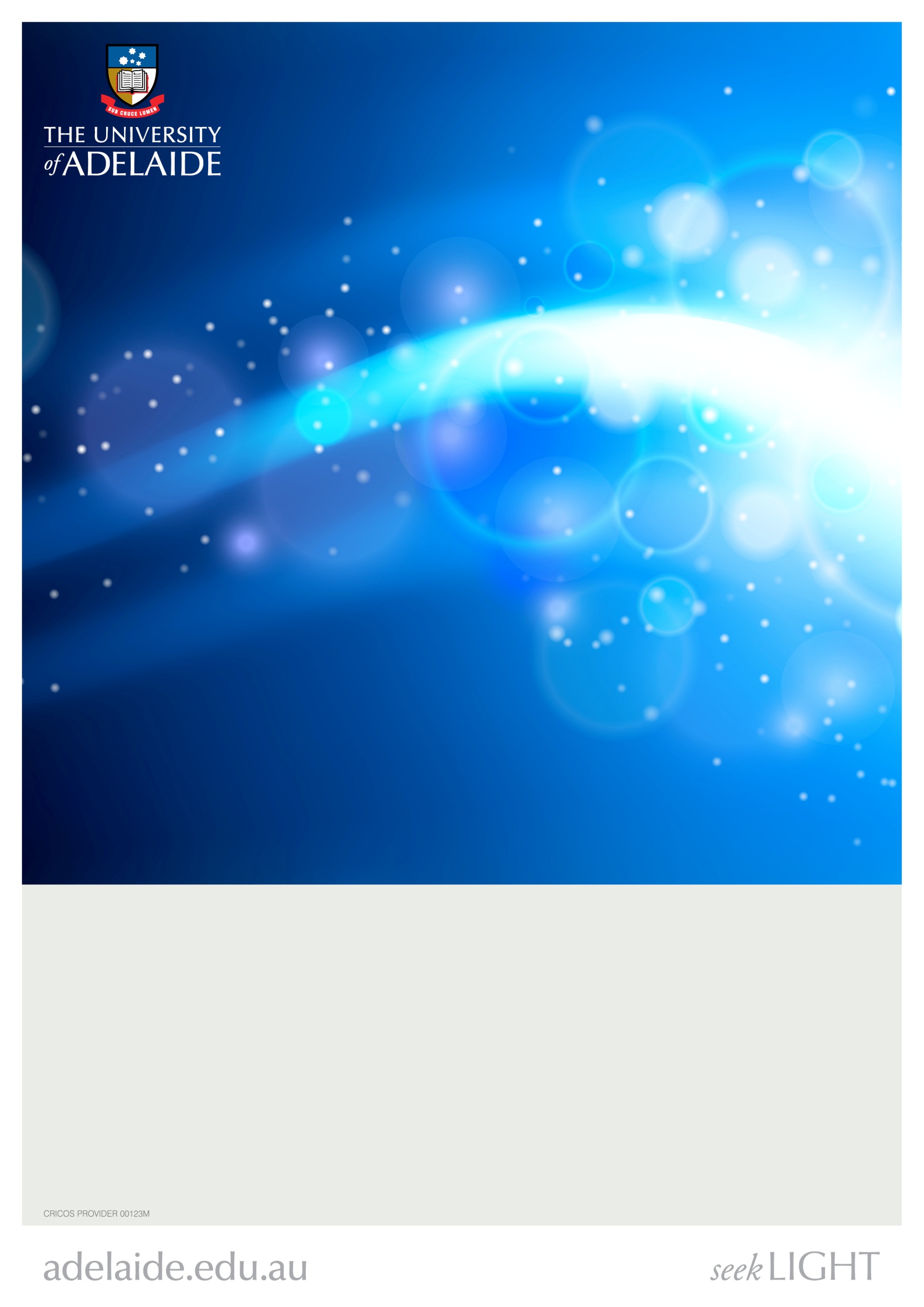
****

**Life Saving Drugs Programme Review: Technical Assessment**

April 2015

## Research Team

*Skye Newton* - Team Leader, Medical HTA1

*Benjamin Ellery* – Research Officer, Horizon Scanning1

*Stefan Fischer* – Health economist, Visiting Fellow2

*Claude Farah –* Senior Research Officer1

*Debra Gum* – Senior Research Officer1

*Zhaohui (Vivian) Liufu* – Senior Research Officer1

*Joanne Milverton* - Research Officer1

*Jacqueline Parsons* – Team Leader, Special Projects1

*Leesa Pridham* - Senior Research Officer1

*Camille Schubert* – Senior Health Economist1{

*David Tamblyn* – Senior Research Officer1

*Tracy Merlin* – Associate Professor and Managing Director1

1Adelaide Health Technology Assessment (AHTA)

School of Population Health

University of Adelaide

Adelaide, South Australia

2Ludwig Boltzmann Institut für Health Technology Assessment, Austria

**Conflicts of interest**

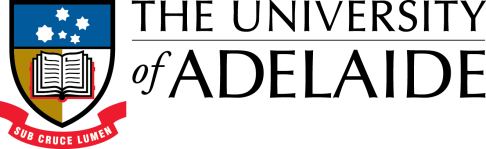
The authors of this document have no financial or other conflicts of interest pertaining to the Life Saving Drug Programme, the drugs reviewed or the conditions assessed.

**Acknowledgements**

Thank you very much to Ms Jenny Ramson from Ampersand Health Science Writing for the plain language summary.

Thank you very much to Professor Deborah Elstein and Professor Raphael Schiffmann for responding so quickly to requests for unpublished information, and to Professor Schiffmann for providing additional data from his 2002 study.

Thank you very much to Mr Thomas Sullivan and Mr Drew Carter for their input on the framework for data collection.

** ****

**contents**

1. Plain language summary 11

2. Technical summary 18

3. INTRODUCTION 34

3.1. The Life Saving Drugs Programme 34

3.2. Objective of the LSDP Review 35

3.3. Scope of the technical assessment 35

4. Systematic literature REVIEW 37

4.1. Systematic review methodology 37

4.2. Critical appraisal of selecte

d evidence 40

4.3. Data extraction and synthesis 41

4.4. Method of review and analysis of currently held data 41

4.5. Data retention and storage 43

4.6. Systematic review results 44

5. Horizon scanning 215

5.1. What is horizon scanning? 215

5.2. Topic eligibility 215

5.3. Method 217

5.4. Results 218

6. International systems comparison 231

6.1. International comparison objective 231

6.2. Research questions 231

6.3. Method 232

6.4. International comparison results 234

6.5. Mechanisms for subsidy 235

7. Appraisal of value metrics 244

7.1. Purpose 244

7.2. Background: Principles of value in the PBS and the LSDP 244

7.3. Method of assessing alternative value metrics 247

7.4. Cost-utility evaluation using QALYs with improved measurement tools and incorporating a broader (societal) perspective 248

7.5. Adjusted Cost-utility analysis: Equity weighted cost-effectiveness 250

7.6. Multi-Criteria Decision Analysis (MCDA) 254

7.7. Input-based pricing 256

7.8. Combined Methods 256

7.9. Summary of advantages and disadvantages of alternative value metrics 256

7.10. Application of value metrics to LSDP drugs 258

7.11. Adjustment to value on basis of uncertainty or risk 264

8. Framework for data collection on rare diseases in Australia 266

8.1. Purpose 266

8.2. Method 266

8.3. Results 267

8.4. Proposed Registry Framework 270

9. Conclusion 289

10. REFERENCES 293

GLOSSARY AND ABBREVIATIONS 323

APPENDIX A 2009 Outcomes of Life Saving Drugs Programme Review 325

Background 325

Appendix B PRISMA flowcharts (ToR 1) 328

Gaucher disease 328

Fabry disease 329

Infantile Onset Pompe Disease 330

Juvenile Onset Pompe Disease 331

Mucopolysaccharidosis Types I, II and VI 332

Paroxysmal Nocturnal Haematuria 333

Appendix C excluded studies (ToR 1) 334

Type I Gaucher disease (imiglucerase and velaglucerase alfa) 334

Miglustat 352

Enzyme Replacement Therapy 357

Fabry disease 368

Infantile Onset Pompe Disease 384

Juvenile Onset Pompe Disease 391

Mucopolysaccharidosis Types I, II & VI 399

Paroxysmal Nocturnal Haematuria 408

APPENDIX D critical appraisal checklists to determine risk of bias (ToR 1) 421

Appendix E study profiles (ToR 1) 426

Medicines to treat Gaucher disease 426

Medicines to treat Fabry disease 430

Alglucosidase alfa to treat Juvenile Onset Pompe disease 439

Medicines to treat MPS I, II, VI 447

Eculizumab to treat Paroxysmal Nocturnal Haematuria 450

APPENDIX F Horizon scanning sources (ToR 2) 465

Appendix G Summary table of drugs which may be relevant to the LSDP (ToR 2) 473

Appendix H International systems comparison data template (ToR 3) 486

Appendix I Summary tables for international comparison 487

Appendix J Quality assurance documentation (ToR 7) 507

Appendix K Example of patient information and consent form for rare diseases registry (ToR 7) 508

**Tables**

Table 1 Terms used to search for evidence to inform the Systematic Review questions (PubMed example) 38

Table 2 NHMRC evidence hierarchy: designations of levels of evidence – (interventional research questions only) 39

Table 3 Interpretation of GRADE evidence ratings (Guyatt et al. 2013) 41

Table 4 Data provided by sponsors 43

Table 5 Criteria for selecting studies to assess the safety and effectiveness of imiglucerase, velaglucerase alfa, and miglustat 47

Table 6 Infection and bleeding risk markers for patients receiving ERT, Vitamin D or a combination 50

Table 7 Adverse events of treatment and Gaucher disease during study period 50

Table 8 Comparison of velaglucerase alfa and imiglucerase on secondary effectiveness measures 52

Table 9 Comparison of adverse events following velaglucerase alfa and imiglucerase 53

Table 10 Quality of life comparison between miglustat and imiglucerase 54

Table 11 Comparison of miglustat and imiglucerase on bone disease markers and bleeding risk 55

Table 12 Comparison of miglustat and imiglucerase on secondary effectiveness measures 56

Table 13 Comparative harms from miglustat and imiglucerase 56

Table 14 Long-term blood count changes with miglustat (after imiglucerase withdrawal) 57

Table 15 Long-term organ volume changes with miglustat (after imiglucerase withdrawal) 58

Table 16 Patients experiencing adverse events during randomised and extension treatment with miglustat 59

Table 17 Most common adverse events from imiglucerase by system organ class (1997-2004) 61

Table 18 Summary of adverse drug reactions associated with velaglucerase alfa 62

Table 19 Summary of adverse drug reactions associated with miglustat 63

Table 20 Number of patients currently treated under the LSDP for Gaucher disease 65

Table 21 Age of those currently receiving treatment on the LSDP 65

Table 22 Gender of patients currently receiving treatment under the LSDP for Gaucher disease 65

Table 23 Doses of imiglucerase on the LSDP for the treatment of Gaucher disease 66

Table 24 Doses of velaglucerase on the LSDP for the treatment of Gaucher disease 66

Table 25 Proportion of Patients with Normal Haemoglobin (g/dL) and improvement from baseline 67

Table 26 Proportion of normal values for Platelet count 67

Table 27 Proportion of patients with normal organ volumes 68

Table 28 Studies included assessing drugs to treat Gaucher disease Type 1 68

Table 29 Criteria for selecting studies to assess the safety and effectiveness of agalsidase alfa and agalsidase beta 73

Table 30 Summary of risk of bias for RCTs assessing the effectiveness and safety of agalsidase-alfa and agalsidase-beta as reported by El Dib 2013 (El Dib, R P, Nascimento & Pastores 2013) 76

Table 31 Comparison of Gb3 levels in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013) 78

Table 32 Creatinine clearance and inulin clearance in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013; Schaefer, Tylki-Szymanska & Hilz 2009; Schiffmann et al. 2001) 79

Table 33 Comparison of changes to glomeruli in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013) (Schiffmann et al. 2001) 80

Table 34 Comparison of ventricular changes in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013; Schaefer, Tylki-Szymanska & Hilz 2009) (Hughes et al. 2008) 81

Table 35 Cardiac outcomes for Fabry patients randomised to receive either agalsidase alfa or placebo (Schaefer, Tylki-Szymanska & Hilz 2009) 82

Table 36 Comparison of Brief Pain Inventory outcomes in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013; Schiffmann et al. 2001) 84

Table 37 Death, Renal events, Cardiac events and cerebrovascular events in Fabry patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) 86

Table 38 Microvascular endothelial Gb3 deposits in patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) (Eng et al. 2001) 87

Table 39 Skin tissue Gb3 deposits in Fabry patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) 88

Table 40 Cardiopulmonary exercise test outcomes in patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) (Schaefer, Tylki-Szymanska & Hilz 2009) 89

Table 41 Pain reported by Fabry patients randomised to receive either agalsidase beta or placebo (Schaefer, Tylki-Szymanska & Hilz 2009) 90

Table 42 Adverse events (rigors, fever, temperature changed sensation and chills) for Fabry patients randomised to receive agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) 92

Table 43 Adverse events (hypertension, vomiting, chest pain, fatigue, headache and pain related to Fabry disease) in Fabry patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) 93

Table 44 Death, cardiac and serious adverse events in Fabry patients randomised to receive either agalsidase alfa or agalsidase beta (El Dib, R P, Nascimento & Pastores 2013) 95

Table 45 Comparison of Gb3 levels in Fabry patients randomised to receive either agalsidase alfa or agalsidase beta (Vedder et al. 2007) 96

Table 46 Changes in creatinine clearance in Fabry patients randomised to receive either agalsidase alfa or agalsidase beta (Vedder et al. 2007) 97

Table 47 Comparison of proteinuria in patients randomised to receive either agalsidase alfa or beta (Schaefer, Tylki-Szymanska & Hilz 2009) (Vedder et al. 2007) 97

Table 48 Left ventricular change in Fabry patients randomised to receive either agalsidase alfa or beta (Vedder et al. 2007) 98

Table 49 Adverse events in Fabry patients randomised to receive agalsidase alfa or agalsidase beta (El Dib, R P, Nascimento & Pastores 2013) 98

Table 50 Summary of safety concerns regarding agalsidase alfa 100

Table 51 Drug-relateda adverse events from Phase III extension studies one Phase IV double-blind study. 102

Table 52 Age of patients currently accessing treatments for Fabry disease on the LSDP 103

Table 53 Average age of first treatment for patients currently accessing treatments for Fabry disease on the LSDP 103

Table 54 Gender of those currently receiving treatment on the LSDP 103

Table 55 Dosing information (mg/kg/2 weeks) for patients currently receiving treatment with agalsidase alfa on the LSDP 104

Table 56 Dosing information (mg/kg/2 weeks) for patients currently receiving treatment with agalsidase beta on the LSDP 104

Table 57 GFR Measures from baseline and 1-2 years after initiation of therapy (first observation only). 105

Table 58 Proportion of patients with normal serum creatinine (SCr) at beginning and last observation by gender 106

Table 59 Concomitant therapies 107

Table 60 Studies included assessing drugs to treat Fabry disease 108

Table 61 Criteria for selecting studies to assess the safety and effectiveness of alglucosidase alfa 111

Table 62 Summary of the results for survival in patients receiving alglucosidase alfa 118

Table 63 Summary of results for ventilation-free survival in patients receiving alglucosidase alfa 119

Table 64 Summary of serious listed adverse events over the period 29 September 2010 to 28 September 2011 123

Table 65 Summary of ADRs– Infantile onset pooled population (Hillmen et al 2007, Nicolino et al 2009) 125

Table 66 Doses of alglucosidase alfa received by Australian patients with infantile onset Pompe disease 129

Table 67 Studies included assessing drug to treat infantile onset Pompe disease 130

Table 68 Natural history survival data for patients with non-classic Pompe’s disease (Winkel, LP et al. 2005) 132

Table 69 Criteria for selecting studies to assess the safety and effectiveness of alglucosidase alfa 133

Table 70 Self-reported physical and mental health scores before and after alglucosidase alfa in patients with JOPD 135

Table 71 Vital capacity before and after alglucosidase alfa in patients with JOPD 136

Table 72 Forced vital capacity before and after alglucosidase alfa in patients with JOPD 137

Table 73 Peak expiratory flow (PEF) and maximum expiratory flow at 50% (MEF 50%) before and after alglucosidase alfa in patients with JOPD 138

Table 74 Forced expiratory volume in 1 second (FEV1) before and after alglucosidase alfa in patients with JOPD 138

Table 75 Pressure, expiratory and inspiratory before and after alglucosidase alfa in patients with JOPD 139

Table 76 Ventilation time before and after alglucosidase alfa in patients with JOPD 140

Table 77 Assisted ventilation requirements before and after alglucosidase alfa in patients with JOPD 140

Table 78 Overnight O2 saturation before and after alglucosidase alfa in patients with JOPD 141

Table 79 Time until hypercapnia before and after alglucosidase alfa in patients with JOPD 141

Table 80 Walking performance on 6MWT (metres) or 10MWT (metres) before and after alglucosidase alfa in patients with JOPD 143

Table 81 Global motor disability on the Modified Walton Scale before and after alglucosidase alfa in patients with JOPD 143

Table 82 Gross motor functioning before and after alglucosidase alfa in patients with JOPD 144

Table 83 Muscle strength measured using hand held dynamometry (HHD) before and after alglucosidase alfa in patients with JOPD 145

Table 84 Manual muscle testing before and after alglucosidase alfa in patients with JOPD 146

Table 85 Muscle functioning outcomes before and after alglucosidase alfa in patients with JOPD 146

Table 86 Motor function measure scale before and after alglucosidase alfa in patients with JOPD 147

Table 87 Grip power before and after alglucosidase alfa in patients with JOPD 147

Table 88 Self- reported fatigue in JOPD patients on FSS before and after alglucosidase alfa 148

Table 89 Changes to gastrointestinal symptoms after alglucosidase alfa in JOPD patients 149

Table 90 Weight changes in JOPD patients after alglucosidase alfa 149

Table 91 Swallowing function before and after alglucosidase alfa in a patient with JOPD 150

Table 92 Walking performance on 6MWT (metres) or 10MWT (metres) before and after alglucosidase alfa in patients with JOPD and adult-onset Pompe disease 150

Table 93 Studies included assessing alglucosidase alfa for juvenile onset Pompe disease 153

Table 94 Criteria for selecting studies to assess the safety and effectiveness of laronidase, idursulfase, and galsulfase 158

Table 95 Lung function and exercise tolerance after laronidase and placebo 161

Table 96 Sleep evaluation, joint movement and level of disability after receiving laronidase or placebo 162

Table 97 Infusion-related reactions to laronidase or placebo 163

Table 98 Development of antibodies and compliance with laronidase or placebo treatment 163

Table 99 Change in liver volume in MPS I patients treated with laronidase (Clarke et al. 2009) 164

Table 100 Changes in clinical endpoints for MPS I patients treated with laronidase (Clarke et al. 2009) 165

Table 101 Summary of changes from baseline to week 53 for MPS II patients randomised to idursulfase weekly, idursulfase every other week or placebo (Muenzer et al. 2006) 168

Table 102 Treatment difference in primary efficacy outcome for MPS II patients randomised to idursulfase weekly, idursulfase fortnightly, or placebo (Muenzer et al. 2006) 169

Table 103 Change in liver and spleen volumes in MPS II patients randomised to idursulfase weekly, idursulfase every other week or placebo (Muenzer et al. 2006) 169

Table 104 Number and percentage of MPS II patients with adverse events occurring at least 9% more frequently in idursulfase-treated patients than in placebo-treated patients (Muenzer et al. 2006) 170

Table 105 Long-term outcomes for MPS II patients receiving idursulfase in a 2 year open label extension study (Muenzer et al. 2011) 171

Table 106 Distance walked in a 12 minute walk test for MPS VI patients randomised to either galsulfase or placebo (Harmatz et al. 2006) 173

Table 107 Distance walked in a 12 minute walk test for MPS VI patients receiving galsulfase in extension study (Harmatz et al. 2006) 173

Table 108 Comparison of 3 minute stair climb for MPS VI patients randomised to either galsulfase or placebo (Harmatz et al. 2006) 174

Table 109 Comparison of 3 minute stair climb for MPS VI patients receiving galsulfase in extension study (El Dib, R P. & Pastores 2009) 174

Table 110 Forced vital capacity and maximum voluntary ventilation in patients randomised to either galsulfase or placebo (Harmatz et al. 2006) 175

Table 111 Number of patients experiencing adverse events during weeks 1 to 24 in MPS VI patients randomised to either galsulfase or placebo (Harmatz et al. 2006) 175

Table 112 Adverse drug reactions to laronidase (Genzyme 2007) 176

Table 113 Adverse reactions to idursulfase during reporting period (Shire Pharmaceuticals 2011) 179

Table 114 Frequency of adverse drug reactions to idursulfase (Shire Pharmaceuticals 2011) 180

Table 115 Summary of important identified and potential risks and missing information for galsulfase (BioMarin Pharmaceuticals Inc. 2014) 181

Table 116 Frequency of adverse drug reactions with galsulfase (BioMarin Pharmaceuticals Inc. 2014) 182

Table 117 Characteristics of patients with MPS and treatment through LSDP 184

Table 118 Studies included assessing drugs to treat mucopolysaccharidoses (MPS) I, II and VI 185

Table 119 Criteria for selecting studies to assess the safety and effectiveness of eculizumab 189

Table 120 The effect of eculizumab on survival in PNH patients 195

Table 121 Effectiveness of eculizumab on transfusion requirements in the TRIUMPH trial 196

Table 122 Mean number of packed red blood cells administered to patients receiving transfusions over the course of the study 197

Table 123 The effect of eculizumab on quality of life in the TRIUMPH trial 199

Table 124 Thromboembolism events in patients with and without eculizumaba 201

Table 125 Effect of 6-month eculizumab treatment on renal function (change in stage of CKD with treatment)\* 202

Table 126 Effect of long-term eculizumab treatment on renal function 203

Table 127 Adverse events in the TRIUMPH trial 205

Table 128 Baseline characteristics across the data sources for patients receiving eculizumab 210

Table 129 Dosing across the data sources for patients receiving eculizumab 211

Table 130 Laboratory outcomes: LDH and Haemoglobin 213

Table 131 Fatigue and hospitalisations 214

Table 132 Studies included assessing drugs to treat paroxysmal nocturnal haemoglobinuria (PNH) 214

Table 133 Incidence of conditions that could be considered rare 216

Table 134 Search terms for horizon scanning 217

Table 135 Direct therapeutic approaches to treat rare genetic diseases 222

Table 136 Search terms to identify policy approaches by international systems (Embase.com example) 233

Table 137 Definition of rare and/or ultra-rare diseases 237

Table 138 Incentives to seek orphan drug designation in Australia, the EU and USA 238

Table 139 Overview of Managed Entry Arrangements (MEAs) identified across five European countries, described by country and design 243

Table 140 Example of different domains included in published MCDA applicable to drug evaluations. 255

Table 141 Advantages and disadvantages of alternative value metrics for the assessment of orphan drugs for reimbursement decisions 257

Table 142 Summary of the value metrics discussed 258

Table 143 Relevant considerations of alternative value methodologies for existing LSDP drugs 259

Table 144 Identification of outcomes identified in the systematic review of clinical evidence, their applicability to quantitative value assessment and other available economic analyses for existing drugs on the LSDP 262

Table 145 Questions to consider regarding the necessity of a registry 272

Table 146 Questions to consider regarding the collection of eligibility data 273

Table 147 Questions to consider regarding the collection of cost data 274

Table 148 Questions to consider regarding the collection of efficacy data 276

Table 149 Commonwealth and State privacy legislation 284

Table 150 Proposed data elements for a drug surveillance register 287

Table 151 Methodological checklist: systematic reviews (AMSTAR; Shea et al 2009) 421

Table 152 Methodology checklist: randomised controlled trials (SIGN 50) 423

Table 153 Methodology checklist: cohort studies (SIGN 50) 424

Table 154 Methodology checklist: case series (NHS CRD; Khan 2001) 425

Table 155 Study profiles for studies on alglucerase/imiglucerase vs standard therapy 426

Table 156 Study profiles for studies on velaglucerase alfa (compared to imiglucerase or extension studies subsequent to trial) 428

Table 157 Study profiles for studies on miglustat (compared to imiglucerase or extension study) 429

Table 158 Study Profiles for systematic reviews assessing agalsidase alfa and agalsidase beta 430

Table 159 Study profiles for studies on alglucosidase alfa 432

Table 160 Study profiles alglucosidase alfa to treat juvenile onset Pompe disease 439

Table 161 Study profiles for studies on laronidase for MPS I 447

Table 162 Study profiles for studies on idursulfase for MPS II 448

Table 163 Study profiles for studies on galsulfase for MPS VI 449

Table 164 Study profiles for included studies on eculizumab 450

Table 165 Demographic and baseline characteristics for patients in the TRIUMPH trial 459

Table 166 Kidney disease outcomes quality initiative (CKD stages) 461

Table 167 Body of evidence profiles (modified GRADE output) 461

Table 168 Summary of findings table (modified GRADE output) 463

Table 169 Overview of systematic reviews (modified GRADE output) 464

Table 170 Horizon scanning sources used to address ToR 2 465

Table 171 Summary table of selected new and emerging drugs that target diseases/conditions of potential relevance to the Life Saving Drugs Program in the future (ToR 2) 473

Table 172 Example of evidence table (ToR 3) 486

Table 173 Funding bodies and coverage 487

Table 174 Mechanisms for the evaluation of drugs for rare diseases, summary by country 489

Table 175 Basis of the decision to reimburse drugs for orphan diseases, summary by country 495

Table 176 Monitoring outcomes of the decision to reimburse, summary by country. 505

Table 177 Example of quality assurance documentation 507

**figures**

Figure 1 Sex distribution across MPS Types for patients receiving drugs through the LSDP 183

Figure 2 Governance structure and direction of information flow 282

Figure 3 PRISMA flowchart for literature on Gaucher Type I disease (imiglucerase, velaglucerase alfa and miglustat) 328

Figure 4 PRISMA flowchart for literature on Fabry disease (agalsidase alfa, agalsidase beta) 329

Figure 5 PRISMA flowchart for Infantile Onset Pompe Disease (alglucosidase alfa) 330

Figure 6 PRISMA flowchart for literature on Juvenile Onset Pompe Disease (alglucosidase alfa) 331

Figure 7 PRISMA flowchart for literature on Mucopolysaccharidosis Types I, II and VI disease (laronidase, idursulfase, galsulfase) 332

Figure 8 PRISMA flowchart for literature on PNH (eculizumab) 333

# Plain language summary

The technical assessment described in this document was carried out to provide information to the Australian Government Department of Health as part of the Life Saving Drugs Programme (LSDP) Review. The objective of the Review was to examine important issues such as access and equity, value for money and the future administration of the LSDP.

The technical assessment included consideration of:

* the effectiveness and safety of drugs currently funded through the LSDP;
* treatments and diseases for which funding through the LSDP may be sought in the future;
* international approaches to defining rare diseases and funding drugs that treat those diseases; and
* the value for money of the currently funded drugs.

The technical assessment also aimed to establish a framework for collecting data on rare diseases in Australia and to assess how this could function internationally.

### What is the LSDP?

The LSDP provides subsidised access for eligible individuals to expensive and potentially life-saving drugs for rare life-threatening diseases. The issues considered during the assessment process involve:

* the review of the evidence presented by the drug sponsor; and
* whether the drug is suitable for listing on the Pharmaceutical Benefits Scheme (PBS) (drugs considered cost-effective are listed on the PBS).

### Clinical effectiveness and safety of currently subsidised medications

To assess whether new information on the safety and effectiveness of drugs currently funded through the LSDP supports the original funding recommendation:

* systematic reviews of the evidence on these drugs were carried out; and
* Australian data on their use was analysed.

The findings of the technical assessment are summarised below.

#### Gaucher disease Type I

Gaucher disease is a rare condition caused by an inherited enzyme deficiency. Type I is the most common form, with symptoms including enlarged spleen and liver, increased risk of bleeding, anaemia and bone complications. Treatments funded through the LSDP include the enzyme-replacement therapies, imiglucerase and velaglucerase, and a substrate reduction therapy, miglustat. The sponsor of miglustat proposed it as an alternative treatment for individuals unable to tolerate or follow a course of enzyme-replacement therapy.

Findings from the systematic review and analysis of Australian data are as follows.

* A small high quality study found that treatment with imiglucerase reduced the risk of disease-related complications compared to use of Vitamin D alone.
* No new studies on velaglucerase were identified. A study previously submitted to the PBAC found velaglucerase to be similar to imiglucerase in reducing the risk of bleeding, bone complications and enlarged liver and spleen, with a slightly higher risk of mild side effects.
* No new studies on miglustat were identified. Some data that had not been submitted to the PBAC showed that patients receiving miglustat had higher chitotriosidase (a marker of disease burden) than patients receiving imiglucerase.
* Australian data showed that individuals receiving enzyme-replacement therapy for Type 1 Gaucher disease have improvements in bleeding risk, anaemia and spleen and liver size following treatment. No patients in Australia are currently receiving miglustat.

The evidence supports the funding of imiglucerase and velaglucerase. The evidence on miglustat did not include any data on the treatment group proposed by the drug’s sponsor.

#### Fabry disease

Fabry disease is a very rare condition caused by an inherited enzyme deficiency. Due to the lack of the enzyme, a substance builds up in multiple organs and tissues and causes kidney and heart disease, stroke, and pain in the hands and feet. Treatments funded under the LSDP include the enzyme-replacement therapies, agalsidase alfa and agalsidase beta.

Findings from the systematic review and analysis of Australian data are as follows.

* Moderate quality evidence found reduced pain with agalsidase alfa treatment compared with placebo. Low quality evidence suggested that there was no difference in heart and kidney function between treatment and placebo.
* A very small study of low quality found that heart function was better in individuals receiving agalsidase beta than in individuals receiving placebo.
* Limited Australian data showed that kidney function was slightly reduced in individuals receiving agalsidase alfa and slightly improved in individuals receiving agalsidase beta.

No new evidence was found to change the conclusion on funding of treatments for Fabry disease.

#### Infantile-onset and Juvenile-late onset Pompe disease

Pompe disease is caused by an inherited enzyme deficiency, which leads to multisystem disease and often to early death. Symptoms of infantile-onset Pompe disease include enlarged heart, low muscle tone, breathing difficulties, muscle weakness, feeding difficulties and failure to thrive. Juvenile-late onset Pompe disease has milder symptoms and tends to progress more slowly. Alglucosidase alfa is funded under the LSDP for the treatment of infantile-onset and juvenile-late onset Pompe disease.

Findings from the systematic review and analysis of Australian data are as follows.

* No new studies were identified but longer-term data provide low quality but consistent evidence that alglucosidase alfa prolongs survival in infants with infantile Pompe disease.
* Very poor quality data suggested that treatment of juvenile-late onset Pompe disease with alglucosidase alfa improves lung and muscle function.
* Australian data on infants receiving treatment for infantile-onset Pompe disease were not analysed due to confidentiality concerns. Treatment for juvenile-late onset Pompe disease has only recently been made available.

No new evidence was found to change the conclusion on funding of treatments for infantile-onset and juvenile-late onset Pompe disease.

#### Mucopolysaccharidosis Types I, II and VI

Mucopolysaccharidoses are severe conditions caused by the absence or reduced function of specific enzymes, which results from gene mutations and leads to the build-up of substances that cause permanent cell damage and progressive deterioration of organs and tissues.

Symptoms include reduced lung and heart function and joint problems for type I; neurological impairment, bone disease and reduced lung and heart function for type II; and skeletal abnormalities and reduced lung, heart and blood vessel function for type VI. Treatments for mucopolysaccharidosis funded under the LSDP include the enzyme-replacement therapies, laronidase (type I), idursulfase (type II) and galsulfase (type VI).

Findings from the systematic review and analysis of Australian data are as follows.

* A follow-up study found that lung function, activities of daily living and mobility improved or remained stable among individuals receiving laronidase over 3.5–4 years.
* A follow-up study found that mobility, joint flexibility and liver and spleen size improved or remained stable in individuals receiving idursulfase over 3 years. Lung capacity improved among individuals aged ≤18 years and decreased slightly among those aged >18 years.
* An extension of a study on galsulfase provided to the PBAC was identified but no new data could be extracted.
* Australian data on individuals with mucopolysaccharidosis types I, II and VI were insufficient to allow conclusions to be made about the effectiveness or safety of treatments.

The new data are unlikely to change the conclusion on the funding of drug for the treatment of mucopolysaccharidosis types I, II and VI.

#### Paroxysmal Nocturnal Haemoglobinuria

Paroxysmal nocturnal haemoglobinuria is a rare, genetically acquired,life-threatening disease in which red blood cells are destroyed by the immune system. Common symptoms include fatigue, breathlessness, recurrent abdominal pain, difficulty swallowing, chest pain and high blood pressure in the blood vessels of the lungs. The risk of blood clots is also increased.

Findings from the systematic review and analysis of Australian data are as follows.

* One new study of poor quality supported the claim that eculizumab treatment extends survival in individuals with paroxysmal nocturnal haemoglobinuria.
* As no baseline data on individuals receiving eculizumab were available, the effect of treatment could not be assessed.

No new evidence was found to change the conclusion on funding of treatments for paroxysmal nocturnal haemoglobinuria.

### Treatments and diseases for which funding may be sought in the future

The technical assessment considered treatments and diseases that could be relevant to the LSDP in the near future. Factors of relevance to the future sustainability of the LSDP include:

* basing inclusion in the LSDP on rarity of the disease — with growing knowledge of the genetic mutations that cause conditions, diseases previously considered common are being divided into many different rare subtypes that can be individually targeted with drugs that may be considered eligible for the LSDP;
* defining ‘rare’ — with a definition of ≤1 in 100,000, some conditions (e.g. cystic fibrosis, Huntingdon’s disease, motor neurone disease) would be too common for drugs to be listed on the LSDP (unless rare subtypes are considered), while with a definition of <1 in 2,000, subtypes of common conditions (e.g. melanoma, lung cancer) could potentially be identified and targeted with drugs that would be eligible for the LSDP;
* emerging clinical treatments for severe diseases —treatment types of growing importance are monoclonal antibodies and gene therapies; and
* treatment of rare diseases with drugs that are already used to treat other more common conditions.

Various drugs were identified that could potentially be relevant to the LSDP. However, the data were too limited to determine the exact nature of the populations being targeted by the sponsors of these drugs.

### International approaches to defining rare diseases and funding drugs

Internationally, ‘rare disease’ is frequently defined by legislation, which often aims to provide incentives for industry to develop and market drugs to prevent, diagnose or treat rare diseases. The definition of rare disease varies between countries, ranging from 1 in 500,000 in China to <1 in 1,500 in the United States. The European Union defines a rare disease as occurring in ≤1 in 2,000 people. For the purpose of orphan drug registration, the Australian Therapeutic Goods Act defines a rare disease as one that has fewer than 2,000 patients, which is approximated as a prevalence of 1 in 10,000 persons.

#### Funding drugs for rare diseases

Australia has no specific evaluation program for drugs for rare diseases (DRDs). However, a DRD can be considered to be reimbursed through the LSDP if the PBAC accepts its clinical effectiveness but rejects its listing on the PBS as the DRD does not meet the cost-effectiveness criterion. Many funding bodies in other countries allow special consideration for drugs developed to treat rare diseases (‘orphan drugs’), including relaxed pharmacoeconomic evaluation requirements, higher cost-effectiveness thresholds, consideration of a broader societal perspective, acceptance of poorer quality evidence, or placement of greater weight in decision-making on the lack of alternative treatments.

Evaluation and funding mechanisms specific to orphan drugs exist in the Netherlands, Italy, England, Wales, and Canada (Ontario and Alberta). In Japan, 56 diseases are considered eligible for public funding. Managed entry schemes are used for orphan drugs in parts of Europe, using either performance-based risk sharing or financial-based schemes.

Approaches to monitoring pricing and funding decisions include requiring submission of a revised report 1.5–3 years after approval (Belgium); reappraisal of evidence after 3 years (the Netherlands) or 5 years (United Kingdom); or limiting listing validity to 5 years (France).

### Assessing value for money

The technical assessment identified published literature on methods to determine ‘value’ that could potentially be applied to orphan drugs and the LSDP. Alternative approaches to routine cost-utility analyses identified were:

* cost-utility evaluation, broadened to include the impact of the disease or condition on family and carers as well as individuals;
* equity-weighted cost-utility evaluation incorporating societal preferences for equity and social justice with greater preference on treatments that are: life-saving; treat more severe diseases; and affect the socio-economically disadvantaged, children, people with dependents etc.;
* Multi-Criteria Decision Analysis, an alternative ‘scoring’ framework that assesses treatments across a range of relevant domains (e.g. effectiveness and safety, economic impact and considerations such as severity of the disease, equity/ethical and social implications of the drug, or current health policy goals); and
* input-based costing, which considers only the costs associated with the development and production of the drug (not the health benefits).

Combinations of methods could be utilised with careful consideration to avoiding duplication.

### Data collection framework

Due to the small number of patients with rare diseases in Australia, it is suggested that Australian physicians and individuals with rare diseases be encouraged to participate in international registries, where they exist.

Elements that should be considered in developing a registry include:

* the purpose of the registry (i.e. evaluating eligibility for ongoing access to drugs, costs of the drug and management of the condition and safety and effectiveness of a drug; using cost, safety and effectiveness measures to facilitate risk-share agreements between sponsors and Government; and ensuring access to data by key stakeholders);
* the best method for data collection (i.e. one that balances ease of use and the amount of detail required, so that the data collected fits the purpose and is not an unreasonable burden on individuals, their families or the treating physician — questions need to be clear and unambiguous, with explicit definitions for each data item);
* quality assurance processes to ensure completeness of data and compliance (e.g. prompts, clear instructions, data dictionaries, automated reminders, cross-checking with external sources, clarification with data provider to correct spurious or missing data, an audit trail of changes, and reporting of common errors to enable ongoing improvements);
* governance structures (including key stakeholders involved in developing and maintaining the registry and reporting to Government, the public and funders of the registry);
* maintenance of privacy and appropriate consent or assent for the collection of data; and
* resourcing and funding (including initial set-up costs and the ongoing running costs).

### Conclusion

This technical assessment has shown that most of the drugs currently funded by the LSDP are clinically effective and with an acceptable safety profile. However, there are warning signs that the LSDP is unlikely to be sustainable in the future, given current patterns of drug development and marketing. Lessons learned from international experience in the public funding of orphan drugs and from economic theory show a range of approaches that might be adopted to work towards a sustainable LSDP. One of these approaches could include the development of a drug surveillance registry to help determine whether each drug performs as expected.

# Technical summary

Purpose

The purpose of this technical assessment was to inform the Life Saving Drugs Programme (LSDP) Review, being undertaken by the Australian Government Department of Health, as part of the Government‘s Post-market Reviews programme.

The objective of the LSDP Review is to examine important issues such as access and equity, value for money and the future administration of the Programme.

Review questions

The Terms of Reference (ToR) for the LSDP Review are given below. This technical assessment addresses those ToRs which are in bold.

1. **Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.**
2. **Review emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future.**
3. **Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.**
4. Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the LSDP.
5. **Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug’s treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.**
6. Review the administration of the LSDP, including the Guidelines with which the programme is administered for each condition, and assess alternative administration systems.
7. **Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.**

Method

With input from the Reference Group, a protocol was developed to guide the conduct of the technical assessment. It outlined the project scope, research questions, and for the systematic review questions it provided the criteria for selecting and critically appraising studies, templates for extracting data and methods for synthesising the results obtained from the evidence-base. The review methods differed depending on the question being addressed.

The protocol was closely followed in order to maintain transparency and, for the systematic review questions, to ensure that there was no bias in study selection, appraisal or interpretation.

## Review of the clinical effectiveness and safety of medicines currently subsidised through the LSDP

All of the evidence on the drugs currently funded through the LSDP was systematically reviewed. The aim was to determine whether new information was available on the safety and effectiveness of these drugs since they were recommended for inclusion on the LSDP. The primary determinant of treatment effectiveness in the systematic reviews was ‘survival’, and secondary outcome measures were ‘quality of life’, other outcomes related to individual disease features, and adverse events related to treatment. Conclusions derived from the evidence were graded according to the degree of confidence in the estimate of effect for each safety and effectiveness outcome. High quality evidence on a directly patient-relevant outcome was rated as GRADE ⨁⨁⨁⨁; and low quality evidence was rated as GRADE ⨁⨀⨀⨀. The new evidence that was obtained (from the literature, as well as an analysis of Australian individual patient data) was assessed as to whether the findings supported, or were likely to change, the original recommendations for these drugs.

### Medicines to treat Gaucher disease – specifically, imiglucerase, velaglucerase and miglustat

| Imiglucerase |
| --- |
| New publications since original recommendations: No formal submission was received for consideration of imiglucerase funding. One randomised controlled trial (RCT) was identified (Schiffmann et al. 2002).  Impact on original recommendation: The trial findings supported the decision to fund alglucerase / imiglucerase for patients with Type 1 Gaucher disease; demonstrating that alglucerase / imiglucerase was superior at reducing the risk of bleeding and indicators of bone disease to receiving vitamin D alone. It is unknown, based on the current data, whether alglucerase / imiglucerase would result in a substantial extension of lifespan.  Australian data: Patients receiving alglucerase / imiglucerase had, on average, improvements in haemoglobin levels, platelet counts and spleen and liver volumes when compared to pre-treatment levels; supporting the use of these enzyme replacement therapies for Type 1 Gaucher disease. |

The funding request for the first drugs under the LSDP – namely, alglucerase, or the drug which superseded it, imiglucerase – was not supported by a formal industry submission. A small but high quality randomised trial was identified during the systematic review that reported that the enzyme replacement therapies were superior to receiving vitamin D alone (a component of standard therapy) in terms of reducing bleeding risk (haemoglobin and platelet count) in splenectomised patients with Type 1 Gaucher disease (GRADE ⨁⨁⨁⨀). Other outcomes, such as bone marrow fat fraction (a surrogate marker for bone disease risk) also favoured treatment with alglucerase / imiglucerase. The evidence therefore supported the decision to fund imiglucerase for Type 1 Gaucher disease.

| Velaglucerase alfa |
| --- |
| New publications since original recommendations: Nil.  Impact on original recommendation: Not applicable.  Australian data: Patients receiving velaglucerase alfa had, on average, improvements in haemoglobin levels, platelet counts and spleen and liver volumes compared to pre-treatment levels, supporting the use of this enzyme replacement therapy for Type 1 Gaucher disease. |

No new randomised trials were identified that assessed velaglucerase alfa. One high quality randomised trial, which was used in the submission to the Pharmaceutical Benefits Advisory Committee (PBAC), showed that velaglucerase alfa was non-inferior to imiglucerase, with no statistically significant differences in measures of bleeding risk (haemoglobin and platelet count), liver or spleen volume, or in a marker of disease burden (chitotriosidase level) (GRADE ⨁⨁⨁⨀). Adverse events were marginally higher in the group receiving velaglucerase alfa than imiglucerase, but were reportedly mild in severity.

| Miglustat |
| --- |
| New publications since original recommendationsImpact on original recommendation: No new *studies* were identified, but data that were not provided in the submission to the PBAC were identified in another publication (European Medicines Agency 2003)  Impact on original recommendation: Patients receiving miglustat had higher chitotriosidase levels (a marker of disease burden) than patients receiving imiglucerase.  Information withheld from this draft report at the request of the drug sponsor.  Australian data: '''''''' '''''''''''''''''''' ''''' ''''''''''''''''''''''' ''''''''' ''''''''''''''''''' '''''''''''''''''''''' ''''''''''''''''''' ''''''''''''''''''' '''''''' '''''''''''''' |

No new randomised trials were identified that assessed miglustat. The sponsor for miglustat proposed that the drug may be used in patients with Type 1 Gaucher disease who cannot tolerate enzyme replacement therapy (ERT; i.e. imiglucerase or velaglucerase alfa), or who are not able to follow the approved treatment regimen for ERT. There were no trials identified in the systematic review that compared miglustat and standard therapy in this proposed population.

An open-label randomised trial, that compared miglustat to imiglucerase, reported that patients who received miglustat had a higher quality of life, with greater convenience associated with use of the oral drug, as compared to the imiglucerase infusion which takes one to two hours (GRADE ⨁⨁⨁⨀). There was a disproportionate loss to follow-up in the miglustat treatment arm, so these results should be interpreted cautiously. Liver and spleen volume changes and haemoglobin levels did not differ significantly between those receiving miglustat, and those receiving imiglucerase, but patients receiving imiglucerase had better platelet counts (GRADE ⨁⨁⨁⨀). Disease burden Risk of bone disease (as measured by a change in chitotriosidase levels) was 33% higher in those receiving miglustat than in those receiving imiglucerase (0.3% decrease in chitotriosidase) (GRADE ⨁⨁⨁⨀). Gastrointestinal adverse events occurred in all patients receiving miglustat, and only in half of those receiving imiglucerase.

### Australian data registry information - imiglucerase, velaglucerase and miglustat

Data were obtained from the Australian Registry on 61 patients with Gaucher disease currently receiving drugs on the LSDP. The mean age of patients currently receiving treatment is 45±17.7 years, and there are a similar number of male and female patients. More than three quarters of patients experienced an improvement in haemoglobin between baseline and follow-up. Only a quarter of patients had normal values for platelet count at baseline (≥150 x 109/L), compared to 64% at last follow-up. At baseline, less than 10% of patients had normal spleen volumes (≤5 multiples of normal), compared to 93% at follow-up.

### Medicines to treat Fabry disease – algalsidase alfa and agalsidase beta

Both agalsidase alfa and agalsidase beta were compared against standard therapy (with/without placebo), and against each other. Two randomised controlled trials (RCTs) were identified in the systematic review that compared agalsidase alfa with standard therapy, three RCTs compared agalsidase beta with standard therapy and one RCT compared agalsidase alfa and beta. All six RCTs and associated open-label extension studies were identified in two published systematic reviews. One of the RCTs identified for agalsidase beta was published after the submission to the PBAC was considered.

| Agalsidase alfa |
| --- |
| New publications since original recommendations: Nil.  Impact on original recommendation: Not applicable.  Australian data: Patients receiving agalsidase alfa had a slightly reduced average glomerular filtration rate (GFR), which is contrary to the claim made in the submission to the PBAC that GFR would improve or remain stable. The Australian results are difficult to interpret given the small sample sizes and varying follow-up times. |

There were no direct measures of survival in the trials comparing agalsidase alfa with standard therapy. Pain severity was measured in one RCT using the Brief Pain Inventory tool and found that severe pain was significantly reduced for patients given agalsidase alfa compared to those given placebo (GRADE ⨁⨁⨁⨀). On a scale of 0 to 10, patients receiving agalsidase alfa reported on average 2 points less than those receiving placebo, which is likely to be clinically important. Patients taking agalsidase alfa lasted an average of 74.5 days without pain medications, compared to those taking placebo, who lasted only 12.9 days without pain medication (p = 0.02). The Brief Pain Inventory was also used to measure quality of life, and the result showed a non-significant trend favouring the agalsidase alfa group (GRADE ⨁⨁⨁⨀).

Kidney function was assessed with surrogate measures of Gb3 levels in plasma and urine sediment, and tissue Gb3 levels in the kidney and myocardium. There was no statistically significant difference found between patients receiving agalsidase alfa or placebo in the small studies identified, but results trended towards favouring agalsidase alfa (GRADE ⨁⨁⨀⨀). Other surrogate measures in the trial also showed minimal or no difference between agalsidase alfa and placebo (creatinine clearance in nmol/g, inulin clearance ml/min, glomeruli nmol/24 hours); although it is likely that the studies were underpowered to find a difference (GRADE ⨁⨁⨀⨀). The group receiving placebo had a reduction in inulin clearance which was three times that in patients receiving agalsidase alfa. Creatinine clearance was marginally improved in those taking agalsidase beta, but significantly declined in those taking placebo (p = 0.02).

In another RCT there was no significant difference between groups on surrogate measures of cardiac function, however, the study only had a total of 14 patients (GRADE ⨁⨁⨀⨀).

| Agalsidase beta |
| --- |
| New publications since original recommendations: One new RCT (Bierer et al. 2006) with 6 patients  Impact on original recommendation : The new RCT supported the evidence already provided in the submission to the PBAC, that cardiac function was better in patients receiving agalsidase beta than placebo (although the study was too small to detect a statistically significant difference).  Australian data: Patients receiving agalsidase beta had a small absolute improvement in average glomerular filtration rate (GFR), supporting the claim that agalsidase beta has clinical advantages over standard management. |

One high quality RCT comparing agalsidase beta with standard treatment plus placebo found that differences in mortality rate between the treatment groups were small (deaths were 1/51 in agalsidase beta group and 0/31 in placebo group), and possibly due to chance (GRADE ⨁⨁⨁⨁). There were no statistically significant differences in the rate of serious adverse event rates (cardiac, cerebrovascular and renal events), although the frequency of renal events, cardiac events and cerebrovascular events were reduced in the agalsidase beta group (GRADE ⨁⨁⨁⨁). Gb3 levels (a surrogate for renal function) were found to be significantly lower in patients randomised to agalsidase beta compared to standard therapy when measured in several ways (including plasma and urine concentrations, skin histological scores, microvascular endothelial deposits); however, the trial from which these results were reported was assessed as having a serious risk of bias (GRADE ⨁⨀⨀⨀).

Cardiopulmonary outcomes were measured in one “RCT” of 6 patients comparing agalsidase beta and standard therapy, and while favouring the group receiving the drug, the low power of the study meant that the difference was not statistically significant (GRADE ⨁⨀⨀⨀). Pain was measured using the McGill Pain Questionnaire in another RCT and found an improvement in both treatment arms, but no significant difference between the groups, so a placebo effect could not be ruled out (GRADE ⨁⨁⨀⨀). Patients randomised to agalsidase beta had a significantly higher risk of fever, rigors, chills, hypertension and temperature changed sensation (GRADE ⨁⨁⨀⨀).

One low quality RCT compared agalsidase alfa and agalsidase beta. No significant differences were found on measures of effectiveness (GRADE ⨁⨀⨀⨀). One death reported in the alfa group was considered to be unrelated to the drug. The frequency of other serious adverse events (atrial fibrillation, other events not requiring hospitalisation), frequency of any adverse event, kidney and cardiac outcomes did not favour either drug (GRADE ⨁⨀⨀⨀).

### Australian data registry information – agalsidase alfa and agalsidase beta

Data relating to drugs for Fabry disease on the LSDP were obtained from Australian Registry Data. ''' ''''''''' ''''' ''''' '''''''''''''''' ''''''''' ''''''''''' ''''''''''''' '''''' '''''''''''''''''' '''''''''''''''' ''''''''''''''''' '''''' ''''''' '''''''''' ''''''' '''''''''''''''' ''''' ''''''''''''''''' '''''' ''''''''''''''' '''''''''''''''''''' '''''' '''' ''' '''''''' '''''''''' ''''' '''''' ''''' '''''''''''''''''''' ''''''''' The mean age of patients at first treatment was 41 years. '''''''' '''''''''' ''''''''' ''''' '''''''''''''''''' ''''''' '''''''' '''''''''' '''''''''''''''''''''''''''''''' ''''''''''' ''''''''''' ''''' '''''' ''''''''''''''''''''''''' ''''''''' ''''' ''''''' '''''''''''''''''''''''''''''''' ''''''' '''''' ''''''''''' ''''''''' ''''' ''''''''''''''''''''' '''''''' ''''''' ''''''''''' '''''''''''''''''''''''''''''''' '''''''''''' '''''' '''''''''''''''''''''''''''''' ''''''''' ''''' ''' ''''''''''''''''''''''''''''''''' Patients receiving agalsidase alfa had a slightly reduced average glomerular filtration rate (GFR), whereas patients receiving agalsidase beta had a small mean absolute increase of GFR. The small sample sizes mean that it is difficult to determine whether these differences are due to chance or whether they are clinically meaningful. The majority of patients (84.7%) had normal serum creatinine at baseline (60-130 µMol/L for males and 40-110 µMol/L for females) (QML Pathology 2009), which was slightly reduced at last follow-up (77.8%). Anti-platelets were commonly prescribed as secondary therapy (73.1% of Fabry patients received them), and statins were used by 69.8% of patients.

### Alglucosidase alfa to treat Infantile Onset Pompe Disease

| Alglucosidase alfa |
| --- |
| New publications since original recommendations: No new studies were identified, but two new publications (Kishnani, P S et al. 2009; Nicolino, M. et al. 2009) provided longer term data for one of the historical control studies presented in the submission to the PBAC.  Impact on original recommendation: The new data supports the conclusion that alglucosidase alfa prolongs survival in infants with infantile onset Pompe disease.  Australian data: Information in this section has been withheld from this draft report at the request of the drug sponsor.  ''''''''''' ''''''''''''''''''' ''''''''''''''''''''' '''''''''''''''''''''''''''''' ''''''''' ''''''''''''''''''' '''''''' ''''''''''''''''' ''''''''''' ''''''''''''''''' ''''''''''' ''''''''''' ''' ''''''''''''''''' ''''' '''''''''''''''''''''''' '''''''''''' '''''' '''''''''''''''''' ''''''''' '''''''''''' ''' ''''''''''''''''''' ''''''''''' ''''''''''' ''''' '''''''''''''' '''''''''''''''''''''''' ''''' '''''''''''' '''''' '''''''''''''''''' ''' '''''''''''' '''''''' '''''' '''''''''''''' ''''''''''''''''''''''''''''' '''''''''''''' '''''''' ''''''''''' ''''''''''''''''' '''''' ''''''''''''''''''''''''' '''''''''''''''''''' ''''''''' ''''''''''''''''''' ''''''''''''' '''''''''''''''' '''''''''''''''''''' ''' '''' ''''''''''' '''''''' '''''''''''''' ''''''''''''''''' ''''''''''''' '''''''''''''''''''''' ''''''''''' '''''''''''''''''''''''''''''' ''''''''''' |

Four historical control studies provided low level but consistent evidence that alglucosidase alfa benefits children with infantile onset Pompe Disease by extending their survival, as well as their ventilation free survival, compared to standard palliative care (GRADE ⨁⨁⨀⨀). Adverse reactions to alglucosidase alfa included life-threatening anaphylactic reactions.

### Australian data registry information – alglucosidase alfa

Information withheld from this draft report at the request of the drug sponsor.

'''''''''''' '''''''' '''''''' ''''''''' ''''''''' '''''''''''''''' '''''''''''''' '''''''' ''''''''''''''''''''''''' ''''''' '''''''''''''''' ''''''' ''''''''' '''''' ''''''''''''''''' ''''''''''' ''''''''''''' ''''''''''''''''' '''''''' ''''''''''''''' ''''''''' '''' '''''' '''''''''''''''' ''''''''''' ''' '''''''''''''' '''' ''''''''''''''''''''''' '''''''''' '''''' ''''''''''' ''''''''''' '''''''''''''' '''''''''' ''''''''' '''' ''''''''' ''''' '''''''''''''' ''' '''''''''' '''''''' ''''' '''''''''' '''''''''''''''''''''' ''''''''''''''' '''''''''''' ''''''''' '''''''''' ''''''' ''''''''''''''''' '''''''''''''' ''''''''' '''''''''''''''' ''' '''''' ''''''''''''''''''' '''''''''''''' '''''''''''''''''' '''''''' ''''''' '''''''' '''''''''''''''' ''' ''''' ''''''''''''''''''''' '''''''''''''''''''' ''' '''''''''''' ''' ''' '''''''''''''''''' ''''''''' '''''''' '''''' '''''''''''''''''''' ''''''''''''''''' '''''' '''''''''''''''' '''''''' ''''''''''''''''' ''''''''' ''''''''''''''''''''''''''' '''''''' '''''''' ''''''''''''''''' ''''''''''''''''' '''''''' ''''''''''''''' ''''''''' '''' ''''''''''''''''''''''''''' ''''''' ''''''''''''''''' '''' ''''''''''''''' ''''''''''''''''' '''''' ''''''''' ''''''' '''''''' '''''''''''''''''''''''''''''''' '''''''''''' ''''''' ''''''''''''''''''''''''' '''''''''' '''' '''''' '''''''''''''''''''''''''''' ''''''''' '''''''' '''' ''''''''''''''' ''''''''''''''''''' '''''''''''''''' ''''''''' '''' '''''' '''''''''

### Alglucosidase alfa to treat Juvenile Onset Pompe Disease

| Alglucosidase alfa |
| --- |
| New publications since original recommendations: The sponsor did not make a specific request for alglucosidase alfa to be provided through the LSDP for patients with the juvenile form of late-onset Pompe disease. Submissions to the PBAC for late-onset Pompe disease did not separate data for patients with juvenile-late onset and adult-onset Pompe disease. One case series and 15 case reports were identified.  Impact on original recommendation: Very poor quality data show that patients improve from baseline when treated with alglucosidase alfa, in terms of respiratory outcomes and muscle functioning. A large amount of heterogeneity between patients and the different outcomes, combined with the low level of evidence, prevent any strong conclusions being made.  Australian data: Only one patient in Australia is currently receiving alglucosidase alfa for juvenile onset Pompe disease. |

Studies on late-onset Pompe disease do not often distinguish between juvenile-late onset and adult-onset Pompe disease. For this reason, data on juvenile-late onset Pompe disease (JOPD) were very scant in the systematic review, limited to one case series (n=7) and 15 case reports (discussing a total of 29 patients). One article discussed the rate of deterioration in the years preceding the initiation of alglucosidase alfa, whereas all the other evidence is based on the change between baseline data (prior to treatment with alglucosidase alfa) and follow-up data, after 6 months to 8 years of treatment.

Natural history data show that patients with late-onset Pompe disease have a longer life-expectancy than patients with infantile-onset Pompe disease, but a reduced lifespan compared to the broader population.

The evidence was too poor to be able to make any statements regarding the impact of alglucosidase alfa on survival in patients with JOPD. Quality of life was only measured using a validated questionnaire in two patients with severe JOPD, treated at ages 28 and 40. Only one of these patients reported a clinically meaningful improvement on the mental subscale of the Short Form-36.

Based on the very poor quality data identified, patients improve, on average, on respiratory functioning (measured by outcomes such as percent predicted vital capacity) and muscle functioning (the most frequently used outcome was the 6-minute walk test) (GRADE ⨁⨀⨀⨀). However, there was a large degree of heterogeneity in treatment effectiveness between patients. Patients who were most likely to benefit from alglucosidase alfa were those who were treated at a younger age, and with less severe disease at baseline (GRADE ⨁⨀⨀⨀).

### Medicines to treat Mucopolysaccharidoses (MPS) I, II, VI – respectively, laronidase, idursulfase, galsulfase

| Laronidase |
| --- |
| New publications since original recommendations: One new extension to an RCT (Clarke et al. 2009), originally included in the submission to the PBAC, was identified in the systematic review.  Impact on original recommendation: Longer term data were not as favourable to laronidase as the trial data were, showing that the majority of the improvement occurs in the first 6 months. Additional distance walked on the 6 minute walk test after 3.5 – 4 years was less than after 6 months. Forced vital capacity (FVC) was reduced from baseline after 3.5 - 4 years. Other outcomes (liver volume, apnoea symptoms, shoulder range of motion, visual acuity and disability index) were improved from baseline. The new data were non-comparative, and it is therefore uncertain how the data compare to an untreated population in the longer-term.  Australian data: The format of the individual data prevented analysis to determine the clinical benefit of laronidase. |

No new trials were identified for the MPS drugs listed on the LSDP. Longer-term data were available for laronidase and idursulfase in extension studies of RCTs included in the submissions to the PBAC.

One RCT reported that 6 months of laronidase significantly improved the distance walked by patients with MPS I, as measured by the 6-minute walk test (6MWT) (GRADE ⨁⨁⨁⨀). However, differences between the patients receiving laronidase and placebo at baseline make it difficult to determine whether this difference was caused by the drug or due to imbalances in confounding factors. Likewise, although respiratory function (measured by forced vital capacity) improved more in the laronidase treatment arm, baseline differences in the treatment groups prevents strong conclusions from being formed (GRADE ⨁⨁⨁⨀). There were no statistically significant differences in the frequency of sleep apnoea or hypopnea symptoms or in joint movement. *Post hoc* analyses of those who had sleep apnoea at baseline, and impaired joint movement at baseline, identified that there were significant differences in sleep apnoea, hypopnea and joint movement that favoured laronidase over placebo (GRADE ⨁⨁⨀⨀). However, after 6 months, the level of disability did not differ between the two treatment groups (GRADE ⨁⨁⨀⨀). Laronidase appeared safe, with a similar safety profile to placebo.

An extension study of the intervention arm in the RCT was identified. Over 3.5 or 4 years of laronidase, measures of respiratory function had worsened from baseline (an average decline of patients’ predicted FVC of 0.78 points per year), and the distance walked in the 6MWT was less than the distance reported in the laronidase arm of the RCT after 26 weeks (GRADE ⨁⨁⨁⨀). Due to the non-comparative nature of the study, it is unclear whether the clinical efficacy of laronidase reduces over time, or whether patients experienced an expected disease-related decline.

| Idursulfase |
| --- |
| New publications since original recommendations: One new extension to an RCT (Muenzer et al. 2011), originally included in the submission to the PBAC, was identified in the systematic review.  Impact on original recommendation: Absolute forced vital capacity continued to improve for patients ≤18 years old with 3 years of treatment with idursulfase. Adult patients (over 18 years) had a slight decrease in absolute forced vital capacity over 3 years. Results on the 6MWT were reasonably similar between 1 year (the length of the RCT) and 3 years. Liver and spleen volume remained stable between 1 and 3 years, and joint flexibility continued to improve between 1 and 3 years. The extension data are therefore consistent with conclusions to fund idursulfase.  Australian data: The format of the individual data prevented analysis to determine the clinical benefit of idursulfase. |

The effectiveness of idursulfase was assessed in one high quality RCT in which MPS II patients received idursulfase weekly or every other week or received placebo. Two deaths in the study population were not considered to be related to treatment. Participants randomised to receive idursulfase weekly had significantly better exercise tolerance (6 MWT) and respiratory function (forced vital capacity; FVC) after one year, than those randomised to placebo (GRADE ⨁⨁⨁⨀). A composite score for both exercise tolerance and respiratory function was greater for all patients receiving idursulfase than for those receiving placebo (GRADE ⨁⨁⨁⨀). Both liver and spleen volumes were reduced significantly in those receiving idursulfase (GRADE ⨁⨁⨁⨀), as were urine glycosaminoglycan (GAG) levels (GRADE ⨁⨁⨁⨀).

At 20 months, there was a significant improvement overall in the distance achieved during a 6 MWT but stratification of results by age showed that most of the improvement was in those aged over 18 (GRADE ⨁⨁⨀⨀). At 36 months, absolute forced vital capacity indicated similar overall improvements, but stratification showed improvement was limited to those participants aged 18 years or younger (GRADE ⨁⨁⨀⨀). Percent predicted forced vital capacity did not significantly change from baseline. Long-term assessment of GAG concentration showed a consistent decrease with time (GRADE ⨁⨁⨀⨀). When the Child Health Assessment Questionnaire was used to measure functional status and disability, there were improvements from baseline for both parent- and child-assessed scores. Adverse events (pruritic rash, infusion site swelling, urticaria, dyspepsia, anxiety, and chest wall pain) reported only in the idursulfase groups, or rarely in the placebo group, may indicate drug side effects.

| Galsulfase |
| --- |
| New publications since original recommendations: One new extension study was identified in the systematic review for the intervention arm of a trial already included in the submission to PBAC; however, no new data could be extracted.  Impact on original recommendation: Not applicable.  Australian data: The format of the individual data prevented analysis to determine the clinical benefit of galsulfase. |

One RCT followed by an open-label extension phase assessed the effectiveness of galsulfase over placebo in MPS VI patients. Patients receiving galsulfase improved a statistically significantly larger amount on the 12 minute walk test than those receiving placebo (p = 0.025) (GRADE ⨁⨁⨀⨀). When endurance was measured using the 3 minute stair climb test there was a non-statistically significant trend favouring galsulfase over placebo (GRADE ⨁⨁⨀⨀). No difference was found over time or between groups on respiratory function (GRADE ⨁⨁⨀⨀). When the numbers of drug-related and infusion-related adverse events were compared between groups at 24 weeks, the outcome favoured the placebo group but was not statistically significant (GRADE ⨁⨁⨁⨀).

### Australian data registry information – laronidase, idursulfase, galsulfase

As of June 2014, there were 35 patients treated for either MPS I (7 patients), MPS II (15 patients) or MPS VI (13 patients). The average dose per patient (at the most recent review) was 0.55 mg/kg/week for laronidase, 0.54 mg/kg/week for idursulfase, and 0.98 mg/kg/week for galsulfase, which is close to the recommended dose for these different drugs (0.58 mg/kg/week for laronidase, 0.5 mg/kg/week for idursulfase and 1 mg/kg/week for galsulfase). Differences are likely due to the necessity to supply whole vials to enable adequate dosing. The format of health outcomes data made it difficult to verify the efficacy or the safety of the drugs used for MPS.

### Medicine to treat paroxysmal nocturnal haemoglobinuria – eculizumab

| Eculizumab |
| --- |
| New publications since original recommendations: One new historical control study (Kelly, RJ et al. 2011) was identified in the systematic review.  Impact on original recommendation: Survival was improved with eculizumab compared to placebo, with a 5-year survival HR of 0.21 (95%CI 0.05, 0.88). Although the study was flawed, the results support the clinical claim and short term data provided in the submission to the PBAC, that eculizumab extends survival in patients with paroxysmal nocturnal haemoglobinuria.  Australian data: Information withheld from this draft report at the request of the drug sponsor.  '''''' ''''''''''''''''''' '''''''''' ''''''''''''' '''''''''''''''''''' '''''' ''''''''''''''''''' '''''''''''''''''''''' '''''''''''''''''''''''''' ''''''''' ''''''''''''''''' ''''''''''''''' ''''' '''''''''''''''''''''' ''''''''''''''''''''''''''' '''''''''''' '''''''''''''''''''''' ''''''' '''''' ''''''''''''''''''''''''' |

One randomised trial provided short term (6 months) evidence that eculizumab improves quality of life and reduces transfusion requirements, compared to placebo, in patients with relatively severe paroxysmal nocturnal haemoglobinuria (PNH) (GRADE ⨁⨁⨁⨁). A before and after study reported that eculizumab reduced the rate of thrombotic events (GRADE ⨁⨁⨀⨀). A *post hoc* analysis showed that patients treated with eculizumab had better outcomes on average than those receiving placebo (GRADE ⨁⨁⨁⨀). Adverse events were more common in those patients receiving eculizumab than taking placebo. Common adverse events were headache, back ache and fatigue. New evidence identified through the systematic review, consisted of a single historical control study, which reported on survival. This study reported that eculizumab prolonged overall survival compared to no treatment; however, due to serious flaws in the design of this study, there are major concerns regarding the validity of this analysis (GRADE ⊕⨀⨀⨀).

### Australian data registry information – eculizumab

LSDP patient summary sheets did not provide data in a format which was easy to aggregate. A registry kept by the sponsor for eculizumab was made available. Information in this registry has been redacted at the request of the drug company for commercial in confidence purposes.

Alexion has indicated its willingness to work with Government to collect and conduct analyses of the Alexion registry data in order to prvide more robust data which could not be submitted to the PBAC.

## Review emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future.

With an increase in knowledge regarding the causative genetic mutations behind many conditions, diseases which have previously been considered common are now being divided into many different rare subtypes. These subtypes can be individually targeted with drugs that may be considered eligible for the LSDP. It is possible that in the future, the majority of drugs being developed will fit this category. Given that the rarity of disease is one of the current criteria for eligibility for the LSDP, an increase in the number of drugs targeting this one criterion may increase the total number of drugs eligible for the LSDP.

The definition of what is defined as ‘rare’ is also likely to have a large impact on the sustainability of the LSDP. The drugs currently listed on the LSDP have a prevalence ≤1 in 100,000. If only conditions with an incidence this rare are considered, then conditions such as cystic fibrosis, Huntingdon’s disease and motor neurone disease would all be considered too common to have drugs listed on the programme (unless rare subtypes are considered, e.g. patients with cystic fibrosis and at least one G551D mutation). Conversely, if a rare condition is considered to be one which affects less than one in 2,000, then relatively common conditions such as melanoma and lung cancer, identified by specific biomarkers, could potentially be targeted by drugs that may satisfy the LSDP criteria for the funding of a drug.

Emerging clinical treatments use a variety of mechanisms to treat severe diseases. Treatment types of growing importance are monoclonal antibodies and gene therapies. Some rare conditions are also being targeted with drugs that are already used for different clinical indications, and this could have implications for the public funding of these treatments.

Various drugs were identified which could potentially be relevant to the LSDP. However, the data were too scant to determine the exact nature of the patient populations being targeted by the sponsors of these drugs.

## Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.

The definition of rare disease varies between countries. The most restrictive is in China, which rare diseases defined as less than 1 in 500,000. The least restrictive is in the United States, with the Food and Drug Administration classifying a rare disease as one which affects less than 200,000 Americans. This equates to less than 1 in 1,500 (this definition is also used to classify ‘orphan subtypes’ of more common diseases). The European Union defines a rare disease as one which occurs in not more than 5 in 10,000 people (i.e. 1:2,000). For the purpose of orphan drug registration, the Australian Therapeutic Goods Act defines a rare disease as one that has fewer than 2,000 patients, which is approximated as a prevalence of 1 in 10,000 persons.

Australia has no specific evaluation program for drugs for rare diseases (DRDs). The Netherlands, Italy, England, Wales, and Ontario (Canada) all have evaluation and funding mechanisms specific to orphan drugs. Alberta has a rare drug program restricted to lysosomal storage disorders and with characteristics similar to the LSDP. Japan has specified 56 different diseases which are considered eligible for public funding.

Many funding bodies allow special consideration of orphan drugs, such as a relaxed requirement for pharmacoeconomic evaluation (Belgium, the Netherlands, Germany, Sweden and France), a higher cost-effectiveness threshold (Sweden), consideration of a broader societal perspective (UK), an acceptance of poorer quality evidence (Belgium, Sweden and France), or placement of greater weight in decision-making on the lack of alternative treatments (Germany, Italy and France).

In Australia, the LSDP does not require a re-assessment of the funding decision on a listing following its initial approval, although this can occur on an ad hoc basis. Pricing and funding decisions are monitored in Belgium, where drug companies are expected to submit a revised dossier 1.5 to 3 years following initial approval; the Netherlands, where evidence is reappraised after 3 years; in France, where a listing is only valid for 5 years; and the United Kingdom, where evidence is assessed after 5 years.

Managed entry schemes are used for orphan drugs in Europe (Belgium, England and Wales, Italy, the Netherlands and Sweden). Performance-based risk sharing is used in Italy, the Netherlands and Sweden, while financial-based schemes are used in Italy, Belgium, England and Wales.

## Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug’s treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.

This ToR was addressed by identifying published literature on methods that determine ‘value’, and that could potentially be applied to orphan drugs and the LSDP. Other than routine cost-utility analyses, alternative approaches identified were:

* Broadened cost-utility evaluation, with improved sensitivity and broadened perspective;
* Equity-weighted cost-utility evaluation, using various weighting criteria, e.g. disease severity (non-specific to orphan drugs), or rarity (specific to orphan drugs);
* Multi-Criteria Decision Analysis (MCDA); and
* Input-based costing.

There is an argument that cost-utility evaluation, taking a societal perspective, should take into account the costs and quality of life for not only the patient, but also their family members and carers, and that this broader inclusion would favour drugs on the LSDP more than the current use of cost-utility evaluation. It remains unlikely, however, that an incremental cost-effectiveness ratio (ICER), using this method, would meet traditional willingness-to-pay thresholds.

There is evidence that societal preferences do not always follow a utilitarian approach of maximising quality adjusted life years (QALYs). Principles such as equity and social justice may cause a preference for non-utilitarian allocation. Preferences have been proposed that place greater value on: i) treatments that are life-saving; ii) treatment for patients with more severe disease; and iii) treatments for populations of social concern such as the socio-economically disadvantaged, children, or people with dependents.

Contradictory information was available on whether society would support additional health spending on the basis of disease rarity. Methods to adapt the equity-adjusted approach to assessing cost-effectiveness include: i) adjusting QALYs based on societal preferences, or ii) adjusting the ICER threshold that is considered cost-effective. Once preference weightings are quantified, these approaches would be mathematically equivalent.

Alternatively, equity concerns can be incorporated into drug assessment and decision-making using an alternative assessment tool such as multi-criteria decision analysis (MCDA). MCDA frameworks have been used for pharmaceutical health technology assessments in Canada, Europe, Malaysia and Thailand. Common criteria across these different frameworks are efficacy / effectiveness, safety, and the economic impact of the drug. Additional criteria used by some frameworks include the severity of the disease, equity / ethical and social implications and a consideration of how treatment aligns with current local health policy targets. Scoring methods for these preferences vary from simple to complex, and can either include the preferences of a committee, or broader societal values derived through surveys. MCDA is an assessment tool which is not specific to health or health technology assessment but has been proposed as a tool which could be useful at quantifying the value of orphan drugs.

Another method of defining the value of orphan drugs is to base value (price) on the cost of developing and producing drugs in order to determine a fair price. This does not link health impacts to price, but could result in the rarity of a disease being linked to the price function. This methodology has not been used to date.

Consideration of the limitations of the available evidence to measure the clinical effectiveness of existing drugs on the LSDP – to inform a value assessment – presents a difficulty, irrespective of the metric used. The level of uncertainty, or risk, itself may be relevant to incorporate into an alternative value metric.

## Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.

The evidence base for drugs on the LSDP is often scant. Drug surveillance registries can therefore be useful to collect data to address uncertainties regarding claims of the efficacy and safety of orphan drugs. The purpose of this form of registry is different from a rare disease registry.

The key purposes of a rare disease registry are: i) to connect affected patients, families and clinicians; ii) to study the natural history of a disease; iii) to support research; and iv) to establish a patient base for evaluating drugs. The main purpose of a drug surveillance registry is to monitor the impact of a drug on the health of individual patients and aggregate the results for the whole patient cohort.

The following elements need to be considered in the development of a registry – the purpose of the registry; data collection; quality assurance; governance and custodianship; ethics, privacy and data security; information output and reporting; and resources and funding.

The design of both types of registry must align with its purpose. The likely objectives of the proposed surveillance registry for drugs being reimbursed through the LSDP are:

1. to verify initial and ongoing eligibility of patients receiving subsidised drugs against the initially determined eligibility criteria;
2. to measure the costs of the drug and management of the programme;
3. to evaluate the safety and effectiveness of the drug against the claims made in the submission for funding through the LSDP;
4. to use cost, safety and effectiveness data to support outcome-based risk-share arrangements between sponsors and Government;
5. to ensure adequate data collection to meet the aims of the registry; and
6. to ensure access to the data by key stakeholders.

Data collection may be from a range of sources, including from scheduled appointments with a single physician, data collection from patients or guardians, and data collections from external sources such as a Births, Deaths and Marriages registry. It is suggested that the eligibility review schedule should be established at the time of entry into the reimbursement programme, with pre-scheduled visits – more aligned with methods used in clinical trials – in order to ensure completeness of the data.

The utility of a registry is dependent on its quality, appropriateness and the completeness of data capture. In order to improve compliance with data collection, forms should be easy to complete, have only relevant data fields, have clear and unambiguous questions, have data validation methods inbuilt into the collection method, have clear and explicit definitions for data, and include prompts and reminders to complete data entry.

The governance of a drug surveillance registry should include the key stakeholders responsible for establishing the registry, as well as those who determine the data that are required, those who develop and maintain the technical systems, and those who collate data and deliver reports to Government or the funders of the registry. Other stakeholders who might be responsible for contributing to the registry include clinical experts and patient or industry representatives. Data security must be compliant with all Federal and State privacy laws, and clear protocols should be developed regarding who may access the data, as well as procedures to ensure compliance, such as the removal of personal identifiers. Reports for the public should not include sufficient information that someone could be identified. Patient consent (or parental consent and patient assent when patients are under 16 years of age) must be sought with regard to the collection of data.

## Conclusion

This technical assessment has shown that most of the drugs currently funded by the LSDP are clinically effective with an acceptable safety profile. However, there are indications that the LSDP is unlikely to be sustainable in the future, given current patterns of drug development and marketing. Lessons learned from international experience in the public funding of orphan drugs and from economic theory suggest that there are a range of approaches that might be adopted to work towards a sustainable LSDP. In cases where there are uncertainties regarding aspects of the safety, effectiveness and cost of the drugs considered eligible for the LSDP, the development of a drug surveillance registry tailored to address these uncertainties would be valuable, particularly when the appropriate governance, technical arrangements and resourcing are in place.

# INTRODUCTION

Adelaide Health Technology Assessment (AHTA), at The University of Adelaide, was commissioned by the Australian Government Department of Health (the Department), to make a technical contribution to the Post-Market Review of the Life Saving Drugs Programme (LSDP)[[1]](#footnote-1).

Through the LSDP, the Australian Government provides subsidised access to expensive and lifesaving drugs for eligible patients. Currently ten medicines are funded that treat seven rare conditions. In 2013-14, 257 patients were treated through the LSDP at a cost of $77.5 million[[2]](#footnote-2).

There was an earlier review of the LSDP in 2008 (Appendix A). This resulted in a number of changes to the criteria for the subsidisation of pharmaceuticals on the LSDP.

## The Life Saving Drugs Programme

The following drugs are subsidised by the LSDP:

* Imiglucerase (Cerezyme®), Velaglucerase (VPRIV®) and Miglustat (Zavesca®) for the treatment of Gaucher disease (Type 1);
* Agalsidase alfa (Replagal®) and Agalsidase beta (Fabrazyme®) for the treatment of Fabry disease;
* Laronidase (Aldurazyme®) for the treatment of Mucopolysaccharidosis Type I (MPS I) disease;
* Idursulfase (Elaprase®) for the treatment of Mucopolysaccharidosis Type II (MPS II) disease;
* Galsulfase (Naglazyme®) for the treatment of Mucopolysaccharidosis Type VI (MPS VI) disease;
* Alglucosidase alfa (Myozyme®) for the treatment of Infantile-onset and Juvenile-late onset Pompe disease; and
* Eculizumab (Soliris®) for the treatment of Paroxysmal Nocturnal Haemoglobinuria (PNH).

Patient eligibility to receive subsidised treatment with these drugs is determined in accordance with the Patient Conditions for Initial and Ongoing Subsidy through the LSDP[[3]](#footnote-3).

During the Review, patients currently treated through the LSDP continued to receive subsidised access to treatment, new patients could continue to apply for access to treatment and applications for new medicines seeking LSDP listing continued to be considered.

## Objective of the LSDP Review

The objective of the LSDP Review was to examine important issues such as access and equity, value for money and the future administration of the Programme.

It was an opportunity to review the current programme in order to ensure that Australians with very rare conditions continue to have subsidised access to much-needed, expensive medicines now and into the future.

It also aimed to update clinical efficacy and safety data for treatments currently subsidised and to incorporate new and emerging evidence.

In order to ensure that people who need these drugs will be able to access them, the programme needs to be as efficient and as evidence-based as possible.

The Review examined the existing LSDP Criteria and Conditions for Funding, identified processes to facilitate data collection for rare diseases and looked at ways to better engage with consumers.

In keeping with the Government’s deregulation agenda, administrative requirements for patients and specialists seeking access to subsidised treatment through the programme are also being reviewed.

On 3 March 2014 the Minister for Health, the Hon Peter Dutton MP approved the final terms of reference (ToR) for the Review. These ToR underwent a consultation process during August 2013 prior to consideration and approval by the Minister.

On 9 April 2014, the Minister announced that the LSDP Review would proceed.

## Scope of the technical assessment

The ToR for the LSDP Review are listed below. The technical assessment addresses ToRs one, two, three, five and seven (bolded):

1. **Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.**
2. **Review emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future.**
3. **Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.**
4. Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the LSDP.
5. **Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug’s treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.**
6. Review the administration of the LSDP, including the Guidelines with which the programme is administered for each condition, and assess alternative administration systems.
7. **Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.**

# Systematic literature REVIEW

A systematic literature review was performed in order to fulfil ToR 1:

1. **Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP**

Six chapters are included in this technical assessment – one each on the clinical effectiveness and safety of:

1. Medicines to treat Gaucher disease – specifically, imiglucerase, velaglucerase and miglustat;
2. Medicines to treat Fabry disease – specifically, agalsidase alfa and agalsidase beta;
3. Alglucosidase alfa to treat Infantile Onset Pompe Disease;
4. Alglucosidase alfa to treat Juvenile Onset Pompe Disease;
5. Medicines to treat MPS I, II, VI – respectively, laronidase, idursulfase, galsulfase; and
6. Eculizumab to treat PNH.

## Systematic review methodology

### Literature search strategy

The search strategy for the systematic review canvassed both the peer reviewed (black) literature and grey literature[[4]](#footnote-4) provided by the sponsors in their original funding submission documents.

The peer reviewed literature was scanned for studies that consider the safety and effectiveness of the drugs currently listed on the LSDP. Scoping searches revealed limited peer-reviewed evidence for some of the patient indications listed and, as such, the systematic review literature search was kept broad to maximise the available information. No restriction was placed on the time period searched because the searches are based on drug name. The search covered the following databases: Orphanet (www.orphanet.net) PubMed (pre-Medline only), Embase.com (includes Medline and Embase), The Cochrane Library, CINAHL, Controlled Trials Meta-Register, Web of Science (Web of Knowledge), Scopus, SciFinder and Toxline. Relevant papers had their reference lists pearled for other studies potentially missed in the searches.

The formal grey literature search was conducted using Google Scholar. However, the search strategy also included pearling of relevant reviews and reports and snowballing techniques to locate potentially relevant articles and reports in obscure locations. In addition to literature obtained through these methods, the submissions provided by the sponsors, prior to the listing of their drugs on the LSDP were cross-checked, and all relevant clinical studies were identified and included in the systematic review.

The search strategy to identify peer reviewed literature is described in Table 1. The search strategy suggested was based on instructional material produced by the US National Library of Medicine (PubMed for Trainers Winter 2013)[[5]](#footnote-5).

Conference abstracts were not included. However, if an abstract was identified that described a relevant high-level study, for which a published article was not also identified, the authors of the study were contacted to see if a full text report of the study findings exists. Likewise, if a relevant study provided information in a graphical format that was not easy to extract data from, the authors were contacted to see if they could provide the original data. Three authors were contacted, two replied, and one of these was able to provide further information.

Table 1 Terms used to search for evidence to inform the Systematic Review questions (PubMed example)

| Drugs | PubMed search terms |
| --- | --- |
| imiglucerase, velaglucerase and miglustat | “imiglucerase”[Supplementary Concept] OR “imiglucerase”[All Fields] OR “cerezyme”[All Fields] OR “velaglucerase”[All Fields] OR “VPRIV”[All Fields] OR “miglustat”[Supplementary Concept] OR “miglustat”[All fields] OR “zavesca”[All Fields] OR  (“Gaucher” OR Gaucher’s) AND (“enzyme replacement therapy” OR ERT OR SRT OR “substrate reduction therapy”) |
| agalsidase alfa and agalsidase beta | “agalsidase alfa”[Supplementary Concept] OR “agalsidase alfa”[All Fields] OR “replagal”[All Fields] OR “agalsidase beta”[Supplementary Concept] OR “agalsidase beta”[All Fields] OR “fabrazyme”[All Fields] |
| alglucosidase alfa for infantile onset pompe disease | “GAA protein, human”[Supplementary Concept] OR “GAA protein, human”[All Fields] OR “alglucosidase alfa”[All Fields] OR “myozyme”[All Fields] |
| alglucosidase alfa for juvenile onset pompe disease | “myozyme”[All Fields] OR “alglucosidase”[All Fields]) OR (Pompe OR Pompe’s OR LOPD OR “glycogen storage disease type II” OR “GAA deficiency”) AND (ERT OR “enzyme replacement therapy”) |
| laronidase, idursulfase, galsulfase | “laronidase”[All Fields] OR “aldurazyme”[All Fields] OR “idursulfase”[Supplementary Concept] OR “idursulfase”[All Fields] OR “elaprase”[All Fields] OR “galsulfase”[Supplementary Concept] OR “galsulfase”[All Fields] OR “naglazyme”[All Fields] |
| eculizumab | “eculizumab”[Supplementary Concept] OR “eculizumab”[All Fields] OR “soliris”[All Fields] |

### Study selection criteria

Studies were assessed for eligibility for inclusion in the systematic review using a staged approach. That is, the “highest level of evidence” available to answer the individual research questions was included in the systematic review. This staged approach targets the research most likely to provide unbiased evidence. The level of evidence was determined by the NHMRC Evidence Hierarchy for Interventional evidence, as described in Table 2 (Merlin, Weston & Tooher 2009). Where even sufficient case series data could not be identified, case reports were included. This hierarchy is used to estimate the risk of bias in study findings as a consequence of how the research was designed. There are, of course, additional matters that also need to be considered when assessing the reliability of study findings (see Section 3.2).

Table 2 NHMRC evidence hierarchy: designations of levels of evidence – (interventional research questions only)

| Level | Interventional study design1 |
| --- | --- |
| I2 | A systematic review of level II studies |
| II | A randomised controlled trial |
| III-1 | A pseudo randomised controlled trial  (i.e. alternate allocation or some other method) |
| III-2 | A comparative study with concurrent controls:  ▪ Non-randomised, experimental trial3  ▪ Cohort study  ▪ Case-control study  ▪ Interrupted time series with a control group |
| III-3 | A comparative study without concurrent controls:  ▪ Historical control study  ▪ Two or more single arm study4  ▪ Interrupted time series without a parallel control group |
| IV | Case series with either post-test or pre-test/post-test outcomes |

1 Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b) and in the accompanying Glossary accompanying Merlin, Weston & Tooher, 2009

2 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

3 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. Utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

4 Comparing single arm studies i.e. Case series from two studies. **Source:** (Merlin, Weston & Tooher 2009).

Literature identified as opinion pieces, editorials or other papers without a clear study design and description of method and results were not included. The study eligibility selection criteria were pre-specified delineated using a PICO structure format (see each relevant section disease chapter in this assessment), based largely on what was provided in the original LSDP funding applications submissions.

Study eligibility was determined. These criteria were applied independently by two researchers and any differences were resolved by consensus. If consensus could not be achieved the decision on study selection was made by a more senior third party.

Only pre-specified outcomes that were reported on have been discussed in the Results section.

### Documenting the literature search

All literature located in the search was documented and presented using flowcharts recommended by the Preferred Reporting of Items in Systematic Reviews and Meta-analyses (PRISMA) statement (Liberati et al. 2009). These flowcharts are given in Appendix B. Studies that met the eligibility criteria but were subsequently excluded are listed in Appendix C according to their reason for exclusion.

## Critical appraisal of selected evidence

Studies were critically appraised according to the likelihood that bias had affected their findings. Study design flaws were appraised using NHMRC levels of evidence and the execution of the research was also evaluated. SIGN 50 checklists were used to critically appraise randomised controlled trials and cohort studies (see APPENDIX D), as recommended by a Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review of appraisal tools[[6]](#footnote-6). Case series were critically appraised using the UK National Health Service Centre for Reviews and Dissemination checklist (NHS CRD) (Khan et al. 2001). Systematic reviews were assessed using the AMSTAR checklist (Assessing the Methodological Quality of Systematic Reviews (Shea et al. 2009)). Case reports were not assessed as their likelihood of bias.

The risk of publication bias could not be assessed, due to the small number of trials identified on each drug.

The quality of the body of evidence reporting on individual health outcomes was rated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Guyatt et al. 2011) (see APPENDIX D). This summation of the body of evidence was performed using the online Guideline Development Tool (McMaster University and Evidence Prime Inc. 2014). The interpretation of the pictorial ratings is given in Table 3. Conclusions derived from the evidence were graded according to the degree of confidence in the estimate of effect for each safety and effectiveness outcome.

Table 3 Interpretation of GRADE evidence ratings (Guyatt et al. 2013)

| GRADE | Quality | Description |
| --- | --- | --- |
| ⨁⨁⨁⨁ | High quality | Further research is very unlikely to change our confidence in the estimate of effect. |
| ⨁⨁⨁⨀ | Moderate quality | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| ⨁⨁⨀⨀ | Low quality | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| ⨁⨀⨀⨀ | Very low quality | We are very uncertain about the estimate. |

## Data extraction and synthesis

Relevant data were extracted from included studies, including detail on the study authors, country/setting, population, intervention drug and dosage details, comparator drug and dosage details, level of evidence, risk of bias, relevant outcome measures and results and follow-up period. These study profiles are shown in Appendix E.

Key outcome data from all of the included studies were extracted in duplicate and independently by two researchers.

Where appropriate, data extracted from the included studies would have been combined in a meta-analysis, but there were insufficient data available. For each review question, the findings were synthesised into an overall narrative, with better quality studies given greater credence in the development of conclusions. This synthesis was informed by the GRADE method of synthesising evidence (Guyatt et al. 2013) (see Appendix E). The findings in each systematic review chapter were reported according to PRISMA reporting standards and incorporate all of the components required by AMSTAR for a high quality systematic review (Shea et al. 2009).

## Method of review and analysis of currently held data

The aim of the data analysis portion of the technical assessment was, for each drug, to:

1. Identify resource use associated with the listing on the LSDP:
   1. Identify and cost resource items related to the data set;
   2. Cross-reference these against the resource items from the submission that are likely to be used for the management of the disease; and
   3. Determine the excess use of testing / monitoring required (if any) for drug administration.
2. Verify clinical and economic claims in the submission:
   1. Identify outcome and other variables in the dataset; and
   2. If the data are sufficient, compare actual use / results in Australia with that presented in the submission.

It was not possible to achieve the aims outlined under point 1, as the data obtained were collected for a different purpose and were not in a format which could easily be extracted.

The extent and format of the obtained data partially supported the stated goals of the proposed data analysis. Data pertinent to the LSDP that are currently held by the Department and in sponsor registries was analysed in an attempt to assess whether the claims of drug safety and effectiveness (made in the sponsors’ funding submissions) were realised in the Australian setting. An attempt was also made to identify the co-administered treatments; however, the format of the data for most drugs could not easily be extracted.

Data were inadequate for the purpose of analysing the costs to the Commonwealth for different treatments, administration costs, the setting of treatment, and the rate of adverse events. An analysis *was* made as to whether the supplied doses of LSDP-subsidised drugs complied with Therapeutic Goods Administration (TGA) recommended dosing from Product Information documents. It was also determined whether any patient health outcomes could be said to differ as a consequence of using an off-label experimental dose rather than the standard drug dose.

The available data were also examined to assess whether they were in a format that would allow a determination of quality of life or an alternative ‘value metric’ chosen by the Reference Group (as discussed in 5.2).

Identified limitations of the data collections were used to inform recommendations for efficient and effective data collection for drugs reimbursed on the LSDP (see Section 6).

The results of the data analysis for the LSDP-subsidised drugs treating each disease or condition are reported subsequent to the systematic review evaluating management of each disease or condition in this technical assessment.

As part of the review process, observational data stored in company databases was requested. The data provided directly from the sponsors are outlined in Table 4.

Table 4 Data provided by sponsors

| Disease | Company and drug | Data provided |
| --- | --- | --- |
| Gaucher disease | Actelion – miglustat | No data available (currently no Australian Patients through LSDP)  Clinical safety reports provided |
| - | Genzyme – Imiglucerase | Gaucher registry Australian annual report 2011 and Global annual report 2014 |
| - | Shire – velaglucerase | Post-marketing outcome survey |
| Fabry disease | Genzyme – agalsidase beta | Fabry Registry Annual Report for Australian patients |
| - | Shire – agalsidase alfa | Annual outcome survey 2013 |
| MPS I disease | Genzyme – laronidase | MPS I Registry annual report |
| MPS II disease | Genzyme – Idursulfase | Annual Hunter Outcome Survey |
| MPS VI disease | BioMarin – Galsulfase | Confidential Report on MPSVI global clinical surveillance programme registry data 2014 |
| Infantile onset Pompe disease | Genzyme – Alglucosidase alfa | Global Pompe registry annual report |
| Juvenile onset Pompe disease | Genzyme – Alglucosidase alfa | No data available (only recently available for this patient group through the LSDP) |
| Paroxysmal Nocturnal Haemoglobinuria | Alexion – Eculizumab | Comprehensive individual patient data from the Alexion PNH registry for patients who have received treatment in Australia (multiple spreadsheets)  Report on the Australian cohort from the international PNH registry |

Most sponsors provided reports derived from registries or surveys.

For Gaucher and Fabry patients, registry data that was available to the Department was used in addition to the Department’s clinical summary assessment spreadsheets.

The only sponsor to provide individual patient data on Australian patients was Alexion who provided data from the PNH registry. Reports on individual patient data in registries are subjected to ethics approval and this can prevent the release of patient data information. Where applicable patient data has been redacted or deleted.

## Data retention and storage

All de-identified data have been treated in the same way as are currently used for commercial or committee-in-confidence material supplied by the PBAC (i.e. storage of data in a highly secure location and all personnel with access to the material are required to sign confidentiality agreements). Raw data will be returned to the Department – or securely destroyed – upon completion of the Post-Market Review.

## Systematic review results

### Medicines to treat Gaucher disease

**In patients with Type 1 Gaucher disease, what is the safety and effectiveness of imiglucerase, velaglucerase alfa, or miglustat compared to standard therapy?**

No formal submission was made to the PBAC requesting funding of alglucerase/imiglucerase. One double-blind randomised trial was identified with a combined imiglucerase/alglucerase intervention and it was found to be superior to standard therapy (vitamin D) on surrogate outcome measures of bone disease (bone marrow fat fraction and disease burden (chitotriosidase level), bleeding risk (haemoglobin, platelet count) and liver size (GRADE ⨁⨁⨁⨀). The evidence therefore supported the decision to fund imiglucerase for Type 1 Gaucher disease.

**In patients with Type 1 Gaucher disease, what is the safety and effectiveness of imiglucerase, velaglucerase alfa, or miglustat when compared to each other?**

The clinical claim made to the PBAC was that velaglucerase alfa was non-inferior to imiglucerase. In the systematic review, no new trials were identified that had not already been presented in the submission to the PBAC. One high quality double-blind randomised trial indicated that velaglucerase alfa and imiglucerase have equivalent effectiveness at reducing bleeding risk (haemoglobin and platelet count), disease burden (as measured by chitotriosidase levels), and hepatosplenomegaly (GRADE ⨁⨁⨁⨀). Velaglucerase was associated with a slightly higher rate of mild to moderate adverse events (47%) than imiglucerase (35%) (GRADE ⨁⨁⨁⨀). The evidence supports the funding of velaglucerase alfa.

The submission to the PBAC proposed that miglustat may be used in patients who cannot tolerate ERT or are not able to follow an approved enzyme replacement therapy (ERT) regimen. The highest level evidence was one open-label RCT comparing miglustat against imiglucerase, which had been included in the submission to the PBAC. This study did not include any evidence on the group of patients in which miglustat has been proposed.

No new trials were identified assessing miglustat. However, additional data were identified on one outcome measure, which showed that miglustat was inferior to imiglucerase according to a marker of disease burden (chitotriosidase level). Other outcome measures (included in the submission to the PBAC) showed that miglustat was non-inferior to imiglucerase in regards to one measure of bleeding risk (haemoglobin), and inferior in regards to another measure of bleeding risk (platelets). Every patient receiving miglustat had gastrointestinal side effects, which was significantly higher than the proportion of patients who received imiglucerase. Quality of life was reported to be higher in those taking miglustat than imiglucerase, which likely relates to the mode of administration (an oral treatment rather than infusions which took one to two hours each week) (GRADE ⨁⨁⨁⨀). It is unknown whether this difference in quality of life would be sustained, given the poorer performance of miglustat compared to imiglucerase on the other surrogate outcome measures.

Australian data on the use of imiglucerase and velaglucerase alfa showed that patients receiving ERT for Type 1 Gaucher disease have, on average, improvements in haemoglobin levels, platelet counts, and spleen and liver volumes compared to their pre-treatment levels. There are no patients in Australia currently receiving subsidised miglustat.

#### Background

##### Gaucher disease

Gaucher disease is the most common lysosomal storage disease, resulting from mutations and rearrangements in the β-glucocerebrosidase gene, located on chromosome 1q21.31 (*GBA* gene). These abnormalities in the gene lead to decreased enzymatic activity, and an accumulation of unmetabolised substrate glucocerebrosidase in the lysosomes of macrophage and monocyte cells, particularly in the liver, spleen and bone marrow (Elstein, Y et al. 2004). There are three clinical sub-types of Gaucher disease, defined by the progression of neurological manifestations. Type 1 Gaucher, which does not have neuropathic complications, is the most common form (Elstein, Y et al. 2004).

The consequences of Gaucher disease may vary enormously from death *in utero*, to no symptoms (Giraldo et al. 2011). Common symptoms involve massive hepatosplenomegaly (enlarged spleen and liver), haematological symptoms (anaemia and thrombocytopenia, resulting from storage of glucocerebrosidase in the spleen), and skeletal involvement (bone pain, osteopenia, osteoporosis) (Elstein, Y et al. 2004).

##### Pre-enzyme replacement therapy

Prior to the introduction of enzyme replacement therapy, Gaucher disease was managed symptomatically through the treatment of pain, splenectomy to relieve the thrombocytopenia caused by hypersplenism, blood transfusions to correct the anaemia of the disease, orthopaedic procedures for fractures and avascular necrosis of the bone, vitamin D supplementation and sometimes bone marrow transplantation for patients with very severe disease (Hayes, RP et al. 1998). Adjunctive therapies of analgesics, anti-inflammatory drugs and bisphosphonates are also used for symptom management.

##### Enzyme replacement therapy and substrate reduction therapy

Options now include enzyme replacement therapies (ERT), or substrate reduction therapies (SRT), which may possibly improve a patients’ functioning and quality of life, maintain it, or slow deterioration, but are not curative. The first enzyme replacement therapy used human placenta cells (alglucerase), which was later replaced by recombinant technology (imiglucerase), reducing the risk of viral contamination (Giraldo et al. 2011). Imiglucerase has been subsidised through the LSDP, and precursors to the LSDP, since 1995. Additional enzyme replacement therapies are velaglucerase alfa, and taliglucerase. Velaglucerase alfa has been subsidised through the LSDP since 2012. A submission was made to the PBAC in 2012 for funding of taliglucerase alfa through the LSDP or Highly Specialised Drug Program, however, the submission did not provide any direct comparative information on taliglucerase alfa compared to placebo or the other forms of ERT for Gaucher disease. The PBAC rejected the submission on the basis of the lack of information on clinical effectiveness (Department of Health, 2012).

Due to the high cost of the drugs, ERT is prepared and delivered with caution. Treatment carries significant burden to the patient despite government funding through the LSDP. Ideally infusion of imiglucerase or velaglucerase alfa should be prepared once the patient arrives at the treatment site, and the prepared solution should be used within 3 hours. Imiglucerase and velaglucerase alfa are both lyophilised powers that must be reconstituted with sterile water and sodium chloride prior to infusion. Both imiglucerase and velaglucerase are dosed at 60 U/kg body weight every 2 weeks by intravenous infusion, which takes 1-2 hours. For those who have received at least three infusions within a hospital, and have tolerated it well, it may be possible to receive the drug at home.

Substrate reduction therapies include miglustat and eliglustat. Miglustat has been subsidised through the LSDP since 2009 for patients with mild to moderate Gaucher disease, for whom ERT is not a therapeutic option due to poor venous access, severe needle phobia, or hypersensitivity. Miglustat is an oral medication which is taken at a dose of 100 mg/kg, three times daily. Patients are likely to experience a benefit from not having the inconvenience of attending hospital for delivery, and being able to avoid hours of waiting and infusion time and the risk of infusion reactions. Miglustat does however increase the risk of gastrointestinal side effects and is recommended to be taken without food.

#### Systematic review inclusion criteria

Table 5 provides the criteria for selecting studies to review the safety and effectiveness of imiglucerase, velaglucerase alfa and miglustat for the treatment of patients with Type 1 Gaucher disease.

Table 5 Criteria for selecting studies to assess the safety and effectiveness of imiglucerase, velaglucerase alfa, and miglustat

| Characteristic | Inclusion criteria |
| --- | --- |
| Study design | The highest level of evidence available (from Table 2) that addressed the research questions. Case reports would have been included if none of the study designs in Table 2 were available. |
| Population | Patients with Type 1 Gaucher disease (absence of CNS involvement), without confounding diagnoses such as Hodgkin lymphoma, or irreversible complications of Gaucher disease (such as avascular necrosis of bone) |
| Interventions | Imiglucerase (Cerezyme®), or  Velaglucerase alfa (VPRIV®), or  Miglustat (Zavesca®)  Subgroup analysis: by dose (e.g. doses consistent with TGA listing, as well as experimental dosing regimens) |
| Comparators | Standard therapy (supportive therapy including total or partial removal of the spleen, blood transfusions, orthopaedic procedures, and occasionally bone marrow transplantation) with/without placebo  Imiglucerase, Velaglucerase alfa, or Miglustat |
| Outcomes | *Safety:* adverse events related to treatments – for example, gastrointestinal problems (e.g. diarrhoea, abdominal pain, nausea); neurological effects; (e.g. peripheral neuropathy); skin reactions; headaches; dizziness; compliance with treatment (i.e. treatment withdrawal or suboptimal dosing)  *Primary effectiveness:* survival  *Secondary effectiveness:* quality of life; bone disease (aseptic bone necrosis, bone pain, fracture, arthritis) or bone disease markers (signs of bone oedema on MRI); Gaucher disease burden (chitotriosidae level); bleeding events (epistaxis or haemorrhage) or bleeding risk (haemoglobin, platelet counts, thrombocytopenia) infection risk (white blood cell counts); splenomegaly (spleen volume); dysphagia (swallowing function); lung function (FEV1, respiratory failure) |
| Language | English language only |
| Research questions | In patients with Type 1 Gaucher disease, what is the safety and effectiveness of imiglucerase, velaglucerase alfa, or miglustat compared to standard therapy?  In patients with Type 1 Gaucher disease, what is the safety and effectiveness of imiglucerase, velaglucerase alfa, or miglustat when compared to each other? |

CNS = central nervous system; TGA = Therapeutic Goods Administration; FEV1 = forced expiratory volume in 1 second

Studies that examined a mix of patients receiving imiglucerase, velaglucerase alfa or miglustat were excluded, unless stratified results were presented. Studies that included a small proportion of patients who received alglucerase, or patients who initially received alglucerase, and then were switched to imiglucerase, were considered eligible for inclusion.

#### Results of the literature search

The highest level of evidence available was from three randomised trials, which addressed the three drugs being assessed:

* A three arm trial that compared (1) alglucerase/imiglucerase (ERT) alone, (2) vitamin D supplementation and ERT, and (3) vitamin D supplementation alone. After the first 6 months of allocated treatment, patients in all treatment arms received ERT (Schiffmann et al. 2002);
* Trial HGT-GCB-039, which compared imiglucerase and velaglucerase alfa (Ben Turkia et al. 2013; Centre for Drug Evaluation and Research 2010); and
* Trial OGT 918-004, which compared imiglucerase and miglustat (Actelion Pharmaceuticals Ltd. 2012; Dechelotte 2003; Elstein, D et al. 2007; Oxford Glycosciences 2002). This study also included a miglustat plus imiglucerase arm, which was excluded for the purposes of this systematic review.

An extension study associated with Trial OGT 918-004 was also included. In this extension study, after the 6 month randomised period, all patients were given the option to receive miglustat, or miglustat in combination with imiglucerase.

Four systematic reviews were identified as meeting the PICO criteria, but were not recent enough or comprehensive enough to be used as the sole evidence base (CADTH 2011; Connock, Burls, et al. 2006; HAYES & Inc 2013; Morris 2012). The reference lists of these documents were pearled to see whether any additional studies were relevant.

Randomised trials comparing one dose of treatment against another dose of the same treatment were not considered as answering the research questions that had been posed (de Fost et al. 2007; Gonzalez et al. 2013; Kishnani, P. S. et al. 2009). Studies which may have met the study eligibility criteria, but were excluded due to higher level evidence being available, are listed in Appendix C.

#### Risk of bias assessment

The randomised controlled trial (RCT) by Schiffmann et al (2002) had a low risk of bias. Participants were block randomised based on gender, bone density and liver size, and it was explicit that both patients and investigators were kept blind to the treatment allocation. It was unclear from the published article whether the results exclude those patients who withdrew from the study (due to pulmonary hypertension, insurance problems, and pregnancy). However, additional data were provided by the lead author, which allowed intention-to-treat data to be used (using last observation carried forward).

Trial HGT-GCB-039, comparing imiglucerase and velaglucerase alfa, was considered to have a low risk of bias, although it was noted that that the method of randomisation was not stated and, although the trial was classed as double-blind, the article did not explicitly state whether treating physicians or study investigators knew which treatment that patients received. The main outcome measures were objective so it is unlikely that any lack of blinding would have an impact on the results. Data were provided in both intention-to-treat format (last observation carried forward for post-baseline measures), and per-protocol.

Trial OGT 918-004, comparing miglustat and imiglucerase was considered to have poorly addressed the likely sources of bias. It was an open-label study, and had a disproportionate number of patients receiving miglustat lost to follow-up due to adverse events. Outcome reporting bias was likely as some non-significant results were not reported. The small sample size increased the likelihood that differences between miglustat and imiglucerase would not be considered statistically significant.

#### Effectiveness of alglucerase/ imiglucerase compared to standard therapy

Schiffmann et al (2002) compared three treatment regimens in patients who had previously undergone a splenectomy. These were ERT (alglucerase / imiglucerase at 60 IU/kg every 2 weeks), ERT plus vitamin D, and vitamin D alone.

Patients who received vitamin D without ERT for the first 6 months had a reduction in their bone marrow fat fraction (a surrogate outcome for bone disease risk), whereas both groups who received ERT had an improved percent of fat fraction over the first 6 months. These results were presented graphically in the publication, and AHTA is still waiting on the author to forward de-identified data on this outcome to present in this technical assessment.

Patients receiving ERT (with/without vitamin D) had significantly better outcomes on surrogate markers of infection and bleeding risk than those who did not receive ERT. On average, patients who received ERT over 6 months had a white blood cell count 2.19 × 109/L lower than those who did not receive ERT over the same time period (p = 0.01) (GRADE ⨁⨁⨁⨀). This put the average white blood cell count for patients receiving ERT within the normal range[[7]](#footnote-7). The mean white blood cell count for patients who did not receive ERT remained above the normal white blood cell count of healthy people. The difference between treatment groups is likely to be clinically important.

Over the same time period, those patients receiving ERT had haemoglobin levels raised an average of 9.5 g/L more than patients without ERT (p = 0.02) (GRADE ⨁⨁⨁⨀). The mean haemoglobin values for all patients were below the normal range for males, but within the normal range for females[[8]](#footnote-8). It is unknown whether the difference between groups would be considered clinically important.

Platelets improved on average by 90.45 x 109/L more in those patients who received ERT over 6 months, compared to those received vitamin D alone (p<0.001) (GRADE ⨁⨁⨁⨀). All the mean platelet counts were within the normal range[[9]](#footnote-9) so it is unlikely that this difference would be considered clinically important.

Table 6 Infection and bleeding risk markers for patients receiving ERT, Vitamin D or a combination

| Outcome | ERT  (N = 8) | ERT plus Vitamin D  (N = 12) | Vitamin D alone  (N = 10) | Difference (ERT vs no ERT) |
| --- | --- | --- | --- | --- |
| White blood cell count (× 109/L mean ± SD)  Baseline  6 months  Change | 12.9 ± 3.86  9.7 ± 2.93  -3.3 ± 1.25 | 12.84 ± 3.28  10.5 ± 2.83  -2.34 ± 2.40 | 12.2 ± 3.35  11.7 ± 4.27  -0.5 ± 2.11 | F(1, 28) = 7.55, p = 0.01  Difference coefficient = -2.19  (95%CI -3.82, -0.56) |
| Haemoglobin (g/L, mean ± SD)  Baseline  6 months  Change | 122 ± 15.6  126 ± 13.5  4.0 ± 13.3 | 128 ± 17.2  135 ± 13.4  6.7 ± 10.8 | 124 ± 13.1  120 ± 11.9  -4.0 ± 6.3 | F(1, 28) = 5.70, p = 0.02  Difference coefficient = 9.5  (95%CI 1.3, 17.6) |
| Platelets (109/L, mean ± SD)  Baseline  6 months  Change | 252.4 ± 69.5  339.0 ± 103.5  86.6 ± 69.8 | 211.6 ± 58.1  276.9 ± 70.8  65.3 ± 48.3 | 246.9 ± 82.3  230.3 ± 70.9  -16.6 ± 51.1 | F(1, 28) = 17.89, p<0.001  Difference coefficient = 90.45 (95%CI 46.64, 134.26 |

Data received via email from Schiffmann, received on 10th November, 2014. Data are intention-to-treat, using last observation carried forward for missing data (one patient in ERT + vitamin D condition did not have 6 month data).

Over the 2 years of the study (including the period where all three groups received ERT), some patients suffered complications, which are outlined in Table 7. No distinction was made in the publication regarding whether the adverse events were considered to be related to Gaucher disease or a complication of treatment. No comparison can be made between ERT and vitamin D alone due to all groups receiving ERT after the first 6 months.

Table 7 Adverse events of treatment and Gaucher disease during study period

| Outcome | ERT  (N = 8) | ERT plus Vitamin D  (N = 12) | Vitamin D alone for 6 months, then plus ERT  (N = 10) | Not stated |
| --- | --- | --- | --- | --- |
| Pulmonary hypertension | 1 | 0 | 1 | - |
| Osteonecrosis of the hip | 1 | 0 | 1 | - |
| Vitamin B12 deficiency | - | - | - | 1 |
| Bone crises (1-3 crises) | 2 | 2 | 3 | - |

#### Additional evidence on imiglucerase compared to standard therapy

Although not formally included in the systematic review due to randomised trial evidence being available, a total of 15 cohort studies were also identified. The findings from these cohort studies support the results of the randomised trial. The effectiveness of imiglucerase (with or without some patients having received alglucerase initially) was compared to receiving standard care (Casal et al. 2002; Donaldson, J et al. 2011; Elstein, Y et al. 2004; Giraldo et al. 2011; Grigorescu-Sido et al. 2010; Hayes, RP et al. 1998; Hollak et al. 2001; Mistry et al. 2002; Oliveira et al. 2013; Stirnemann et al. 2010; Stirnemann et al. 2012; Terk, Dardashti & Liebman 2000; van Dussen, Biegstraaten, Dijkgraaf, et al. 2014; Wyatt et al. 2012b; Zimran et al. 2009). In the majority of these studies ERT was found to be superior to no ERT (and supportive therapy).

Cohort studies, where patients are recommended to receive, or not to receive, ERT based on how severe their symptoms are, have a high risk of selection bias. Three of the cohort studies reported that health outcomes were worse in those patients who had undergone ERT, than those who had not received ERT (Elstein, Y et al. 2004; Giraldo et al. 2011; Hayes, RP et al. 1998). Giraldo et al (2011) reported that during an imiglucerase shortage, patients were either given a reduced dose, or discontinued treatment, depending on the severity of their symptoms. During follow-up, those receiving a reduced dose of imiglucerase had more bone pain, and more need for supportive therapy than those who had discontinued ERT treatment. However, given the differences in baseline disease severity, these results should not be considered to reflect a lack of treatment effect. In this same study, when baseline differences were taken into account, chitotriosidase levels increased more in the group of patients who had discontinued treatment with imiglucerase during the ERT shortage, compared to those who had been on a reduced dose (i.e. favouring ERT) (Giraldo et al. 2011).

One study reported that postpartum haemorrhage was more common in those patients with symptoms serious enough to continue ERT throughout their pregnancy (Elstein, Y et al. 2004). This was consistent with another study that reported that Gaucher-related and non-Gaucher related complications were far more common in women who continued to take ERT during pregnancy, compared to those who were untreated (Zimran et al. 2009).

In a cross-sectional study of 35 patients quality of life was higher in patients who received ERT, although this was only statistically significant on one domain (Oliveira et al. 2013). Gaucher disease burden, as measured by chitotriosidase activity (Casal et al. 2002; Grigorescu-Sido et al. 2010), was reduced. Changes in haemoglobin levels (Grigorescu-Sido et al. 2010; Wyatt et al. 2012b; Zimran et al. 2009), frequency of menorrhagia (Zimran et al. 2009), and intracerebral bleeding (Grigorescu-Sido et al. 2010) indicated a lower bleeding risk.

Bone events were fewer after ERT treatment, than prior to receiving (or without) ERT (Stirnemann et al. 2010; Stirnemann et al. 2012; van Dussen, Biegstraaten, Dijkgraaf, et al. 2014). Those patients who had ERT had increased bone marrow fat fractions after treatment, whereas those who were untreated had no increase in fat fraction (Hollak et al. 2001).

ERT was associated with a reduced risk of an enlarged liver (Grigorescu-Sido et al. 2010; Terk, Dardashti & Liebman 2000; Wyatt et al. 2012b) and an enlarged spleen (Terk, Dardashti & Liebman 2000) and patients had a reduced incidence of a splenectomy (van Dussen, Biegstraaten, Dijkgraaf, et al. 2014).

Patients receiving ERT also had a reduced risk of pulmonary hypertension (Mistry et al. 2002).

#### Effectiveness of imiglucerase compared to velaglucerase

Ben Turkia et al (2013) performed a non-inferiority trial comparing 60 units/kg/2 weeks of velaglucerase alfa and imiglucerase (trial HGT-GCB-039).

Velaglucerase alfa was pre-specified to be non-inferior to imiglucerase if a one-sided t-test comparison of the haemoglobin levels between treatment groups resulted in a 97.5% confidence interval, with the lower end exceeding -10 g/L. Over 9 months patients in both the velaglucerase alfa and imiglucerase groups improved in regards to haemoglobin levels (a surrogate outcome for bleeding risk), and the difference between the two groups was very small, with the lower confidence limit exceeding the pre-defined non-inferiority margin. Patients in both treatment groups improved on the other outcome measures, such as platelet count (bleeding risk surrogate), a marker of disease burden (reduced chitotriosidase), and decreased hepatosplenomegaly (reduced spleen and liver volume). No statistically significant differences were detected between the drugs (see Table 8) (GRADE ⨁⨁⨁⨀ for all outcomes).

Table 8 Comparison of velaglucerase alfa and imiglucerase on secondary effectiveness measures

| Outcome | Velaglucerase alfa | Imiglucerase | Mean difference | One-sided 97.5% CI |
| --- | --- | --- | --- | --- |
| Haemoglobin (g/L)  Median baseline (range)  Mean change from baseline | N = 17  114 (97 – 144)  16.24 | N = 17  106 (81 – 131)  14.88 | 1.35 | (-5.96, ∞) |
| Platelets (x109/L)  Median baseline (range)  Mean change from baseline | N = 17  172.0 (44.0 – 310.5)  108.0 | N = 17  188 (63.0 – 430.5)  146.7 | -38.71 | 95% 2-sided CI  (-88.42, 10.99) |
| Liver volume, % body weight  Median baseline (range)  Mean change from baseline | N = 17  3.90 (1.9 – 12.2)  -1.24 | N = 17  4.00 (1.7 – 7.0)  -1.17 | -0.07 | (-0.43, 0.29) |
| Spleen volume, % body weight  Median baseline (range)  Mean change from baseline | N = 7  1.90 (1.4-6.3)  -1.86 | N = 7  1.40 (0.6-8.9)  -1.94 | 0.08 | (-0.52, 0.68) |
| Chitotriosidase (nmol/mL/h)  Median baseline  Mean change from baseline | N = 15  27 145  -27 622 | N = 16  34 362  -28 691 | 1069 | (-7446, 9583) |

Data from (Centre for Drug Evaluation and Research 2010)

A slightly higher number of patients receiving velaglucerase alfa suffered from treatment-related adverse events when compared to patients receiving imiglucerase (GRADE ⨁⨁⨁⨀). The study was not powered to detect differences in adverse event rates but the authors report that the majority of adverse events were mild to moderate in severity (Ben Turkia et al. 2013).

Table 9 Comparison of adverse events following velaglucerase alfa and imiglucerase

| Adverse events | Velaglucerase alfa | Imiglucerase |
| --- | --- | --- |
| Drug-related adverse events | 8/17 (47.1%) including:  1 patient had allergic dermatitis 30 weeks after first dose (resolved without sequelae)  1 patient had 2 episodes of severe prolonged activated partial thromboplastin time (resolved without sequelae)  1 patient had generalised tonic-clonic seizures following week 17 treatment. Recovered within 2 hours following anti-convulsant treatment. Considered unrelated to drug.  0 patients developed anti-drug antibodies | 6/17 (35.3%) including:  1 case of severe chills  4 patients developed anti-drug antibodies |
| Infusion related events | 5/8 | 4/6 |
| Deaths or discontinuations due to adverse events | 0 | 0  1 withdrew consent citing multiple infusion-related reactions |

#### Effectiveness of imiglucerase compared to miglustat

One randomised trial compared the effectiveness of imiglucerase relative to miglustat in the treatment of patients with Type 1 Gaucher disease (Trial OGT 918-004) (Elstein, D et al. 2007). Patients randomised to miglustat were administered one 100mg capsule 3 times a day, whereas patients randomised to imiglucerase predominantly received an infusion of 30 units/kg/month (n=33), with a small proportion of patients (n=3) receiving 60 units/kg/month. Dosing changes to miglustat due to adverse events were permitted, whereas no changes to the dose or frequency of imiglucerase were allowed.

##### Quality of life

Patients who switched from imiglucerase to miglustat reported an improvement in quality of life, whereas those who entered the trial and were randomised to continue receiving imiglucerase reported a mean decrease in quality of life. Quality of life was measured using the Short Form-36 (SF-36, with a scale of 0 – 100, where higher scores represent better quality of life; Table 10) (GRADE ⨁⨁⨁⨀). These differences were considered statistically significant. Miglustat was considered more convenient (GRADE ⨁⨁⨁⨁), being able to be taken as an oral treatment, rather than administered intravenously, over one or two hours. The remaining SF-36 items and subscales were not statistically different between groups or when compared to baseline (data not reported) (Elstein, D et al. 2007). Some caution should be applied when considering these results, given the slightly higher loss to follow-up in the group of patients that received miglustat.

Table 10 Quality of life comparison between miglustat and imiglucerase

| Quality of life (SF-36) | Miglustat | Imiglucerase | p-Valueb |
| --- | --- | --- | --- |
| Overall change from baseline to 6 months | +8.7% | -8.5% | p = 0.057 |
| Treatment convenient | 77.8% | 33.3% | p = 0.028 (Fisher exact test between three arms) |
| Overall treatment satisfaction | 77.8% | 33.3% | p = 0.053 |

Note: p-value calculated for comparison between the three arms (i.e. including miglustat plus imiglucerase, which had a mean reduction in SF-36 of 8.1%). SF-36 scale: 0 – 100, where a higher score relates to higher quality of life).

##### Markers of disease burden and bleeding risk

Indicators of bleeding risk differed as to whether miglustat and imiglucerase were equivalent or not, depending on what surrogate outcome measure was used. Haemoglobin concentration was marginally decreased (a worsening of bleeding risk) from baseline in both groups, but the difference between groups was not considered statistically significant or likely to have any clinical impact (GRADE ⨁⨀⨀⨀). However, platelet count was *reduced* by an average of 21.6 x109/L in the group who switched to miglustat, whereas it *increased* an average of 15.3 x109/L in the group who remained on imiglucerase. The loss of platelets in the miglustat group resulted in the average platelet count in this group being less than the healthy reference range of 150 – 450 x 109/L (QML Pathology 2009). This would potentially have a clinical impact, and was statistically significant (p<0.05) (GRADE ⨁⨁⨀⨀).

'''''''''''''''''''''''''' '''''''''''''''' ''''' ''' '''''''''''''' ''''' ''''''''''' '''''''''''''' '''''''' ''''''''''''''''' '''' ''''''''''' ''''''''' ''''''''''''''''' '''' '''''''''''''''''' '''''''''''''''' ''''''''''''' '''''''''''' '''' ''''''''''' '''''' '''''''''''''''''''''''''' ''''''''''''''''' '''''''''''''''''''''''' ''''' ''' '''''''''''' '''''''''''''''''''' ''''''''''''''''''' '''''''''''''' ''''''''''' '''''''''''''''' ''''''''''''''''''' ''''''''' ''''''''''''''' '''''''' ''''''''' ''''''' '''''''''''''''''''

Table 11 Comparison of miglustat and imiglucerase on markersof disease burden and bleeding risk

| Outcome | Miglustat | Imiglucerase | Difference |
| --- | --- | --- | --- |
| Haemoglobin concentration (g/L)  '''''''''''''''''''  Absolute change from baseline (g/L, mean±SD) | N = 10  '''''''''''''''''''''''  -3.1±5.5 | N = 12  '''''''''''''''''''''''''''  -1.5±3.9 | NS |
| Percent change from baseline (%, mean±SD) | -2.4±4.1 | -1.2±3 | NS |
| Platelet count (x109/L)  ''''''''''''''''''''''  Absolute change from baseline (x109/L, mean±SD) | N = 10  '''''''''''''''''''''''''''  -21.6±37.4 | N = 12  '''''''''''''''''''''''''''''  15.3±26.2 | '''''''''''  ''''''''''''''''' ''''''''''''''' '''''''''''' |
| Percent change from baseline (%, mean±SD) | -9.6±15.1 | 10.1±16.7 | NR |
| Chitotriosidase activity  Baseline range (approximate; nmol/mL/hr)  Percent change from baseline (% mean) | 1000 – 15 000  33.0 | 1000 – 15 000  -0.3 | p = 0.004 |

Data from (Actelion Pharmaceuticals Ltd. 2012) (Elstein, D et al. 2007) (European Medicines Agency 2003); NS = not significant; NR = not reported

Data extracted from the submission to the PBAC (Actelion Pharmaceuticals Australia Pty Ltd. 2007) and are Committee in Confidence and have been redacted.

##### Spleen and organ volume

There were no significant differences in the change from baseline values measuring liver volume or spleen volume between those patients who switched to miglustat, and those who remained on imiglucerase (see Table 12; GRADE ⨁⨁⨀⨀ for both outcomes).

Table 12 Comparison of miglustat and imiglucerase on secondary effectiveness measures

| Organ volume | Miglustat | Imiglucerase | Difference |
| --- | --- | --- | --- |
| Liver volume, L  Baseline (mean) | N = 10  1.53±0.32 | N = 11  1.81±0.57 |  |
| Absolute change from baseline | -0.05±0.12 | 0.04±0.16 | '''''''''''''' ''''''''''''''''' ''''''''''''''' ''''''''''''''' ''' ''' '''''''''' |
| Percent change from baseline (%, mean±SD) | -2.9±7.9% | 3.5±9% | ''''''''' '''''''''''''''''' ''''''''''''' '''''''''' ''' '''' ''''''''''' |
| Spleen volume, L  Baseline (mean) | N = 7  0.63±0.43 | N = 8  0.74±0.56 |  |
| Absolute change from baseline (Litres, mean±SD) | -0.27±0.07 | -0.02±0.06 | '''''''''''' '''''''''''''''''' ''''''''''''' ''''''''''''''' '''' '''' ''''''''''''' |
| Percent change from baseline (%, mean±SD) | -4.8±7.8% | -2.1±4.8% | '''''''' ''''''''''''''''''' '''''''''''''' ''''''''''''''' ''' '''' ''''''''''' |

Data from (Actelion Pharmaceuticals Ltd. 2012); NS = not significant

Data extracted from the submission to the PBAC (Actelion Pharmaceuticals Australia Pty Ltd. 2007) and are Committee in Confidence and have been redacted

##### Comparative safety

Gastrointestinal adverse events (i.e. diarrhoea) occurred in all patients who switched to miglustat, and occurred in only half of those who continued on imiglucerase (RR = 1.92, 95%CI 1.10, 3.35; GRADE ⨁⨁⨁⨀). The intensity of adverse events was mild to moderate, and diarrhoea decreased from weeks 0-4 to after week 13 of the study (Dechelotte 2003).

Two patients receiving miglustat withdrew from the trial. One patient wished to start a family, and also had a transient tremor of the hand, while the other withdrew due to being dissatisfied with her quality of life, having malaise and fatigue, which were attributed to infectious mononucleosis (European Medicines Agency 2003; Oxford Glycosciences 2002).

Table 13 Comparative harms from miglustat and imiglucerase

| Adverse events | Miglustat | Imiglucerase | Comparison |
| --- | --- | --- | --- |
| Abnormalities on electromyography and nerve conduction velocity (not associated with symptoms) | 3/12 (25%) | 2/12 (16.7%) | RR = 1.5  (95%CI 0.30, 7.43) |
| Severe adverse events | 0 | 0 | - |
| At least one adverse event in the gastrointestinal system | 12/12 (100%) | 6/12 (50%) | RR = 2.0 (1.14, 3.52) |
| Withdrew from study | 2/12 | 0/12 | NC |

Source: (Dechelotte 2003); NC = not calculable

##### Extension period

After the 6 month period of randomisation, all patients enrolled in OGT 918-004 were given the option to receive miglustat for an additional 18 month extension trial. Those who had been originally randomised to receive miglustat therefore had 24 months of miglustat in total. Patients who switched from imiglucerase or combination imiglucerase and miglustat to miglustat alone had 18 months of miglustat treatment in the extension trial. Baseline was defined as the start of the trial for those participants who received miglustat alone in the randomised period, and month 6 for patients who were initially randomised to a condition including imiglucerase.

Patients on miglustat had deterioration in their mean haemoglobin concentration after imiglucerase withdrawal, to a statistically significant degree at months 6, 9, 12 and 24 (see Table 14; GRADE ⨁⨀⨀⨀). It was stated that no patients had haemoglobin low enough to be considered clinically significant (Actelion Pharmaceuticals Ltd. 2012) although the mean haemoglobin concentration was under the reference range for health males[[10]](#footnote-10). Similarly, a small statistically significant decrease in platelet levels was observed after imiglucerase withdrawal (see Table 14; GRADE ⨁⨀⨀⨀). Mean platelet levels dropped from being within the normal range[[11]](#footnote-11), to being under the normal range for three out of four post-baseline time-points. One patient had clinically significant low platelet levels, although this was also observed at baseline (Actelion Pharmaceuticals Ltd. 2012).

Table 14 Long-term blood count changes with miglustat (after imiglucerase withdrawal)

| **Time** | **Mean ±SD Haemoglobin concentration (g/L)** | **Mean ±SD % change from baseline** | **Mean ±SD platelet count (x 109/L)** | **Mean ±SD % change from baseline** |
| --- | --- | --- | --- | --- |
| **Baseline (n = 31)** | 127.5±14.6 | N/A | 171.70±86.5 | N/A |
| **6 months (n = 29)** | 124.0±11.5 | -2.14±5.51 | 147.6±78.6 | -12.0±14.2 |
| **12 months (n = 28)** | 123.8±12.4 | -2.48±5.59 | 146.6±77.5 | -14.8±14.9 |
| **18 months (n = 20)** | 127.6±14.3 | -1.63±7.69 | 153.2±77.9 | -16.9±17.6 |
| **24 months (n = 6)** | 129.7±10.9 | 1.49±5.30 | 144.2±37.4 | -7.8±19.6 |

(Actelion Pharmaceuticals Ltd. 2012); SD = standard deviation; N/A = not applicable

Mean liver and spleen volumes did not significantly over time change while patients were on miglustat (see Table 15; GRADE ⨁⨀⨀⨀).

Table 15 Long-term organ volume changes with miglustat (after imiglucerase withdrawal)

| **Time** | **-** | **Liver volume (L)** | **-** | **-** | **Spleen volume (L)** | **-** |
| --- | --- | --- | --- | --- | --- | --- |
| **-** | **N** | **Mean ±SD** | **% change from baseline** | **N** | **Mean** | **% change from baseline** |
| **Baseline** | 29 | 1.78±0.46 | N/A | 20 | 0.66±0.38 | N/A |
| **6 months** | 29 | 1.78±0.42 | (N = 27)  -1.69±10.27 | 21 | 0.86±0.61 | (N = 19)  3.32±16.31 |
| **12 months** | 8 | 1.58±0.34 | -0.75±6.44 | 6 | 0.52±0.25 | -6.13±6.33 |
| **18 months** | 9 | 2.04±0.43 | -3.89±7.67 | 6 | 0.74±0.41 | -0.10±9.69 |
| **24 months** | 5 | 1.47±0.33 | -2.68±9.19 | 4 | 0.46±0.27 | -0.79±15.75 |

(Actelion Pharmaceuticals Ltd. 2012); SD = standard deviation; N/A = not applicable

In patients who had stable Type 1 Gaucher disease, maintenance therapy with miglustat was considered effective in 11/15 patients for an average of 19 months. Four patients showed signs of deterioration, i.e. an increase in organ volume or chitotriosidase and/or reduction in platelet or haemoglobin level (Actelion Pharmaceuticals Ltd. 2012; Elstein, D et al. 2007). No patients had bone events, avascular necrosis or fracture over the time that they were treated with miglustat (GRADE ⨁⨁⨀⨀) (Actelion Pharmaceuticals Ltd. 2012).

Side effects from miglustat during either the randomised period or the extension period are shown in Table 16 (GRADE ⨁⨁⨀⨀). The most common adverse events experienced after miglustat were diarrhoea (88%), decreased weight (82%), musculoskeletal and connective tissue disorders (59%), flatulence (50%), abdominal pain (47%) and tremors (35%).

Table 16 Patients experiencing adverse events during randomised and extension treatment with miglustat

| Outcome | 0 to 6 months | 6 to 12 months | 12 to 18 months | 18 to 24 months | Overall |
| --- | --- | --- | --- | --- | --- |
| Subjects at beginning of time interval | 34 | 28 | 26 | 19 | 34 |
| Subjects with at least 1 AE during time interval | 34 (100) | 27 (96) | 25 (96) | 18 (95) | 28 (100) |
| **Gastrointestinal disorders, no. patients (%)** | 32 (94) | 15 (54) | 14 (54) | 11 (58) | 32 (94) |
| Diarrhoea | 30 (88) | 14 (50) | 9 (35) | 8 (42) | 30 (88) |
| Flatulence | 14 (41) | 6 (21) | 6 (23) | 4 (21) | 17 (50) |
| Abdominal pain | 13 (38) | 8 (29) | 6 (23) | 4 (21) | 16 (47) |
| Constipation | 6 (18) | 3 (11) | 2 (8) | 2 (11) | 8 (24) |
| Nausea | 3 (9) | 1 (4) | 2 (8) | 2 (11) | 5 (15) |
| Vomiting | 1 (3) | 2 (7) | 2 (8) | 0 | 5 (15) |
| **Nervous system disorders, no. patients (%)** | 12 (62) | 7 (25) | 6 (23) | 4 (21) | 22 (65) |
| Tremor | 10 (29) | 2 (7) | 3 (12) | 3 (16) | 12 (35) |
| Dizziness | 8 (24) | 0 | 1 (4) | 0 | 9 (26) |
| Headache | 8 (24) | 2 (7) | 1 (4) | 1 (5) | 8 (24) |
| Fatigue | 5 (15) | 6 (21) | 4 (15) | 1 (5) | 9 (26) |
| Weakness | 7 (21) | 2 (7) | 2 (8) | 1 (5) | 9 (26) |
| Decreased weight, no. patients (%) | 23 (68) | 25 (89) | 21 (81) | 16 (84) | 28 (82) |
| Musculoskeletal and connective tissue disorders, no. patients (%) | 13 (38) | 9 (32) | 7 (27) | 5 (26) | 20 (59) |
| Respiratory, thoracic, and mediastinal disorders, no. patients (%) | 4 (12) | 5 (18) | 2 (8) | 3 (16) | 10 (29) |
| Skin and subcutaneous tissue disorders, no. patients (%) | 6 (18) | 6 (21) | 4 (15) | 2 (11) | 9 (26) |

AE = adverse event

#### Extended assessment of harms

The summary of safety provided in this section for velaglucerase alfa and miglustat is based on Periodic Safety Update Reports (PSURs) presented in confidential submissions to the Post Market Review (PMR) of the Life Savings Drugs program (LSDP). The summary of safety experience with imiglucerase is based on a review of data between 1994 and 2004 by Starzyk et al (2007), which provides more comprehensive data than available in the PSUR for the time period 2001 – 2002.

##### Imiglucerase (Cerezyme® / Sponsor: Genzyme):

Adverse events reported spontaneously between 1994 and 2004 were reviewed and categorised using the System Organ Class (SOC). Between 1994 and 1997 only limited data were available, and specific rates are not presented. A total of 59 adverse events were reported during this period, and 44 of these were reported as related to imiglucerase or not able to be assessed. Adverse events that were reported four or more times were: nausea, vomiting, headache, pruritus, urticaria, rash, chest pain or chest tightness, fatigue or asthenia, malaise, flushing or dyspnoea (Starzyk et al. 2007). Most of these were managed successfully by using a slower rate of infusion and/or by pre-treating patients with anti-pyretics or antihistamines.

Between 1997 and 2004, imiglucerase was used more widely. By the end of 1997, there were 2,184 patients receiving enzyme replacement therapy, 753 (34%) with alglucerase, and 1,431 (66%) with imiglucerase. The majority of patients receiving imiglucerase (80%) had transferred from treatment with alglucerase, 17% were ERT naïve prior to imiglucerase treatment, and 3% had received imiglucerase during a clinical trial. By 2004, approximately 4,200 patients were receiving imiglucerase world-wide (Starzyk et al. 2007).

The most common adverse events reported are shown in Table 17, categorised by System Organ Class, and by whether the adverse event was likely related to imiglucerase. Each of these adverse events occurred in less than 1% of the total treated patient population. Significant adverse events, such as anaphylaxis, were very rare. The most frequent adverse events were non-serious infusion-associated reactions, which were managed by decreasing the rate of infusion and through the use of antihistamines. In patients with significant reactions, temporary dose reductions were used, but most patients returned to the regular infusion rate without additional pre-treatment. Four patients who had experienced severe infusion reactions discontinued treatment with imiglucerase. It is not known whether the discontinuation was due to tolerability (Starzyk et al. 2007).

Table 17 Most common adverse events from imiglucerase by system organ class (1997-2004)

| **System organ class and adverse event** | **Related events** | **All events** |
| --- | --- | --- |
| **General disorders and administration site reactions** | 161 | 455 |
| Pyrexia | 25 | 80 |
| Chills | 21 | 55 |
| Chest discomfort | 22 | 44 |
| **Skin and subcutaneous tissue disorders** | 117 | 325 |
| Pruritus | 28 | 82 |
| Rash | 23 | 67 |
| Urticaria | 24 | 60 |
| **Respiratory, thoracic, and mediastinal disorders** | 88 | 75 |
| Dyspnoea | 28 | 75 |
| Cough | 12 | 32 |
| Throat irritation | 9 | 11 |

Source: (Starzyk et al. 2007)

Antibody testing was voluntary, so only 1,633 patients were tested and 1,134 patients had a baseline sample and at least one post-treatment sample taken. The cumulative rate of seroconversion for IgG antibody formation was 15.6% between 1994 and 2005. Most patients who developed antibodies did so within the first 6 months of treatment. This rarely occurred after 12 months of treatment (Starzyk et al. 2007).

Updated safety data on velaglucerase alfa and miglustat were provided in confidence to the LSDP expert reference group.

Information was withheld from this draft report at the request of the sponsors.

Table 18 Summary of adverse drug reactions associated with velaglucerase alfa

| System/Organ class | Incidence Category | Adverse Drug Reaction |
| --- | --- | --- |
| '''''''''''''''''''''' '''''''''''''''''' ''''''''''''''''''''' | '''''''''' '''''''''''''''''''' | '''''''''''''''''''''''' '''''''''''''''''''''' |
| '''''''''''''''''''''''''''''''''' '''''''''''''''''''''''' | ''''''''''' '''''''''''''''''' | '''''''''''''''''''''''''' ''''''''' '' ''''''''''''''''''''''''' '''''''''' '''''''''''''' |
|  | ''''''''''''''''''''''' | '''''''''''''''''''' |
| '''''''''''''''''''''''''''''''''' '''''''''' '''''''''''''''''''''''' ''''''''''''' ''''''''''''''''''''''' | ''''''''''' ''''''''''''''''''''' | '''''''''''''' '''''''''''' ''''''''''''''''''''''' ''''''''''' '''''''''' |
| '''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''' | '''''''''''''''''''' '''''''''''''''' '''''''''''''''''''''''''''''''' '''''''''' '''''''''''''''''''''''' ''''''''''''''''''''''''''' '''''''''''''''''' ''''''''''''''''''' |
| ''''''''''''''''''' ''''''''''''''''''''''' '''''''''' ''''''''''''''''''''''''''''''''' '''''''' ''''''''''''''''''''''' | '''''''''' ''''''''''''''''''''' | '''''''''''''''''''''''''''''''''''''' ''''''''''''''''''' ''''''''''''''''''''' '''''' '''' ''''' ''''''''''''''' ''''''''''' '''''''''' ''''' ''''''''''''''''''''''' '''''''''''''''''''' '' '''''''''''''''' '''''''''''''''' '' '''''''''''' '''''''''''''''''''''''''''' ''''''''''''''''''''''' |
| '''''''''''''''''''''' '''''''''''''''''''''''' | ''''''''''''''''''''''' | '''''''''''''''''''' ''''''''''''''''''''''''''''''''' ''''''''''''''''''''''''''''''' |
| ''''''''''''''''''' '''''''''''''''''''''''' | ''''''''''''''''''''' | '''''''''''''''''''''''''''' |
| ''''''''''' ''''''''' ''''''''''''''''''''''''''''''''''' '''''''''''''' '''''''''''''''''''' | ''''''''''''''''''''''' | ''''''''''''''' '''''''''''''''''''' |
| ''''''''''''''''''' '''''''''''''''' ''''''''''''''''''''' | '''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''' ''''''''''''''''''' ''''''''''''''''''''' ''''''''''''''''''''''' '''''''''''''''' '''''''''' ''''''''''''''''''''''''''''''''''' '''''''''''''''''''''' |

##### Miglustat (Zavesca® / Sponsor: Actelion Pharmaceuticals)

###### Exposure from clinical trials and marketing experience:

'''''''' '''''''''' ''''' ''''''''''''''''''' ''''''''''''''''' '''''' '''''''''''''' '''''''''''''''''' ''''' '''''''''''''''' ''''''''' '''''''' '''''' ''''''''''''''''' ''''''''''' '''''''' ''''''''''' '''''''' ''''''''' ''''''''''''''''' '''''''' '''''''''''''''''''' ''''''''''''' '''''' ''''''' ''''''''''''''''''' ''''''''''''' ''''''' '''''''''' ''''''' '''''''''''''''''''''' '''' '''''''''''''''''' '''' ''''''''''' ''''''''' ''''''''''' ''' ''' ''''''''''''''''''''' '''''''' '''''''''''' ''''''''''''''''' ''''''''' ''''''''''' ''''''''''''''''' '''' '''''''''''''''''''' '''''''''''''''' '''''' '''''''''' ''''''''''''''''' '''''''''' '' ''''' '''''''''''''''''''''''' '''''''' ''' '''''''''''''' ''''' '''''''''''''''''' ''' '''''''' ''''' ''''''' ''''''''''''''''' '''''''''' ''''''''' ''''''''''''''' '''' '''''''''''''''' '''' '''''''''''''' '''''''''' ''''' ''''''''''' '''''''' ''''''' ''''''''''''''''' ''''''''''''' ''''''''' ''' ''''''''''''''''''' '''''''''''''''''''''''''''' '''''''' ''''''''''''

'''''''''''''' ''''''' ''''''''''' ''' '''''''''''''''''''''' ''''''''' '''' '''''''''' '''''''' '''''''''''''' '''''''''' '''''''''' '''''''''''''' ''''''''' ''''''' '''''''''''''''''' ''''' ''''''''''' ''''''' ''''''''' ''''''''''''''''' ''''''''''''''''''''''''''''' ''''''''''''''''' '''''''''''''''''''' '''''''''''''''''''' '''''''' ''''''' ''''''''''''''''''' '''''''' ''''''' ''''''''' ''''''''''''''''' '''''''''''''''''' '''''''''' ''''''''''''''' '''' ''''''''''''''''''''''''''''' ''''''' ''''''''''''''''''''' ''' '''''''''' ''''' '''''''' '''''''''' ''''''' ''' '''''''' ''''''''''''''''' ''''''''''''''''' '''''''''''''''''''''''''''' ''''''' ''''''''''''

###### Summary of safety concerns

''' ''''''''''''''''''' '''' ''''''''''' '''''''''''''''' '''''''''''' '''' '''''' ''''''' ''''' '''''''''''''''''' ''' ''''''''''''''''''' '''' '''''''''' '''''' ''''''''''''''''''''' ''''''''' ''''''' ''''''''''' ''''' ''''''''''''''' '''''''''''''''' ''''''''''''' ''' ''''''''''''''''' ''''''''''' '''''''''''''''' '''''''''''''''''''''''''''''''' ''''''' ''''''''''''

Table 19 Summary of adverse drug reactions associated with miglustat

| **Classification of risk** | **Adverse drug reactions** |
| --- | --- |
| **Important identified risks** | **Clinical**  ''''''''''''''''''''''' '''''''' ''''''''''''' '''''''''''''''''''''''''''''''''''''' '''''''''''''''''''' '''''''''''''''''''''''  '''''''''''''''''''' '''''''''''''''' ''''''''''''''' '' '''''''''''''''' '''''''''''' ''''' '''''''''''''''' ''''''''''''''''''''''' ''''''''''''''''''''''' ''''''''''''''''''''''''' '''''''''''''''''''  ''''''''''''''' ''''''''''  '''''''''''''''''''''' '''''''''''''''' '''''''''''' |
| **Important potential risks** | **Non-clinical**  ''''''''''''''''''''' '''''''''''''''' '''' '''''''''''''''''''''''''''''''''''''''' '''''''''' ''''''''''''''' ''''''''''''''''''''''''''''''' '''''''''' '''''''''''''''''' ''''''''''''''''  '''''''''''''''''''''''''''''' ''''''''''''''''' '''''''''''''''''''''' ''''''''''''''''''  ''''''''''''''''''''' '''''''''''''''''''''' '''' ''''''''''' '''''''''''''''''''' ''''''''''''''''''''''''''''' '''''''''''''''''''''''' ''''''''' ''''''''''''''''''''''''''''''''''''''''' ''''' '''''''''''''''' '''''''''''' '''''''' ''''''''''''''''''''''''' '''' ''''''''''''''' '''' '''''''''''''''''''' '''''''''''''''''''''' '''''''''''''''''' '''''''''''''''' ''''' ''''''''''''''''''''''''' ''''''''''''''''''''' '''' '''''''' '''''''''''''''''' '''''''''''' |
| **Important missing information** | ''''''''''''' '''' ''''' ''''''''''''''''''''''' '''''''''''''''' ''''''''''''''''''''''' '''''''''''''''''''''''' ''''''''''' '''''''''' '''''''''''''''''''''''''''' '''' '''''''''''''''' '''''''''''''''''''''''''' '''''''''''''''''''''''' ''''''''' ''''''' '''''''''''''''' ''''' ''''''''''''''''' ''''''''''''' '''' ''''''''' ''' ''''''''''''''''''' '''''''''''''''''''''' ''''''''' '''''''''''''''''' ''''''''' '''' '''''''''''''' '''' '''''''''''''''''''''''' ''''''''''''''''''''''''''''''''' '''''''''''''''''''''' '''''''''''''''''''' '''''''''''''''''''''''''''''' '''''''''''''' ''''''''''''''''''''' |

'''''''''''''''''''' '''''''''''''''''''' '''''''''''''''''''''''''''''''''''''''' ''''''''' ''''''''''''

''''''''''''' '''''' ''''''''''''''' ''''''''''' ''''''''''''''''' ''''''''''''' ''''''''''''''''''''''''' ''' ''' ''''''''''''''''''' '''''''' ''''''''' ''''''''''''''''' ''''''''''''''''' '''''''''''''''''''' ''''''''''''''''''' ''''''' ''''''' '''''''' ''''''''''''' ''''''''' ''''''''''''''''''' ''''' ''''''''''' '''''' '''''''' ''' ''''''''' ''''''''''''''''' ''''''''''''' '''''' ''''''''''''''''' '''''''''''' '''''''''''' '''' ''''''''''''' ''''''''''''' '''' ''''''''''''''' '''''''''''''' ''''''''''''''''''' ''''''''''''''''''''''''''''''' ''''''''''''''''' ''''''''''' '''''''''''''''''' '''' '''''''''''' '''' ''''''''''' '''''''''''''' ''''''''''''''''' '''''' '''''''''''''''''''''''''''' '''''''' '''''''''''''''''''''' '''' '''''''''''' ''''' ''''''''''''' '''''''' '''''''''''''''''''''''' ''' '''''''''' '''' ''''''''''' '''''''''''''''' '''''''''''''''''''''''''''' ''''''' ''''''''''''

''''''' ''''''''' ''''''''''''''''''' '''''''''''''''' '''''''''''''''' ''''''''''' '''''''''' '''''''''''''''' '''''''' '''''''''''''''''' '''''' '''''''''' ''''''''''''' ''''''' '''''''''''''''''' '''''''''''''''' '''''''' ''' '''''''''''''''''''' ''''''''' ''''''' ''''''''''''''''' '''''''' ''''''''' '''''''''''' ''''''''''' '''''''''' '''''''' ''''''''' ''''''''' '''' ''''''''''''''' '''''''''' '''''''''''''''''''''''''''' '''''''''''''' ''''''''''''' '''''''''''''''''''' '''' '''''''''''''' ''''''''''''''''' '''''''' '''''''''''''''''''''''''' '''''''' ''''''''''' ''''''''''''''' '''' '''''''''''' '''''' '''''''''''''''' ''''''''''''' ''''' '''''''''''''''' '''''''''''''' ''''''' '''''''''''' ''''''''''''''''''''''''' ''''''''''' ''''''''''''''''''' ''''''''''''''''' '''''''''''' ''''''''''''' '''''''''''' ''''''''''''''''''''''''''' ''''''''''''''''' ''''''''''''''''''' ''''''''''''''''''''''''''''''''' '''''''' ''''''''''''

'''''''''''' '''''''''''' ''''''''' '''''' '''''''' ''''''''''''''' ''''''''''''' ''''' ''''''''''''''''''''''''''''''' '''''''''''''' ''''''''''''''' ''''''''''''''''''''''''''''' '''''''''''''' ''''''''''''''' '''' '''''''''''' ''''' ''''''''''''''' '''''''''''''''''' ''''''''''''''''''' '''''''''''''''' '''''''''''''''''' '''''''''''' '''''''''''''''''' '''''''''''''' ''''''''''''''''''' '''''''' '''''''''''''''' ''''''''''''''''' ''''''''''' ''''''' '''''''''''' '''''''''''''''''''''' ''''''''' ''''''''''''''' ''''''''''''''''''' '''''''''''''''''''''''''''''' ''''''' '''''''''''

'''''''''''''''' ''''''''''''''' ''''''''''''''''' '''''''''' '''''''''''''''''' '''' ''''''''''''' '''' ''''''' '''''''' ''''''''''''''''' '''''''''''''''''''' '''''''''''''''' ''' ''' '''''''' ''''''''''''''' ''''''''''' '''''''''''''''''' ''''''''''''''' ''''''''''''''''' ''''''''''''''''' '''''''''''''''' '''''''''''''''''''''' '''''''''''' '''''''''''''''' ''''''''''''''' ''''''''''''''''''''' '''''''''''''''''''''' '''''''''''''' '''''''' ''''''''''''' '''''''''''''''''''''' ''''''''''''' '''''''''' '''''''''''''''''''''''''' ''''''''' '''''''''''''' '''''''' ''''''' ''''''''' ''''''''''''''''''' ''''''''''''''''' '''''''''''''''' ''''''''''''''''''''''''''' ''''''' ''''''''''' '''' '''''''''''' ''''''''' ''''''''' '''''''''''''''''' ''''''''''' '''''''''' ''' ''''''''' '''' ''''''' ''''''''' '''' ''''''''''''''''''' '''''''''''''''''''' ''''''''' ''''''' ''''''''' '''''''''''''''' '''''' '''' '''''''''''''''' '''''''' ''''''''' '' '''''''''''''''''' '''''''' '''''''''''''''' ''''''''''''''''' '''' '''''''''' ''''''''''''''' '''''''''''''''' '''''''''''''''''''''' '''''' '''''''''''''' '''''''' ''''''''''''''''''' ''''''' '''''''''''''''''''''''' '''''''''''''''''''''''' '''' ''''''''''''''''''''''''''''''' ''''''''''''''''''' ''''''' '''''''' '''''''''''''''''''''''' ''''''''''''''''' '''''''''''''' '''''''' ''''''''''''''''''''' ''''''''''''' ''''''' ''''''''' ''' '''''''''''''''' ''''''''''''''''' '''''''' ''''''''''''''' ''''''''''''' '''''''''''''''''''''''' '' ''''''''''''''''''''''' '''''' '''''''''''' ''''''' ''''''''''''''''''''''' '' ''''''''''' '' '''''''''''' '''''''''''''''''''''' '''' '''''''''''' ''''''''''''''''''' '''''''''''''''''''' '''''' '''''''' ''' ''''''''''''''''''' '''''''''''''''''' ''''''''''' ''''''''''''''''' '''''' '''''''''''''''''' ''''''''''''' ''''''''' '''''''' '''''''''''''''''''''' ''''''''''''''''''''' ''''' '''''''''''''''''''' '''''''''''''''''''''' '''''''''''''''' ''''''''' ''''''''''''''''''' ''' '''''''''' '''' ''''''''''''''''''''''' ''''''''' '' '''''''' '''''''''''''''''''''' ''''''''''''''''''''''' ''''' ''''''''''''''''''''''' '''''''' ''''''''''' ''''''''''''''''''''''''' '''''''''''''''''''''''''''''' ''''''' ''''' ''''''''''' '''''''''''''''' ''''''''''''''' ''''''''''''' '''''''' '''''''' '''''' ''''''''''''''''''''''''''''''''''' ''''''''''''''''' '''''''''''''''''''''''''''''' '''''''' '''''''''''''

'''''''''''' '''''''' ''''''''' ''''' ''''''''' '''''''''''''''' ''''''' ''''''''''''''''' ''''''''''''''' ''''''''''''''' '''''''' ''' '''''''''''''' '''''''''''''''''' '''''''''' ''''' ''''''''''''''''' ''''''''''' '''''''''''''' ''''''''''''''''' ''' '''''''' ''''' ''''''''''''''' '''' '''''''''''''''''' '''''''''' '''''''''' '''''''''' '''''' ''''''''' '''''''' ''''''''''''''''' ''''''''''' '''''''''' ''''''''''''''''''''''''''' '''''''''''''' '''' '''''''''''''' ''''''' ''''''' ''''' ''''''''''''''''' '''' ''''''''' '''''''''''''' ''''''''' ''''''' '''''''' ''''' '''''''''' '''''''''''''''''''''''' '''''' '''''''''''''''''' '''''''' '''''''''''''''''''' '''''''' ''''''' '''''''''''' ''''''' ''' '''''''''''''' ''''''' '''' '''''' '''''''''' ''''''''''''''''' '''''''''''''''' '''''''''''''''''''''''''''' '''''''' '''''''''''

''''''''''''''''' '''''''''''''' '''''''''' ''''''''''''''''' '''' ''''''''' '''' '''''''''''''' ''''''''''''' '''''''' ''''''''''''''''''' ''''''''' '''''' '''''''''''''' ''''''''''' '''''''''''''''''''''''''''' '''''''' ''''''''''' '''' '''''''''''''''''''''''''''''''' '''''''''''''' '''''''''''''' ''''''''''''''' '''''''''' ''''''''' ''''''''''''''''' ''''''''''' ''''''''''' ''''' '''''''''''' ''''' '''''''''' '''' ''''''''''''''' '''''''' '''''''''' ''' ''''''''''''''' ''''''''''''' ''''''' '''''''''''''''' ''''' ''''''''''' '''' ''''''''''''''''''''''''''''''''''''' ''''' '''''''''' '''' '''''''''''''''''''' '''''''''''''' '''''''''''' ''' ''''''''' ''''' '''''''''''''''''''''''''''' ''' '''''''''' '''' '''''''''' '''''''''''''' ''''''''''''''''' ''''''' ''' ''''''''' '''' ''''''''''''''''''''''''''' ''''''''''''''''''' ''''' ''' '''''''''''''' ''''''''' ''''''''''' '''''''''''''''' '''''''''''''''''''''''' '''''''''''''''''''''''''''' '''' '''''''''' ''''''''''''' ''' '''''''''''''' '''''''''' ''''''' '''''''''''''' '''''''''''''''' ''''' '''''''''' '' '''''''''''''''' '''''''''''''''' ''''''''''' ''''''''''''''' '''''''''''''''' ''''''' ''''''''''''''''''''''''''''''' ''''''''''''''' '''''''''''''''''''''''''''' '''''''' '''''''''''

'''''''''''''''' '''''''''' '''''''''' '''''''''''''''''' '''' ''''''''''''''''' '''''''' ''''''''' ''''''''''''''' ''''''''''' ''''''''''''''''''' '''''' '''''''' '''' '''''''''''''' ''''''''' '''''''' ''' ''''''''''''''''' '''''''''''''''' '''''''''''''''' '''''''''' '''''''''' ''''''''' '''''' '''''''''''''''' '''''''''' '''' ''''''''''''''''''' ''''' ''''''''''''''''' '''' '''''''' ''' '''''''''''''''' '''''''''''''''' '''''''''''''''' '''''''''' ''''''''''''''''''' ''''''''''''''''' '''''''''''''''''''''''''''''' ''''''' ''''''''''''

#### Australian data registry information

There are currently three drugs listed for the treatment of Gaucher disease on the LSDP; namely, imiglucerase, velaglucerase and miglustat. No patients are currently receiving treatment with miglustat under the LSDP.

Data relating to the drugs subsidised through the LSDP for Gaucher Disease were obtained from registry data held by the Australian Government Department of Health. The number of patients currently receiving drugs for Type 1 Gaucher disease through the LSDP is shown in Table 20.

Information withheld from this draft report at the request of the drug sponsor.

Table 20 Number of patients currently treated under the LSDP for Gaucher disease

| Outcome | Imiglucerase | Velaglucerase | All |
| --- | --- | --- | --- |
| Number of patients receiving treatment through LSDP | 17 | ''''' | ''''' |

The median age of patients’ currently receiving treatment on the LSDP for Gaucher disease is 45 years of age. There are currently ''''''''' patients aged less than 18 years currently receiving treatment.

Table 21 Age of those currently receiving treatment on the LSDP

| Outcome | Imiglucerase | Velaglucerase | All |
| --- | --- | --- | --- |
| Mean age ± SD | 40.6±20.2 | 46.3±16.4 | 45±17.7 |
| Minimum | 5 | 3 | 3 |
| Maximum | 82 | 84 | 84 |
| Number of patients under 18 years of age | ''' | ''' | ''' |

Source: Australian registry data; SD = Standard Deviation

Slightly more females (55%; ''''''''''' than males (45%; '''''''''') accessed drugs used to treat Gaucher disease on the LSDP (Table 22).

Table 22 Gender of patients currently receiving treatment under the LSDP for Gaucher disease

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Imiglucerase | Velaglucerase | All |
| Female ''''' | 52.9% '''''' | 56.8% ''''''' | 55.7% '''''''''' |
| Male ''''' | 47.1% ''''' | 43.2% '''''''' | 44.3% '''''''''' |

Weight and height information was available for all patients and has been used to calculate the average dose per patient (U/kg/fortnight). ''' ''''''''''''''''''' '''' '''''' '''''''''''''''''' ''''''''''''''''' '''''''''''''' ''''''''''''''''''''''''''''''' '''''' ''''' ''''''''' '''''''''''''''' ''''''''' ''' '''''' '''''''''''' ''''''''''' '''''''''''''''' '''''''''''''''' ''''''''''''''''' ''''' '''''' ''''''''''''' '''' ''''''''''' '''' ''''''''''' '''''' ''''''' ''''''''''' '''''. The mean doses received by patients on the registry '''''''''' ''''''''''''''''''''''''''' '''''' ''''''''''''''''''''''' ''''''' '''''''' ''''''''''''''''''''''''''' '''''' ''''''''''''''''''''''''' '''''''' were lower than the doses used by Schiffmann et al (2002) and Ben Turkia et al (2013) (60 U/Kg/fortnight) in the key trials assessing imiglucerase and velaglucerase alfa. A lower dose was used in the trial by Elstein et al (2007) (30 U/Kg/month of imiglucerase in 33 patients, 60 U/Kg/month in 3 patients), that compared imiglucerase to a 100mg capsule of miglustat, taken 3 times per day. The TGA Product Information states that imiglucerase doses should be individualised and may range from 2.5U/kg 3 times per week, to 60U/kg/fortnightly (Therapeutic Goods Administration 2010a). The Australian doses are within this range. The TGA Product Information for velaglucerase alfa recommends dosing at 60 U/kg/fortnightly (Therapeutic Goods Administration 2012b) ''''''''''' ''' ''''''''''''''''''''' ''''''''''''' '''''' ''''''''' '''''''''''''''' ''''' ''''''' '''''''''''''''''' ''''''''''''''.

Table 23 Doses of imiglucerase on the LSDP for the treatment of Gaucher disease

|  | **BMI <27** | **BMI >27 (A)** | **BMI > 27 (B)** | **ALL (A)** | **ALL (B)** |
| --- | --- | --- | --- | --- | --- |
| Number of observations^ | 10 | 4 | 4 | 14 | 14 |
| Mean dose U/kg/fortnight  (± SD) | 23.3 ± 11.7 | 22.4 ± 2.06 | 19.4 ± 2.1 | 23.1 ± 10.0 | 22.2 ± 10.1 |
| Median | 19.3 | 23.3 | 20.3 | 20.2 | 19.7 |
| Minimum dose | 14.3 | 19.0 | 15.8 | 14.3 | 14.3 |
| Maximum dose | 52.8 | 24.0 | 21.3 | 52.8 | 52.8 |

SD = standard deviation

BMI>27 (A) = weight for patients with a BMI greater than 27 was adjusted so that their weight (given their height) would equal a BMI of 27.

BMI>27 (B) = the patient’s weight has not been adjusted in this calculation.

^Analysis has been restricted to those patients aged over 18 years '''''''''''''''''

Source: Australian registry data

Table 24 Doses of velaglucerase on the LSDP for the treatment of Gaucher disease

**Commercial in confidence-redacted at the request of the sponsor**

|  | **''''''''' '''''''** | **'''''''' ''''''' ''''''** | **''''''' ''' ''''' '''''''** | **''''''''' '''''''** | **''''''''' '''''''** |
| --- | --- | --- | --- | --- | --- |
| ''''''''''''''''' '''' ''''''''''''''''''''''''''''''''''' | '''''' | '''''' | ''''' | '''''' | '''''' |
| '''''''''''''' '''''''''''' '''''''''''''''''''''''''''''''  '''' ''''''' | '''''''''' '''' '''''''''' | ''''''''''' '''' '''''''''''' | '''''''''' '''' ''''''' | ''''''''''' '''' ''''''''''' | ''''''''''' '''' ''''''''''' |
| '''''''''''''''''' | '''''''''' | '''''''''' | '''''''''' | '''''''''''' | '''''''''' |
| ''''''''''''''''''''''' '''''''''' | '''''''''' | ''''''''''' | '''''''''' | ''''''''''' | ''''''''''' |
| ''''''''''''''''''''''' ''''''''''''' | '''''''''''' | '''''''''' | ''''''''''' | '''''''''' | ''''''''''' |

'''''''' '''' ''''''''''''''''''''' ''''''''''''''''''''''

'''''''''''''''''' ''''''' '''' ''''''''''''''' '''''' '''''''''''''''''' ''''''''' '''' '''''''''' '''''''''''''''' '''''''''' '''''' '''''''''' '''''''''''''''''''' '''''' ''''''''' ''''''''''' ''''''''''''''' '''''''''''''' ''''''''' ''''''''''''''' ''''''''''''' '''''''''''' ''' ''''''''''' '''' '''''''

'''''''''''''''''''' ''''''' ''' '''''''' '''''''''''''''''' ''''''''''''''' '''''''' '''''''' ''''''''''''' '''''''''''''''''''' ''''' '''''''' ''''''''''''''''''''''''

''''''''''''''''''''' '''''''' '''''''''''' ''''''''''''''''''''' '''' '''''''''''' '''''''''''''''''' '''''''''''' '''''''''' ''''''' '''''''''''' ''''''''''''''''''

''''''''''''''''' ''''''''''''''''''''''''' '''''''''''''''''' '''''''''''

Baseline and follow up data regarding haemoglobin levels (g/L) were available for 57 patients currently receiving treatment for Gaucher disease on the registry (Table 25). It is not certain that the baseline information for each patient is pre-enzyme replacement therapy. More than half of these patients had normal haemoglobin levels at baseline (56.1%; n = 32). At last follow up, the vast majority (93.5%; n = 53) also had normal haemoglobin levels. More than three-quarters of patients experienced an improvement in haemoglobin (g/L) between baseline and follow-up.

Table 25 Proportion of Patients with Normal Haemoglobin (g/dL) and improvement from baseline

| Outcome | Female | Male | Total |
| --- | --- | --- | --- |
| **Proportion of Patients with Normal Haemoglobin (g/L)** | **--** | **--** | **--** |
| Baseline, % (n) | 59.3% (16) | 53.3% (16) | 56.1% (32) |
| Latest, % (n) | 92.6% (25) | 93.3% (28) | 93% (53) |
| **Haemoglobin (g/dL), improvement from baseline** | **-** | **-** | **-** |
| Improvement, % (n) | 77.8% (21) | 83.3% (25) | 80.7% (46) |
| Worse, % (n) | 22.2% (6) | 16.7% (5) | 19.3% (11) |

Normal values for haemoglobin: <11.5 g/dL for children aged 3-14; , <11.5 g/dL for females aged over 15 years; 13.5 g/dL for men aged 15-55 years; 13 g/dL for men aged 56-70 years; <12.5 g/dL for men aged over 71 years (QML Pathology 2009)

Source: Australian registry data

Baseline and follow up platelet counts were available for 56 patients on the Australian registry. A quarter of patients had a normal platelet count at baseline. It is not certain that the baseline information for each patient is pre-enzyme replacement therapy. By end of follow up, most patients experienced an improvement, with 64.3% of patients with platelet counts in the normal range (Table 26).

Table 26 Proportion of normal values for Platelet count

| Time | Female | Male | Total |
| --- | --- | --- | --- |
| Baseline | 25.9% (7/27) | 24.1% (7/29) | 25% (14/56) |
| Last follow up | 77.8% (21/27) | 51.7% (15/29) | 64.3% (36/56) |

Normal Value defined as ≥ 150 x 109/L (QML Pathology 2009)

Source: Australian registry data

Baseline and follow up data for spleen volume was available for 27 patients. At baseline, less than 10% of patients had normal spleen volumes (≤5 multiples of normal). By the end of follow up, this had improved to approximately 93%. Liver volume baseline values were available for 34 patients, with follow up data available for 35 patients. Approximately 40% of patients had a normal liver volume (≤1.25 multiples of normal) at baseline. Females were more likely to have an abnormal liver volume than were males (23.5% vs 58.8%). By the end of follow up, almost all (94.3%) of the patients had a liver volume within the normal range.

Table 27 Proportion of patients with normal organ volumes

| Outcome and time | Female | Male | Total |
| --- | --- | --- | --- |
| **Proportion of patients with normal spleen volumes** | **-** | **--** | **--** |
| Baseline | 9.1% (1/11) | 6.3% (1/16) | 7.4% (2/27) |
| Last follow up | 90.9% (10/11) | 93.8% (15/16) | 92.6% (25/27) |
| **Proportion of patients with normal liver volumes** | **-** | **--** | **--** |
| Baseline | 23.5% (4/17) | 58.8% (10/17) | 41.2% (14/34) |
| Last follow up | 94.1% (16/17) | 94.4% (17/18) | 94.3% (33/35) |

Normal spleen volume = ≤5 multiples of normal (Elstein, D et al. 2007); Normal liver volume ≤1.25 multiples of normal (Elstein, D et al. 2007)

#### Impact of findings

To determine whether the findings of the systematic review and the analysis of the Australian data would likely have an impact on the decisions made to fund the drugs on the LSDP, the results were compared against claims made in the submissions to the PBAC as well as against the minutes of the relevant PBAC meeting(s) (where the basis of the decision to recommend that the drugs be considered for the LSDP was outlined).

A summary of the evidence identified through this systematic review, highlighting the new information included (not included in the relevant submissions to the PBAC) is shown in Table 28.

Table 28 Studies included assessing drugs to treat Gaucher disease Type 1

| Drug | Results | References | Evidence not included in submission to the PBAC |
| --- | --- | --- | --- |
| Imiglucerase | 1 RCT vs no ERT | Schiffmann et al (2002) | No formal industry-sponsored submission was made to the PBAC for imiglucerase. Schiffmann et al reported that ERT was statistically superior to vitamin D alone on measures of haemoglobin, white blood cell count and platelets. |
| Velaglucerase alfa | 1 RCT vs imiglucerase | HGT-GCB-039, Ben Turkia et al (2013) | No additional evidence. |
| Miglustat | 1 RCT vs imiglucerase + non-comparative extension | OGT 918-004, Elstein et al (2007) | Chitotriosidase data were not included in the submission to the PBAC.  Patients receiving miglustat had a 33% increase on chitotriosidase vs 0.3 drop with imiglucerase |

RCT = randomised controlled trial; ERT = enzyme replacement therapy (in this study: alglucerase or imiglucerase); PBAC = Pharmaceutical Benefits Advisory Committee

##### Imiglucerase / alglucerase

The funding request for the first drugs under the LSDP – namely, alglucerase, or the drug which superseded it, imiglucerase – was not supported by a formal industry submission.

The evidence identified in the systematic review supported the decision to fund imiglucerase for patients with Type 1 Gaucher disease; demonstrating that imiglucerase, and the drug which preceded it, alglucerase, were superior to receiving vitamin D alone at reducing the risk of bleeding and indicators of bone disease.

Patients receiving alglucerase and imiglucerase had, on average, improvements in haemoglobin levels, platelet counts and spleen and liver volumes when compared to pre-treatment levels; supporting the use of these enzyme replacement therapies for Type 1 Gaucher disease. The Australian data were not in a format which did not allow information on the rate of concomitant therapies to be easily extracted.

##### Velaglucerase alfa

No new randomised trials on the use of velaglucerase alfa to treat Type 1 Gaucher disease have been published since the submission to the PBAC. The Australian data showed that on average, patients receiving velaglucerase alfa improved on surrogate measures of bleeding risk, and spleen and liver volumes compared to pre-treatment levels, supporting the continued funding.

##### Miglustat

Since the submission to the PBAC there have been no new randomised trials have been published on the use of miglustat to treat Type 1 Gaucher disease. However, a small amount of additional data were identified in another publication of the same trial originally included in the submission to the PBAC (European Medicines Agency 2003). Patients whose disease status was considered stable after receiving imiglucerase, continued to have stable chitotriosidase activity (a marker of disease burden) if they were randomised to remain on imiglucerase. However, those patients who were randomised to switch to miglustat, had a 33 per cent increase in chitotriosidase level, indicating a higher disease burden. It is unknown whether this difference would be clinically important. These new data would support the conclusion that miglustat is inferior to enzyme replacement therapy (imiglucerase or velaglucerase alfa). The new evidence further supports the restriction of the use of miglustat, to those who cannot tolerate, or who do not respond to enzyme replacement therapy. However, there were no trials identified that assessed the effectiveness of miglustat in the restricted population (as all participants in the trial had stable disease following imiglucerase treatment).

'''''''''' '''''' ''''' '''''''''''''''''' '''''''''''''''' '''''''''''''''' '''''''''''''''' '''''''''''''''''''' '''''''''''''''''' '''''''''''''' '''''''''''''''' '''''''''''''' ''''''''' '''''''''''''''''' ''''''''''' ''' ''''''''''''''''''''''''''' '''''''''''''' ''''''''''''''''' '''''''' ''''''''''' ''''''''''''''''' '''' ''''''''''''''''''''''' ''''' ''''''''''''''''''''''''' ''''''' '''''''' ''''''''''''''''''''''' ''''''''''''''''''''''''''' '''''''' ''''''''''''

### Medicines to treat Fabry disease

**In patients with Fabry disease, what is the safety and effectiveness of agalsidase alfa compared to standard therapy?**

The clinical claim made by the sponsors in their submission to the PBAC, was that agalsidase alfa was superior to standard (palliative) therapy. Two systematic reviews reported on the original two RCTs presented to the PBAC that compared agalsidase alfa and placebo. No measure of survival was reported.

There was no difference found between the groups for cardiovascular function and most surrogate measures of renal function (Gb3 levels), although one assessment of renal function was statistically significant, favouring the agalsidase alfa group when using nmol/24 hours of mean Gb3 clearance as the measure (GRADE ⨁⨁⨀⨀).

Scores on the Brief Pain Inventory for Severity were significantly better for patients receiving agalsidase alfa, rather than placebo and standard therapy, at 3 time periods during treatment. Patients receiving agalsidase alfa reported a 2 point reduction in pain on a scale of 0 to 10. The Brief Pain Inventory – Quality of Life score also favoured treatment with agalsidase alfa at the later time period of 5-6 months, with a mean difference of over 2 on a scale of 0 to 10 (GRADE ⨁⨁⨁⨀).

The submission for agalsidase alfa claimed that glomerular filtration rate (GFR) would improve or remain stable in patients taking the drug at 24 weeks. However, based on the data obtained on 12 Australian patients, GFR was slightly reduced (13%; 3.4 mL/min/1.73m2).

In 2009, the PBAC took the view that although a survival benefit was not strictly proven, it would be reasonable to expect this, along with a lessening of morbidity, given the action of agalsidase alfa and the pathophysiology of the disease. No new literature was identified to support or negate this view.

**In patients with Fabry disease, what is the safety and effectiveness of agalsidase beta compared to standard therapy?**

The submission to the PBAC for agalsidase beta claimed that the new drug had significant clinical advantages over standard management, but was associated with more toxicity. In 2002, the PBAC decided that the pathophysiological mechanisms in Fabry disease are highly specific, and the link between the surrogate outcomes presented in the submission and clinical endpoints were plausible. One very small randomised trial has been published since the submission to the PBAC and is unlikely to alter the conclusions of the PBAC, as it showed a trend towards favouring agalsidase beta over placebo in terms of cardiac function.

Two systematic reviews assessed 3 RCTs and found that the difference in survival between agalsidase beta and placebo was consistent with chance, given the small sample size (GRADE ⨁⨁⨁⨁). Likewise, differences between renal events, cardiac events and cerebrovascular events between treatment arms was no greater than chance – and larger sample sizes would be required to demonstrate any differences – all three analyses reported a higher frequency of disease-related events in the placebo group (GRADE ⨁⨁⨁⨁).

Most of the renal function measures (Gb3 levels in the kidney, heart and skin endothelium) were found to be significantly improved in patients randomised to agalsidase beta compared to placebo (GRADE ⨁⨁⨀⨀).

There was no difference shown between treatment groups for cardiopulmonary exercise test outcomes, or another surrogate for renal function (GFR; short or long-term) although GFR was found to remain stable in both groups (GRADE ⨁⨀⨀⨀). Pain was found to be reduced in both the agalsidase beta and placebo groups and so a placebo effect could not be ruled out (GRADE ⨁⨁⨀⨀).

A comparison of adverse events between groups showed that rigors, fever, temperature changed sensation; hypertension and vomiting were much more likely to occur in patients randomised to agalsidase beta than placebo. These adverse events were considered likely to be drug side-effects (GRADE ⨁⨁⨀⨀).

Australian data, based on 20 patients, showed that patients taking agalsidase beta had a small absolute improvement in GFR between baseline and follow-up (4.6%; 0.93 mL/min/1.73m2).

**In patients with Fabry disease, what is the safety and effectiveness of agalsidase alfa and agalsidase beta when compared to each other?**

Two systematic reviews reported on one RCT comparing agalsidase alfa and agalsidase beta. There was no significant difference in the survival of patients randomised to receive either of these treatments (GRADE ⨁⨀⨀⨀).

Renal and cardiac function markers appeared to favour agalsidase beta but the differences were not statistically significant (GRADE ⨁⨀⨀⨀).

Adverse events were more frequent in patients receiving agalsidase beta when compared to agalsidase alfa, although the difference was not statistically significant (GRADE ⨁⨀⨀⨀).

#### Background

##### Fabry disease

Fabry (Anderson-Fabry) disease (FD) is glycolipid storage disorder caused by a deficiency of the enzyme alpha-galactosidase A. The rare and debilitating genetic disorder is X-linked and recessive, predominantly affecting males, but is also seen in a more varied form in females. The enzyme deficiency results in an accumulation at a cellular level of the metabolite globotriaosylceramide (Gb3) in multiple organs and tissues and it is this substance which leads to a progressive dysfunction of systems. Cardiac and renal failures are common causes of premature death, but peripheral nerve, proteinuria, gastrointestinal and cerebrovascular complications are also features of FD. The disease is most often diagnosed in young adults but symptoms can occur as young as five years, or later than adolescence, depending on the form of the disease.

##### Pre-enzyme replacement therapy

Until agalsidase-beta and agalsidase-alfa were developed and approved for use in Europe in 2001, there was no specific treatment for FD.

Management of proteinuria is a priority for patients with FD. Adjunctive therapies are recommended to control blood pressure and nephropathy including angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Neuropathic pain management can be complex and may require analgesics, antiepileptic drugs and/or amino butyric acid analogues. Anti-platelet drugs and blood pressure control are among the recommended treatments for vascular disease in Fabry patients. Disease progression can lead to dialysis, renal transplantation and neurotropic analgesics.

##### Enzyme replacement therapy

Agalsidase alfa and beta have been subsidised through the LSDP for patients with FD since 2004. The rationale behind enzyme replacement therapy is to administer sufficient enzyme to the patient to enable metabolism of Gb3, thereby reducing its accumulation and slowing progression of the disease (Alegra T et al. 2012; Schaefer, Tylki-Szymanska & Hilz 2009).

The two genetically engineered drugs are now produced by different companies but are virtually identical – the beta form produced by Genzyme Corp. is cultured in a hamster cell line, and the alfa form is produced by TKT in a human cell-line. Due to a world-wide shortage of agalsidase-beta in 2009, many patients decreased or ceased treatment and transferred to agalsidase-alfa (Smid et al. 2011). In the United States, orphan drug laws prevented the approval of both drugs, and agalsidase-beta was approved by the FDA in 2003 after consideration of the trial evidence for both drugs (Desnick 2004).

Administration of ERT carries considerable burden for the patient. Agalsidase beta is administered by intravenous infusion at a recommended dose of 1mg/kg very two weeks. The initial infusion rate is cautiously slow (no more than 15 mg per hour) as infusion reactions are not uncommon, however once a patient has established tolerance to the treatment, infusion rate can be increased. At maximum rate, infusion times vary from 2 hours for a child of 30 kg to 5 hours in a 75 kg adult. The recommended dose for agalsidase alfa is 0.2 mg/kg every 2 weeks with an infusion time of 40 minutes. Pre-treatment with antihistamines or corticosteroids to reduce infusion reaction is common and would be applied if a prior infusion resulted in a reaction.

A home infusion program is provided by the sponsor for both drugs; however a patient must undergo their first three infusions in a hospital setting. Once the patient has been assessed by the treating physician as having infusion reactions controlled, home infusion may be considered.

#### Systematic review inclusion criteria

Table 29 provides the criteria for selecting studies that assess the safety and effectiveness of agalsidase alfa or beta for the treatment of patients with Fabry disease.

Table 29 Criteria for selecting studies to assess the safety and effectiveness of agalsidase alfa and agalsidase beta

| Characteristic | Inclusion criteria |
| --- | --- |
| Study design | The highest level of evidence available (from Table 2) that addresses the research questions. Case reports would have been included if none of the study designs in Table 2 were available. |
| Population | Patients with Fabry disease (Anderson-Fabry disease, *angiokeratoma corporis diffusum* or α-galactosidase A deficiency) |
| Interventions | 1. Agalsidase alfa (Replagal®), or  2. Agalsidase beta (Fabrazyme®)  Subgroup analysis: by dose (e.g. doses consistent with TGA listing, as well as experimental dosing regimens) |
| Comparators | 1. Supportive care (including analgesics) plus placebo  2. Agalsidase alfa (Replagal®) or agalsidase beta (Fabrazyme®) |
| Outcomes | *Safety:* adverse events related to treatments – for example, nausea, vomiting, diarrhoea, inability to gain weight, fatigue, vertigo, tinnitus, anaphylaxis; and compliance with treatment (i.e. treatment withdrawal or suboptimal dosing)  *Primary effectiveness:* survival  *Secondary effectiveness:* quality of life; pain (peripheral neuropathy/acroparaesthesia); cerebrovascular outcomes (stroke/TIAs); renal function (globotriaosylceramide\* (Gb3 or GL-3) levels, GFR, urinary protein:creatinine ratio); cardiovascular function (hypertension, left ventricular measures, exercise capacity) |
| Language | Studies in languages other than English would only be translated if it appeared from the abstract that the study represented a higher level of evidence than that available in English. |
| Research questions | Is agalsidase alfa safe and effective compared to supportive care and placebo for treating patients with Fabry disease?  Is agalsidase beta safe and effective compared to supportive care and placebo for treating patients with Fabry disease?  Is agalsidase beta safe and effective compared to agalsidase alfa for treating patients with Fabry disease? |

TGA = Therapeutic Goods Administration; TIA = transient ischaemic attack; GFR = glomerular filtration rate

#### Results of the literature search

The highest level of evidence obtained in the literature search was three systematic reviews (Alegra T et al. 2012; El Dib, R P, Nascimento & Pastores 2013; Schaefer, Tylki-Szymanska & Hilz 2009) and one health technology assessment (HTA) (Connock et al. 2008) which assessed the safety and effectiveness of agalsidase alfa and beta. Of these studies, the evidence in the two systematic reviews (SRs) (El Dib, R P, Nascimento & Pastores 2013; Schaefer, Tylki-Szymanska & Hilz 2009) were considered to be of higher quality and containing the most relevant trials and are discussed here. The SR by Alegra et al (2012) was excluded as the results of the key randomised trials (RCTs) were not able to be separated from additional data, and the HTA by Connock et al (2008) was excluded as it provided limited evidence from Fabry disease drug trials and was published earlier than the two included SRs.

All RCTs included in the SRs were also identified in our literature search, with the exception of Eng et al (2001) which was identified through pearling of the SRs. An additional RCT was identified by pearling the references of a PSUR report but was excluded as there was insufficient information reported in it (TKT010 (TKT 2003)). Preliminary results of this multicentre trial (TKT010) of 80 patients randomised to either agalsidase-alfa or placebo found that there was no statistically significant difference in kidney function between treatment arms.

El Dib (2013) included RCTs and quasi-randomised controlled clinical studies only in the SR, whereas Schaefer (2009) included any prospectively designed clinical study, whether blinded or open label. Data were stratified in Schaeffer (2009) enabling the inclusion of the RCT results in this review. The SR by El Dib et al (2013) included six RCTs comparing agalsidase alfa and placebo, agalsidase-beta and placebo, or agalsidase alfa with agalsidase beta. In addition to the RCTs included in El Dib’s (2013) study, Schaeffer et al (2009) listed studies by Thurberg et al (Thurberg et al. 2004), Moore et al (Moore, David F. et al. 2002) and Schiffmann et al (Schiffmann et al. 2006) as RCTs; however, these are extension studies to the other RCTs. The RCTs and extension studies used to report outcome data are listed below[[12]](#footnote-12).

Agalsidase-alfa compared to placebo:

* RCT by Hughes et al (2008) (Hughes et al. 2008)
* RCT by Schiffmann et al (2001) (Schiffmann et al. 2001), and extension studies (Moore, David F. et al. 2002; Moore, D. F. et al. 2001; Schiffmann et al. 2006)

Agalsidase-beta compared to placebo:

* RCT by Banikazemi et al (2007) (Banikazemi, M. et al. 2007)
* RCT by Bierer et al (2006) (Bierer et al. 2006)
* RCT by Eng et al (2001) (Eng et al. 2001), and extension studies (Thurberg et al. 2004; Thurberg et al. 2002; Wilcox et al. 2004)

Agalsidase-alfa compared to agalsidase-beta:

* RCT by Vedder et al (2007) (Vedder et al. 2007)

Studies which may have met the inclusion criteria, which were subsequently excluded, are shown in Appendix C.

#### Risk of bias assessment

Quality appraisal was conducted on the two included systematic reviews using the AMSTAR checklist described by Shea and associates (Shea et al. 2009). The SR by El Dib et al (2013) was considered to be high quality. It provided a good description of the literature search and selection criteria *a priori*, eligibility screening and data extraction were conducted in duplicate, and included studies were well described and assessed for scientific quality. Risk of bias was assessed in all of the included RCTs for randomisation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources. The SR by Schaefer et al (2009) was considered to be moderate quality. While this study provided a good description of the search and eligibility criteria, duplicate screening of studies and data extraction was not reported, it was unclear whether grey literature were included, and a list of excluded articles was not provided. The characteristics of the included RCTs were described; however, assessment and reporting of the risk of bias in the studies was lacking.

A summary of the assessment of risk of bias of the individual RCTs as reported by El Dib et al (2013) is given in Table 30.

Table 30 Summary of risk of bias for RCTs assessing the effectiveness and safety of agalsidase-alfa and agalsidase-beta as reported by El Dib 2013 (El Dib, R P, Nascimento & Pastores 2013)

| Comparison and Study Author | Generation of randomised sequence | Allocation concealment | Blinding | Incomplete outcome data | Selective reporting | Other potential sources of bias |
| --- | --- | --- | --- | --- | --- | --- |
| **Agalsidase-alfa versus placebo** | - | - | - | - |  | - |
| Hughes 2008 | Not described, risk unclear | Not described, risk unclear | Described, low risk | Not described, risk unclear | No selectivity, low risk | None identified |
| Schiffmann 2001 | Not fully described, risk unclear | Described, low risk | Not described, risk unclear | Sufficiently described, low risk | No selectivity, low risk | None identified |
| **Agalsidase-beta versus placebo** | - | - | - | - |  | - |
| Banikazemi 2007 | Reported, low risk | Described, low risk | Described, low risk | Not fully described, unclear risk | No selectivity, low risk | None identified |
| Bierer 2006 | Not described, risk unclear | Not described, risk unclear | Not fully described, unclear risk | Not described, unclear risk | No selectivity, low risk | None identified |
| Eng 2001 | Not described, risk unclear | Not described, risk unclear | Not fully described, risk unclear | Not described, unclear risk | No selectivity, low risk | Possible source identified, risk unclear |
| **Agalsidase alfa versus beta** | - | - | - | - |  | - |
| Vedder 2007 | Fully described, low risk | Described, low risk | Not blinded, high risk | Described, high risk | No selectivity, low risk | None identified |

#### Effectiveness of agalsidase alfa compared to placebo

Two RCTs (Hughes et al. 2008; Schiffmann et al. 2001) met the inclusion criteria for assessing agalsidase alfa with reference to placebo. In the trial reported by Schiffmann et al (2001), 26 male US residents were randomised – 14 received algalsidase alfa and 12 received placebo. The more recent (2008) RCT (Hughes et al. 2008) randomised 15 males, with seven allocated the treatment arm and 8 receiving placebo. Both trials administered algalsidase alfa at a dose of 0.2 mg/kg once per fortnight for a period of 6 months. Placebo was administered using an identical method to drug infusion. The studies did not describe any additional standard therapies. A 24 month open-label extension study of patients in the smaller trial was conducted (Hughes et al, 2008), which was completed by 10 of the 15 participants.

El Dib et al (2013) reported outcomes as mean differences with confidence intervals and these data have been synthesised using the GRADE approach. Where an outcome was assessed in more than one trial, a pooled analysis is presented. Outcomes that were reported by Schaeffer et al (2009) that were additional to those in El Dib et al (2013) have been included in the GRADE evidence summary. Schaefer et al (2009) reported mean baseline and endpoint data with standard deviations. P values, with or without confidence intervals, were reported for some of the outcomes.

##### Primary effectiveness

Patient survival was not reported in the two included SRs.

##### Secondary effectiveness

##### Renal function

Renal function was assessed through the surrogate measures of plasma Gb3 levels, creatinine clearance and inulin clearance, and by the number of glomeruli that had undergone changes.

A comparison of the change in plasma Gb3 levels between patients randomised to agalsidase alfa or placebo was undertaken in two RCTs (Hughes et al. 2008; Schiffmann et al. 2001) at the end of a six month treatment period. A pooled analysis of Gb3 concentration indicates that there was no statistically significant difference between treatment groups. There was also no statistically significant difference in urine sediment or kidney Gb3 concentration (Schiffmann et al. 2001), or myocardial Gb3 levels (Hughes et al. 2008). These indirect outcome measures (Table 31) were assessed as *low* quality (GRADE ⨁⨁⨀⨀).

Table 31 Comparison of Gb3 levels in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Plasma Gb3 at up to 6 months** assessed with: nmol/ml follow up: mean 6 months | 39 (2 RCTs) 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean plasma Gb3 at up to 6 months ranged across control groups from **10.19 – 0.63** nmol/ml | MD **2.07 lower** (6.64 lower to 2.5 higher) |
| **Urine sediment Gb3** assessed with: nmol/ml follow up: mean up to 6 months | 25 (1 RCT) up to 6 months | ⨁⨁⨀⨀ LOW 1 3 | The mean urine sediment Gb3 in the control group was **2495** nmol/ml | MD **812 lower** (1897 lower to 273 higher) |
| **Kidney Gb3** assessed with: nmol/mg tissue follow up: up to 6 months | 25 (1 RCT) up to 6 months | ⨁⨁⨀⨀ LOW 1 3 | The mean kidney Gb3 in the control group was **18.1** nmol/ml | MD **2.5 lower** (9.47 lower to 4.47 higher) |
| **Myocardial Gb3** assessed with: nmol/ug follow up: 3-6 months | 14 (1 RCT) 3-6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean myocardial Gb3 in the control group was **0.63** nmol/ug | MD **0.07 higher** (0.35 lower to 0.49 higher) |

CI = confidence interval; Gb3 = globotriaosylceramide; RCT = randomised controlled trial; MD = mean difference between agalsidase alfa and placebo (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than placebo, and conversely “higher” means that the effect size is higher in agalsidase alfa than in placebo). In this instance, a lower Gb3 level is beneficial to patients; NR = not reported

1. Small participant numbers

2. Inadequate reporting

3. Surrogate outcome

There was no statistically significant difference in creatinine clearance and inulin clearance between patients receiving agalsidase alfa or placebo when measured by mL/min/1.73 m2 (Schiffmann et al. 2001) (Table 32). When creatinine clearance was assessed according to nmol/24 hours, there was a statistically significant difference favouring the agalsidase alfa group (mean±SE = 1052±457; placebo, mean±SD = -25±NR, p = 0.047)(Hughes et al. 2008). The comparisons between treatment groups on these surrogate outcomes were assessed as *low* quality (GRADE ⨁⨁⨀⨀).

Table 32 Creatinine clearance and inulin clearance in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013; Schaefer, Tylki-Szymanska & Hilz 2009; Schiffmann et al. 2001)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with Supportive care plus placebo** | **-Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Creatinine clearance** assessed with: mL/min/1.73m2 follow up: up to 6 months | 24 (1 RCT) up to 6 months | ⨁⨁⨀⨀ LOW 1 3 | The mean creatinine clearance in the control group was **84.5** ml/min/1.73m2 | MD **10.3 higher** (15.37 lower to 35.97 higher) |
| **Inulin clearance** assessed with: mL/min/1.73m2 follow up: up to 6 months | 24 (1 RCT) up to 6 months | ⨁⨁⨀⨀ LOW 1 3 | The mean inulin clearance in the control group was **71.5** ml/min/1.73m2 | MD **0.05 lower** (21.36 lower to 20.36 higher) |
| **Creatinine clearance**  assessed with: nmol/24h follow up: median 6 months | 15 (1 RCT) 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean creatinine clearance in the control group was **-25** nmol/24h | p **0.047 lower** (CI NR) |

CI = confidence interval; RCT = randomised controlled trial; MD = mean difference between agalsidase alfa and placebo (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than placebo, and conversely “higher” means that the effect size is higher in agalsidase alfa than in placebo). In this instance, a lower clearance rate is beneficial to patients; NR = not reported

1. Small participant numbers

2. Inadequate reporting

3. Surrogate outcome

When changes to glomeruli in patients (i.e. the number of glomeruli with mesangial widening, segmental sclerosis or that were obsolescent) were compared between the agalsidase alfa and placebo treatment arms, there were no statistically significant differences (GRADE ⨁⨁⨀⨀). There was also no consistent trend in the direction of these changes (Schiffmann et al. 2001) (Table 33).

Table 33 Comparison of changes to glomeruli in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013) (Schiffmann et al. 2001)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Fraction of glomeruli without mesangial widening** assessed with: % follow up: up to 6 months | 21 (1 RCT) up to 6 months | ⨁⨁⨀⨀ LOW 1 2 | The mean fraction of glomeruli without mesangial widening in the control group was **40.4** % | MD **14.7 lower** (36.72 lower to 7.32 higher) |
| **Fraction of glomeruli without segmental sclerosis** assessed with: % follow up: up to 6 months | 21 (1 RCT) up to 6 months | ⨁⨁⨀⨀ LOW 1 2 | The mean fraction of glomeruli without segmental sclerosis in the control group was **3** % | MD **3.8 higher** (2.35 lower to 9.95 higher) |
| **Fraction of non-obsolescent glomeruli** assessed with: % follow up: mean up to 6 months | 21 (1 RCT) up to 6 months | ⨁⨁⨀⨀ LOW 1 2 | The mean fraction of non-obsolescent glomeruli in the control group was **13** % | MD **6.5 higher** (8.93 lower to 21.93 higher) |

RCT = randomised controlled trial; MD = mean difference between agalsidase alfa and placebo (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than placebo, and conversely “higher” means that the effect size is higher in agalsidase alfa than in placebo). In this instance, a lower fraction of damaged glomeruli is beneficial to patients.

1. Small participant numbers

2. Surrogate outcome

##### Cardiovascular function

One RCT (Hughes et al. 2008) used echocardiography to compare ventricular changes (a surrogate measure of cardiovascular function) in Fabry patients after 6 months of treatment. The trial included only a small number of participants, reducing its power. There was no significant difference found between groups randomised to agalsidase alfa or placebo for mean left ventricular wall thickness, left ventricular internal diameter (diastolic), left ventricular internal diameter (systolic) and left ventricular ejection fraction (GRADE ⨁⨁⨀⨀) (Table 34).

Table 34 Comparison of ventricular changes in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013; Schaefer, Tylki-Szymanska & Hilz 2009) (Hughes et al. 2008)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Left ventricular wall thickness**  assessed with: mm follow up: 3 to 6 months | 14 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean left ventricular wall thickness in the control group was **13.4** mm | MD **0.79 lower** (3.62 lower to 2.04 higher) |
| **Left ventricular internal diameter (diastolic)** assessed with: mm follow up: 3 to 6 months | 14 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean left ventricular internal diameter (diastolic) in the control group was **52.1** mm | MD **3.7 lower** (11.73 lower to 4.33 higher) |
| **Left ventricular internal diameter (systolic)** assessed with: mm follow up: 3 to 6 months | 14 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean left ventricular internal diameter (systolic) in the control group was **30.4** mm | MD **2.7 lower** (9.91 lower to 4.51 higher) |
| **Left ventricular ejection fraction** assessed with: % follow up: 3 to 6 months | 14 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean left ventricular ejection fraction in the control group was **79.12** % | MD **1.88 higher** (4.68 lower to 8.44 higher) |

RCT = randomised controlled trial; MD = mean difference between agalsidase alfa and placebo (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than placebo, and conversely “higher” means that the effect size is higher in agalsidase alfa than in placebo). In this instance, lower left ventricular measures are beneficial to patients.

1. Small participant numbers

2. Inadequate reporting

3. Surrogate outcome

Further cardiac outcomes were reported in the SR by Schaefer et al (2009) (Table 35). Left ventricular mass index (LVMI) measured by MRI at baseline, 13 weeks and 6 months found a significant difference in LVMI change between groups, favouring the treatment group (p=0.02). This result should be considered with caution as Scheffer et al comment that at 13 weeks the decrease in LV mass in the agalsidase alfa group could be attributed almost entirely to one patient. One patient in the placebo group, who showed the largest decrease in LV mass, was also excluded from the analysis.

Mean change in QRS[[13]](#footnote-13) was assessed in two RCTs. There was no difference between patients randomised to agalsidase alfa or placebo at the 6 month follow-up for mean QRS change in one RCT (Hughes et al. 2008) (GRADE ⨁⨁⨀⨀) (Table 35) and no effect measure was reported in the other (Schiffmann et al. 2001).

Table 35 Cardiac outcomes for Fabry patients randomised to receive either agalsidase alfa or placebo (Schaefer, Tylki-Szymanska & Hilz 2009)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Change in QRS**  assessed with: ms follow up: 6 months | 15 (1 RCT) 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean change in QRS in the control group was **4** ms | p **0.8 lower** (CI NR) |
| **Left Ventricular Mass Index change** assessed with: g/m2 follow up: 6 months | 15 (1 RCT) 6 months | ⨁⨁⨀⨀ LOW 1 2 3 | The mean Left Ventricular Mass Index change in the control group was **12** g/m2 | p **0.02 lower** (CI NR) |
| **Change in QRS** assessed with: ms follow up: 6 months | 26 (1 RCT) 6 months | ⨁⨁⨀⨀ LOW 1 3 | The mean change in QRS in the control group was **3.6** ms | MD **6 lower** (CI NR) |

CI = confidence interval; RCT = randomised controlled trial; NR = not reported; QRS = (see footnote 13)

1. Small participant numbers

2. Inadequate reporting

3. Surrogate outcome

##### Pain

Schiffmann (2001) measured pain – as the primary outcome – using the Brief Pain Inventory at 1 to 3 months, 3 to 5 months and 5 to 6 months (Table 36) (Schiffmann et al. 2001). When the Inventory was used to measure pain severity (on a scale of 0 to 10), there was a statistically significant difference between patients randomised to agalsidase alfa and placebo at all three time points, with results indicating reduced pain in those receiving the drug. The mean difference between groups was -2.10 (95%CI -3.79 to -0.41) over 1-3 months, -1.90 (95%CI -3.65 to -0.15) over 3-5 months and -2.00 (95%CI -3.66 to -0.34) over 5-6 months. Schiffmann (2001) also reported that 4 out of 11 (36%) patients in the agalsidase alfa group were able to cease neuropathic pain medication after an average of 30.5 days of treatment, compared to 0 out of 11 (0%) patients in the placebo group (p = 0.03). In addition patients taking agalsidase alfa lasted longer without pain medications than those receiving placebo (74.5 days versus 12.9 days, p = 0.02) (Schiffmann et al. 2001). These differences in pain tolerance are likely to be important to patients.

There was a statistically significant difference in quality of life, as measured with the Brief Pain Inventory, over 5-6 months, again favouring the agalsidase alfa group (mean difference -2.1, 95%CI -3.92 to -0.28). The outcomes at 1-3 months and 3-5 months were not statistically significant but also favoured the agalsidase alfa treatment arm. The Brief Pain Inventory results were considered to be direct patient-relevant outcomes, with findings of *moderate* quality (GRADE ⨁⨁⨁⨀).

Table 36 Comparison of Brief Pain Inventory outcomes in patients randomised to receive either agalsidase alfa or placebo (El Dib, R P, Nascimento & Pastores 2013; Schiffmann et al. 2001)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Pain severity** assessed with: The Brief Pain Inventory Severity score follow up: 1 to 3 months | 26 (1 RCT) 1 to 3 months | ⨁⨁⨁⨀ MODERATE 1 | The mean pain severity in the control group was **5.2** (Severity scale 0-10) | MD **2.1 lower** (3.79 lower to 0.41 lower) |
| **Pain severity** assessed with: The Brief Pain Inventory Severity score follow up: 3 to 5 months | 26 (1 RCT) 3 to 5 months | ⨁⨁⨁⨀ MODERATE 1 | The mean pain severity in the control group was **5.2** (Severity scale 0-10) | MD **2 lower** (3.65 lower to 0.15 lower) |
| **Pain severity** assessed with: The Brief Pain Inventory Severity score follow up: 5 to 6 months | 26 (1 RCT) 5 to 6 months | ⨁⨁⨁⨀ MODERATE 1 | The mean pain severity in the control group was **4.7** (Severity scale 0-10) | MD **2 lower** (3.66 lower to 0.34 lower) |
| **Pain related quality of life** assessed with: The Brief Pain Inventory Quality of Life score follow up: 1 to 3 months | 26 (1 RCT) 1 to 3 months | ⨁⨁⨁⨀ MODERATE 1 | The mean pain related quality of life in the control group was **4.1** (Quality of life scale 0-10) | MD **0.9 lower** (2.73 lower to 0.93 higher) |
| **Pain related quality of life** assessed with: The Brief Pain Inventory Quality of Life score follow up: 3 to 5 months | 26 (1 RCT) 3 to 5 months | ⨁⨁⨁⨀ MODERATE 1 | The mean pain related quality of life in the control group was **4.6** (Quality of life scale 0-10) | MD **1.8 lower** (3.77 lower to 0.17 higher) |
| **Pain related quality of life** assessed with: The Brief Pain Inventory Quality of Life score follow up: 5 to 6 months | 26 (1 RCT) 5 to 6 months | ⨁⨁⨁⨀ MODERATE 1 | The mean pain related quality of life in the control group was **4.2** (Quality of life scale 0-10) | MD **2.1 lower** (3.92 lower to 0.28 lower) |

RCT = randomised controlled trial; Brief Pain Inventory Severity scale 0 – 10, where 0 = no pain, and 10 = pain as bad as you can imagine; Brief Pain Inventory Quality of Life scale 0 – 10, where 0 = pain does not interfere, and 10 = pain completely interferes; MD = mean difference between agalsidase alfa and placebo (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than placebo, and conversely “higher” means that the effect size is higher in agalsidase alfa than in placebo). In this instance, a lower pain level is beneficial to patients.

1. Small participant numbers

2. Inadequate reporting

3. Surrogate outcome

#### Comparative safety

No data on comparative safety were reported in the two RCTs assessing agalsidase alfa and placebo in Fabry patients (Hughes et al. 2008; Schiffmann et al. 2001).

#### Effectiveness of agalsidase beta compared to placebo

Systematic reviews by El Dib et al (2013) and Schaeffer et al (2009) assessed the effectiveness of agalsidase beta compared to placebo in patients with FD. Three RCTs and relevant extension studies were identified which contributed outcome data to this question. The earliest RCT (Eng et al. 2001) was a multicentre, double blind study in which 58 patients were randomised to agalsidase beta or placebo (29 to each group). The trial was followed by an on-going open labelled study (Thurberg et al. 2004; Thurberg et al. 2002; Wilcox et al. 2004). A second RCT was a small study (Bierer et al. 2006) which was designed to assess the impact of ERT on cardiopulmonary exercise. Six patients were randomised 2:1 to receive agalsidase beta or placebo, and received serial cardiopulmonary exercise tests every three months for up to 18 months. In the third RCT (Banikazemi, M. et al. 2007) 82 patients from several centres were randomised 2:1 to drug or placebo. All three RCTs administered the agalsidase beta at a dose of 1 mg per kilogram of body weight, once fortnightly. The study populations were predominantly male.

Outcomes in the SR by El Dib et al (2013) were reported as mean differences with confidence intervals and are presented below in a GRADE evidence summary. Most findings were reported in one RCT only. Where an outcome was assessed in more than one trial, a pooled analysis is presented. Any additional findings reported by Schaefer et al (2009) were used to supplement the results presented by El Dib (2013). Schaefer et al (2009) reported mean baseline and endpoint data with standard deviations. Statistical differences were reported as p values for some outcomes; however, not always with confidence intervals.

##### Primary effectiveness

##### Survival and serious disease-related events

Survival (reported as number of deaths per randomised group) and the frequency of cardiac, renal and cerebrovascular events were compared between those randomised to either agalsidase beta or placebo in one RCT (Banikazemi, M. et al. 2007) (Table 37). There was one death out of the 51 patients given agalsidase beta, and no deaths in the placebo group of 31 patients. The difference between groups was consistent with chance, given the small sample size (GRADE ⨁⨁⨁⨁).

The frequency of renal events (defined as 33% increase in serum creatinine level, end stage renal disease) was slightly lower in patients receiving agalsidase beta as compared to placebo (19.6% versus 22.6%, RR 0.87, 95%CI 0.37 to 2.04) although the difference was not statistically significant (GRADE ⨁⨁⨁⨁). Similarly the differences in cardiac events (5.9% versus 12.9%, RR 0.46, 95%CI 0.11 to 1.90) and cerebrovascular events (0% versus 6.5%, RR 0.12, 95%CI 0.01 to 2.48) were not statistically significant (GRADE ⨁⨁⨁⨁). While the differences between treatment arms were no greater than chance – and larger sample sizes would be required to demonstrate any differences – all three analyses reported a higher frequency of disease-related events in the placebo group.

Table 37 Death, Renal events, Cardiac events and cerebrovascular events in Fabry patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Relative effect (95% CI)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase beta** |
| --- | --- | --- | --- | --- | --- |
| **Death – ITT** assessed with: n follow up: 6 months | 82 (1 RCT) 6 months | ⨁⨁⨁⨁ HIGH | **RR 1.85** (0.08 to 43.96) | 0 per 1000 | **20 more per 1000** (18 fewer to 58 more) |
| **Renal events** assessed with: n follow up: 6 months | 82 (1 RCT) 6 months | ⨁⨁⨁⨁ HIGH | **RR 0.87** (0.37 to 2.04) | 226 per 1000 | **30 fewer per 1000** (213 fewer to 150 more) |
| **Cardiac events** assessed with: n | 82 (1 RCT) | ⨁⨁⨁⨁ HIGH | **RR 0.46** (0.11 to 1.9) | 129 per 1000 | **70 fewer per 1000** (205 fewer to 64 more) |
| **Cerebrovascular events** assessed with: n follow up: 6 months | 82 (1 RCT) 6 months | ⨁⨁⨁⨁ HIGH | **RR 0.12** (0.01 to 2.48) | 65 per 1000 | **64 fewer per 1000** (151 fewer to 22 more) |

CI = confidence interval; RCT= randomised controlled trial; ITT = intention to treat population; RR = relative risk; risk difference was calculated using STATA; importance of outcome was critical

##### Secondary effectiveness

##### Changes in globotriaosylceramide (Gb3) levels in plasma and tissue

Gb3 levels were used as a surrogate outcome for renal function. Changes in Gb3 levels were reported in different ways in one RCT (Eng et al. 2001) with results shown in Table 38. Microvascular endothelial Gb3 levels were reported for heart, kidney and a composite measure after 5 months of treatment. Gb3 levels were significantly lower favouring the agalsidase beta group for all three measures (kidney: MD -1.70, 95%CI -2.09 to -1.31; heart: MD -0.90, 95%CI -1.18 to -0.62; composite: MD -4.80, 95%CI -5.45 to -4.15). These results were given a quality rating of *very low* (GRADE ⨁⨀⨀⨀) as risk of bias, indirectness and imprecision were considered to be serious.

Table 38 Microvascular endothelial Gb3 deposits in patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) (Eng et al. 2001)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase beta** |
| --- | --- | --- | --- | --- |
| **Microvascular endothelial Gb3 deposits: Kidney** assessed with: Gb3 score follow up: 3 to 6 | 58 (1 RCT) | ⨁⨀⨀⨀ VERY LOW 2 | The mean microvascular endothelial Gb3 deposits: Kidney in the control group was **0** | MD **1.7 lower** (2.09 lower to 1.31 lower) |
| **Microvascular endothelial Gb3 deposits: Heart** assessed with: Gb3 score follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨀⨀⨀ VERY LOW 1 2 | The mean microvascular endothelial Gb3 deposits: Heart in the control group was **0** | MD **0.9 lower** (1.18 lower to 0.62 lower) |
| **Microvascular endothelial Gb3 deposits: Composite** assessed with: Gb3 score follow up: 3 to 6 | 58 (1 RCT) | ⨁⨀⨀⨀ VERY LOW 1 2 | The mean microvascular endothelial Gb3 deposits: Composite in the control group was **0** | MD **4.8 lower** (5.45 lower to 4.15 lower) |

RCT = randomised controlled trial; Gb3 = globotriaosylceramide; MD = mean difference between agalsidase beta and placebo (i.e. a mean difference “lower” means that the effect size in the agalsidase beta arm is lower than placebo, and conversely “higher” means that the effect size is higher in agalsidase beta than in placebo). In this instance, a lower Gb3 deposit is beneficial to patients; Gb3 score was defined as 0 for specimens with no or trace amounts of Gb3, 1 if the majority of vessels had evidence of a single endothelial inclusion, 2 if multiple vessels with single or multiple aggregate inclusions, and 3 for specimens with larger accumulations of inclusions and bulging of the vessel lumens.

1. Possible conflict of interest

2. Surrogate outcome

Gb3 levels in skin were measured in biopsy samples and were given a histological score. A score of 0 was given if there was no Gb3 or only trace amounts found. The percentage of patients with reduced Gb3 deposits or a score of zero were compared between randomised groups for a range of skin tissues. Patients randomised to receive agalsidase beta rather than placebo had a significantly lower Gb3 level in superficial endothelial cells (100% versus 34.5%, RR 2.81, 95%CI 1.72 to 4.59) as well as deep endothelial cells (100% versus 34.6%, RR 2.79, 95%CI 1.67 to 4.67). Results were not significantly different for smooth muscle cells and perineurium, given the small sample size, but the direction of the difference was consistent for all analyses (GRADE ⨁⨀⨀⨀) (Table 39).

Table 39 Skin tissue Gb3 deposits in Fabry patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Relative effect (95% CI)** | **Risk with Supportive care plus placebo** | **-Risk difference with Agalsidase beta** |
| --- | --- | --- | --- | --- | --- |
| **Participants achieving zero score or reduction in skin: Superficial endothelial cells** follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 2.81** (1.72 to 4.59) | 345 per 1000 | **655 more per 1000** (482 more to 828 more) |
| **Participants achieving zero score or reduction in skin: Deep endothelial cells** follow up: 3 to 6 months | 52 (1 RCT) 3 to 6 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 2.79** (1.67 to 4.67) | 346 per 1000 | **654 more per 1000** (471 more to 837 more) |
| **Participants achieving zero score or reduction in skin: Smooth muscle cells** follow up: 3 to 6 months | 6 (1 RCT) 3 to 6 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 1.5** (0.1 to 22.62) | 0 per 100 | **333 fewer per 100** (200 fewer to 867 more) |
| **Participants achieving zero score or reduction in skin: Perineurium** follow up: 3 to 6 months | 47 (1 RCT) 3 to 6 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 1.49** (0.68 to 3.25) | 292 per 1000 | **143 more per 1000** (129 more to 415 more) |

CI = confidence interval; RCT = randomised controlled trial; RR = relative risk

1. Possible conflict of interest

2. Surrogate outcome

##### Cardiopulmonary test

Cardiopulmonary testing was conducted in one “RCT” that randomised 6 patients (Bierer et al. 2006), with outcomes discussed by El Dib (2013). Overall, the patients randomised to agalsidase beta tended to have better cardiac function than patients receiving placebo i.e. a higher average heart rate reserve, average oxygen uptake at peak exercise, maximum oxygen uptake at peak exercise, oxygen pulse at peak exercise and decrease in diastolic pressure (Table 40). Unsurprisingly, given the sample size, the differences between treatment arms were not statistically significant (GRADE ⨁⨁⨀⨀).

Table 40 Cardiopulmonary exercise test outcomes in patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013) (Schaefer, Tylki-Szymanska & Hilz 2009)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Relative effect (95% CI)** | **Risk with Supportive care plus placebo** | **-Risk difference with Agalsidase beta** |
| --- | --- | --- | --- | --- | --- |
| **Cardiopulmonary exercise test: Average heart rate reserve** assessed with: beats/min follow up: 18 months | 6 (1 RCT) 18 months | ⨁⨁⨀⨀ LOW 1 2 | - | The mean cardiopulmonary exercise test: Average heart rate reserve in the control group was **21** beats/min | MD **21.3 higher** (1.28 lower to 43.88 higher) |
| **Cardiopulmonary exercise test: Average maximum oxygen uptake measured at peak exercise** assessed with: L/minutes follow up: 18 months | 6 (1 RCT) 18 months | ⨁⨁⨀⨀ LOW 1 2 | - | The mean cardiopulmonary exercise test: Average maximum oxygen uptake measured at peak exercise in the control group was **1.35** L/min | MD **0.22 higher** (0.94 lower to 1.38 higher) |
| **Cardiopulmonary exercise test: Maximum oxygen uptake measured at peak exercise** assessed with: ml/kg/minutes follow up: 18 months | 6 (1 RCT) 18 months | ⨁⨁⨀⨀ LOW 1 2 | - | The mean cardiopulmonary exercise test: Maximum oxygen uptake measured at peak exercise in the control group was **NR** | MD **2.6 higher** (13.16 lower to 18.36 higher) |
| **Cardiopulmonary exercise test: Oxygen pulse average at peak exercise** assessed with: Volume O2/heart rate follow up: 18 months | 6 (1 RCT) 18 months | ⨁⨁⨀⨀ LOW 1 2 | - | The mean cardiopulmonary exercise test: Oxygen pulse average at peak exercise was **NR** | MD **2.1 higher** (3.67 lower to 7.87 higher) |
| **Cardiopulmonary exercise test: Decrease in diastolic pressure** follow up: 18 months | 6 (1 RCT) 18 months | ⨁⨁⨀⨀ LOW 1 2 | **RR 1.5** (0.34 to 6.7) | 500 per 1000 | **250 more per 1000** (330 fewer to 2850 more) |

CI = confidence interval; RCT = randomised controlled trial; MD = mean difference between agalsidase beta and placebo (i.e. a mean difference “lower” means that the effect size in the agalsidase beta arm is lower than placebo, and conversely “higher” means that the effect size is higher in agalsidase beta than in placebo). In this instance, a higher level of cardiac output is beneficial to patients; RR = relative risk; NR = not reported; risk difference calculated using STATA

1. Possible conflict of interest

2. Small participant numbers

##### Pain

Pain was assessed in one trial (Eng et al. 2001) reported by Schaefer et al (2009). The short form of the McGill Pain Questionnaire was used to assess sensory pain, affective pain, pain measured on a visual analogue scale and present pain intensity. The total pain score, which is a sum of the sensory pain and affective pain scores, is reported in Table 41. Surprisingly, there were improvements in pain scores in both agalsidase beta and placebo groups, so a placebo effect cannot be ruled out (GRADE ⨁⨁⨀⨀).

Table 41 Pain reported by Fabry patients randomised to receive either agalsidase beta or placebo (Schaefer, Tylki-Szymanska & Hilz 2009)

| Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Risk with Supportive care plus placebo | Risk difference with Agalsidase beta |
| --- | --- | --- | --- | --- |
| **Total pain** assessed with: McGill Pain Questionnaire follow up: 5 months | 58 (1 RCT) 5 months | ⨁⨁⨀⨀ LOW 1 | The mean total pain ranged across control groups was **NR** | p >**0.05 higher2** (CI NR) |

CI = confidence interval; RCT = randomised controlled trial; NR = not reported

1. Possible conflict of interest

2. Neither group favoured

##### Extension studies

##### Glomerular filtration rate

Schaeffer et al reported long term follow-up outcomes for GFR from two RCTs (Banikazemi, M. et al. 2007; Eng et al. 2001). Only baseline data were published for this outcome, but Schaefer et al (2009) reported that long-term measures reflected a stable filtration rate over 54 months and 35 months for individual RCTs (GRADE⨁⨀⨀⨀).

#### Comparative safety

A comparative assessment of frequency of adverse events was conducted in the SR by El Dib, 2013. Results can be seen here in Table 42 and Table 43. The GRADE quality of each outcome ranged between low and high, depending on whether the RCT from which the result was taken was assessed as serious risk of bias or not, and whether imprecision was assessed as serious or not serious. These factors were affected by lack of reporting of randomisation and concealment methods, and patient withdrawal and drop data (Eng et al. 2001) and the possibility of conflict of interest for authors (Eng et al. 2001).

Rigors and fever were assessed in two RCTs (Banikazemi, M. et al. 2007; Eng et al. 2001) at different time points (3 to 6 months, and 24 months) and the results were analysed together here. Rigors were 16 times more likely to occur in the patients randomised to agalsidase beta than those in the placebo group (40% versus 1.7%, RR 16.12, 95%CI 3.35 to 77.95). Fever was another adverse event assessed in two RCTs at different time points. When assessed together it was found that fever was 7.84 times more likely to occur in the agalsidase group than the placebo group (26.6% versus 3.3%, RR 3.04, 95%CI 1.88 to 32.68) (GRADE ⨁⨁⨀⨀). Temperature changed sensation (reported in Banikazemi 2007) and chills (reported in Eng 2001) were also more likely to occur in the patients who received the drug (respectively 9.8% versus 3.2%, RR 3.04, 95%CI 0.37 to 24.82; 13.8% versus 0%, RR 9.00, 95%CI 0.51 to 159.94) (GRADE ⨁⨁⨀⨀).

Table 42 Adverse events (rigors, fever, temperature changed sensation and chills) for Fabry patients randomised to receive agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Relative effect (95% CI)** | **Risk with Supportive care plus placebo** | **-Risk difference with Agalsidase beta** |
| --- | --- | --- | --- | --- | --- |
| **Adverse event: Rigors** assessed with: n follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 | **RR 29** (1.81 to 464.38) | 0 per 1000 | **483 more per 1000** (301 fewer to 667 more) |
| **Adverse event: Rigors** assessed with: n follow up: 24 months | 82 (1 RCT) 24 months | ⨁⨁⨁⨁ HIGH | **RR 10.94** (1.54 to 77.95) | 32 per 1000 | **321 more per 1000** (175 more to 466 more) |
| **Adverse event: Rigors, Total** assessed with: n follow up: 3 to 24 months | 140 (2 RCTs) 3 to 24 months | ⨁⨁⨀⨀ LOW 1 | **RR 16.12** (3.35 to 77.58) | 17 per 1000 | **252 more per 1000** (390 more to 12760 more) |
| **Adverse event: Fever** assessed with: n follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 | **RR 7** (0.92 to 53.36) | 34 per 1000 | **207 more per 1000** (38 more to 376 more) |
| **Adverse event: Fever** assessed with: n follow up: 24 months | 82 (1 RCT) 24 months | ⨁⨁⨁⨁ HIGH | **RR 8.51** (1.18 to 61.58) | 32 per 1000 | **242 more per 1000** (105 more to 380 more) |
| **Adverse event: Fever** assessed with: n follow up: 3 to 24 months | 140 (2 RCTs) 3 to 24 months | ⨁⨁⨀⨀ LOW 1 | **RR 7.84** (1.88 to 32.68) | 33 per 1000 | **228 more per 1000** (290 more to 10560 more) |
| **Adverse event: Temperature changed sensation** assessed with: n follow up: 24 months | 82 (1 RCT) 24 months | ⨁⨁⨁⨁ HIGH | **RR 3.04** (0.37 to 24.82) | 32 per 1000 | **66 more per 1000** (37 fewer to 168 more) |
| **Adverse event: Chills** assessed with: n follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 | **RR 9** (0.51 to 159.94) | 0 per 1000 | **138 more per 1000** (12 more to 263 more) |

CI = confidence interval; RCT = randomised controlled trial; RR = relative risk; risk difference calculated using STATA

1. Possible conflict of interest

Table 43 Adverse events (hypertension, vomiting, chest pain, fatigue, headache and pain related to Fabry disease) in Fabry patients randomised to receive either agalsidase beta or placebo (El Dib, R P, Nascimento & Pastores 2013)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Relative effect (95% CI)** | **Risk with Supportive care plus placebo** | **Risk difference with Agalsidase beta** |
| --- | --- | --- | --- | --- | --- |
| **Adverse event: Hypertension** assessed with: n follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 | **RR 7** (0.38 to 129.74) | 0 per 1000 | **103 more per 1000** (1 fewer to 380 more) |
| **Adverse event: Hypertension** assessed with: n follow up: 24 months | 82 (1 RCT) 24 months | ⨁⨁⨁⨁ HIGH | **RR 2.13** (0.47 to 9.6) | 65 per 1000 | **73 more per 1000** (55 fewer to 201 more) |
| **Adverse event: Hypertension** assessed with: n follow up: 3 to 24 months | 140 (2 RCTs) 3 to 24 months | ⨁⨁⨀⨀ LOW 1 | **RR 2.94** (0.8 to 10.86) | 33 per 1000 | **65 more per 1000** (70 fewer to 3290 more) |
| **Adverse event: Vomiting** assessed with: n follow up: 24 months | 82 (1 RCT) 24 months | ⨁⨁⨁⨁ HIGH | **RR 8** (0.47 to 137.27) | 0 per 1000 | **118 more per 1000** (29 more to 206 more) |
| **Adverse event: Chest pain** assessed with: n follow up: 24 months | 82 (1 RCT) 24 months | ⨁⨁⨁⨁ HIGH | **RR 6.77** (0.39 to 118.36) | 0 per 1000 | **98 more per 1000** (16 more to 180 more) |
| **Adverse event: Fatigue** assessed with: n follow up: 24 months | 82 (1 RCT) 24 months | ⨁⨁⨁⨁ HIGH | **RR 6.77** (0.39 to 118.36) | 0 per 1000 | **98 more per 1000** (16 more to 180 more) |
| **Adverse event: Headache** assessed with: n follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 | **RR 2.5** (0.53 to 11.86) | 69 per 1000 | **103 more per 1000** (62 fewer to 269 more) |
| **Adverse event: Pain related to Fabry Disease** assessed with: n follow up: 3 to 6 months | 58 (1 RCT) 3 to 6 months | ⨁⨁⨀⨀ LOW 1 | **RR 3** (0.33 to 27.18) | 34 per 1000 | **69 more per 1000** (60 fewer to 198 more) |

CI = confidence interval; RCT = randomised controlled trial; RR = relative risk; risk difference calculated using STATA

1. Possible conflict of interest

Hypertension was another adverse event assessed in two RCTs (Banikazemi, M. et al. 2007; Eng et al. 2001) again at time points of 3 to 6 months and 24 months (see Table 43). When analysed together there was found to be a three times greater risk of hypertension for those patients taking the drug, than those on placebo, although the effect was still consistent with chance despite the pooled sample size (12.5% versus 3.3%, RRp 2.94, 95%CI 0.80 to 10.86) (GRADE ⨁⨁⨀⨀). Vomiting, chest pain and fatigue events (Banikazemi, M. et al. 2007) were similarly associated with the drug, occurring in 9.8%-11.8% of patients, with no events occurring in patients taking placebo (GRADE ⨁⨁⨁⨁). Headache and pain related to Fabry disease (Eng et al. 2001) were also more likely to occur in the agalsidase beta group than the placebo group (GRADE ⨁⨁⨀⨀).

#### Effectiveness of agalsidase alfa compared with agalsidase beta

One RCT (Vedder et al. 2007) randomised 36 Fabry patients to receive treatment with either agalsidase alfa or beta (0.2 mg/kg/2 weeks). Two patients withdrew after 6 months of treatment. While the method of randomisation and concealment of allocation was adequate for this trial, there was no blinding to the treatment received, therefore this trial was considered at high risk of bias. In addition there was incomplete outcome data following a variance in withdrawal rates between groups.

##### Primary effectiveness

##### Survival, serious adverse events and disease related events

Survival was reported in Vedder (2007) as the number of deaths at an extended follow-up period of 24 months. There was one death in the agalsidase alfa group and no deaths in the beta group (Table 44). The single death was reported to be as a result of multiple cerebral infarctions after 20 months of treatment (GRADE ⨁⨀⨀⨀).

Cardiac events were assessed at 42 months in 29 patients. There were 3 occurrences of atrial fibrillation, 2 events in the beta group compared with 1 in the alfa group (Table 44). There were also more serious adverse events (defined as events requiring hospitalisation or initiation of medication and which did not fulfil the criteria for treatment failure) in the agalsidase beta group compared to the alfa group (GRADE ⨁⨀⨀⨀). The differences between treatment arms were not statistically significant for each of these outcomes.

Table 44 Death, cardiac and serious adverse events in Fabry patients randomised to receive either agalsidase alfa or agalsidase beta (El Dib, R P, Nascimento & Pastores 2013)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Relative effect (95% CI)** | **Risk with agalsidase beta** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- | --- |
| **Death** assessed with: n follow up: 24 months | 36 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 3** (0.13 to 69.09) | 0 per 1000 | **56 more per 1000** (50 fewer to 161 more) |
| **Cardiac events** assessed with: n follow up: 42 months | 29 (1 RCT) 42 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 0.47** (0.05 to 4.6) | 143 per 1000 | **76 fewer per 1000** (299 fewer to 146 more) |
| **Any serious adverse event** assessed with: n follow up: 24 months | 34 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 0.3** (0.03 to 2.57) | 188 per 1000 | **132 fewer per 1000** (351 fewer to 87 more) |

CI = confidence interval; RCT = randomised controlled trial; RR = relative risk; risk difference calculated using STATA; Death, cardiac events and serious adverse events are considered critical, any adverse events is considered important

1. No blinding

2. Incomplete outcome data

##### Changes in globotriaosylceramide Gb3 concentrations

Changes in Gb3 levels in plasma and urine were reported by Vedder (2007). The results in Table 45 have been calculated from raw data published by the author. Differences between the agalsidase alfa and beta groups were not statistically significant (GRADE ⨁⨀⨀⨀).

Table 45 Comparison of Gb3 levels in Fabry patients randomised to receive either agalsidase alfa or agalsidase beta (Vedder et al. 2007)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with agalsidase beta** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Change in plasma Gb3** assessed with: umol/L follow up: 24 months | 29 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 3 | The mean change in plasma Gb3 in the control group was -**1.1** umol/L | MD **0.42 higher** (1.04 lower to 1.87 higher) |
| **Change in urine Gb3** follow up: 24 months | 27 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 3 | The mean change in urine Gb3 in the control group was 371 umol/L | MD **587 higher** (450 lower to 1624 higher) |

RCT = randomised controlled trial; Gb3 = globotriaosylceramide; MD = mean difference between agalsidase alfa and agalsidase beta (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than in agalsidase beta, and conversely “higher” means that the effect size is higher in agalsidase alfa than in agalsidase beta). In this instance, a lower Gb3 level is beneficial to patients.

1. No blinding

2. Incomplete outcome data

3. Surrogate outcome

##### Renal function

Renal function was assessed as changes in GFR through creatinine clearance (Table 46) and proteinuria (Table 47). The GFR was calculated from raw data published by Vedder et al (2007). It was higher in patients receiving agalsidase beta compared to alfa but the difference was not statistically significant. Proteinuria values also favoured the beta group but again the result was consistent with chance (GRADE ⨁⨀⨀⨀).

Table 46 Changes in creatinine clearance in Fabry patients randomised to receive either agalsidase alfa or agalsidase beta (Vedder et al. 2007)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with agalsidase beta** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Change in glomerular filtration rate (based on creatinine clearance)** assessed with: ml/min follow up: 24 months | 29 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 3 | The mean change in glomerular filtration rate (based on creatinine clearance) in the control group was **107** ml/min | MD **0.11 higher** (8.25 lower to 8.46 higher) |

RCT= randomised controlled trial; MD = mean difference between agalsidase alfa and agalsidase beta (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than agalsidase beta, and conversely “higher” means that the effect size is higher in agalsidase alfa than in agalsidase beta). In this instance, a lower creatinine clearance rate is beneficial to patients.

1. No blinding

2. Incomplete outcome data

3. Surrogate outcome

Table 47 Comparison of proteinuria in patients randomised to receive either agalsidase alfa or beta (Schaefer, Tylki-Szymanska & Hilz 2009) (Vedder et al. 2007)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Mean change with agalsidase beta** | **Difference in mean change with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Proteinuria** assessed with: g/24h follow up: 24 months | 29 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 3 | The mean change in proteinuria in the control group was -**0.09** g/24h | p **0.33a** |

RCT = randomised controlled trial; Outcome considered not very important; a Trend favours agalsidase beta

1. No blinding

2. Incomplete outcome data

3. Surrogate outcome

##### Cardiac outcomes

There was a mean difference of 31.25g in the change in left ventricular mass between the treatment groups reported by Vedder (2007). This favoured the agalsidase beta group but the difference was not statistically significant (GRADE ⨁⨀⨀⨀) (Table 48).

Table 48 Left ventricular change in Fabry patients randomised to receive either agalsidase alfa or beta (Vedder et al. 2007)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Risk with agalsidase beta** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- |
| **Left ventricular mass** assessed with: g follow up: 24 months | 29 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 3 | The mean left ventricular mass in the control group was **308** g | MD **31.3 lower** (104.5 lower to 42 higher) |

RCT = randomised controlled trial; MD = mean difference between agalsidase alfa and agalsidase beta (i.e. a mean difference “lower” means that the effect size in the agalsidase alfa arm is lower than agalsidase beta, and conversely “higher” means that the effect size is higher in agalsidase alfa than in agalsidase beta). In this instance, a lower left ventricular mass is beneficial to patients.

1. No blinding

2. Incomplete outcome data

3. Surrogate outcome

##### Comparative safety

Vedder (2007) reported on the frequency of adverse events in the two agalsidase treatment groups (Table 49). Events in this category included: infusion related chills, fever, grade 1 or 2 nausea, dizziness, headache and diarrhoea. Increased adverse events were observed in the agalsidase beta group but the difference between alfa and beta was not statistically significant (GRADE ⨁⨀⨀⨀).

Table 49 Adverse events in Fabry patients randomised to receive agalsidase alfa or agalsidase beta (El Dib, R P, Nascimento & Pastores 2013)

| **Outcomes** | **№ of participants (studies) Follow-up** | **Quality of the evidence (GRADE)** | **Relative effect (95% CI)** | **Risk with agalsidase beta** | **Risk difference with Agalsidase alfa** |
| --- | --- | --- | --- | --- | --- |
| **Any adverse event** assessed with: n follow up: 24 months | 34 (1 RCT) 24 months | ⨁⨀⨀⨀ VERY LOW 1 2 | **RR 0.36** (0.08 to 1.59) | 313 per 1000 | **201 fewer per 1000** (471 fewer to 68 more) |

CI = confidence interval; RCT = randomised controlled trial; RR = relative risk; risk difference calculated using STATA

1. No blinding

2. Incomplete outcome data

#### Extended assessment of harms

The summary of safety provided in this section based on Periodic Safety Update Reports (PSURs) have been provided in confidence to the LSDP expert reference group. The summary has been redacted at the request of the sponsors.

#### Australian data registry information

There are currently two drugs on the LSDP program for the treatment of Fabry disease; agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme).

Data relating to the treatment of Fabry disease on the LSDP was obtained from registry data held by the Australian Government Department of Health.

A total of ''''' patients are currently receiving treatment for Fabry disease on the LSDP. Approximately two thirds of Fabry patients currently receiving treatment under the auspices of the LSDP are male (65.5%; ''' ''' ''''''), with the average age of those currently receiving treatment approximately 49 years of age. The average age at first treatment was 41 years of age. Table 52 – Table 54 contain summary demographic information on the patients receiving treatment on the LSDP.

Table 52 Age of patients currently accessing treatments for Fabry disease on the LSDP

| **Age** | **''''''''''''''''''''''' '''''''** | **''''''''''''''''''''' '''''''''** | **All patients** |
| --- | --- | --- | --- |
| Average | 49 | 48 | 49 |
| Median | 50 | 49 | 49 |
| Min | 15 | 17 | 15 |
| Max | 75 | 69 | 75 |
| ''''''''''''''''''''' '''' '''''''''''''''''''''''''''''''' '''''''''' | '''''' | ''''''' | ''''''' |

Source: Australian Data Registry

Table 53 Average age of first treatment for patients currently accessing treatments for Fabry disease on the LSDP

| **Age at first treatment** | **Agalsidase alfa** | **Agalsidase beta** | **All patients** |
| --- | --- | --- | --- |
| Average | 41 | 41 | 41 |
| Median | 40 | 41 | 40 |
| Min | 13 | 21 | 13 |
| Max | 69 | 69 | 69 |
| ''''''''''''''''''' ''''' '''''''''''''''''''''''''''''' ''''''''''' | ''''''' | '''''' | '''''' |

Source: Australian Data Registry

Table 54 Gender of those currently receiving treatment on the LSDP

| **Gender** | **Agalsidase alfa** | **Agalsidase beta** | **All patients** |
| --- | --- | --- | --- |
| Male | 65.5% '''''''''' | 84.6% '''''''''' | 71.6% '''''''''' |
| Female | 34.5% '''''''''' | 15.4'''''' ''''''' | 28.4% '''''''''' |
| Number of observations (n=) | 100.0% '''''''''' | 100.0% ''''''''' | 100.0% '''''''''' |

Source: Australian Data Registry

The average dose for agalsidase alfa was ''''''''''''' ''''''''''''''''''''''''''''''''''''' (using an adjusted weight for patients with a BMI greater than 27, see table notes), which is only marginally above the recommended dose of 0.2 mg/kg/fortnight (Therapeutic Goods Administration 2010c), and consistent with the randomised trials identified; these all used doses of 0.2 mg/kg/fortnight (Hughes et al. 2008; Schiffmann et al. 2001; Vedder et al. 2007).

The average dose for agalsidase beta was 0.966 mg/kg/fortnight (using an adjusted weight for patients with a BMI greater than 27, see table notes), which was slightly lower than the recommended dose of 1 mg/kg/fortnight (Therapeutic Goods Administration 2010b). The maximum dose received was 1.072 mg/kg/fortnight. For comparison, the trials comparing agalsidase beta against placebo all used a dose of 1 mg/kg/fortnight (Banikazemi, Maryam et al. 2007; Bierer et al. 2006; Eng et al. 2001), while the trial of agalsidase beta against agalsidase alfa used a dose of 0.2 mg/kg/fortnight (Vedder et al. 2007).

Table 55 Dosing information (mg/kg/2 weeks) for patients currently receiving treatment with agalsidase alfa on the LSDP

|  | **BMI <27** | **BMI >27 (A)\*** | **BMI >27 (B)** | **All (A)\*** | **All (B)** |
| --- | --- | --- | --- | --- | --- |
| Number of observations^ | ''''' | '''''' | '''''' | ''''' | '''''''''' |
| Mean Dose mg/kg/fortnight  ± SD | 0.22 ± 0.04 | 0.21 ± 0.02 | 0.17 ± 0.03 | 0.22 ± 0.04 | 0.20 ± 0.04 |
| Median | 0.21 | 0.21 | 0.18 | 0.21 | 0.20 |
| Maximum dose | 0.40 | 0.23 | 0.213 | 0.40 | 0.40 |
| Minimum dose | 0.19 | 0.14 | 0.11 | 0.14 | 0.11 |

BMI>27 (A) = weight for patients with a BMI greater than 27 was adjusted so that their weight (given their height) would equal a BMI of 27.

BMI>27 (B) = the patient’s weight has not been adjusted in this calculation.

\*Weight of patients with a BMI greater than 27 has been adjusted so that their weight (given their height) equals a BMI of 27.

^While dosing information was available for all patients currently receiving treatment with agalsidase ''''''''' '''''''''''''''' '''''''''''''''' '''''''''' '''''''''''''' '''''''''''''''''''''''''''''''''' '''''''''''' ''''''''''' '''''''''''''''''''' '''''' ''''''' ''''''''''''''''''''

†Weight was available for an additional three patients which were also missing height values (and were therefore not included in analysis A)

Table 56 Dosing information (mg/kg/2 weeks) for patients currently receiving treatment with agalsidase beta on the LSDP

|  | **BMI <27** | **BMI >27 (A)\*** | **BMI >27 (B)** | **All (A)\*** | **All (B)** |
| --- | --- | --- | --- | --- | --- |
| Number of observations^ | '''''' | '''' | ''' | '''''' | '''''''''' |
| Mean Dose mg/kg/fortnight  ± SD | 0.95 ± 0.22 | 0.97 ± 0.04 | 0.86 ± 0.04 | 0.97 ± 0.17 | 0.91 ± 0.18 |
| Median | 1.03 | 0.97 | 0.87 | 1.00 | 0.95 |
| Maximum dose | 1.07 | 1.01 | 0.98 | 1.07 | 1.07 |
| Minimum dose | 0.27 | 0.87 | 0.70 | 0.27 | 0.27 |

BMI>27 (A) = weight for patients with a BMI greater than 27 was adjusted so that their weight (given their height) would equal a BMI of 27.

BMI>27 (B) = the patient’s weight has not been adjusted in this calculation.

\*Weight of patients with a BMI greater than 27 has been adjusted so that their weight (given their height) equals a BMI of 27.

^While dosing information was available for all patients currently receiving treatment with agalsidase beta '''''''''''''''''' '''''''''''''''' '''''''''' ''''''''''''''' '''''''''''''''''''''''''''''''' ''''''''''''' ''''''''' '''''''''''''''''''' ''''''' '''''' ''''''''''''''''''''

†Weight was available for one additional patient that was also missing a height value (and was therefore not included in analysis A)

'''''''''' ''''''''''''''''''''''''''''' '''''' ''''''''''''''''''''''''''' '''''''''' '''''''''''''''''''' ''''''''' '''''''''''''''''''''''' '''''''''''''''''' '''''''''' '''''''''''''''' ''''''' '''''''''''''''''''' '''''' ''''''''''''''' ''''''''''''' ''''' '''''''''''''''' ''''''''''''' ''''''' '''''''''' '''' '''''' ''''''''''''''' ''''' '''''''' '''''''''''''''''' ''''' '''''''''''''''''''''''''' ''''''''''' ''''''''''''''' ''''''''''''''''''' ''''''' ''''''''''''''''''''''''''''''''''''''''''' ''''''''''''''''''''''''' '''''' ''''''''' '''''''''''''''''''''''' '''' ''' '''''''''''''''' ''''' ''''''''''''''''''''''''''''''''''''' ''''''''''' ''''''''''''' '''''''' '''''''''''''''''' The guidelines for Fabry disease previously required treating physicians to submit a re-application form once a year. On this basis, it was decided to compare GFR results at baseline and at the first observation to occur after 12 months. Of patients who had both baseline and follow up data within 24 months of first treatment, 44 patients had used the same GFR estimation method at both time points. The majority of these patients had estimated the GFR (eGFR) based on the CKD-EPI method (33 patients). For this sub-group of patients, there was a small absolute *decrease* in eGFR between baseline and follow up (4.6%; 0.93 mL/min/1.73m2). When stratifying this result by drug, agalsidase beta had a small improvement (0.5%; 1 mL/min/1.73m2), while agalsidase alfa revealed a small decrease (13%; 3.4 mL/min/1.73m2). These analyses are difficult to interpret given the small sample sizes and varying follow-up times. A summary of this analysis is given in Table 57.

Table 57 GFR Measures from baseline and 1-2 years after initiation of therapy (first observation only).

|  | ALL | Agalsidase beta | Agalsidase alfa |
| --- | --- | --- | --- |
| Baseline and follow up use has same GFR estimation method | 44 | - | - |
| Only those estimating GFR based on the CKD-EPI method and those with primary therapy information | 331 | 20 | 12 |
| Average Absolute Improvement (mL/min/1.73m2) | -0.93 | 1.00 | -3.42 |
| Average Proportion Improvement (mL/min/1.73m2) | -4.6% | 0.5% | -13.0% |

1One patient included in this category’ had changed therapies between baseline and one year. This patient has been excluded from the ‘by drug’ analysis.

Analysis of the number of patients with normal serum creatinine (SCr) at baseline and current follow-up revealed that the majority (53.2%%; n = 50) of patients had serum creatinine (SCr) within normal ranges (60-130 µMol/L for males and 40-110 µMol/L for females) at baseline (Table 58). The proportion of patients with normal SCr level increased at the latest follow up (68.2%; ''' ''' '''''').

Table 58 Proportion of patients with normal serum creatinine (SCr) at beginning and last observation by gender

|  | Female | Male | Total |
| --- | --- | --- | --- |
| **Beginning of treatment** | **-** | **-** | **-** |
| % Lower | 25.9% '''''''''''' | 41.8% '''''''''''''''''' | 37.2% '''''''''''''''' |
| % Normal | 70.4% ''''''''''''''''' | 46.3% '''''''''''''''''' | 53.2% '''''''''''''''' |
| % High | 3.7% ''''''''''''' | 11.9% ''''''''''''''' | 9.6% ''''''''''''' |
| **End of treatment** |  |  |  |
| % Low | 16.7% ''''''''''''' | 10.3% '''''''''''' | 12.2% '''''''''''''''''' |
| % Normal | 79.2% '''''''''''''''' | 63.8% '''''''''''''''''' | 68.3% ''''''''''''''''' |
| % High | 4.2% ('''''''''''' | 25.9% ''''''''''''''''' | 19.5% '''''''''''''''' |

Normal defined as: (60-130 µMol/L for males and 40-110 µMol/L for females) (QML Pathology 2009)

Secondary therapies for patients being treated under the LSDP were analysed according to therapeutic class. Two analyses were undertaken: one relating to any secondary therapy received, regardless of whether it is currently being used; and those that are currently being used. Unsurprisingly, anti-platelets were the most commonly prescribed secondary therapy, with 73.1% of LSDP patients receiving them, and 76.5% of current patients. Statins are also widely used by patients receiving treatment under the LSDP (69.8% of all patients; 57.4% patients currently being treated).

Table 59 Concomitant therapies

| Drug Category | All\* | Current^ |
| --- | --- | --- |
| ACE inhibitors | 51.2% (44) | 32.4% (22) |
| Anti-arrhythmic | 5.8% (5) | 2.9% (2) |
| Anti-coagulants | 19.8% (17) | 13.2% (9) |
| Anti-depressants | 43% (37) | 33.8% (23) |
| Anti-diarrheals | 8.1% (7) | 4.4% (3) |
| Anti-epileptic (for Fabry-related pain) | 15.1% (13) | 16.2% (11) |
| Anti-migraine | 1.2% (1) | 1.5% (1) |
| Anti-platelets | 73.3% (63) | 76.5% (52) |
| ARBs (angiotensin II reception blockers) | 51.2% (44) | 38.2% (26) |
| Beta blockers | 39.5% (34) | 30.9% (21) |
| Calcium channel blockers | 24.4% (21) | 19.1% (13) |
| Digestive enzymes | 2.3% (2) | 2.9% (2) |
| Digitalis | 5.8% (5) | 2.9% (2) |
| Diuretics | 26.7% (23) | 22.1% (15) |
| Folic Acid | 5.8% (5) | 5.9% (4) |
| Motility agents | 16.3% (14) | 14.7% (10) |
| Narcotic pain medicine (for Fabry-related pain) | 5.8% (5) | 7.4% (5) |
| Non-narcotic/analgesic (for Fabry-related pain) | 2.3% (2) | 2.9% (2) |
| Statins | 69.8% (60) | 57.4% (39) |
| Vitamin D | 9.3% (8) | 10.3% (7) |
| Number of patients | 100% (86) | 100% (68) |

\*Includes all concomitant therapies taken at any time and that have been recorded in the Australian Registry Data. ^Includes only those concomitant therapies that were reported as continuing at the time of data cut-off (i.e. excludes therapies that were ceased prior to the latest visit, or in patients no longer receiving a drug through the LSDP).

#### Impact of findings

The systematic review did not identify any new high-level evidence on the use of agalsidase alfa to treat Fabry disease, published since the drug was listed on the LSDP (Table 60).

One small randomised trial was identified on the use of agalsidase beta, which was not included in the agalsidase beta submission to PBAC; however, this trial only randomised six patients. Although the trial showed a trend towards favouring agalsidase beta over placebo at improving cardiac functioning, the study was not sufficiently powered for the difference to be considered statistically significant. The findings from this evidence are in keeping with the initial recommendation to fund agalsidase beta.

The submission to the PBAC for funding of agalsidase alfa, claimed that patients’ glomerular filtration rate (GFR; a surrogate for kidney function) will improve or remain stable in patients taking the drug. However, the Australian data showed that patients receiving agalsidase alfa had a 13% deterioration in GFR between baseline and 1-2 years of treatment. Patients who received agalsidase beta had on average, stable GFR estimates (a 0.5% improvement). These results are difficult to interpret given the small number of patients and varying follow-up times, but may suggest the need for consistent methods of estimation of GFR at different time points.

Table 60 Studies included assessing drugs to treat Fabry disease

| Drug | Results | References | Evidence not included in submission to the PBAC |
| --- | --- | --- | --- |
| Agalsidase alfa | 2 RCTs vs placebo + non-comparative extensions | Hughes et al (2008), Schiffmann et al (2001), Moore et al (2001) | No additional evidence |
| Agalsidase beta | 3 RCTs | Banikazemi et al (2007), Bierer et al (2006), Eng et al (2001) + extensions (Thurberg et al (2002, 2004) and Wilcox et al (2004)) | Study was Bierer et al (2006) was not included in the submission to the PBAC. However, this study was very small (6 patients). This study reported that cardiac function was better in patients treated with agalsidase beta than placebo (but not statistically significant). |
| Agalsidase alfa vs agalsidase beta | 1 RCT | Vedder et al (2007) | No additional evidence |

RCT = randomised controlled trial

### Medicine to treat Infantile Onset Pompe Disease

**Is alglucosidase alfa safe and effective compared to standard palliative care with/without placebo for treating patients with Infantile Onset Pompe Disease?**

The submission to the PBAC claimed that alglucosidase alfa is superior to standard (palliative) therapy. The PBAC considered that alglucosidase alfa met the criteria for the LSDP as it extended survival in patients with infantile-onset Pompe disease, although survival did not extend beyond early childhood. No new studies were identified to alter this conclusion, although longer term data were available for one of the historical control studies.

Three historic control studies provide low quality, but consistent, evidence that alglucosidase alfa prolongs survival in infants with infantile onset Pompe disease, across a range of populations varying in respect to the severity and stage of development of the disease (GRADE ⨁⨁⨀⨀). Two of these studies also provide low quality evidence that alglucosidase alfa also prolongs invasive ventilation-free survival (GRADE ⨁⨁⨀⨀). The effectiveness of alglucosidase alfa on survival beyond the limited duration of these studies has not been assessed.

There is evidence to suggest that the presence of cross-reactive immunologic material or a high antibody titre may have a deleterious effect on response to ERT.

There are no data on the comparative safety of alglucosidase alfa versus standard palliative care in these patients. Serious hypersensitivity reactions, including life-threatening anaphylactic reactions, have been observed in infantile-onset Pompe patients during alglucosidase alfa treatment.

#### Background

##### Pompe disease

Pompe disease is a progressive neuromuscular disorder caused by an autosomal recessively inherited deficiency of the lysosomal enzyme that degrades acid alfa-glucosidase (GAA) (Chakrapani et al. 2010). The resulting lysosomal and cytoplasmic accumulation of glycogen disrupts the cytoarchitecture and function of affected cells, leading to multisystem disease and often to early death (Kishnani, PS, Hwu, et al. 2006).

In a retrospective, multinational study on the natural history of infantile onset Pompe disease, based on retrospective chart reviews of 168 patients with documented GAA deficiency, the median age at symptom onset was 2.0 months, and infants were a median of 4.7 months old at diagnosis, 5.9 months at first ventilator support, and 8.7 months at death (Kishnani, PS, Hwu, et al. 2006). Survival rates were 25.7% at 12 months of age and 12.3% at 18 months of age, while the corresponding ventilator-free survival rates were 16.9% and 6.7%. Symptoms included cardiomegaly (92%), hypotonia (88%), respiratory distress (78%), muscle weakness (63%), feeding difficulties (57%), and failure to thrive (53%) (Kishnani, PS, Hwu, et al. 2006).

##### Pre-enzyme replacement therapy

Prior to enzyme replacement therapy being available for infantile onset Pompe disease, there was no specific treatment to treat the disease. Supportive care and palliative care (including intensive respiratory support, cardiac care, dietary therapy and rehabilitative services) were therefore the only options available.

##### Enzyme replacement therapy

Enzyme replacement therapy with alglucosidase alfa (Myozyme®) was first included in the Australian Register of Therapeutic Goods (ARTG) in March 2008, and subsidised through the LSDP since 2010. Alglucosidase alfa is a purified form of the lysosomal enzyme GAA, which is produced by recombinant DNA technology in a Chinese hamster ovary cell line (Therapeutic Goods Administration 2012a). The TGA recommended dosage regimen for alglucosidase alfa is 20mg/kg of body weight administered once every 2 weeks as an intravenous infusion (Therapeutic Goods Administration 2012a). It is supplied as a lyophilised powder, which requires reconstitution with water and sodium chloride. There is potential for severe infusion reactions, so the infusion rate should start at no more than 1 mg/kg/hour, which may be increased, after patient tolerance is established, to a maximum rate of 7 mg/kg/hour. Even at the maximum infusion rate, administration of the drug takes approximately 4 hours. Medical support should be readily available in case of severe infusion reactions.

#### Systematic review inclusion criteria

Table 61 outlines the criteria for selecting studies that assess the safety and effectiveness of alglucosidase alfa for the treatment of patients with infantile onset Pompe disease.

Table 61 Criteria for selecting studies to assess the safety and effectiveness of alglucosidase alfa

| Characteristic | Inclusion criteria |
| --- | --- |
| Study design | The highest level of evidence available (from Table 2) that addressed the research questions. Case reports would have been included if none of the study designs in were available. |
| Population | Patients with Infantile Onset Pompe Disease (glycogen storage disease type II, or acid maltase deficiency; presentation within first 24 months of life) |
| Intervention | Alglucosidase alfa (Myozyme®)  Subgroup analysis: by dose (e.g. doses consistent with TGA listing, as well as experimental dosing regimens); by whether immunosuppressives (e.g. infliximab, prednisolone) were co-administered |
| Comparator | Standard palliative care (including intensive respiratory support, cardiac care, dietary therapy and rehabilitative services) with/without placebo |
| Outcomes | *Safety:* adverse events related to treatment – for example, urticaria, pyrexia, anaphylactic shock; and compliance with treatment (i.e. treatment withdrawal or suboptimal dosing)  *Primary effectiveness:* survival  *Secondary effectiveness:* quality of life; cardiorespiratory functioning (ventilator free survival, supplementary oxygen, apnoea/hypopnoea, sleep apnoea, CPAP requirements: nocturnal or all day); cardiovascular function (hypertension, left ventricular measures, exercise capacity, heart failure); gross motor functioning; swallowing; audiology outcomes; neurological outcomes. |
| Language | Studies in languages other than English would only have been translated if it appeared from the abstract that they represented a higher level of evidence than that available in English. |
| Research question | Is alglucosidase alfa safe and effective compared to standard palliative care with/without placebo for treating patients with Infantile Onset Pompe Disease? |

TGA = Therapeutic Goods Administration; CPAP = continuous positive airway pressure

#### Results of the literature search

One randomised trial comparing the effectiveness of two different doses of alglucosidase alfa was identified, both of which were also compared with an untreated historical control group (Kishnani, P S et al. 2009; Kishnani, PS et al. 2007). As this trial did not include a direct comparison with an appropriate comparator (standard palliative care or placebo), for the purposes of this report, it has been assessed as an historic control study (Level III-3 evidence). An additional three historic control studies also fulfilled the study eligibility criteria (Chen et al. 2009; Chien et al. 2009; Nicolino, M et al. 2009). These four studies represent the highest level of evidence assessing the effectiveness of alglucosidase alfa for the treatment of infantile onset Pompe disease. No studies comparing the safety of alglucosidase alfa with an appropriate comparator in patients with infantile onset Pompe disease were identified.

#### Description of the included studies

##### Kishnani et al. (2007), Kishnani et al (2009)

This was a multi-centre, open-label, randomised trial comparing two doses of alglucosidase alfa. A comparison with an untreated historical control group was also performed to assess differences in survival (overall survival and ventilator-free survival). The initial study included a minimum follow-up of 52 weeks (Kishnani, PS et al. 2007), after which patients were eligible to participate in an extension study, where they continued to receive alglucosidase alfa at the same dose to which they were originally assigned (Kishnani, P S et al. 2009). The overall duration of follow-up differed between patients, ranging from 60 to 150 weeks.

Eligible patients were randomised to receive an IV infusion of either 20mg/kg (n=9) or 40mg/kg (n=9) alglucosidase alfa every two weeks. Patients were required to be no older than 26 weeks at enrolment, and to have documented symptoms of infant onset Pompe disease, including skin fibroblast GAA activity <1% of the normal mean and hypertrophic cardiomyopathy (left ventricular mass index ≥65g/m2 by ECG). Exclusion criteria included respiratory insufficiency (including use of any ventilation), a major congenital abnormality, or clinically significant intercurrent illness unrelated to Pompe disease. These criteria restricted eligibility to young infants at the more severe end of the disease spectrum, in whom alglucosidase alfa treatment was initiated at a relatively early stage of disease progression (Nicolino, M et al. 2009).

The historical control group was identified by applying the study eligibility criteria to a cohort of 168 patients included in a study of the natural history of infantile onset Pompe disease (Kishnani, PS, Hwu, et al. 2006). The patients included in the natural history study were identified by retrospective chart review; the only eligibility criteria were documented GAA enzyme deficiency or GAA gene mutation(s), and onset of signs or symptoms by 12 months of age (Kishnani, PS, Hwu, et al. 2006).

A total of 18 patients from 13 primary sites in the United States, Europe, Taiwan and Israel were enrolled in the randomised trial, nine patients in each of the two alglucosidase alfa dosage groups. The historical control group consisted of 62 infants, from 33 sites in nine different countries, with birth dates ranging from before 1985 to 2002 (55% were born in 1995 or later) (Kishnani, PS, Hwu, et al. 2006).

Of the 18 alglucosidase alfa treated patients, one died before the end of the initial 52-week study (at age 20 months) and one patient did not enrol in the extension study. A further three patients died during the extension phase (aged 30 months, 34 months and 41 months). In total, 13 (72%) completed the extension study, 7 from the 20mg/kg dose arm and 6 from the 40mg/kg dose arm. One additional death was reported after completion of the study (age 44 months). All treated patients were included in the analyses (ITT analysis). The median duration of treatment over the entire study was 121 weeks (range 60-150 weeks). One of the 62 (1.6%) patients in the historical control group was excluded from the survival analysis as the date of death was not available (Kishnani, P et al. 2008).

At baseline, the treatment group differed from the historical control group in that it contained a higher proportion of male patients (61.1% vs 45.2%), and had a different racial distribution. The mean age (± SD) at first symptoms in the study group was 1.6 ± 1.8 months (range 0.0-5.5 months), the age at diagnosis was 3.7 ± 2.2 months (range 0.2-6.8 months) and the age at first infusion was 4.6 ± 1.7 months. In the historical control group, the age at first symptoms (1.9 ± 1.8 months) and at diagnosis (3.6 ± 1.9 months) were reasonably similar to those in the treatment group. Due to the lack of details for the control group, it is not possible to compare the distribution of all potential confounders across the two groups.

A comparison between treated patients and the historical control group was performed for the primary outcome, the Kaplan-Meier estimation of the proportion of patients alive and free of invasive ventilation at 18 months of age, and for overall survival (with or without ventilator use) (Kishnani, PS et al. 2007). Similar analyses were performed at 24 months and 36 months of age during the extension study (Kishnani, P S et al. 2009) (see Results section below).

##### Nicolino et al (2009)

This was a multicentre, open-label, study of the effectiveness and safety of alglucosidase alfa in patients with infant onset Pompe disease over a minimum duration of 52 weeks. An untreated historical cohort was used as control for survival endpoints (Nicolino, M et al. 2009).

Eligibility criteria included documented onset of Pompe disease symptoms by 12 months of age, aged 6-36 months at enrolment, skin fibroblast GAA activity ≤2% of the normal mean, and abnormal left ventricular mass indices. Patients could be dependent on ventilator support or ventilator-free at enrolment. Exclusion criteria included clinical signs or symptoms of cardiac failure with ejection fraction <40%, major congenital anomaly, or intercurrent organic disease. These criteria are more inclusive than those in Kishnani et al (2007), resulting in a more heterogeneous study population who were at variable stages of disease progression when treatment was initiated (Nicolino, M et al. 2009).

The source group for the historical control was the same cohort of 168 patients with infant onset Pompe disease as that used in Kishnani et al (2007) (Kishnani, PS, Hwu, et al. 2006). This group was screened with additional inclusion and exclusion criteria to resemble the clinical characteristics of the treated study population.

All treated patients initially received IV alglucosidase alfa at a dose of 20mg/kg every two weeks. After a minimum of 26 weeks of treatment, the dose could be increased to 40mg/kg every two weeks if the patient’s clinical condition had significantly deteriorated relative to baseline. This occurred in 8 patients. The median duration of treatment was 120 weeks (range, 0.6-168 weeks).

Twenty-two patients were enrolled but one patient died before receiving any treatment. Four age-related protocol deviations were reported: three patients were older than 36 months of age (36.6, 37.3, and 43.1 months) and one was 3.7 months of age at initiation of treatment. The historical control group included 84 (50%) of the 168 patients in the source population. The racial distribution of the study population differed from the historical control group, with more Caucasians (71% vs 47%) and fewer Asians (14% vs 33%). In the study population, the mean ages (±SD) at first symptoms, at diagnosis and at first infusion were 3.9 ± 2.8 months (range 0.0-12.6 months), 8.8 ± 5.4 months (range 1.5-22.6 months), and 15.7 ± 11.0 months (range 3.7-43.1 months), respectively; in the historical control group the age at first symptoms and at diagnosis were 3.1 ± 2.8 months and 5.8 ± 3.8 months, respectively. Five of the 21 treated patients (24%) required invasive ventilation at baseline, and an additional 10% required non-invasive ventilation.

Effectiveness outcomes, for which a comparison with the historical control group was made, included survival and ventilation-free survival over the course of treatment (see Results section below).

##### Chen et al (2009)

Chen et al (2009) performed a single-centre study in which outcomes in patients with infant onset Pompe disease who received 20mg/kg alglucosidase alfa fortnightly were compared to a historical cohort of patients who died before the availability of enzyme replacement therapy (Chen et al. 2009). In addition, the effectiveness of alglucosidase alfa in asymptomatic infants with Pompe disease, identified by a national screening program, was compared to that in patients who were clinically symptomatic at the commencement of therapy.

The study included all patients diagnosed with infantile onset Pompe disease included in the patient database of a single Taiwanese hospital from January 1983 to March 2008. Diagnosis was confirmed by GAA enzyme activity <5% of the normal mean in mononuclear cells. The dosing regimen for alglucosidase alfa was not reported.

Fourteen patients were treated with alglucosidase alfa. These patients were subdivided into three groups: asymptomatic patients identified through a national screening program, (NBS group, N = 5), symptomatic patients who commenced ERT before 5 months of age (Clin-E, N = 4), and symptomatic patients who commenced treatment later (Clin-L, N = 5). The cut-off age of 5 months was based on the observation that systolic dysfunction appeared only after 5 months of age in untreated patients. The median age at diagnosis was 19 days, 3.0 months and 4.1 months in the NBS group, Clin-E group and the Clin-L group, respectively, while the corresponding median age at commencement of therapy was 0.87, 3.18 and 5.87 months, respectively. Twenty-six patients who died before the availability of ERT (December 2002) were included in the historical control group. No details are provided for the control group.

The median duration of treatment was 1.1 years (range 0.3-1.8 years) in the NBS group, 1.0 years (range 0.3-2.0 years) in the Clin-E group, and 4.2 years (range 1.2-5.2 years) in the Clin-L group.

The only outcome measures for which a comparison with the historical control group was made were survival and the requirement of ventilator support.

##### Chien et al (2009)

Chien et al (2009) was a single-centre study, to evaluate the impact of early treatment in infant onset Pompe disease patients diagnosed by a newborn screening program (Chien et al. 2009), and this appears to be a follow-up study to that reported by Chen et al (2009). Outcomes were compared with an untreated historical control group.

Diagnosis of infant onset Pompe disease was confirmed by GAA activity in whole blood and clinical evaluation. Patients with confirmed cardiomyopathy at diagnosis immediately commenced treatment with alglucosidase alfa; asymptomatic patients were treated when Pompe-associated symptoms appeared. Eleven patients from the same centre were used as an untreated control group. They had died before the availability of ERT and were included in the study of 168 patients from which both Kishnani et al (2007, 2009) and Nicolino et al (2009) sourced their historical cohorts(Kishnani, PS, Hwu, et al. 2006).

Alglucosidase alfa was administered by intravenous infusion at a dose of 20mg/kg every other week. All patients were followed until the end of the study, at which time they ranged in age from 18 months to 40 months.

Of 206,088 newborns screened, six had a confirmed diagnosis of infantile onset Pompe disease; five of these appear to be the NBS patients included in Chen et al (2009). The infants were aged 7 days to 40 days at diagnosis. In five patients with cardiomyopathy at diagnosis, treatment was initiated at ages ranging from 12 to 34 days, while the sixth commenced treatment at 14 months of age. GAA activity in fibroblasts ranged from 0.06 to 0.64 nmol/mg per hour (normal range >60nmol/mg per hour). No details are provided for the untreated control group but the inclusion criteria for the study from which they were sourced included documented GAA enzyme deficiency or GAA gene mutation(s), and onset of signs or symptoms by 12 months of age (Kishnani, PS, Hwu, et al. 2006).

Comparison with the untreated control group was performed for the endpoints of survival, survival free of ventilation, time to independent walking, and time to walking.

##### Prater et al (2012)

In the studies outlined above, only three patients were followed beyond 5 years of age (Nicolino, M et al. 2009). A non-comparative case-series reported on outcomes in long-term survivors with infantile onset Pompe disease (Prater et al. 2012). Patients were identified by a retrospective review of medical records from July 1999 to June 2011. The majority of the inclusion criteria for this study were similar to those in Kishnani et al 2007: onset of symptoms by ≤6 months of age, GAA activity in skin fibroblasts and/or muscle biopsy <1% of the control mean value, the presence of cardiomyopathy, absence of ventilator support before the start of ERT, and initiation of ERT ≤ 6 months by corrected gestational age. In addition, eligible patients must have survived to age ≥ 5 years at the most recent assessment (MRA) (Prater et al. 2012).

The source population for the study included a total of 17 patients with infantile onset Pompe disease treated with 20 - 40mg/kg alglucosidase alfa every two weeks, some of whom had participated in the original clinical studies of alglucosidase alfa. Eleven patients were cross-reactive immunological material (CRIM) positive, and 6 were CRIM negative. None of the CRIM negative patients met the inclusion criteria of survival to ≥ 5 years of age.

Of the 11 patients included in the study, all were CRIM positive. The median age at the study database lock was 8.0 years (range 5.4 to 12.0 years); while median age at diagnosis was 3.2 months (range -0.5 to 5.5 months; and at ERT initiation was 4.9 months (range 0.2 to 6.0 months).

None of the included studies reported whether patients were receiving concomitant immunosuppressive therapy.

#### Results of the included studies

##### Primary effectiveness: Survival

Kishnani et al (2007, 2009) reported that none of the 18 alglucosidase alfa treated patients included in the study died before the age of 18 months, and only one died before the age of 24 months. The Kaplan-Meier survival estimate at 24 months was 94.4% (95%CI: 83.9, 100), while the survival rate at 36 months was 72% (95%CI: 47.9, 96.0) (Kishnani, P S et al. 2009). At the end of the extension study, the median age of surviving patients was 35.7 months (range: 27.1 to 41.5 months). Only one of the 61 patients in the historical control group survived to the age of 18, 24 and 36 months (Kishnani, P S et al. 2009; Kishnani, PS et al. 2007).

The risk of death for treated patients compared to the untreated historical control group was analysed using a Cox proportional hazards analysis with model terms of age at diagnosis, age at symptom onset, and treatment as a time-varying covariate. Survival over the duration of the study was significantly improved in the treatment group compared with the untreated historical control group, with a hazard ratio (HR) for death of 0.05 (95%CI: 0.02, 0.14) (Kishnani, P S et al. 2009) (GRADE ⨁⨁⨀⨀). No difference in the effects of alglucosidase alfa on survival or ventilator-free survival was observed between the two alglucosidase alfa dose groups (GRADE ⨁⨁⨀⨀).

In the study reported by Nicolini et al (2009), six of the 21 patients treated with alglucosidase alfa died during the study. These patients ranged in age from 3.7 to 13.0 months at first infusion and from 7.7 to 27.1 months at time of death (Nicolino, M et al. 2009). Five patients died before 18 months of age and before Week 28 of treatment; the sixth patient died at 27 months of age, after 100 weeks of treatment. The median age of surviving patients at the end of the study was 47.8 months (range: 34.7 to 80.3 months). The Kaplan-Meier survival estimate at 104 weeks was 71.1% (95%CI: 51.6, 90.6%) for treated patients, compared with 26.3% (95%CI: 6.5, 46.1%) in the historical control group. A Cox proportional hazards analysis, similar to that performed in Kishnani et al (2009), resulted in an estimated hazard ratio for death of 0.21 (95%CI: 0.08, 0.52) for treated patients compared to the untreated historical control group (GRADE ⨁⨁⨀⨀).

Chen et al (2009) stated that survival was substantially improved with ERT, compared to the untreated control group (Chen et al. 2009). While the methods section states that analysis of time to event was performed with the Kaplan-Meier method, no statistical results were provided to support this statement. The study was insufficiently powered to detect any difference in survival between the three treatment sub-groups (GRADE ⨁⨀⨀⨀).

In a follow-up to Chen et al. (2009), Chien et al (2009) reports that all of the six patients identified by newborn screening survived until the end of the study, at which time their ages ranged from 15 to 40 months (Chien et al. 2009). Kaplan-Meier analysis indicated that survival in these patients was significantly improved compared to the untreated historical cohort (p = 0.001) (GRADE ⨁⨀⨀⨀).

The comparative results for survival are summarised in Table 62. Due to the non-randomised nature of these studies, the lack of details provided for the historical control groups (e.g. CRIM status), and the improvements in supportive therapy over time, there is considerable potential for confounding. In addition, due to the rarity of the disease, the sample size in each of the studies was small. While the reported magnitude of the treatment effect is uncertain and likely to vary between different populations, the large effect sizes, and the consistency of results across the studies, suggest that alglucosidase alfa significantly prolongs survival, compared to standard care, in patients with infant onset Pompe disease.

Table 62 Summary of the results for survival in patients receiving alglucosidase alfa

| Study | Population | Duration of treatment  Dose (fortnightly) | HR for deatha  (95% CI) | p-valueb |
| --- | --- | --- | --- | --- |
| Kishnani et al (2009)  N = 18  ⨁⨁⨀⨀ | Infants ≤26 weeks of age  Skin fibroblast activity <1% of normal mean  Treatment initiated at a relatively early stage  No ventilation at baseline  78% CRIM positive | Median 121 weeks  Range 60-150 weeks  20mg/kg (n=9)  40mg/kg (n=9) | 0.05 (0.02, 0.14) | NR |
| Nicolino et al (2009)  N = 21  ⨁⨁⨀⨀ | Onset of symptoms by 12 months  Aged 4-43 months at initiation of treatment.  Skin fibroblast activity ≤2% of normal mean  Could be dependent on ventilation | Median 120 weeks  Range 0.6-168 weeks  20mg/kg  n=8 receiving 40mg/kg after 26 weeks | 0.21 (0.08, 0.52) | 0.0009c |
| Chien et al (2009)  N = 6  ⨁⨀⨀⨀ | Patients diagnosed by newborn screening program  Early initiation of treatmentc  100% CRIM positive | Range 14-33 months  20mg/kg | NR | 0.001c |

CI = confidence interval; CRIM = cross-reactive immunological material; GRADE = grading of recommendations assessment, development and evaluation; HR = hazard ratio; NR = not reported

a Cox proportional hazards analysis

b Kaplan-Meier analysis.

c Treatment was initiated within 7 days of diagnosis if evidence of cardiomyopathy was present; asymptomatic patients commenced treatment when Pompe-associated symptoms first developed

##### Conclusions

Three historic control studies provided low quality, but consistent, evidence that alglucosidase alfa prolongs survival in infants with infantile onset Pompe disease, across a range of populations varying in respect to the severity and stage of development of the disease (GRADE ⨁⨁⨀⨀).

The effectiveness of alglucosidase alfa on survival beyond the limited duration of these studies has not been assessed (see “Long-term outcomes in patients surviving beyond infancy”).

##### Secondary effectiveness outcomes

##### Ventilation free survival

Kishnani et al (2007, 2009), Nicolino et al (2009) and Chien et al (2009) all reported ventilation-free survival in patients on ERT compared to a historical untreated control group.

Kishnani et al (2007) reported a Kaplan-Meier invasive ventilation-free survival rate of 88.9% (95%CI: 74.4%, 100%) at the age of 18months; this fell to 66.7% (95%CI: 44.9%, 88.4%) at age 24 months and 49.4% (95%CI: 26.0, 72.8) at 36 months of age (Kishnani, P S et al. 2009). In Nicolino et al (2009) 44% (7/16) of those invasive-ventilation free at baseline remained so at the end of the study (median treatment duration of 120 weeks).

The results of the comparison of treated patients versus the historical control group for each of these studies are summarised in Table 63. Both Kishnani et al (2009) and Nicolino et al (2009) reported that survival free of invasive ventilation was significantly prolonged in treated patients compared to the untreated control group (Kishnani, P S et al. 2009; Nicolino, M et al. 2009). In contrast to Kishnani (2009) and Chien et al (2009), Nicolino et al (2009) failed to show any significant difference between groups for the outcome of survival free of any ventilation. This may have been due to differences between the study populations; Nicolino et al (2009) was the only study which enrolled patients who were already dependent on ventilation at baseline (33% of patients).

Table 63 Summary of results for ventilation-free survival in patients receiving alglucosidase alfa

| **Outcome** | **GRADE** | **N** | **Duration of treatment**  **Median (range)** | **HRa**  **(95% CI)** | **p-valueb** |
| --- | --- | --- | --- | --- | --- |
| **Invasive ventilation or death** |  |  |  |  |  |
| Kishnani et al (2009) | ⨁⨁⨀⨀ | 18 | 121 weeks (60-150) | 0.09 (0.04, 0.22) | NR |
| Nicolino et al (2009) | ⨁⨀⨀⨀ | 21 | 120 weeks (0.6-168) | 0.42 (0.20, 0.88) | 0.02 |
| **Any ventilation or death** |  |  |  |  |  |
| Kishnani et al (2009) | ⨁⨁⨀⨀ | 18 | 121 weeks (60-150) | 0.13 (0.06, 0.29) | NR |
| Nicolino et al (2009) | ⨁⨀⨀⨀ | 21 | 120 weeks (0.6-168) | 0.53 (0.25, 1.15) | 0.11 |
| Chien et a l (2009) | ⨁⨀⨀⨀ | 6 | (14-33 months) | NR | 0.008 |

CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation; HR = hazard ratio; NR = not reported

a Cox proportional hazards analysis

b Kaplan-Meier analysis

##### Conclusions

There is low quality evidence that alglucosidase alfa prolongs invasive ventilation-free survival in patients with infantile onset Pompe disease (GRADE ⨁⨁⨀⨀).

There is low quality evidence that alglucosidase alfa may prolong survival free of any assisted ventilation in infantile onset Pompe patients in whom treatment is commenced at an early stage of the disease, prior to requiring any assisted ventilation (GRADE ⨁⨁⨀⨀).

##### Time to independent walking/walking

Chien et al (2009) reported earlier independent walking in the newborn screening group compared to the untreated historical cohort (p = 0.009) (GRADE ⨁⨀⨀⨀), while there was no statistical difference in time to walking between the groups (p = 0.22) (Chien et al. 2009).

##### Long-term outcomes in patients surviving beyond infancy

Prater et al (2012) reported that all of the 11 CRIM positive patients receiving 20 – 40 mg/kg every 2 weeks who, having survived to 5 years of age, were included in the study, remained alive and ventilator-free at the last study assessment at a median age of 8.0 years (range 5.4 to 12.0 years)(Prater et al. 2012). Three assessments of cardiovascular function were conducted. The baseline cardiomegaly in all 11 patients resolved approximately 5 months after the start of ERT; at all subsequent time points, median left ventricular mass index (LVMI) values remained within control limits over a median duration of treatment 69 months (range 28-110 months). Seven (64%) of the 11 patients were independently ambulatory without assistive devices; three required walkers on either a full-time or part-time basis. Nine patients had some degree of hearing loss: seven used hearing aids and three had tympanostomy tubes/grommets. The majority (10/11) had motor speech deficits (hypernasal speech). Seven patients had an exclusively oral mode of nutritional intake, while four used a combination of oral and gastrostomy tube feeds; five had dysphagia with aspiration on fluoroscopic swallow examination; and three had gastroesophageal reflux disease (Prater et al. 2012).

##### Effect of CRIM status on response to therapy

There is evidence to suggest that the presence or absence of cross-reactive immunologic material (CRIM) may affect response to ERT. A retrospective analysis of data from clinical studies, including 11 CRIM-negative patients and 21 CRIM-positive patients, found that CRIM-negative patients, after an initial period of improvement, subsequently showed an attenuated response to alglucosidase alfa, compared to CRIM-positive patients, in all outcome measures including survival and ventilator-free survival (Kishnani, PS et al. 2010). The clinical decline in CRIM-negative patients was observed to coincide with the development of high sustained anti-recombinant human GAA (rhGAA, Myozyme®) antibody titres.

Data from clinical studies suggests that approximately 20% of cases of infantile onset Pompe disease are CRIM-negative (Kishnani, PS et al. 2010). CRIM-negative patients have two deleterious GAA gene mutations which result in complete absence of native GAA enzyme and, therefore, lack of immunological exposure to the GAA protein. It is suggested that these patients are not immune tolerant to GAA and mount an antibody response to the enzyme when given as ERT (Banugaria et al. 2011). In contrast, most CRIM-positive patients produce some native enzyme which establishes some degree of immune tolerance, with antibody titres generally remaining relatively low or declining from modest levels with continued exposure to alglucosidase alfa.

Further studies have shown that the minority of CRIM-positive patients who develop high sustained antibody titres also have poor clinical outcomes (Banugaria et al. 2011). Similar to the observations in CRIM-negative patients, CRIM-positive patients with high antibody titres showed a period of improvement in the first 6 months of alglucosidase alfa treatment, after which they declined across all measures. As for CRIM-negative patients, antibody titres persisted above 1:51,200 at or beyond 6 months post-ERT initiation, and correlated with the observed clinical decline.

As a result of these findings, a number of small studies have assessed the use of immune tolerance induction (ITI) regimens aimed at increasing ERT effectiveness in CRIM-negative patients (Banugaria et al. 2013; Elder et al. 2013; Messinger et al. 2012).

In Messinger et al (2012), two CRIM-negative patients with pre-existing anti-GAA antibodies were treated therapeutically with rituximab, methotrexate, and gammaglobulins, while two additional CRIM-negative patients were treated prophylactically with a course of rituximab and methotrexate at initiation of ERT. At the end of the study, all four patients were immune tolerant to rhGAA, were off immune therapy, had responded to ERT, and were continuing to receive treatment at ages ranging from 18 to 56 months (Messinger et al. 2012).

Similarly, Banugaria et al (2013) used a combination of rituximab, methotrexate and immunoglobulin in seven CRIM-negative patients. At baseline, three patients were invasively ventilated, two required supplementary oxygen, one required bi-level positive airway pressure, and one required no respiratory support. Four patients remained antibody-free, one died from respiratory failure and two required another course of the ITI regimen. After a median duration of treatment of 79 weeks (range48-101 weeks), two of the six surviving patients required no respiratory support, three required positive airway pressure only at night, and one patient who required invasive ventilation at baseline was able to come off the ventilator for 10-12 hours each day(Banugaria et al. 2013).

A further four subjects, three of whom were CRIM-negative, received rituximab and sirolimus both before and during ERT (Elder et al. 2013). After 17-36 months of treatment, all patients lacked antibodies to GAA. Despite this, two of the CRIM-negative patients progressed to requiring invasive ventilation, while the other, who required assisted ventilation at diagnosis, subsequently became ventilator-independent through 22 months of ERT. In contrast, the CRIM-positive patient never required invasive ventilation and had no evidence of respiratory deterioration at the end of study after 17 months of ERT (Elder et al. 2013).

##### Summary of comparative effectiveness

There is low quality evidence that alglucosidase alfa prolongs overall survival improves cardiorespiratory function (invasive ventilator-free survival) in patients with infantile onset Pompe disease, compared to standard care. Alglucosidase alfa may also improve survival free of any ventilator use in patients in whom treatment is initiated at an early stage of the disease. Due to the considerable potential for confounding, the magnitude of the treatment effect is uncertain, and is likely to vary across different populations, depending on the average severity of the disease (including the proportion of CRIM negative patients) and the stage of progression at commencement of ERT.

There are minimal data on patients who survive to ≥5 years of age. One small case series reported the outcomes in 11 patients up to a median age of 8.0 years (range 5.4 to 12.0 years) (Prater et al. 2013). The median LVMI values remained within control limits over a median duration of treatment of 69 months and 7/11 patients were able to walk unassisted. The majority of patients had hearing and speech deficits, and 5/11 had dysphagia with aspiration.

#### Safety of alglucosidase alfa in the treatment of infantile onset Pompe disease

##### Comparative safety of alglucosidase alfa

There are no data on the comparative safety of alglucosidase alfa versus standard palliative care in patients with infantile onset Pompe disease.

##### Extended assessment of harms

The summary of safety provided in this section is based on Periodic Safety Update Reports (PSURs) presented in Submissions to the Post Market Review (PMR) of the Life Savings Drugs program (LSDP).

##### Serious adverse events

The most common serious treatment-emergent adverse events observed in the clinical studies were pneumonia, respiratory failure, respiratory distress, catheter related infection, respiratory syncytial virus infection, gastroenteritis, and fever. The most common treatment-emergent adverse events were fever, diarrhoea, rash, vomiting cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation (Myozyme PI)(Therapeutic Goods Administration 2012a).

In the most recent PSUR for alglucosidase alfa (Myozyme®), the commercial patient exposure for the period 29 September 2010 to 28 September 2011 was estimated at 1,515 patient-years (Genzyme Australasia Pty Ltd 2011). Serious adverse events (AEs) listed during this period are summarised in Table 64. Alglucosidase alfa is indicated for all treatment of patients with the forms of Pompe disease; the data are not specifically for the infantile onset form of the disease.

Table 64 Summary of serious listed adverse events over the period 29 September 2010 to 28 September 2011

| Body system | Preferred term | Number of serious adverse events |
| --- | --- | --- |
| Cardiac disorders | Bradycardia | 3 |
|  | Cardiac arrest | 2 |
|  | Cardio-respiratory arrest | 1 |
|  | Cardiopulmonary failure | 1 |
|  | Cyanosis | 5 |
|  | Tachycardia | 10 |
|  | Subtotal | 22 |
| Gastrointestinal disorders | Abdominal pain upper | 1 |
|  | Lip oedema | 1 |
|  | Nausea | 2 |
|  | Oedema mouth | 1 |
|  | Swollen tongue | 2 |
|  | Vomiting | 9 |
|  | Subtotal | 16 |
| General disorders and administration site conditions | Chills | 5 |
|  | Fatigue | 1 |
|  | Feeling hot | 1 |
|  | Pyrexia | 10 |
|  | Subtotal | 17 |
| Immune system disorders | Anaphylactic reaction | 10 |
|  | Hypersensitivity | 2 |
|  | Subtotal | 12 |
| Investigations | Blood pressure decreased | 4 |
|  | Blood pressure increased | 1 |
|  | Body temperature increased | 1 |
|  | Heart rate increased | 2 |
|  | Oxygen saturation decreased | 6 |
|  | Subtotal | 14 |
| Musculoskeletal and connective tissue disorders | Arthropathy | 1 |
|  | Myalgia | 1 |
|  | Subtotal | 2 |
| Nervous system disorders | Dizziness | 1 |
|  | Headache | 1 |
|  | Subtotal | 2 |
| Psychiatric disorders | Agitation | 1 |
|  | Subtotal | 1 |
| Respiratory, thoracic and mediastinal disorders | Apnoea | 1 |
|  | Bronchospasm | 3 |
|  | Cough | 1 |
|  | Dyspnoea | 8 |
|  | Hypoxia | 4 |
|  | Laryngeal oedema | 1 |
|  | Respiratory distress | 5 |
|  | Tachypnoea | 4 |
|  | Wheezing | 2 |
|  | Subtotal | 29 |
| Skin and subcutaneous tissue disorders | Erythema | 2 |
|  | Hyperhidrosis | 1 |
|  | Pruritis | 1 |
|  | Rash | 6 |
|  | Rash generalised | 2 |
|  | Urticaria | 9 |
|  | Subtotal | 21 |
| Vascular disorders | Flushing | 2 |
|  | Hypertension | 2 |
|  | Hypotension | 5 |
|  | Pallor | 1 |
|  | Subtotal | 10 |
| Total |  | 146 |

Source: Myozyme PSUR, 29 September 2010 to 28 September 2011(Genzyme Australasia Pty Ltd 2011).

##### Adverse drug reactions

The most common adverse drug reactions (ADRs) in the two main infantile onset clinical studies were infusion associated reactions (IARs) (Myozyme PI)(Therapeutic Goods Administration 2012a).

Kishnani et al (2009) reported that 11 (61%) of the 18 patients experienced 224 infusion associated reactions (IARs) over the course of the study (median duration of treatment 121 weeks; range 60-150 weeks) (Kishnani, P S et al. 2009). IARs were defined as any treatment related AE that occurred during an infusion or within 2 hours after the infusion. All IARs were mild or moderate in intensity; no severe reactions occurred. The most common IARs were urticarial (47 events, fever (27 events), and decreased oxygen saturation (24 events. IARs were managed by slowing or interrupting infusions, and all patients recovered without sequelae. More IARs were reported in the 40mg/kg dose group than in the 20mg/kg dose group.

In Nicolino et al (2009), 11 (52%) of the 21 patients experienced 42 IARs, defined as AEs occurring on the day of infusion and assessed by the investigator as being related to treatment (Nicolino, M et al. 2009). The most common IARs were skin and subcutaneous disorders (13 events), vascular disorders (10 events), and oxygen saturation, blood pressure increase, heart rate increase or respiratory rate increase (7 events). Reactions were managed by slowing or temporarily interrupting the infusion and administrating symptomatic treatment. All patients recovered without sequelae. Six of the patients died during the treatment period; none of the deaths were attributed to treatment.

Other ADRs reported in the clinical trials that were not assessed as IARs and occurred in more than one patient included increased blood creatinine phosphokinase MB. All ADRs are summarised in Table 64.

Due to the non-blinded nature of the studies, there is potential for bias in the reporting of treatment-related AEs.

Table 65 Summary of ADRs– Infantile onset pooled population (Hillmen et al 2007, Nicolino et al 2009)

| **System Organ Class**  **Preferred terma** | **Number of patientsb (N = 39)**  **n (%)** | **Number of AEs**  **N** |
| --- | --- | --- |
| Any adverse event | 24 (61.5) | 222 |
| Skin and subcutaneous tissue disorders | 12 (30.8) | 65 |
| Urticaria | 6 (15.4) | 23 |
| Rash | 5 (12.8) | 11 |
| Rash maculopapular | 3 (7.7) | 5 |
| Rash macular | 2 (5.1) | 13 |
| Rash popular | 2 (5.1) | 3 |
| Erythema | 2 (5.1) | 2 |
| Pruritis | 2 (5.1) | 2 |
| Investigations | 13 (33.3) | 38 |
| Oxygen saturation decreased | 7 (17.9) | 21 |
| Blood creatinine phosphokinase MB increased | 2 (5.1) | 2 |
| Blood pressure increased | 2 (5.1) | 2 |
| General disorders and administration site conditions | 11 (28.2) | 33 |
| Pyrexia | 10 (25.6) | 28 |
| Rigors | 2 (5.1) | 3 |
| Respiratory, thoracic and mediastinal disorders | 8 (20.5) | 27 |
| Cough | 5 (12.8) | 17 |
| Tachypnoea | 5 (12.8) | 8 |
| Vascular disorders | 8 (20.5) | 20 |
| Flushing | 5 (12.8) | 11 |
| Hypertension | 3 (7.7) | 4 |
| Pallor | 2 (5.1) | 3 |
| Gastrointestinal disorders | 4 (10.3) | 17 |
| Vomiting | 3 (7.7) | 8 |
| Retching | 2 (5.1) | 7 |
| Cardiac disorders | 4 (10.3) | 10 |
| Tachycardia | 4 (10.3) | 7 |
| Cyanosis | 2 (5.1) | 3 |
| Psychiatric disorders | 5 (12.8) | 8 |
| Agitation | 2 (5.1) | 4 |
| Irritability | 2 (5.1) | 2 |
| Nervous system disorders | 2 (5.1) | 3 |
| Tremor | 2 (5.1) | 3 |
| Injury, poisoning and procedural complications | 1 (2.6) | 1 |

AE = adverse event

a Number of events by preferred term are only listed for events occurring in more than one patient

b Percentages are based on the total number of patients treated in the studies.

Source: Myozyme PI(Therapeutic Goods Administration 2012a)

#### Extended assessment of safety

Alglucosidase alfa is currently authorised in a total of 53 countries, and has been commercially available in Europe since 29 March 2006 and in the US since 28 April 2006. The cumulative commercial exposure since 2006 is estimated at 4,845 patient-years, while the total cumulative exposure (commercial and clinical) is estimated at 5,599 patient-years (Myozyme PSUR)(Genzyme Australasia Pty Ltd 2011).

The only listed adverse event of special interest for alglucosidase alfa is anaphylaxis and significant hypersensitivity reactions (Myozyme PSUR, 29 September 2010 to 28 September 2011). In addition, the following precautions are included in the TGA-approved Product Information (PI): risk of cardiac arrhythmia and sudden cardiac death during general anaesthesia for central venous catheter placement; risk of acute cardiorespiratory failure; infusion associated reactions (IARs), and immunogenicity (Therapeutic Goods Administration 2012a).

##### Anaphylaxis and significant hypersensitivity reactions

Serious hypersensitivity reactions, including life-threatening anaphylaxis reactions, have been observed in infantile and late-onset Pompe patients during alglucosidase alfa treatment, some of which were IgE-mediated. A small number of patients (<1%) in clinical trials and in the commercial setting developed anaphylactic shock and/or cardiac arrest during infusion that required life-support measures (Therapeutic Goods Administration 2012a).

In clinical trials and expanded access programs with alglucosidase alfa, 38 out of 380 (14%) patients treated with alglucosidase alfa developed infusion reactions that involved at least 2 of 3 body systems, cutaneous, respiratory or cardiovascular systems. These events included cardiovascular events (hypotension, cyanosis, hypertension, tachycardia, ventricular extrasystoles, bradycardia, pallor, flushing, nodal rhythm, peripheral coldness), respiratory events (tachypnoea, wheezing/bronchospasm, rales, throat tightness, hypoxia, dyspnoea, cough, respiratory tract irritation, oxygen saturation decrease), and cutaneous events (angioneurotic oedema, urticarial, rash, erythema, periorbital oedema, pruritis, hyperhidrosis, cold sweat, livedo reticularis). Of the 38 patients with infusion reactions, 8 patients experienced severe or significant hypersensitivity reactions (Myozyme PI)(Therapeutic Goods Administration 2012a).

Additional infusion associated reactions reported from worldwide post-marketing sources after marketing approval included: cardiac arrest, bradycardia, angioneurotic oedema, pharyngeal oedema, peripheral oedema, chest pain, chest discomfort, dyspnoea, muscle spasm, fatigue and conjunctivitis (Therapeutic Goods Administration 2012a).

##### Risk of cardiac arrhythmia and sudden cardiac death during general anaesthesia for central venous catheter placement

The Myozyme® PI states that cardiac arrhythmia, including ventricular fibrillation, ventricular tachycardia and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been observed in infantile onset Pompe patients with cardiac hypertrophy, associated with the use of general anaesthesia for the placement of a central venous catheter intended for a Myozyme infusion. Caution has been recommended when administering general anaesthetic for the placement of a central venous catheter in infantile onset Pompe disease patients with cardiac hypertrophy (Therapeutic Goods Administration 2012a).

##### Risk of acute cardiorespiratory failure

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed after infusion with Myozyme in one patient with infantile onset Pompe disease and underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of Myozyme (Therapeutic Goods Administration 2012a).

##### Infusion associated reactions (IARs)

Severe infusion reactions reported in more than one patient in clinical studies and in the expanded access program include: pyrexia, decreased oxygen saturation, tachycardia, cyanosis, and hypotension. Other infusion reactions reported in more than one patient include rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnoea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritis, retching, rigors, tremor, hypotension, bronchospasm, erythema, face oedema, feeling hot, headache, hyperhidrosis, increased lacrimation, livedo reticularis, nausea, periorbital oedema, restlessness, and wheezing (Myozyme PI) (Therapeutic Goods Administration 2012a).

##### Immunogenicity

In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. There does not appear to be a correlation between the onset of IARs and the time of antibody formation. There is evidence to suggest that patients developing sustained titres of ≥ 12,800 of anti-alglucosidase alfa antibodies may have a poorer clinical response to treatment, or may lose motor function as antibody titres increase (Myozyme PI). A small number of patients tested positive for alglucosidase alfa-specific IgE antibodies. The effect of antibody development on the long-term efficacy of alglucosidase alfa is not fully understood (Myozyme PI) (Therapeutic Goods Administration 2012a).

In clinical studies, infusion reactions appear to be more common in antibody-positive patients: 8 out of 15 patients with high antibody titres experienced infusion reactions, whereas none of three antibody-negative patients experienced infusion reactions.

Nephrotic syndrome was observed in a few Pompe patients treated with alglucosidase alfa who had high IgG antibody titres (≥102,400). In these patients, renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption (Myozyme PI) (Therapeutic Goods Administration 2012a).

#### Australian data registry information

The Infantile Onset Pompe Disease data available in the Patient Summary sheets maintained by the Department of Health were analysed and provided to the LSDP Reference Group. The data has been redacted in this report to protect the privacy of patients.

''''''''' ''''''''''''''''' '''''''''' '''''''''''''''' ''''''''''''''''''''' ''''''''''''''''''''''' '''''' '''''''''''''' ''''''' '''''''''' ''''' '''''''''''''''''' '''''''''''''' ''' '''''''''''''''' ''''' '''''''''' ''''''''''' '''''''''''''' ''''''''''''''' ''''' ''''''''''''''''''' ''''''''''''''' '''''' ''''''''' '''''''''''''' '''''''' '''''''''' '''''' ''''''''' ''''''' ''' '''''''''''''' ''''''' ''''''''''''''''''' ''''''' ''''''' ''''''''' '''''''''''''''' '''''''''' '''''''''''' ''''''''''''' '''''''''''' '''''' ''''''' ''''' ''''''''''''''' '''' '''''''' '''''''' '''''''''''''' '''''''''''''''' ''''''''''''''''''''''' ''''''' '''''' ''''''''''''''' ''''' ''''''''''' '''''''' ''''''''''''''' ''''''' '''''''''''''''' '''''''''''' ''' ''''''''' ''''''''' '''''''''''''''''''''' '''''''' '''''''''''''' '''' '''''' '''''''' '''''''''''''' ''''''' ''''''''' ''''' ''''' '''''''''''''' '''' '''''''' ''' ''''''''''''''' ''''''''' '''''''''''''''''' '''' ''''''''''''''''''''' '''''''''''' '''''''' Two year survival in an untreated population as estimated in the systematic review was 26.3% (Table 62, page 118).

The PBAC minutes indicated that treatment effectiveness was assessed in terms of survival and dependence on ventilator support. The current systematic review also identified low quality evidence for a reduced time to walking. '''''''''''' '''''''''''''''''' '''''''''''''' ''''' '''''''''''''''''''' '''''''''' '''''' '''''''' '''' '''''' '''''''''''''' ''''''''''''''''''' ''''''''''''

There are insufficient numbers of patients to conclude whether any benefit has been derived from alglucosidase alfa, nor to quantify the extent of such benefit. However, given the duration of survival of the patients receiving alglucosidase alfa through the LSDP, it is likely that some benefit, and perhaps substantial benefit, has been observed.

The clinical studies assessed alglucosidase alfa at doses of 20 mg/kg/2 weeks or 40 mg/kg/2 weeks (Chien et al. 2009; Kishnani, PS, Nicolino, et al. 2006; Nicolino, M et al. 2009). One study did not report dosing regimens (Chen et al. 2009). The TGA recommended dosage regimen for alglucosidase alfa is 20mg/kg of body weight administered once every 2 weeks (Therapeutic Goods Administration 2012a). ''''' ''''''' '''''''''' '''''''''''' ''''''''''''''' ''''''''''' '''''''' ''''' ''''''''' '''''''''''''' ''''''''''''''' ''' ''''''''''''' '''''''''' '''''''' ''''''''''''''''''''''''''''' ''''''''' '''''''' ''''' ''''''''' ''''''''''''''''''' '''''''' '''' '''''''''''''''''''''' '''''''''''' '''''''

Table 66 Doses of alglucosidase alfa received by Australian patients with infantile onset Pompe disease

| **Characteristics** | ''''''''''''' ''' | ''''''''''''' ''' | ''''''''''''''' ''' | ''''''''''''''' ''' |
| --- | --- | --- | --- | --- |
| **Age at start of treatment** | ''' '''''''''''''''' | ''''' '''''''''''''' | '''' ''''''''''''''''' | ''' ''''''''''''''' |
| **Age at most recent review** | ''''' ''''''''''' | ''' '''''''''''' | '' | '''''' '''''''''''''''' |
| **Age at death** | '' | '' | '''' ''''''''''''''' | '' |
| **Dose at most recent review** | '''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''' |
| **Weight at most recent review** | ''''''''''''''' | ''''''''''''' | ''''''''''''''' | ''''''' |
| **Dose at most recent review** | '''''''''''''''''''''''''''''''''''''''' | '''''''' ''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''''''''''''' | '''''''''''''''''''''''''''''''''''' |
| **Predicted dose**  **(at 20mg/kg)** | ''''''''''''' '' '''''''''''''''''''''' | ''''''''''''''' | ''''''''''''' | ''''''''''''''' |

'''''''''' '''''''''''''''''''' ''''''' ''''''''''''''''''''' ''' ''''''''' ''''' ''''''''''''''''''' '''''' ''''''''''''''''''' ''' '''''''''' ''''' '''''''''''''' ''''''' ''''''''''''''''' ''''''''''' '''''''''' ''''''''''''' ''''' ''''''' ''''''''''''''' ''' ''''''''''''''''''''''''''

#### Impact of findings

No new trials were identified comparing alglucosidase alfa with placebo in patients with infantile onset Pompe disease. However, two new publications were identified, that provided longer term data from those treated with alglucosidase alfa. Survival rates were considerably higher than what was documented prior to alglucosidase alfa being available, supporting the decision to fund the drug for patients with infantile onset Pompe disease.

There were only data available on '''''''' patients with infantile onset Pompe disease who have received treatment through the LSDP. '''''''' ''''''''''''''' '''''''' ''''''''' ''' '''''''''''''' ''''' ''''''''''''''''''' '''''''''' '''''' ''''''''''''''''' '''''''' '''''''''' ''' ''''''''''''''''' ''''''''' ''''''''' '''' ''''''''''' ''''''''''''''''' ''''' ''''''''' ''''' '''''''''''''' ''' '''''''''' '''''''' ''''' '''''''''''' Given the poor survival of untreated patients with infantile onset Pompe disease, it is likely that these patients have benefited from alglucosidase alfa.

Table 67 Studies included assessing drug to treat infantile onset Pompe disease

| Drug | Results | References | Evidence not included in submission to the PBAC |
| --- | --- | --- | --- |
| Alglucosidase alfa | 4 historical control studies | Kishnani et al (2007), Kishnani et al (2009)  Chen et al (2009)  Chien et al (2009)  Nicolino et al (2009) | Kishnani et al (2009) was extension study of Kishnani et al (2007). Provided longer term data. Survival estimate at 24 months was 94.4% (95%CI 83.9, 100); at 36 months was 72% (95%CI 47.9, 96.0). Median age of surviving patients was 35.7 months (range 27.1 to 41.5 months).  Nicolino et al (2009) reported that median survival at 104 weeks was 71.1% (95%CI 51.5, 90.6) in treated group, 26.3% (95%CI 6.5, 46.1%) in untreated group. |

### Alglucosidase alfa to treat juvenile onset Pompe disease

**Is alglucosidase alfa safe and effective compared to standard palliative care with/without placebo for treating patients with Juvenile late-Onset Pompe Disease?**

Submissions made to the PBAC for consideration of alglucosidase alfa for late-onset Pompe disease have combined the data from juvenile-late onset and adult-onset patients. No separate submission has been made for juvenile-late onset Pompe disease.

There were no data on the comparative safety of alglucosidase alfa versus standard palliative care in these patients.

Identified case reports suggest that respiratory function may improve, or be maintained in the early months of ERT, but that after 2 or more years respiratory function declines (GRADE ⨁⨀⨀⨀).

Case reports also suggest that the need for assisted ventilation may be decreased with the use of ERT. Improvements may occur in gastrointestinal function and fatigue with the use of ERT (GRADE ⨁⨀⨀⨀).

Poor quality but consistent evidence suggests that muscle functioning improves with alglucosidase alfa, with the largest benefits seen in the first 6 to 12 months. Those patients who were treated at a younger age, and had a less severe baseline status, responded to a larger degree than patients who were treated as adults, and had severe disease status at baseline (GRADE ⨁⨀⨀⨀).

The evidence from case reports is low level and unreliable, and possibly subject to publication bias.

#### Background

##### Juvenile late onset Pompe disease

Patients diagnosed with Pompe disease at an age older than 2 years tend to have a varied amount of GAA activity, and considerable clinical heterogeneity. This late-onset form of Pompe disease can fall into the category of either juvenile or adult, depending on the age at diagnosis and has an incidence of around 1 in 57 000, with variations depending on ethnicity (Bembi et al. 2010). Categorisation may be confused by the patient’s age at onset of symptoms, which may occur years after diagnosis if the patient was identified through genetic characterisation, or well before diagnosis, if symptoms were not associated with the disease in their early stages. Additionally, in the literature the categorisation of juvenile late- onset Pompe disease (JOPD) varies in starting age from 1 to 2 years, with upper limits of 16 to 20 years old. This review has used the criteria of onset of symptoms between the ages of 2 and 18 years for JOPD. Further criteria for systematic review of the effects of ERT in the treatment of JOPD can be seen in Table 69.

JOPD has been found to have somewhat milder symptoms than the classic infantile form of Pompe disease, and disease progression tends to be slower. Limited evidence suggests that the earlier the age at which symptoms of Pompe occur, the worse the prognosis is likely to be and hence adult onset disease tends to be less severe again than JOPD. A collection of 225 case reports from 19 countries was compiled by Winkel et al (2005) to determine the natural history of Pompe disease in patients who did not show the classic infantile phenotype (Table 68).

Table 68 Natural history survival data for patients with non-classic Pompe’s disease (Winkel, LP et al. 2005)

| Age at onset | 0 – 1 years (n = 32) | 1 – 6 years (n = 24) | 6 – 18 years (n = 30) | 18 years or older (n = 139) |
| --- | --- | --- | --- | --- |
| Mean age at diagnosis (range) | 3.8 years  (0.1 – 17) | 7 years  (1.6 – 32) | 17 years  (6 – 61) | 43 years  (18 – 71) |
| Mean age at death (range) | 6.1 years (n = 12)  (0.9 – 24) | 22.6 years (n = 4)  (6.5 – 28) | 25.1 years (n = 5)  (15 – 40.5) | 44.9 years (n = 15)  (25 – 66) |

Likewise, average age at first ventilation requirement and age of wheelchair use was positively associated with age at onset (Winkel, LP et al. 2005). Symptoms which are found in classic infantile-onset Pompe disease were more likely to occur in patients presenting with symptoms at a younger age. However, within each age group, there was wide variation in the course of disease (Winkel, LP et al. 2005).

##### Pre-enzyme replacement therapy

Prior to alglucosidase alfa becoming available, there was no treatment for patients with juvenile late-onset Pompe disease, so their management involved supportive care and palliation (including intensive respiratory support, cardiac care, dietary therapy and rehabilitative services).

Enzyme replacement therapy

Alglucosidase alfa has been subsidised for patients with juvenile late-onset Pompe disease through the LSDP since December 2014.

#### Systematic review

The systematic review for this section searched for data on juvenile onset patients of any age, including those currently of adult age. Where studies included both adult and juvenile onset patients, an attempt was made to separate data for JOPD. One RCT (Van Der Ploeg et al. 2010) and one SR (Toscano & Schoser 2013) were identified, both of which studied populations including juvenile late-onset and adult onset Pompe disease, however the data were not separated, nor were the proportions of each population published. This “higher level” evidence was therefore not included here. Lower level evidence (case series and case reports) have been used to provide evidence for the effectiveness of ERT (alglucosidase alfa) for JOPD. There are no comparator groups for studies of this level of evidence.

Table 69 outlines the criteria for selecting studies that assess the safety and effectiveness of alglucosidase alfa for the treatment of patients with JOPD.

Table 69 Criteria for selecting studies to assess the safety and effectiveness of alglucosidase alfa

| Characteristic | Inclusion criteria |
| --- | --- |
| Study design | Randomised trials, pseudo-randomised trials, cohort studies and historical control studies. In the absence of comparative evidence, case series and case reports were included. |
| Population | Patients with Juvenile Onset Pompe Disease (glycogen storage disease type II, or acid maltase deficiency; presentation when 2 to 18 years old) |
| Intervention | Alglucosidase alfa (Myozyme®)  Subgroup analysis: by dose (e.g. doses consistent with TGA listing, as well as experimental dosing regimens); by whether immunosuppressives (e.g. infliximab, prednisolone) were co-administered |
| Comparator | Standard palliative care (including intensive respiratory support, cardiac care, dietary therapy and rehabilitative services) with/without placebo |
| Outcomes | *Safety:* adverse events related to treatment – for example, urticaria, pyrexia, anaphylactic shock; and compliance with treatment (i.e. treatment withdrawal or suboptimal dosing)  *Primary effectiveness:* survival  *Secondary effectiveness:* quality of life; cardiorespiratory functioning (ventilator free survival, supplementary oxygen, apnoea/hypopnoea, sleep apnoea, CPAP requirements: nocturnal or all day); cardiovascular function (hypertension, left ventricular measures, exercise capacity, heart failure); gross motor functioning; swallowing; audiology outcomes; neurological outcomes. |
| Language | Studies in languages other than English would only have been translated if they appeared from the abstract to represent a higher level of evidence than that available in English. |
| Research question | Is alglucosidase alfa safe and effective compared to standard palliative care with/without placebo for treating patients with Juvenile Onset Pompe Disease? |

TGA = Therapeutic Goods Administration; CPAP = continuous positive airway pressure

#### Results of the literature search

The literature search identified one case series (Bembi et al. 2010) and 15 case report studies which provided separate data for JOPD patients (Bernstein et al. 2010; Deroma et al. 2014; Fecarotta et al. 2013; Furusawa et al. 2014; Furusawa et al. 2012; Ishigaki et al. 2012; Kobayashi et al. 2010; Korpela et al. 2009; Merk et al. 2009; Orlikowski et al. 2011; Papadimas et al. 2011; Sugai et al. 2010; van Capelle et al. 2010; van Capelle et al. 2008; Winkel, LP et al. 2005). Two studies reported on the same two JOPD patients, one at 3 years and one at 8 years follow-up (van Capelle et al. 2008; Winkel, LP et al. 2005). One case report (Furuwasa et al. 2014) did not state the dose of alglucosidase alfa, but all the other studies were consistent, and used a dose of 20 mg/kg per fortnight.

The case series included 24 late-onset PD patients in total, seven of whom had JOPD. Outcomes were reported separately at baseline and 12 month intervals up to 3 years from the initiation of ERT for juvenile patients, and some data synthesis was performed. The case reports provided before and after ERT data on one to five JOPD patients. A summary of the study profiles can be seen in Table 160. Outcome measures were similar between studies and were focused on determining muscle strength and function, and respiratory function. Less common outcomes reported assessed fatigue and gastrointestinal function. Due to the low level of evidence identified, formal quality assessment was not performed.

Patients in the included studies were either juvenile at onset *and treatment*, or juvenile at onset, but *adults* at age of treatment. The age of symptom onset varied from 2 to 17 years of age, and the age at first treatment with alglucosidase alfa varied from 2.3 years to 44 years.

There were a high number of case reports on late-onset Pompe disease presented at conferences, of which only a small proportion appear to have been published as journal articles. It is unknown whether the cases published are representative of the body of patients who receive alglucosidase alfa, or whether there is publication bias, which may influence the results.

#### Results of the included studies

##### Primary effectiveness: Survival

There were no data specific to patients with JOPD which addressed whether ERT would extend survival or not. Individual case reports mentioned age at death, but given the wide variability in the natural history of the disease, nothing can be concluded from individual data.

##### Quality of life

Quality of life was discussed in two articles. Orlikowski et al (2011) presented results for two patients with JOPD, who were treated at ages 28 and 40. Self-reported physical and mental health scores were given, which were measured using the Short form-36 (36-item Short Form Health Survey, SF-36, scale 0 – 100, where 0 = maximum disability, and 100 = no disability). Both JOPD patients had been invasively ventilated for at least 5 years prior to baseline, and patient 5 was bed-ridden. The two patients both reported an improvement from baseline after 1 year of ERT in the mental component of the survey. For the physical component, one patient score increased, while the other decreased, although neither of these changes is likely to be considered large enough to be clinically meaningful (Table 70).

Table 70 Self-reported physical and mental health scores before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **1 year ERT** | **Change** |
| --- | --- | --- | --- | --- |
| Orlikowski 2011  SF-36 Physical component score (points) | Patient 1  Patient 5 | 34.9  26.1 | 33.8  30.8 (week 38) | -1.1  4.7 |
| Orlikowski 2011  SF-36 Mental component score (points) | Patient 1  Patient 5 | 55.9  39.4 | 64.4  65.9 (week 38) | 8.5  -26.5 |

ERT = enzyme replacement therapy; NR = not reported; SF-36 = 36 item Short Form Health Survey

Although no validated tool was used by Winkel et al (2004) to measure quality of life, the authors described an increase in quality of life in two JOPD patients treated at ages 16 and 32. Both JOPD patients required less ventilation. Patients 1 and 2 were more severe, and remained wheelchair bound. However, patient 1 was able to resume her education, and participate in social life, with the requirement for ventilation decreasing from 18 to 10 hours per day. Prior to ERT, patient 2 was bedridden for 21 hours of the day, which reduced to 11 hours after 3 years of treatment, allowing him to go out (Winkel, LPF et al. 2004).

##### Cardiorespiratory function

Cardiorespiratory function was measured in nine case reports using a number of surrogate assessment methods. The most commonly used measures were slow vital capacity (VC), which may be measured in the supine or sitting position, and forced vital capacity (FVC). Other surrogate measures reported were peak expiratory flow, maximum expiratory flow, forced expiratory volume, inspiratory pressure, and expiratory pressure.

Vital capacity was measured in seven case reports, two of which (Orlikowski et al. 2011; Papadimas et al. 2011) measured VC in sitting and supine positions (Table 71). All measurements taken at the 6 month time-point from baseline showed an increase in VC. Both JOPD patients discussed by Orlikowski et al (2011) had severe Pompe symptoms at baseline, and remained on continuous ventilation support 24 hours per day throughout the study.

At 1 year after the initiation of ERT results are more varied with some patients still measuring an increase in %VC and others showing a decline. Measurements at 2 years or more after baseline are also inconsistent. FVC was measured in 5 patients from one study (Deroma et al. 2014) after 4 to 5 years of ERT (Table 72). FVC scores over 80% are considered to be within the normal range (Lachmann & Schoser 2013), so at baseline, three out of five patients were considered to have normal respiratory functioning. One patient who had much lower capacity at baseline than the others indicated a significant increase in capacity over that time period (increase from 14% to 30%). The four other patients were within the normal range at follow-up.

Winkel et al (2004) performed piece-wise linear regression (“broken-stick” method) to compare the difference in the rate of change prior to receiving ERT, and after ERT. Patients 1 and 2 had both had a significant decline of vital capacity in the 6 to 9 years prior to starting ERT (Patient 1 *r* = -0.99, p<0.001; Patient 2, *r* = -0.98, p=0.02). After the start of treatment, the slope of VC changed significantly (Patient 1 p=0.002; Patient 2 p=0.021), favouring the use of alglucosidase alfa.

Table 71 Vital capacity before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **Duration of treatment** | **Follow-up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| Winkel et al 2004  VC, % of predicted | Patient 1  Patient 2 | 14  9 | 3 years  3 years | NR  16 | r NR  p = 0.002a  7, r = 0.58b  p = 0.024a |
| Orlikowski et al 2011  VC, supine (% of predicted) | Patient 1  Patient 5 | 8  0 | 6 months  1 year  6 months  week 38 | 11  12  5  4 | 48%  Not evaluable |
| Orlikowski et al 2011  VC, sitting (%of predicted) | Patient 1  Patient 5 | 7  6 | 6 months  1 year  6 months  week 38 | 15  11  6  5 | 56%  -16% |
| Furusawa 2012  VC, % of predicted | Patient 4  Patient 5 | 17.6  13.1 | 1 year  2 years  1 year  2 years | Not taken  9.2  19.5  21.4 | NR  NR |
| Korpela 2009  VC, % of predicted | Patient 1 | 26 | 6 months | NR | increased |
| Ishigaki 2012  VC, sitting (% of predicted) | Patient 1 | 57 | 4 months  18 months | 65  NR | return to baseline |
| Furusawa 2014  VC, % of predicted | Patient 1 | 65 | 4 years | 9.2 | NR |
| Papadimas 2011  VC, sitting (% of predicted) | Patient 2 | 32 | 3 years | 31 | NR |
| Papadimas 2011  VC, supine (% of predicted) | Patient 2 | 23 | 3 years | 22 | NR |

NR = not reported; VC = vital capacity; ERT = enzyme replacement therapy; JOPD = juvenile late -onset Pompe disease

a Change in slopes pre and post ERT initiation using Broken Stick analysis

b Spearman’s correlation coefficient

Table 72 Forced vital capacity before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **Duration of treatment** | **Follow-up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| Deroma 2014  FVC (% predicted) | Patient 3  Patient 4  Patient 5  Patient 6  Patient 7 | 138  14 (tracheostomy)  88  83  75 | 4-5 years | 119  30  87  91  91 | NR |
| Furusawa 2012  FVC (% predicted) | Patient 4  Patient 5 | 14.2  10.3 | 2 years  1 year  2 years | 7.0  17.7  20.4 | NR |
| Korpela 2009  FVC (% predicted) | Patient 1 | 29 | 6 months | increased | 16% |

NR = not reported; FVC = forced vital capacity; ERT = enzyme replacement therapy; JOPD = juvenile late onset Pompe disease

Peak expiratory flow (PEF) and Maximum expiratory flow (MEF) were each measured in one study (Table 73). An increase of 65% in MEF (measured at 50% exhalation of FVC) was measured after 6 months of ERT in one patient. When PEF was measured at 2 years after the initiation of ERT, results were inconsistent, with one patient showing improvement and the other showing deterioration. Forced expiratory volume (FEV1) increased in two out of three patients from different studies, when measured after 6 months of ERT (Table 74). After 3 years of ERT, one patient showed only a slight decrease in FEV1 in both the sitting and supine positions. Inspiratory and expiratory pressure was measured in three patients from two studies (Table 75). Results after 6 months of ERT were inconsistent, but after 1 year, results in showed improvement in both patients tested.

Table 73 Peak expiratory flow (PEF) and maximum expiratory flow at 50% (MEF 50%) before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **6 months ERT** | **1 year ERT** | **2 years ERT** | **Change** |
| --- | --- | --- | --- | --- | --- | --- |
| Furusawa 2012  PEF (L/s) | Patient 4  Patient 5 | 0.58  1.24 | -  - | Not taken  1.63 | 0.25  1.70 | NR |
| Korpela 2009  MEF | Patient 1 | NR | increased | - | - | 65% |

ERT = enzyme replacement therapy; PEF = peak expiratory flow; NR = not reported; MEF 50% = maximum expiratory flow when 50% of the forced vital capacity has been exhaled; JOPD = juvenile late onset Pompe disease

Table 74 Forced expiratory volume in 1 second (FEV1) before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **Follow-up length** | **Follow-up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| Korpela 2009  FEV1 (ml) | Patient 1 | NR | 6 months | Increased | 16% |
| Merk 2008  FEV1 (ml) | Patient 1 | 550 | 6 months | 580 | 30 |
| Papadimas 2011  FEV1, sitting  (% predicted) | Patient 2 | 29 | 3 years | 28 | -1 |
| Papadimas 2011  FEV1, supine  (% predicted) | Patient 2 | 21 | 3 years | 21 | 0 |

ERT = enzyme replacement therapy; FEV1 = forced expiratory volume in 1 second; NR = not reported; JOPD = juvenile late onset Pompe disease

Table 75 Pressure, expiratory and inspiratory before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **6 months ERT** | **1 year ERT** | **Change** |
| --- | --- | --- | --- | --- | --- |
| Orlikowski 2011  Pemax (cmH2O) | Patient 1  Patient 5 | 7  2 | 10  2 | 13  3 (week 38) | 86%  50% |
| Orlikowski 2011  Pimax (cmH2O) | Patient 1  Patient 5 | 8  1 | 13  2 | 15  3 (week 38) | 88%  200 |
| Merk 2008  Pimax, (kPa)  (% of rated value) | Patient 1 | 1.59  (14) | 1.82  (16) | - | NR |
| Merk 2008  Pi0.1 (kPa)  (% of rated value) | Patient 1 | 0.43  (505) | 0.35  (345) | - | NR |

ERT = enzyme replacement therapy; Pemax = maximum expiratory pressure; Pimax = maximum inspiration pressure; Pi0.1 = inspiration pressure 0.1 seconds after the onset of inspiration; JOPD = juvenile late onset Pompe disease

In summary, the results presented for cardiorespiratory function in JOPD patients after 4 to 6 months of ERT reflect an improvement using the majority of assessment methods for vital capacity, inspiration and expiration volume, flow and pressure. It should be noted that the 16 measurements described in Table 71 to Table 75 were conducted in only five JOPD patients. The exceptions to improvement at the 4 to 6 month time point were seen in three measurements from two patients. One patient remained stable for measurements of slow %VC and Pemax (patient 5, Orlikowski et al 2011). This patient, whose first symptom appeared at age 14 years, was bed-ridden at baseline (age 40) but was able to sit in a wheelchair by the end of the study (12 months ERT) according to the authors. A second patient (aged 41 at treatment initiation) had a decrease in Pi0.1 at 6 months, despite showing improvements in other measurements (Pimax, FEV1) (Merk 2009). This patient was reported to have chronic respiratory insufficiency at baseline. Her age at first symptom onset was 15 years.

At 1 year post ERT initiation 11 measurements reflect an improvement in respiratory function in 2 patients and a decline in one. The patient showing a decline was described in the paragraph above (patient 5, Orlikowski et al 2011). Results reported after 2 or more years of ERT tend to reflect either stabilisation or decline in patient condition, possibly indicative of the disease progression in competition with effects of enzyme replacement.

Further studies gave narrative reports of JOPD cases. In a Chinese case report of 15 patients, 5 of 8 patients (65%) for whom there were data showed improvement or no deterioration in FVC after 12 months ERT (Yang et al. 2011). After 3.8 years of ERT however, only 2 patients did not show deterioration. In another study two patients who were assessed before and after 48 weeks of ERT showed stabilisation or mild improvement in both %FVC and %FEV1 (Park et al. 2014). A further study which included one JOPD case reported an overall decline in FVC from baseline after 18 months of ERT (Angelini et al. 2009).

Single case studies reported on other surrogate measures of cardiorespiratory function - patient ventilation time (van Capelle et al. 2008), patient need for assisted respiration (Kobayashi et al. 2010), periods of low overnight O2 saturation (Ishigaki et al. 2012) and time until hypercapnia (measured in the sitting and supine positions) (Orlikowski et al. 2011). Results are reported here in Table 76 to Table 79. Ventilation time was found to be reduced moderately in one patient (aged 16 at treatment initiation) and remained consistent in another after 8 years of ERT (aged 32 at treatment initiation). Changes to requirements for ventilation assistance requirements showed improvement for three out of four patients after 12 months of ERT (age at treatment onset 17 to 44 years), as their status changed from ‘nocturnal dyspnoea’ to ‘normal’. Patient 1, aged 28 at treatment onset, deteriorated after 12 months ERT, requiring intermittent mechanical ventilation rather than non-invasive ventilation at baseline. All other patients had some reduction for the requirement of ventilation support on alglucosidase alfa, although there were differences between patients to the degree of improvement (GRADE ⨁⨀⨀⨀).

Table 76 Ventilation time before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **Treatment duration** | **Follow-up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| van Capelle 2008  Ventilation time (hours) | Patient 1  Patient 2 | 16-18  24 | 3 years  8 years  3 years  8 years | 11-12  11-12  23.5  23.5 | 4-6 hours less  4-6 hours less  ½ hour less  ½ hour less |

ERT = enzyme replacement therapy; NR = not reported; JOPD = juvenile late onset Pompe disease

Table 77 Assisted ventilation requirements before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **12 months ERT** | **Change** |
| --- | --- | --- | --- | --- |
| Kobayashi 2010  Respiratory assistance required | Patient 1  Patient 2  Patient 3  Patient 4  Referencea | Non-invasive ventilation  Nocturnal dyspnoea  Nocturnal dyspnoea  Nocturnal dyspnoea  Non-invasive ventilation 40%  Intermittent mechanical ventilation 60% | Intermittent mechanical ventilation  Normal  Normal  Normal  Non-invasive ventilation 20%  Intermittent mechanical ventilation 80% | NR |

ERT = enzyme replacement therapy; NIV = non-invasive ventilation; IMV = intermittent mechanical ventilation (tracheotomy); NR = not reported; JOPD = juvenile late onset Pompe disease

a Average data of Expanded Access Program (Genzyme Co., n-5)

Table 78 Overnight O2 saturation before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **4 months ERT** | **18 months ERT** | **Change** |
| --- | --- | --- | --- | --- | --- |
| Ishigaki 2012  Low overnight O2 saturation  (no. of periods at 90% or less) | Patient 1 | 2-3 | < 2-3 | increased | NR |

ERT = enzyme replacement therapy; NR = not reported; JOPD = juvenile late onset Pompe disease

Table 79 Time until hypercapnia before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **6 months ERT** | **Change** | **1 year ERT** | **Change** |
| --- | --- | --- | --- | --- | --- | --- |
| Orlikowski 2011  Time until hypercapnia, sitting (min) | Patient 1  Patient 5 | 6:55  2:00 | 12:00  >20:00 | 5:05  >18:00 | 22:00  10:00 | 15:05  8:00 |
| Orlikowski 2011  Time until hypercapnia, supine (min) | Patient 1  Patient 5 | 1:45  0:00 | 3:20  2:00 | 1:35  2:00 | 15:00  Not done | 13:15 |

ERT = enzyme replacement therapy; NR = not reported; JOPD = juvenile late onset Pompe disease

An overview of cardiorespiratory function assessed by the ventilation needs measured in case reports of JOPD patients suggests an overall trend of stabilised or decreasing need (GRADE ⨁⨀⨀⨀). Ventilation time decreased in one patient indicating improvement after 12 months of ERT and remained stable in another at the same time point. After 8 years of ERT the same two patients showed no further change. These results support the hypothesis that ERT generates improvement the first few months of administration and thereafter sustains stabilisation. Patient need for assisted ventilation requirements are more varied. Out of four cases in one study, three showed improvement after 1 year of ERT but one increased their need for assisted ventilation.

Other measures also showed long-term improvement or stabilisation: overnight O2 saturation improved after 18 months ERT in one patient, and time to hypercapnia indicated improved respiration after 1 year ERT. Three patients in a study by Parks et al, 2014 (Park et al. 2014) were reported to have no change in terms of respiratory patterns or duration of artificial ventilation during ERT compared to baseline. In contrast a patient severely affected by JOPD at baseline required continuous intermittent mandatory ventilation through tracheostomy and O2 supplementation for about 8 hours per night on most nights, throughout the 20 week ERT treatment period and subsequently died (Rossi et al. 2007).

##### Gross motor function

Objective muscle weakness and functioning was measured in a variety of ways by the studies included, such as the 6MWT, global motor functioning and disability, gross motor functioning, muscle strength, motor testing, and levels of fatigue. These assessments are considered together here as surrogate measures of gross-motor function. Fatigue and 6MWT can also be indicators of cardiovascular function.

##### Distance walked

Six articles published data on how far patients with JOPD could walk on the 6MWT or ten minute walk test (10MWT) before and after treatment with alglucosidase alfa (Bembi et al 2010; Deroma et al 2014; Merk et al 2008; Ishigaki et al 2012; von Capelle et al 2010; Korpela et al 2009).

Similar improvements were seen across most cases, with clinically important improvements observed over time[[14]](#footnote-14), particularly in the short term (GRADE ⨁⨀⨀⨀). There were two exceptions to this, Patient 7, discussed by Deroma et al (2014) (a patient who was not considered to have any significant muscle impairment at baseline) and the single case reported by Merk et al (2008). Merk et al (2008) reported on a 41 year old woman, whose symptoms of PD started at age 15 years. She had seriously impaired mobility, which did not allow her to perform the 6MWT at either time point, despite respiratory improvements.

Bembi et al (2010) reported that all juvenile patients (mean age at onset was 2.5 years) had an improvement in walking performance on the 6MWT over 3 years, with the greatest change seen in the first 12 months. After three years of alglucosidase alfa, JOPD patients were able to walk an average of 192 metres further than at baseline, which is similar to the improvement reported by van Capelle (2010) (mean improvement 157.7 metres) and Deroma et al (2014) (mean of 209.2 metres improvement) after 4-5 years. In all three studies, the patients were treated when they aged between 5.9 years and 15.2 years.

Ishigaki et al (2012) reported on a single case, which first showed symptoms of JOPD at age 2, and started to receive ERT at age 10. He improved on the 6MWT over the first 8 months, at which point his progress halted (results presented graphically). For a healthy child aged between 6 and 8 years, the reference range is 577.8 ± 56.1 metres, and for a child aged 9 to 11 years, the reference range is 672 ± 61.6 metres (Ishigaki et al. 2012).

Table 80 Walking performance on 6MWT (metres) or 10MWT (metres) before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Sample** | **Baseline** | **Follow-up length** | **Follow-up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| (Bembi et al. 2010)  6MWT | n=7 | 434.7 ± 260.8 | 12 months  24 months  36 months | 590.6 ± 213.6  599.6 ± 240.9 (n=6)  614.3 ± 233.1 (n=6) | 155.9 ± 195.9  188.0 ± 201.1  192.4 ± 203.7 |
| Deroma et al 2014  6MWT | Patient 3  Patient 4  Patient 5  Patient 6  Patient 7  Mean ± SD | 617  15  580  690  636  507.6 ± 278.2 | 4-5 years | 821  510  830  782  641  716.8 ± 138.2 | 204  495  250  92  5  209.2 ± 186.3 |
| Merk et al (2008)  6MWT | Patient 2 | Not possible | 6 months | Not possible | NR |
| Ishigaki et al 2012  6MWT | Patient 1 | 320 | 4 months | 500 | 180 |
| (van Capelle et al. 2010)  6MWT | Patient 1  Patient 2  Patient 4 | 340  470  400 | 3 years | 530  580  570 | 190  110  170 |
| Korpela et al (2009)  10MWT | Patient 1 | wheelchair bound | 6 months  12 months | 93  87 | 93  87 |

6MWT = 6-minute walk test; 10MWT = 10-minute walk test

##### Global motor functioning

Deroma et al (2014) assessed the benefit of ERT in five JOPD patients, four of whom were asymptomatic at baseline. Therapy was started when the patients were between 9.6 years and 11.9 years old. After 4 to 5 years of treatment, no deterioration or improvements, in global motor disability on the Modified Walton Scale were noted (GRADE ⨁⨀⨀⨀).

Table 81 Global motor disability on the Modified Walton Scale before and after alglucosidase alfa in patients with JOPD

| **Study** | **Sample** | **Baseline** | **Follow up length** | **Follow up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| (Deroma et al. 2014)  MWS | Patient 3  Patient 4  Patient 5  Patient 6  Patient 7 | 2  2.5  0  0  0 | 4-5 years | 2  2.5  0  0  0 | 0  0  0  0  0 |

\*MWS = Modified Walton Scale, which measures global motor disability, 0=normal to 7=wheelchair bound. Scores≤2 indicate no significant muscle function impairment.

Van Capelle et al (2008) reported that gross motor function improved slightly over the 3 to 8 years of the study, with the patients’ scoliosis being corrected during this period. The overall level of handicap (measured on the Rotterdam 9-item Handicap Scale; RHS) was decrease slightly in both patients, with patient 1 being able to resume education. Patient 2 was able to perform domestic activities outdoors and leisure activities independently, with no limitations on participating in social activities (van Capelle et al. 2008).

Table 82 Gross motor functioning before and after alglucosidase alfa in patients with JOPD

| Study  Measure | Sample | Baseline | 3 year follow-up | Change | 8 year follow-up | Change |
| --- | --- | --- | --- | --- | --- | --- |
| Van Capelle et al (2008)  GMFM (%) | Patient 1 (sitting)  Patient 1 (lying)  Patient 1 (crawling)  Patient 2 (total) | 47  67  21  12 | 80  78  33  13 | 33  11  12  1 | 83  73  36  12 | 36  6  15  0 |
| Van Capelle et al (2008)  RHS | Patient 1  Patient 2 | NR  NR | 16  18 | NR | 25  20 | NR |

GMFM = gross motor function assessment, reference value = 100

RHS = Rotterdam handicap scale

##### Muscle strength

Muscle strength was measured by hand held dynamometry (HHD), manual muscle testing (MMT), motor function measure (MFM), and the quick motor function test.

Three articles used the HDD method of measuring muscle strength. A small improvement was seen after one year of treatment in a 26 year old, who had had symptoms of PD since age 15 (Sugai et al. 2010). She had relatively severe disease, requiring invasive ventilation and lower limbs were ‘severely difficult to move’.

Larger improvements were seen over 3 and 8 years of treatment in patients aged 5.9 to 32 years at the start of treatment (age of onset between 2.5 years and 10 years) (van Capelle et al. 2010; van Capelle et al. 2008). However, muscle strength remained below normal values, with van Capelle et al (2008) providing age-appropriate reference values for their patients after 8 years, as 3356 Newtons for patient 1, and 4759 Newtons for Patient 2 (van Capelle et al. 2008). Comparisons across these studies, would suggest that the patients treated at an earlier stage of disease progression (i.e. with better baseline scores, and at a younger age; Patients 1, 2 and 4 in van Capelle et al 2010 and Patient 1 in van Capelle et al 2008) show larger improvements than those treated when they are adults (Patient 2 in the study by van Capelle et al 2008 and the patient treated by Sugai et al 2010) (GRADE ⨁⨀⨀⨀).

Table 83 Muscle strength measured using hand held dynamometry (HHD) before and after alglucosidase alfa in patients with JOPD

| **Study** | **Sample** | **Baseline HHD sumscore (Newtons)** | **Follow-up length** | **Follow-up HHD sumscore (Newtons)** | **Change** |
| --- | --- | --- | --- | --- | --- |
| van Capelle (2010) | Patient 1  Patient 2  Patient 4 | 521.5  521  608 | 3 years | 750  865  1158 | 228.5  344  550 |
| (van Capelle et al. 2008) | Patient 1  Patient 2 | 751  199 | 3 years  8 years  3 years  8 years | 848  1371  305  349 | 97  620  106  150 |
| Sugai et al 2010 | Patient 1 | 123.2 | 1 year | 141.9 | 18.7 |

HHD = hand-held dynamometry, conducted using a hand-held dynamometer; van Capelle et al HHD values represent the sum score of the following muscle groups: neck flexion and extension, shoulder abduction, elbow flexion and extension, wrist extension, hip flexion and abduction, knee extension and flexion, ankle dorsiflexion and plantar flexion

Sugai et al HDD sumscore combines elbow extension and flexion, knee extension, key pinch and palmar pinch

Muscle strength was measured by three studies using manual muscle testing (MMT). There was a large amount of heterogeneity in both baseline values and response to treatment in the cases reported, although all patients either remained stable, or improved (GRADE ⨁⨀⨀⨀). It is unknown whether there would have been further deterioration in the absence of treatment.

In the study by van Capelle et al (2010), muscle strength increased significantly to near normal values (van Capelle et al. 2010). These patients were aged between 5.9 and 12.7 years at treatment.

In the study by Furuwasa et al (2012), patients were aged 32 and 38 at initiation of alglucosidase alfa. Their age of symptom onset was 7-8 years, both patients had required ventilation for over 5 years, and one was completely wheelchair-bound. These more severe patients did not show any noticeable improvement on the MMT, although patient 4 was reported to be able to stand with less effort after 6 months of treatment, and patient 5 could move her hip from floor to chair unaided after 44 weeks of treatment, which she had been unable to do for several years (Furusawa et al. 2012).

Ishigaki et al (2012) similarly reported that a 10 year old boy (first signs of JOPD at age 2) showed only minimal change on the MMT.

Table 84 Manual muscle testing before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **Follow-up length** | **Follow-up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| van Capelle (2010)a  MMT sumscore, % maximum | Patient 1  Patient 2  Patient 4 | 86  79  79 | 3 years | 92  93  100 | 16  14  21 |
| Furusawa et al (2012) a  MMT sumscore, % maximum | Patient 4  Patient 5 | 30  28 | 1 year  2 years  1 year  2 years | 30  30  28  29 | 0  0  0  1 |
| Ishigaki et al (2012)b  MMT rawscores | Patient 1 | proximal: 3+  distal: 4  neck: 2  trunk: 2 | 6 months | proximal: 4  distal: 4-5  neck: 2  trunk: 2 | proximal: 1  distal: 0-1  neck: 0  trunk: 0 |

a MMT = manual muscle testing, scored by an 11-point modified version of the Medical Research Council scale, % of maximum score (i.e. 0 to 100%)

b Raw scores on 5 point scale

The quick motor function test (QMFT) is a 16-item scale, which was developed and validated for use in patients with PD by van Capelle et al (2012) to assess clinical severity and motor function (van Capelle et al. 2012) (scores are as a percent of maximum possible). Over 3 years all three patients had considerable improvements in muscle functioning. The time it took patients to rise from supine to standing position, and to run 10 metres all decreased marginally, but would only be considered clinically important in one out of three patients.

Table 85 Muscle functioning outcomes before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Sample** | **Baseline** | **3 year follow-up** | **Change** |
| --- | --- | --- | --- | --- |
| van Capelle et al (2010)  Rising (sec)a | Patient 1  Patient 2  Patient 4 | 4.4  5.1  6.2 | 3.94  4.13  3.2 | -0.46  -0.97  -3.0 |
| van Capelle et al (2010)  10-metre running (sec)b | Patient 1  Patient 2  Patient 4 | 4.1  4.2  4.5 | 4.0  4.0  3.8 | -0.1  -0.2  -0.7 |
| van Capelle et al (2010)  QMFT | Patient 1  Patient 2  Patient 4 | 70.3  73.4  67.2 | 95.3  92.2  92.2 | 25  18.8  25 |

a Time taken to rise from a supine position to standing position

b 10 metre running time

c QMFT = quick motor function test, % of maximum possible (i.e. 0 to 100%), covering: raising the torso, neck flexion, hand across midline, hip and knee flexion, extending the legs, sit up, extending the arms, standing from a chair, standing up from half knee, squatting, standing up from squatting, picking up an object, standing on one leg, walking in ten metres, jumping, and walking up steps.

A single case series of 5 severe PD patients (including two with JOPD, treated at ages 28 and 40) assessed muscle functioning on the motor function measure (MFM) scale (Orlikowski et al. 2011). Both JOPD patients required invasive ventilation 24 hours a day. Patient 5, who was bed-ridden at baseline, was able to sit in his wheelchair at follow-up, although the MFM scale detected no improvements for this patient. Patient 1 experienced only minor improvements.

Table 86 Motor function measure scale before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **Follow-up length** | **Follow-up** | **% Change** |
| --- | --- | --- | --- | --- | --- |
| Orlikowski et al (2011) MFM scale, standing and transfers | Patient 1  Patient 5 | 0  0 | 52 weeks  38 weeks | 3  0 | 3  0 |
| Orlikowski et al (2011)  MFM scale, sitting and proximal | Patient 1  Patient 5 | 44  25 | 52 weeks  38 weeks | 56  25 | 12  0 |
| Orlikowski et al (2011)  MFM scale, distal | Patient 1  Patient 5 | 95  81 | 52 weeks  38 weeks | 95  76 | 0  -5 |
| Orlikowski et al (2011)  MFM scale, total | Patient 1  Patient 5 | 38  27 | 52 weeks  38 weeks | 43  26 | 5  -1 |

MFM = motor function measure, % of maximum (i.e. 0 to 100%)

Muscle strength was measured by grip power (Dynamometer®) in one study (Furusawa et al. 2012). Two patients in a case series of five were juvenile onset patients who were followed up for two years. The patients were both female and aged 7 and 8 years of age at onset, but treated at ages 32 and 38. Both had relatively serious disease with one wheelchair bound and requiring ventilation for most of the day, and the other was partially wheelchair bound and required ventilation at night. Patient 4 was very ill during the treatment period, experiencing severe dyspnoea and recurrent pneumothorax after 64 weeks of treatment and emphysema at 80 weeks of treatment. She also was treated with parenteral hyperalimentation for a month due to inability to eat. After recovery from emphysema she remained bedridden and lost ambulation. Grip strength only improved marginally in this patient. For patient 5, grip power increased by 7.5kg after 2 years.

Table 87 Grip power before and after alglucosidase alfa in patients with JOPD

| **Study**  **Measure** | **Patient** | **Baseline** | **52 weeks** | **Change** | **104 weeks** | **Change** |
| --- | --- | --- | --- | --- | --- | --- |
| Furusawa et al (2012)  Grip power, kg: | Patient 4  Patient 5 | 17.0  17.5 | 18.0  23.9 | 1.0  6.4 | 17.7  25.0 | 0.7  7.5 |

##### Fatigue (self-reported patient outcomes)

Three included studies published results for self-reported fatigue using the Fatigue Severity Scale (FSS) (Orlikowski et al. 2011; Papadimas et al. 2011; van Capelle et al. 2008) in a total of five patients (Table 88). In van Capelle’s study, two JOPD patients were found to have a decrease in self-reported fatigue after 8 years of ERT compared to 3 years of ERT. There was no baseline fatigue level recorded. In the second study, Orlikowski et al also found there was a decrease in fatigue in two patients after 1 year of ERT compared to baseline. In a third case report one patient reported a decrease in fatigue 3 years after ERT initiation. In summary, fatigue was consistently reduced in five JOPD patients who used the self-reported FSS tool. Other single case studies report a decrease in fatigue levels following ERT (Bernstein et al. 2010; Fernandez et al. 2012) (GRADE ⨁⨀⨀⨀).

Table 88 Self- reported fatigue in JOPD patients on FSS before and after alglucosidase alfa

| **Study**  **Measure** | **Patient** | **Baseline** | **Duration of treatment** | **Follow-up** | **Change** |
| --- | --- | --- | --- | --- | --- |
| van Capelle et al 2008  Fatiguea (FSS) | Patient 1  Patient 2 | NR  NR | 3 years  8 years  3 years  8 years | 5.6  3.9  6  4.2 | NR  NR  NR  NR |
| Orlikowski et al 2011  Fatigue (FSS) | Patient 1  Patient 5 | 4.6  4.7 | 1 year  1 year | 3.1  3.2 | -1.5  -1.5 |
| Papadimas et al 2011  Fatigue (FSS) | Patient 2 | 5.9 | 3 years | 4.9 | -1.0 |

ERT = enzyme replacement therapy; FSS = Fatigue severity scale; NR = not reported

a Reference value 2.9 (general population); scale 1 to 7, where 1 = no fatigue or interference from fatigue in everyday life, and 7 = large amount of fatigue and interference with functioning from fatigue in everyday life

##### Summary of gross motor function

The collection of case reports and one case series were relatively consistent across outcome measures, that on average, patients with JOPD experienced improvements in muscle functioning and strength with alglucosidase alfa compared to baseline figures, prior to receiving treatment. Only one patient deteriorated from baseline on a muscle functioning measure, and all other patients, on all other muscle functioning/strength outcomes either remained or stable or improved. The improvements were larger in patients who had less severe JOPD at baseline, and who were treated at an earlier age (GRADE ⨁⨀⨀⨀).

##### Swallowing and gastrointestinal symptoms

Poor digestive function and weight loss are common symptoms among PD patients. Three case studies published data on gastrointestinal symptoms in a total of five JOPD cases (Bernstein et al. 2010; Fecarotta et al. 2013; Sugai et al. 2010). Bernstein et al 2010 recorded time to resolution of gastrointestinal symptoms in three JOPD patients and found that all symptoms were resolved after initiation of ERT in 3 to 10 months (Table 89) (GRADE ⨁⨀⨀⨀). The same three patients were found to have gained weight after 6-12 months on ERT compared to baseline (Table 90). The authors comment that patient 1 had only one episode of bowel movement urgency, and patient 2 and 3 remain free of gastrointestinal symptoms after 2-3 years of ERT.

A second case study also reported on weight changes and found that one patient increased their weight after 13 months ERT compared to baseline. Swallowing function was measured in one patient using the dysphagia severity scale (DSS) and found to be improved after 6 months ERT (Fecarotta et al. 2013) (Table 91) (GRADE ⨁⨀⨀⨀).

Table 89 Changes to gastrointestinal symptoms after alglucosidase alfa in JOPD patients

| **Study**  **Measure** | **Patient** | **Symptoms at start of ERT** | **Time to resolution of symptoms** |
| --- | --- | --- | --- |
| Bernstein 2010  Time to resolution of symptoms (months) | Patient 1 | Diarrhea, constipation, cramps, abdominal pain, bloating, early satiety/fullness, bowel urgency/incontinence, unable to chew, swallowing difficulty, weight loss | 10 |
| Bernstein | Patient 2 | Diarrhoea, cramps, abdominal pain, bloating, early satiety/fullness, anorexia, weight loss | 3 |
| Bernstein | Patient 3 | Chronic, synchronous diarrhea and vomiting, constipation, early satiety, abdominal pain, postprandial bloating, weight fluctuation | 5 |

ERT = enzyme replacement therapy; JOPD = juvenile late onset Pompe disease

Table 90 Weight changes in JOPD patients after alglucosidase alfa

| **Study**  **Measure** | **Patient**  **(height in cm)** | **Baseline** | **6-12 months ERT** | **Change** |
| --- | --- | --- | --- | --- |
| Bernstein 2010  Weight (kg) | 1 (201)  2 (157.5)  3 (154.8) | 73  48  56 | 78  56  58 | 5  8  2 |
| Sugai 2010  Bodyweight (kg) | 1 | 36.0 | 40.1 (13 months) | 11.4% |

ERT = enzyme replacement therapy; JOPD = juvenile late onset Pompe disease; NR = not reported

Table 91 Swallowing function before and after alglucosidase alfa in a patient with JOPD

| **Study**  **Measure** | **Patient** | **Before ERT** | **6 months ERT** | **Change** |
| --- | --- | --- | --- | --- |
| Fecarotta 2013  Dysphagiaa  (DSS grade) | 1 | 1 | 0 | NR |

DSS = dysphagia severity scale adapted by Gates et al, 2006; ERT = enzyme replacement therapy

aDysphagia investigated by Videofluroscopy Swallowing Study

Although the evidence is limited and poor quality, results are consistent in showing that gastrointestinal symptoms improve after several months of ERT and this condition is maintained for 2 to 3 years of ERT. Weight gain in four patients on ERT also reflects improved gastrointestinal function (GRADE ⨁⨀⨀⨀).

### Medicines to treat Mucopolysaccharidoses (MPS) I, II, VI

**Is laronidase safe and effective compared to standard medical management plus placebo in the treatment of patients with Mucopolysaccharidosis Type I (Hurler-Scheie syndrome)?**

The submission to the PBAC asserted that improvements in forced vital capacity (FVC) and a 6-minute walk test (6MWT) would translate into lesser cardiorespiratory morbidity and mortality in MPS I. The PBAC considered it may be reasonable to expect that improvements in FVC may lead to increasing lifespan, and other benefits, such as a reduction in sleep apnoea and liver side would favour laronidase. A new extension trial was identified, which provides longer term outcome clinical data for patients treated with laronidase.

One double-blind randomised placebo-controlled trial reported that 6 months of laronidase treatment was effective at improving cardiac function (assessed with 6MWT) and respiratory function (assessed with FVC) by a significantly greater amount than placebo (GRADE ⨁⨁⨁⨀) However, these results are difficult to interpret, due to baseline differences favouring placebo. *Post hoc* analyses also showed reductions in sleep apnoea and improvement in joint movement, although these were only statistically significant in the sub-group who had severe symptoms at baseline and may have been affected by confounding (GRADE ⨁⨁⨀⨀). Laronidase appears safe, with a very similar profile of adverse events to placebo infusions.

An extension to the randomised trial assessed the benefit of laronidase over 3.5 to 4 years, and found that % predicted normal FVC was reduced from baseline by a small amount (i.e. the 4.9% benefit observed in the first 6 months of treatment during the trial was not maintained on average during the extension). In 29/40 patients FVC improved or remained stable over 3.5-4 years, while the remaining11 patients declined by ≤15%. Similarly, the distance walked in the 6MWT (which improved by an average of 19.7 metres during the randomised trial), improved only 17.1 metres on average from baseline in the extension trial, which was an improvement of ≥ 54 metres in 50% of patients, limited increase or decrease in 28% of patients, and a reduction of ≥ 54 metres in 23% of patients. Given the lack of comparative data for the longer-term, it cannot be determined whether the poorer outcomes at 3.5-4 years (as compared to after 6 months in the laronidase arm of the randomised trial) are due to lack of longer-term efficacy, or normal disease-related decline.

Data on the baseline status of Australian patients receiving laronidase were scant, and the benefit of laronidase could not be assessed.

**Is idursulfase safe and effective compared to standard medical management plus placebo in the treatment of patients with Mucopolysaccharidosis Type II (Hunter syndrome)?**

The submission to the PBAC claimed that improvements on surrogate endpoints of FVC and the 6MWT compared to placebo are clinically meaningful. The PBAC accepted that it was sufficiently likely that treatment with idursulfase would improve survival in patients with MPS II. Longer term data were available from one new extension trial, following the randomised trial which was included in the submission to the PBAC.

A high quality double-blind randomised placebo-controlled trial found that MPS II patients taking idursulfase weekly had significantly better physical functional capacity (6MWT) and respiratory function (absolute FVC) after one year than patients who received placebo (GRADE ⨁⨁⨁⨀). Liver and spleen volumes, and urinary GAG were also significantly reduced in patients taking idursulfase compared to those taking placebo (GRADE ⨁⨁⨁⨀). Improvements were less pronounced in patients taking idursulfase every other week than in those who received idursulfase weekly. An extension study reported that improvements in 6MWT and absolute FVC were largely maintained with treatment for a further 24 months (GRADE ⨁⨁⨀⨀).

Adverse events were more common in the patients taking idursulfase compared to those taking placebo and some are likely to be drug-related (GRADE ⨁⨁⨁⨁).

Data on the Australian patients receiving idursulfase could not be collated due to the lack of consistency in reporting.

**Is galsulfase safe and effective compared to standard medical management plus placebo in the treatment of patients with Mucopolysaccharidosis Type VI (Maroteaux-Lamy syndrome)?**

The submission claimed that galsulfase had significant advantages in effectiveness over placebo (plus standard medical management) and similar or less toxicity. The PBAC accepted that galsulfase had significant clinically effectiveness over placebo for the primary outcome of 12-minute walk test (12MWT) over 24 weeks, but more toxicity. No new data were identified through the systematic review.

One randomised double-blind trial detected a statistically significant difference favouring galsulfase on the 12-minute walk test, and a non-statistically significant trend favouring galsulfase on the 3-minute stair climb (GRADE ⨁⨁⨀⨀). No significant improvements were detected on respiratory functioning over the 24 weeks (GRADE ⨁⨁⨀⨀). While there were more adverse events in the galsulfase group than the placebo group, these were predominantly infusion-related, and the difference was not shown to be statistically significant (GRADE ⨁⨁⨁⨀).

Data on the Australian patients receiving galsulfase were not comprehensive enough to determine the clinical impact of treatment.

#### Background

##### Mucopolysaccharidoses

The mucopolysaccharidoses are severe progressive lysosomal storage disorders caused by the absence or reduced function of specific lysosomal enzymes. The enzymes are required for different steps of glycosaminoglycan (GAG) catabolism. The lack of enzyme function is the result of gene mutations and leads to the build-up of GAGs, specifically dermatan sulphate and heparin sulphate. Accumulation of GAGs within lysosomes leads to permanent cell damage and progressive deterioration of organs and tissues.

Mucopolysaccharidosis I (MPS I) is a chronic, life-threatening disorder in which a deficiency in enzyme α-L-iduronidase results in an accumulation of GAGs, compromising organs and tissues (Wraith, J. E. et al. 2004). Mutations in the α-L-iduronidase gene are inherited in a recessive autosomal fashion, affecting males and females equally. Common causes of morbidity and mortality in MPS I are respiratory insufficiency, cardiac compromise, and joint problems. Clinically, MPS I can be classified into three syndromes, namely Hurler (the most severe), Scheie (least severe) and Hurler-Scheie syndrome; however, the three groups are not distinct.

Deficiency in the lysosomal enzyme iduronate-2-sulfatase (I2S) is the cause of Mucopolysaccharidosis II (MPS II), also called Hunter syndrome. I2S is involved in the breakdown of GAGs and a deficiency leads to progressive tissue and organ dysfunction. The gene encoding I2S is X-linked and the disease occurs primarily, although not exclusively, in males. Phenotypic variation is high but GAG accumulation commonly leads to neurological impairment, bone disease, decreased respiratory function and impaired cardiac function. Physical abnormalities worsen with age and severely affect quality of life.

Mutations in a third enzyme, N-acetylgalactosamine-4-sulfatase, cause Mucopolysaccharidosis VI (MPS VI), also known as Maroteaux-Lamy syndrome. Enzyme deficiency leads to dermatan sulphate accumulation and consequent tissue and organ damage. MPS VI is inherited in an autosomal recessive pattern. Skeletal abnormalities are common and patients experience compromised pulmonary and cardiovascular function. Progression of disease often results in the death of patients who are aged in their teens or early 20s.

##### Pre-enzyme replacement therapies

Most treatments for MPS I are aimed at symptom relief. Prior to the development of ERT these treatments involved orthopaedic, otolaryngological, cardiac ophthalmological and neurosurgical interventions. Haemopoietic stem cell transplantation (HSCT) has been used with some success alone and in combination with ERT to treat patients and has been found to maintain their intellectual function.

HSCT and bone marrow transplant have been attempted but have not been found to prevent neurodegeneration and are not routine treatment options for MPS II.

For patients with MPS VI, there has been some success with bone marrow transplant and HSCT in patients with severe somatic disease, but with little benefit to bone tissue, and there is a reported high mortality (Braunlin et al. 2013; Harmatz et al. 2006).

##### Enzyme replacement therapies

The use of laronidase ERT attempts to target the underlying cause of the disorder (El Dib, R. P. & Pastores 2007; Jameson, Jones & Wraith 2013). Laronidase has been subsidised through the LSDP since 2007. The standard intravenous dose for laronidase is 100 U/kg (0.58mg/kg) weekly. Different dilutions are applied to patients who weigh ≤ or > 20 kg. In order to minimise reactions the infusion rate is begun at 2 U/kg/hour and is doubled every 15 minutes, provided it is tolerated. The initial dose of 100 U/kg would take 5.5 hours to deliver, but subsequent infusions may be administered more quickly over 3 to 4 hours.

ERT with idursulfase aims to reduce the level of GAGs and thereby reduce disease progression in patients (All Wales Medicines Strategy Group 2007; da Silva et al. 2014). Idursulfase has been subsidised through the LSDP since 2008. Idursulfase, which has a recommended dose of 0.5 mg/kg weekly, is delivered at an initial rate of 8 mL/ hour for the first 15 minutes. Once tolerance is established the rate may be increased incrementally to a maximum of 100 U/hour, leading to a delivery time of between one and three hours.

Galsulfase is an ERT that is intended to reduce GAG levels in MPS VI patients. Galsulfase has been subsidised through the LSDP since 2008. The recommendation for galsulfase is for delivery at 1 mg/kg weekly by intravenous infusion, following pre-treatment with antihistamines (with or without antipyretics) 30 to 60 minutes prior to the start of infusion. Infusion time should be no less than 4 hours.

It is important to note that although ERT provides a possible treatment option for MPS, it is not without burden for the patients. The drugs are delivered through intravenous infusion, and infusion reactions are not uncommon. To reduce the reactions, protocols are provided for drug delivery whereby the first dose is delivered under the supervision of a pjysician experiences in the management of patients with MPS or other inhereited metabolic diseases. Administration of ERT should be carried out in an appropriate setting where resuscitation equipment to manage clinical emergencies would be readily available..

If reactions occur, infusion is stopped and the patient may not receive further therapy until the next dose is due. In some instances, infusion may be restarted when the reaction is under control. Drug infusions must be prepared in correct dilutions from concentrated vials immediately prior to patient delivery. Due to the high cost of the drugs, wastage due to discontinuation of infusions or non-attendance of a patient for treatment is to be avoided if at all possible.

#### Systematic review inclusion criteria

Table 94 presents the criteria for selecting studies that assessed the safety and effectiveness of laronidase, idursulfase and galsulfase for the treatment of patients with mucopolysaccharidosis.

Table 94 Criteria for selecting studies to assess the safety and effectiveness of laronidase, idursulfase, and galsulfase

| Characteristic | Inclusion criteria |
| --- | --- |
| Study design | The highest level of evidence available (from Table 2) that addressed the research questions. Case reports would have been included if none of the study designs in Table 2 were available. |
| Populations | Patients with Mucopolysaccharidosis (MPS)  Type I (MPS I; MPS HIS; Hurler-Scheie syndrome, but not Hurler syndrome or Scheie syndrome)  Type II (MPS II; Hunter syndrome) or  Type VI (MPS VI; Maroteaux-Lamy syndrome) |
| Interventions | Laronidase (Aldurazyme®)  Idursulfase (Elaprase®)  Galsulfase (Naglazyme ®)  Subgroup analysis: by dose (e.g. doses consistent with TGA listing, as well as experimental dosing regimens) |
| Comparator | Standard medical management plus placebo |
| Outcomes | *Safety:* adverse events related to treatment – for example, abdominal pain, dyspnoea, rigors, chest pain; and compliance with treatment (i.e. treatment withdrawal or suboptimal dosing)  *Primary effectiveness:* survival  *Secondary effectiveness:* quality of life; pain; respiratory function (supplementary oxygen, CPAP (nocturnal or all day), sleep disordered breathing: apnoea/hypopnoea); cardiac functioning (ejection fraction, fraction shortening, LV hypertrophy, heart failure); joint movement. |
| Language | Studies in languages other than English would have been translated if it appeared from the abstract that they represented a higher level of evidence than that available in English. |
| Research questions | Is laronidase safe and effective compared to standard medical management plus placebo in the treatment of patients with Mucopolysaccharidosis Type I (Hurler-Scheie syndrome)?  Is idursulfase safe and effective compared to standard medical management plus placebo in the treatment of patients with Mucopolysaccharidosis Type II (Hunter syndrome)?  Is galsulfase safe and effective compared to standard medical management plus placebo in the treatment of patients with Mucopolysaccharidosis Type VI (Maroteaux-Lamy syndrome)? |

TGA = Therapeutic Goods Administration; CPAP = continuous positive airway pressure; LV = left ventricular

One randomised trial reporting on idursulfase beta (Hunterase®) was excluded, as it was considered a different drug to idursulfase (Elaprase®).

#### Results of the literature search

Randomised trials were identified for all three MPS types and drugs of interest. Non-randomised evidence was therefore not included in the systematic review, with the exception of extension studies of the included RCTs, providing longer term data.

One publication was identified through pearling of the reference lists of included studies (Harmatz et al 2006). The included evidence is described below:

##### MPS I

* One randomised, double-blind placebo controlled trial comparing 100 U/kg of body weight of laronidase against placebo, administered once weekly by a 4-hour intravenous infusion, for a period of 6 months (Wraith, J. E. et al. 2004).
* A 3.5 year open-label extension study to the above (Clarke et al. 2009).

##### MPS II

* A randomised, double-blind placebo-controlled trial of idursulfase, administered once weekly (0.5mg/kg) or every two weeks (0.5 mg/kg), compared to weekly placebo infusions, for a period of a year (TKT024) (Muenzer et al. 2006).
* A 2-year open-label extension study to the above RCT - including 3 year data from patients in active treatment arms from the randomised trial (Muenzer et al. 2011).

##### MPS VI

* A double-blind, placebo-controlled trial of galsulfase over 24 weeks (Phase 3 trial), plus an open-label extension study over 24 weeks (Harmatz et al. 2006).
* Long-term outcomes of 3 clinical trials (including the RCT above), providing data after 97 – 260 weeks (Harmatz et al. 2010), and on cardiac outcomes (Braunlin et al. 2013), but these were excluded, due to the inclusion of patients from outside the included clinical trial.

#### Risk of bias assessment

##### MPS I

The double-blind placebo-controlled trial of laronidase had a low risk of bias, although it was not reported how patients were randomised, or the methods used to ensure blinding was maintained. The baseline characteristics of the two randomised groups were well balanced, and it is expected that the only difference between the two groups is the active treatment in the laronidase arm.

##### MPS II

In this trial of 96 MPS II patients, all participants were blinded by receiving weekly dosing, whether in the idursulfase weekly group, idursulfase every other week group (i.e. receiving placebo in alternate weeks) or placebo group. The study was rated as having a moderate risk of bias. Professionals unrelated to the trial used a standardised protocol and detailed operational manual to conduct assessments. Allocation concealment and randomisation methods were not clearly described. There was a risk of selective reporting noted as some important clinical outcomes (e.g. score of height and weight, left ventricular mass index (LVMI) and overnight AHI) were not reported.

##### MPS VI

Patients, investigator and staff supervising the infusions were blinded in the 2006 galsulfase trial. Eleven of the 39 randomised patients did not fulfil the eligibility criteria set *a* priori, but were included, despite the fact they exceeded the 12 minute walk test limit (n = 7), were too young (n = 3) or had a serious prior medical condition (n = 1). Those in the placebo arm could walk an average of 154 metres further at baseline than those in the galsulfase arm. Groups could therefore not be considered equal at baseline. There was a risk of selective reporting, as results on other unspecified tertiary outcome measures, which did not show a change with galsulfase, were not reported.

#### Effectiveness and safety of laronidase for treating MPS type I

One high quality randomised trial compared laronidase and placebo in patients at least 5 years old, with MPS (Wraith, J. E. et al. 2004). Patients randomised to receive laronidase were dosed at 100 U/kg of body weight (0.58mg/kg), in a solution of 100 mmol/L sodium phosphate, 150 mmol/L sodium chloride, and 0.001% polysorbate-80. Patients in the placebo condition received the same solution without the laronidase. Both placebo and laronidase solutions were administered in 0.1% human serum albumin in normal saline, administered intravenously over 4-hours, once a week. To reduce the chance of infusion-related adverse events, patients were also given an antipyretic and an antihistamine before each infusion. The proportion of participants that were clinically diagnosed as Hurler-Scheie syndrome comprised 82% in the laronidase group and 83% in the placebo group. Results were not separated according to clinical syndromes.

The two primary outcomes were lung function, as measured by the percent of normal forced vital capacity (FVC), and exercise tolerance, as measured by the distance covered in the 6-minute walk test (6MWT). FVC and 6MWT can be considered surrogate measures for respiratory and cardiac function respectively. On average, patients taking laronidase improved by 4.9% in FVC, whereas those in the placebo group decreased slightly (-0.7%). This difference of 5.6% was considered statistically significant but may not be clinically important (GRADE ⨁⨁⨁⨀). Patients on laronidase were able to walk an average of 19.7 metres further in 6 minutes, whereas those receiving placebo infusions walked on average 18.4 fewer metres than at baseline. The difference of 38 metres was statistically significant. However, due to a potentially meaningful difference in baseline values on the 6MWT (those receiving placebo could walk a further 47 metres than those receiving laronidase), these results are difficult to interpret (GRADE ⨁⨁⨁⨀).

Table 95 Lung function and exercise tolerance after laronidase and placebo

| Outcome | Laronidase (N = 22) | Placebo (N = 23) | Difference |
| --- | --- | --- | --- |
| Forced vital capacity (% of predicted normal; mean ± SD) | - | - | - |
| Baseline | 48.4±14.5 | 54.2±16.0 |  |
| Week 26 | 53.3±18.5 | 53.5±14.2 |  |
| Change from baseline to week 26 | 4.9±8.7 | -0.7±5.9 | 5.6, p = 0.007a |
| 6-minute walk test (mean±SD) | - | - | - |
| Baseline | 319.1±131.4 | 366.7±113.7 |  |
| Week 26 | 338.8±127.1 | 348.3±128.8 |  |
| Change from baseline to week 26 | 19.7±68.6 | -18.4±67.5 | 38.1, p = 0.039 |

aANCOVA analysis of covariance, prospectively conducted to account for disease heterogeneity and baseline differences between groups. SD = standard deviation

On average, there was no difference between patients treated with laronidase or placebo, in terms of the change in total apnoea events (no airflow for ≥10 seconds) or hypopnea events (≥50% airflow reduction) (GRADE ⨁⨁⨀⨀). However, *post hoc* analyses of those patients who had abnormal baseline sleep studies on the apnoea/hypopnea index (AHI; sleep apnoea defined by score of ≥10 for ages ≤15 years, and ≥15 for ages >15 years) suggested that laronidase decreased the number of events after 6 months by an average of 6 events per hour, whereas those in the placebo group had a slight increase in the number of apnoea and hypopnea events per hour (0.3; p = 0.014). These outcomes are surrogate outcomes for respiratory function.

Similarly, mean change in joint movement, measured by shoulder flexion, did not differ to a significant degree between groups (GRADE ⨁⨁⨀⨀). A *post hoc* analysis of those whose flexion was limited at baseline showed an improvement while receiving laronidase, whereas those on placebo had a reduction on average in shoulder flexion.

The results of both of these subgroup analyses may have been affected by confounding.

Differences from baseline to follow-up were small on the CHAQ/HAQ Disability Index, and did not differ significantly between conditions (GRADE ⨁⨁⨀⨀).

Table 96 Sleep evaluation, joint movement and level of disability after receiving laronidase or placebo

| Outcome | Laronidase (N = 22) | Placebo (N = 23) | Difference |
| --- | --- | --- | --- |
| Apnoea and hypopnea (mean number of events/hour of sleep, based on a nocturnal polysomnogram)  Change from baseline to 26 weeks (mean) | Decrease of 3.6 events per hour | Not stated | p = 0.145 |
| *Post-hoc* analysis of patients whose baseline AHI suggested sleep apnoea | (n = 10)  Mean decrease 6.0 events per hour of sleep | (n = 9)  Mean increase of 0.3 events per hour of sleep | 11.4 events per hour treatment benefit  p = 0.014a |
| Shoulder flexion (mean of both shoulders) | NR | NR | NS |
| *Post-hoc* analysis of patients with baseline should flexion below median of 90.5” | (n = 7)  9.6” | (n = 12)  -4.8” | Trend towards significance |
| Childhood Health Assessment Questionnaire (≤18 years), or Health Assessment Questionnaire (>18 years) |  |  |  |
| Baseline | 2.0 | 1.9 |  |
| Changes | NR | NR | NS |

a ANOVA model of between-group differences in adjusted mean change; NR = not reported; NS = not significant; AHI = apnoea/hypopnea index

CQAQ/HAQ scale 0 to 3, with 3 being most disabled

Overall, adverse events reported were considered to be related to the disease, more than the treatment. The rates of adverse events were similar between patients receiving laronidase or placebo (Table 97). Compliance with treatment was equivalent between the two groups (Table 98).

Table 97 Infusion-related reactions to laronidase or placebo

| Infusion-related reaction | Laronidase (N = 22)  No. of patients (%) | Laronidase  No. of events | Placebo (N = 23)  No. of patients (%) | Placebo  No. of events |
| --- | --- | --- | --- | --- |
| Any infusion-related reaction | 7 (32) | 66 | 11 (48) | 82 |
| Flushing | 5 (23) | 48 | 4 (17) | 47 |
| Fever | 1 (5) | 1 | 3 (13) | 8 |
| Headache | 2 (9) | 4 | 2 (9) | 3 |
| Rash | 1 (5) | 1 | 2 (9) | 2 |
| Back pain | 1 (5) | 2 | 1 (4) | 1 |
| Sweating increased | 1 (5) | 1 | 1 (4) | 1 |
| Temperature change sensation | 1 (5) | 2 | 1 (4) | 1 |
| Vomiting | 1 (5) | 1 | 1 (4) | 1 |
| Coughing | 1 (5) | 1 | 0 | 0 |
| Face oedema | 1 (5) | 1 | 0 | 0 |
| Hypotension | 1 (5) | 1 | 0 | 0 |
| Paraesthesia | 1 (5) | 2 | 0 | 0 |
| Tachycardia | 1 (5) | 1 | 0 | 0 |

The majority of patients receiving laronidase developed IgG antibodies (Table 98).

Table 98 Development of antibodies and compliance with laronidase or placebo treatment

| Outcomes | Laronidase (N = 22) | Placebo (N = 23) |
| --- | --- | --- |
| Development of IgG antibodies | 20/22 (91%) | Not stated |
| Compliance with treatment | >97% | >97% |

##### Extension study

An extension of the Wraith et al study was published by Clarke et al (2009). Those MPS I patients (n = 45) who successfully completed the 26-week randomised placebo-controlled trial of laronidase entered the 3.5 year extension study, and received laronidase at weekly doses of 100 U/kg of body weight (0.58 mg/kg), diluted with saline and serum albumin, and infused over a period of 4 hours[[15]](#footnote-15). Forty patients completed the open-label phase, these receiving 80% or more of scheduled infusion treatments. There was one death during the trial and four patient withdrawals. Reasons given for withdrawal were a needle phobia, problems scheduling infusion due to school attendance, pregnancy, and an anaphylactic reaction. The death occurred in a patient with viral pneumonia and was considered unrelated to treatment. Measures of effectiveness included change in urinary GAG, hepatomegaly, respiratory function, mobility, and limitations in activities of daily living. Change in liver volume is reported in Table 99. Liver volume improved at a smaller rate of 38% ± 3% from baseline to final assessment. Reduction in liver volume was more rapid in the first year of the trial and declined after that.

Table 99 Change in liver volume in MPS I patients treated with laronidase (Clarke et al. 2009)

| Outcome | Patients with abnormal value % (n) | Baselinea Mean value ± SD | Finala  Mean value  ± SD (n) | Mean change  ± SD (n) | Response by individual patients |
| --- | --- | --- | --- | --- | --- |
| Liver volume (cc/g) | 68 (44) | 3.54 ± 1.02 | 2.04 ± 0.36 (38) | 38% ± 3% (38) improvement | 95% had normal values  92% of those with abnormal values attained normal values |

n = number of with available data

###### Changes in clinical endpoints

Table 100 provides data for a range of clinical outcomes measured in the laronidase extension trial. Respiratory function was assessed by percent predicted forced vital capacity (%FVC) and this outcome indicated patient decline from baseline to final assessment, albeit a slow decline of approximately one percentage point per year (not meeting the minimum clinically important difference is defined as a %FVC ≥15%). The other clinical measurements showed improvement from baseline to final assessment. The score with the greatest number of improved patients was the CHAQ/HAQ disability index which measures physical disability and limitations in activities of daily living on a scale of 0 to 3. The authors defined the minimum clinically important difference as a change of 0.24 (Clarke et al. 2009). The index remained stable or improved gradually over time from a level of severe at baseline (overall baseline index score 1.91) in 27 out of 35 patients by the final assessment, with a mean decrease of 0.31 being clinically important (GRADE ⨁⨁⨁⨀). In addition there was improvement in pain in 30 patients when the Pain Index was used to assess this outcome (a subscale of the CHAQ/HAQ, also on a scale of 0 to 3) (baseline mean value 0.93 ± 0.84; final mean value 0.56 ± 0.52, mean decrease 0.34 ± 0.14. It is likely that this reflects a clinically meaningful difference (GRADE ⨁⨁⨁⨀). There were also improvements in mobility. An improvement on the 6MWT was defined as being able to walk at least an extra 54 metres. The average improvement over the study period was only 17.1 metres. Overall 31 out of 40 patients showed improvement or stabilisation in the 6MWT outcome at the final assessment compared to baseline (GRADE ⨁⨁⨁⨀). Shoulder range of movement was meaningfully improved in 46% of patients (improvement by ≥20°) and remained stable in 49% over the same period (GRADE ⨁⨁⨀⨀).

Table 100 Changes in clinical endpoints for MPS I patients treated with laronidase (Clarke et al. 2009)

| Outcome | Patients with abnormal value % (n) | Baselinea Mean value ± SD | Finala  Mean value  ± SD (n) | Mean change  ± SD (n) | Improved % | Stable % | Declined % |
| --- | --- | --- | --- | --- | --- | --- | --- |
| % predicted normal FVC | 100(45) | 49.9 ± 13.9 | 48.3 ± 13.7 (40) | 0.78 ± 0.32 percentage point decline per year (45)b | 18 | 55 | 28 |
| Distance walked in the 6MWT (m) | 33 (45) | 334.0 ± 129.5 | 373.3 ± 133.0 (40) | 17.1 ± 16.8 improvement (45)b | 50 | 28 | 23 |
| AHI (events per hour) | 51 (39) | 17.5 ± 15.5 | 12.1 ± 16.6 (34) | 4.4 ± 2.3 improvement (32) | 31 | 63 | 6 |
| Shoulder range of motion (o) | 100 (44) | 90.1 ± 31.7 | 108.1 ± 20.8 (40) | 17.4 ± 3.6 improvement (37) | 46 | 49 | 5 |
| Corrected visual acuityc | 93 (43) | 1.66 ± 0.34 | 1.60 ± 0.34 (39) | 0.03 ± 0.03 improvement (39) | 24 | 66 | 10 |
| CHAQ/HAQ disability index | 100 (44) | 1.91 ± 0.61 | 1.53 ± 0.77 (35) | 0.31 ± 0.11 improvement (35) | 57 | 20 | 23 |

6MWT = 6 minute walk test; AHI = apnoea/hypopnea index; CHAQ = child health assessment questionnaire (scale = 0 to 3, where higher scores indicate greater disability); FVC = forced vital capacity; HAQ = health assessment questionnaire (scale = 0 to 3, where higher scores indicate greater disability); n = number of with available data; SD = standard deviation

a Baseline and/or final assessment values were not available in all clinical domains

b 45 patients contribute data to the regression model that estimates this result

c Snellen visual acuity values were log-transformed; 1.66 corresponds to 20/46; 1.6 corresponds to 20/40

###### Safety

While all patients experienced at least one adverse event, only 30 patients experienced adverse events that appeared related to laronidase treatment. In total there were 682 adverse events related to treatment during the extension study; however, 414 (61%) of these were infusion associated reactions (IARs) experienced by one patient.

The most common adverse events related to treatment were: rash (22%), arthralgia (20%), headache (18%), flushing (16%), injection site reaction (13%), fever (13%), arthropathy (11%), abdominal pain (11%), back pain (11%), skeletal pain (11%) and nausea (11%). There were 9 serious adverse events in total which occurred in 3 patients – 7 IARs (2 patients), back pain (1 patient) and vein disorder (1 patient). One death occurred in a 7 year old boy which was unrelated to the treatment.

Of the 45 patients in the trial, 42 (93%) developed IgG antibodies to laronidase with 13 of these testing seronegative at their final assessment. Development of IgG antibodies did not appear to coincide with IARs and most IARs occurred following seroconversion. One patient who had an anaphylactic shock was found to be IgE positive and was withdrawn from the trial.

#### Effectiveness and safety of idursulfase for treating MPS type II

One high quality double-blind RCT (Muenzer et al. 2006) and one open-label extension study were identified which compared idursulfase with placebo in MPS II patients. The RCT randomised 96 patients to receive idursulfase weekly (0.5 mg/kg), idursulfase every other week (EOW)(0.5mg/kg) or placebo weekly. The patients in the trial arm receiving idursulfase EOW received placebo infusions on the alternate week to maintain blinding. Patients who developed infusion reactions were treated with antihistamines and/or corticosteroids. Other than these treatments, standard medical management was not described. Participants were all males, and 45% were between the ages of 5 and 11 years, with 25% being over 18 years. An open label extension (Muenzer et al. 2011) provided 2 year follow-up data on 94 patients who completed the double-blind RCT.

##### Primary effectiveness

##### Survival

There were two deaths in the study population within one year of treatment. One was a 24 year old from the idursulfase weekly group who died from a cardiac arrest 5 weeks after his first infusion. This followed the development of a pulmonary infection and respiratory insufficiency. The second death was a 6 year old from the placebo group who developed streptococcus pneumonia and suffered a lung haemorrhage at 34 weeks. Neither death was attributed to treatment allocation (da Silva et al. 2014; Muenzer et al. 2006).

##### Secondary effectiveness

##### 6 minute walk test and forced vital capacity

The primary outcome measures of the RCT by Muenzer et al (2006) were the six-minute walk test (6MWT) which claimed to estimate physical functional capacity, and the percent predicted forced vital capacity (%FVC) which provides a surrogate measure of respiratory function. In some studies 6MWT may be considered to be a surrogate measure of cardiac function. A two-component composite score was also reported which was a combination of %FVC and 6MWT. Additional comparisons between groups were reported of liver and spleen volumes. An intention-to-treat analysis of the population was conducted (Muenzer et al. 2006) (Table 101).

Table 101 Summary of changes from baseline to week 53 for MPS II patients randomised to idursulfase weekly, idursulfase every other week or placebo (Muenzer et al. 2006)

| Outcome  (observed mean ± SEM) | Idursulfase weekly (n = 32) | Idursulfase EOW (n = 32) | Placebo (n = 32) | Difference  (vs placebo, p)b |
| --- | --- | --- | --- | --- |
| 6MWT (metres ± SEM) | B = 392 ± 19  C = 44.3 ± 12.3 | B = 401 ± 18  C = 30.3 ± 10.3 | B = 392 ± 19  C = 7.3 ± 9.5 | Weekly p = 0.0131  EOW p = 0.0732 |
| FVC, (% predicted ± SEM) | B = 55.3 ± 2.8  C = 3.45 ± 1.77 | B = 55.1 ± 2.5  C = 0.004 ± 1.32 | B = 55.6 ± 2.2  C = 0.75 ± 1.71 | Weekly p = 0.0650  EOW p = 0.9531 |
| Absolute FVC (L ± SEM) | B = 1.19 ± 0.10  C = 0.22 ± 0.05a | B = 1.17 ± 0.10  C = 0.07 ± 0.03 | B = 1.09 ± 0.09  C = 0.06 ± 0.03 | Weekly p = 0.0011  EOW p = 0.3735 |

% FVC = percent predicted forced vital capacity; 6MWT = 6-minute walking test; EOW = every other week; SEM = standard error of the mean; B = baseline; C = change

a P = 0.0176 compared to EOW dosing

b P-values are based on ANCOVA for the comparison to placebo.

Patients in the idursulfase weekly group walked significantly further in 6 minutes than those in the placebo group for the 6 minute walk test (6MWT; 44.3 ± 12.3m versus 7.3 ± 9.5m, p = 0.0131) and had significantly better absolute Forced Vital Capacity (FVC) compared to the placebo group (0.22 ± 0.05% versus 0.06 ± 0.03%, p = 0.0011) after 53 weeks. The % predicted FVC increased more in the idursulfase weekly group compared to placebo but the difference was not statistically significant. When the same outcomes were compared between the idursulfase every other week (EOW) and placebo groups, none reached statistical significance, although the 6MWT showed a trend in favour of idursulfase EOW. The authors also reported that there was a statistically significant difference in the absolute FVC when the idursulfase weekly and EOW groups were compared (p = 0.018).

In Table 102 the data for treatment difference between randomised groups for the two-component composite score is reported. The score gives a combined measure of respiratory function and physical function capacity using the O’Brien analysis procedure[[16]](#footnote-16). Using an ITT analysis, the score was significantly higher in the idursulfase weekly group compared to placebo (treatment difference 19.96 ± 6.47, 9 = 0.0049), and the difference was smaller but still significant between the idursulfase EOW group compared to placebo (treatment difference 12.86 ± 6.17, p = 0.0416). There was no difference between Weekly and EOW dosing of idursulfase (GRADE ⨁⨁⨁⨀).

Table 102 Treatment difference in primary efficacy outcome for MPS II patients randomised to idursulfase weekly, idursulfase fortnightly, or placebo (Muenzer et al. 2006)

| Outcome  (ITT analysis) | Idursulfase weekly versus placebo (n = 32) | Idursulfase EOW versus placebo (n = 32) | Weekly versus EOW (n = 32) |
| --- | --- | --- | --- |
| Treatment difference for the two-component composite scorea | 18.96 ± 6.47  p = 0.0049 | 12.86 ± 6.17  p = 0.0416 | 10.84 ± 7.11  p = 0.1329 |

% FVC = percent predicted forced vital capacity; 6MWT = 6-minute walking test; EOW = every other week; ITT = intention to treat

a The composite score combines 6MWT and %FVC

##### Change in liver and spleen volumes

The % change in liver and spleen volumes were measured after 53 weeks of treatment (Table 103). Liver volumes decreased by more than 20% in both idursulfase groups but remained unchanged in the placebo group. Hepatomegaly was defined as a liver volume of >3.5% of body weight in patients aged 5 – 12 years, >2.2% in patients 13 – 17 years, and >2.6% in patients >18 years. Approximately 80 percent of patients who had hepatomegaly at baseline, and were treated with idursulfase, had a normal liver volume after 18 weeks and 53 weeks. In contrast, only one patient out of 23 with baseline hepatomegaly who received placebo had a normal liver volume at week 53 (GRADE ⨁⨁⨁⨀).

Spenomegaly was defined as having a spleen volume greater than the 95th percentile of normal distribution of children. The majority of patients had normal spleen volumes at baseline. Spleen volumes were similarly reduced in both the idursulfase weekly and EOW groups compared to placebo (GRADE ⨁⨁⨁⨀).

Table 103 Change in liver and spleen volumes in MPS II patients randomised to idursulfase weekly, idursulfase every other week or placebo (Muenzer et al. 2006)

| Outcome  (observed value ± SE) | Weekly (n = 32) | EOW (n = 32) | Placebo (n = 32) | Difference  (vs placebo, p)a |
| --- | --- | --- | --- | --- |
| Liver volume (mL) (mean±SE)  % change | B = 1262 ± 50  C = -25.3 ± 1.6 | B = 1191 ± 48  C = -24.0 ± 1.7 | B = 1198 ± 48  C = -0.8 ± 1.6 | Weekly p<0.0001  EOW p<0.0001 |
| Spleen volume (% change ± SE) | B = 316 ± 39  C = -25.1 ± 2.4 | B = 251 ± 26  C = -19.8 ± 3.2 | B = 288 ± 30  C = 7.2 ± 4.2 | Weekly p<0.0001  EOW p<0.0001 |

EOW = every other week; SE = standard error; B = baseline; C = change from baseline

a P-values are based on ANCOVA for the comparison to placebo.

##### Comparative safety

Muenzer et al (2006) reported adverse events that occurred in the idursulfase trial at least 9% more frequently in the idursulfase groups than in the placebo group (Table 104; GRADE ⨁⨁⨁⨁). Adverse events of pruritic rash, infusion site swelling, urticarial, dyspepsia, anxiety and chest wall pain occurred only in the patients randomised to idursulfase, or only rarely in the placebo group, and may therefore be indicated as drug side effects. Whilst more frequent in the idursulfase groups headache, nasopharyngitis, abdominal pain, arthralgia and pruritus also occurred frequently in the placebo group, thus are possibly disease related. Fever, headache, cough, pharyngitis, upper respiratory tract infection, nasal congestion, nausea, vomiting, abdominal pain and diarrhoea were reported to be the most common adverse events overall.

Table 104 Number and percentage of MPS II patients with adverse events occurring at least 9% more frequently in idursulfase-treated patients than in placebo-treated patients (Muenzer et al. 2006)

| Adverse event | Idursulfase weekly (n = 32)  N (%) | Idursulfase EOW (n = 32)  N (%) | Placebo (n = 32)  N (%) |
| --- | --- | --- | --- |
| Headache | 19 (59%) | 21 (66%) | 14 (44%) |
| Nasopharyngitis | 17 (53%) | 19 (59%) | 15 (47%) |
| Abdominal pain | 16 (50%) | 19 (59%) | 13 (41%) |
| Arthralgia | 10 (31%) | 14 (44%) | 9 (28%) |
| Pruritus | 10 (31%) | 6 (19%) | 5 (16%) |
| Rash pruritic | 5 (16%) | 5 (16%) | 0 |
| Infusion site swelling | 4 (13%) | 4 (13%) | 1 (3%) |
| Urticaria | 5 (16%) | 4 (13%) | 0 |
| Dyspepsia | 4 (13%) | 4 (13%) | 0 |
| Anxiety | 2 (6%) | 4 (13%) | 0 |
| Chest wall pain | 4 (13%) | 0 | 0 |

##### Extension study

All 94 patients who completed the double-blind phase enrolled in a 2 year open label trial extending the total study time to 36 months (Muenzer et al. 2011). Idursulfase was received weekly at a dose of 0.5 mg/kg and assessments were made 4 monthly. Eighty five patients completed the extension study. For the endpoint data analysis, baseline was defined as the most recent assessment before the start of treatment, i.e. for patients who had been in the placebo group in the original trial the baseline was at the final assessment of the double-blind phase. Results are reported in Table 105.

Statistically significant improvements from baseline were seen overall for the 6MWT and at several time points. When results were stratified by age group it was found that patients aged over 18 had improved the most at the final assessments (GRADE ⨁⨁⨀⨀). Absolute FVC was assessed at 36 months. For the whole population there was an increase in capacity from baseline of 0.31 L absolute FVC, indicating an improvement in respiratory function. This is a further improvement from what was observed in the randomised trial (change of 0.07 L in idursulfase EOW group, and 0.22 L in idursulfase weekly group). The improvement was found to be restricted to the < 12 and 12 -18 year old age groups (increases of 0.39 ± 0.09 and 0.45 ± 0.11 L respectively) (GRADE ⨁⨁⨀⨀).

Table 105 Long-term outcomes for MPS II patients receiving idursulfase in a 2 year open label extension study (Muenzer et al. 2011)

| Outcome  (observed value ± SEM) | Baseline  (mean ± SE) | Change from baseline at  4 months | Change from baseline at  20 months | Change from baseline at  36 months |
| --- | --- | --- | --- | --- |
| 6MWT (metres ± SE), all patients  < 12 yrs  12-18 yrs  > 18 yrs | 400 ± 10  428 ± 11  103 ± 18  351 ± 27 | 14 ± 5  -  -  - | 42 ± 10  -  -  - | -  8 ± 6  0.7 ± 7  48 ± 13 |
| Absolute FVC (L ± SE), all patients  < 12 yrs  12-18 yrs  > 18 yrs | 1.18 ± 0.06  -  -  - | -  -  -  - | -  -  -  - | 0.31 ± 0.06, p<0.05a  0.39 ± 0.09  0.45 ± 0.11  -0.04 |

6MWT – 6-minute walking test; SE = standard error of the mean; FVC= forced vital capacity

a P-value based on ANCOVA for the comparison to placebo

Further long-term outcomes were discussed by Muenzer et al (2011); however, some results which were not significantly different from baseline were not published and this may have introduced some reporting bias into the study. Percent predicted FVC was found to be no different from baseline at all-time points except one (month 16). There were improvements in joint range of motion that indicated a progressive and statistically significant change from baseline for the shoulder (p ≤ 0.005), but no consistent changes for elbow, wrist, digits, hip, knee or ankle. The Child Health Assessment Questionnaire (CHAQ) tool was used to assess functional status and showed clinically important changes from baseline. When parents assessed their children using the CHAQ Disability Index Score (DIS) there were statistically significant improvements at 8, 16, 20, 24 and 30 months. For the child-assessed DIS similar improvements from baseline were seen at 20, 24, 30, and 36 months (n = 48 children at baseline). No comment was made as to whether measurements indicating non-significant changes were in the positive or negative direction from baseline, or whether there were statistically significant changes indicating patient decline.

#### Effectiveness and safety of galsulfase for treating MPS type VI

One randomised double-blind multicentre study (Harmatz et al. 2006) compared galsulfase with placebo in patients with MPS VI. Thirty nine patients from 6 clinical sites were randomised to either galsulfase (rhASB 1.0 mg/kg) or placebo for 24 consecutive weeks. Both drug and placebo were administered with the same method. No description of standard medical management was provided. After 24 weeks, all participants received weekly infusions of galsulfase and were assessed again at the end of 48 weeks. The RCT was given a quality appraisal of moderate. While the study met criteria for blinding, randomisation method and allocation concealment method were not reported. More than 25% of randomised patients (11/39 patients) did not fulfil the study eligibility criteria with reasons being they exceeded the walk distance eligibility criteria (n = 7), were <7 years old (n = 3) or had an earlier medical complication (n = 1). Measures of efficacy were analysed using an ITT analysis. The safety outcome analysis was limited to those who received at least one dose. One patient withdrew after the 24 week time point.

Long term cardiac and pulmonary outcomes were assessed after open label treatment extension in two studies (Braunlin et al. 2013; Harmatz et al. 2010) in which patients were assessed at intervals up to 240 weeks. The extension group included patients who participated in earlier dose-comparison and open label studies and data for trial populations could not be separated for consideration here.

The primary outcome of the RCT and extension period was the 12 minute walk test (12MWT) which provided a measure of endurance and was conducted 6 weekly from baseline to 24 weeks, then 12 weekly to 48 weeks follow-up. This measure may also be considered a surrogate outcome for cardiac and pulmonary function. Secondary measures were the 3 minute stair climb (3MSC) and measures of respiratory function (forced vital capacity and the maximum voluntary ventilation).

##### Primary effectiveness

##### Survival

There was no comparison of survival between patients randomised to galsulfase or placebo. No deaths were reported in either group.

##### Secondary effectiveness

##### Endurance

A comparison of functional endurance between patients in the galsulfase and placebo groups was measured with 12MWT (Table 106). Despite randomisation, the difference between groups at baseline was statistically significant, with the placebo group able to walk the further distance (227 ± 170 versus 381 ± 202 m, p = 0.014) (Harmatz et al. 2006). When the change in 12MWT at week 24 was compared between groups using a longitudinal analysis, with the covariates of baseline values and site, the estimated difference between groups was 92 metres in favour of galsulfase (GRADE ⨁⨁⨀⨀).

Between 24 and 48 weeks, those who received placebo in the first 24 weeks increased the number of metres walked by a larger amount than those who had received galsulfase in the first 24 weeks (Table 107).

Table 106 Distance walked in a 12 minute walk test for MPS VI patients randomised to either galsulfase or placebo (Harmatz et al. 2006)

| Time point | Galsulfase  Mean ± SD | Placebo  Mean ± SD | Estimated mean difference (95%CI )  p-value |
| --- | --- | --- | --- |
| Baseline | 227 ±170 | 381 ± 202 | - |
| Week 24 | 336 ± 227 | 399 ± 217 | - |
| Week 24-Baseline (absolute change) | 109 ± 154 | 26 ± 122 | 92 (11, 172)  p = 0.025 |

SD = standard deviation

Table 107 Distance walked in a 12 minute walk test for MPS VI patients receiving galsulfase in the extension study (Harmatz et al. 2006)

| Time point | Galsulfase/ galsulfase  Mean ± SD | Placebo/ galsulfase  Mean ± SD |
| --- | --- | --- |
| Week 24 | 336 ± 227 | 399 ± 217 |
| Week 48 | 372 ± 240 | 482 ± 206 |
| Week 48-Week 24 (absolute change) | 36 ± 97 | 66 ± 133 |

Another secondary measure of efficacy in the RCT was the 3MSC, with results paralleling those for 12MWT. There was a trend towards a statistically significant difference between groups in stairs climbed in 3 minutes at 24 weeks (p = 0.53), favouring galsulfase. (Table 108) (GRADE ⨁⨁⨀⨀). In the open-label study between weeks 24 and 48, patients continued to increase the number of stairs they were able to climb within 3 minutes, with the greatest increase seen in those newly treated with galsulfase (Table 109).

Table 108 Comparison of 3 minute stair climb for MPS VI patients randomised to either galsulfase or placebo (Harmatz et al. 2006)

|  |  |  |  |
| --- | --- | --- | --- |
| Time point | Galsulfase  Mean ± SD | Placebo  Mean ± SD | Difference  p-value |
| Baseline | 19.4 ± 12.9 | 31.0 ± 18.1 | - |
| Week 24 | 26.9 ± 16.8 | 32.6 ± 19.6 |  |
| Week 24/Baseline (absolute change) | 7.4 ± 9.9 | 2.7 ± 6.9 | 5.7 ± 2.9  p = 0.053 |

SD = standard deviation

Table 109 Comparison of 3 minute stair climb for MPS VI patients receiving galsulfase in the extension study (Harmatz et al. 2006)

| Time point | Galsulfase/ galsulfase  Mean ± SD | Placebo/ galsulfase  Mean ± SD |
| --- | --- | --- |
| Week 24 | 26.9 ± 16.8 | 32.6 ± 19.6 |
| Week 48 | 29.8 ± 16.0 | 39.6 ± 19.5 |
| Week 48/Week 24 (absolute change) | 2.9 ± 7.2 | 5.9 ± 7.9 |

SD = standard deviation

##### Respiratory function

Respiratory function, as assessed by forced vital capacity, forced expiratory volume in 1 second (FEV1, data not reported), or the maximum voluntary ventilation (MVV), did not improve over the course of the study, with a large amount of variability between patients.

Table 110 Forced vital capacity and maximum voluntary ventilation in patients randomised to either galsulfase or placebo (Harmatz et al. 2006)

| Outcome | Galsulfase (N=17, 15) | Placebo (N = 19, 17) | Difference |
| --- | --- | --- | --- |
| Forced vital capacity L; mean ± SD) | - | - | - |
| Baseline | 0.65 ± 0.40 | 0.50 ± 0.24 | - |
| Week 24 | 0.63 ± 0.47 | 0.45 ± 0.13 | - |
| Week 24/Baseline (absolute change) | -4 ± 19 | 3 ± 21 | Not significant |
| MVV (L/min) | - | - | - |
| Baseline | 16.8 ± 8.9 | 15.9 ± 5.4 | - |
| Week 24 | 20.5 ± 11.4 | 15.9 ± 4.6 | - |
| Week 24/Baseline (absolute change) | 13 ± 29 | 8 ± 37 | Not significant |

MVV=maximum volume ventilation

#### Safety

The number of patients experiencing adverse events from galsulfase relative to placebo is reported for weeks 1 to 24 (Harmatz et al. 2006). There were more drug-related adverse events, adverse events during infusion, and drug-related adverse events during infusion, in the galsulfase group than in the placebo group but the differences were not statistically significant (Table 111) (GRADE ⨁⨁⨁⨀). A trend was observed towards harms from drug-related adverse events during infusion in patients receiving galsulfase.

Table 111 Number of patients experiencing adverse events during weeks 1 to 24 in MPS VI patients randomised to either galsulfase or placebo (Harmatz et al. 2006)

| Time point | Galsulfase  n/N of patients | Placebo  n/N of patients | RR (fixed)  (weight %) | 95% CI |
| --- | --- | --- | --- | --- |
| Deaths | 0/19 | 0/20 | Not estimable | - |
| Drug-related adverse events | 11/19 | 6/20 | 1.93 (100) | 0.89, 4.17 |
| Serious and severe adverse events | 7/19 | 8/20 | 0.92 (100) | 0.42, 2.04 |
| Adverse events during infusion | 11/19 | 8/20 | 1.45 (100) | 0.75, 2.80 |
| Drug-related adverse events during infusion | 10/19 | 4/20 | 2.63 (100) | 0.99, 6.98 |

RR = relative risk

#### Extended assessment of safety

PSURS were used to examine non-comparative safety data regarding drugs for MPS I, II and VI.

##### MPS I

The PSUR provided for laronidase covered the period 1 May 2006 to 30 April 2007. Laronidase first received marketing approval on 30 April 2003 (Genzyme 2007).

It is estimated that during the reporting period, four patients were receiving laronidase within clinical trials, and 553 were receiving laronidase commercially. During the same period, 140 case reports were received, of which 135 were medically confirmed. The majority (127) were from spontaneous reporting sources, 6 were identified through the literature, and 2 were from clinical trials(Genzyme 2007).

A summary of the 59 serious and 76 non-serious reported events between May 2006 and April 2007 is shown in Table 112. Other adverse reactions were only reported in individual cases.

Table 112 Adverse drug reactions to laronidase (Genzyme 2007)

| Category | Description (No. of events between May 2006 and April 2007) |
| --- | --- |
| Serious unlisted adverse drug reactions | Complications of bone marrow transplantation (graft versus host disease) (8)  Pyrexia (8)  Oxygen saturation decreased (6)  Dyspnoea and respiratory failure (4)  Chills (3)  Coughs (3)  Respiratory distress (3)  Sepsis (3)  Vomiting (3)  Central line infection (2)  Intracranial pressure increased (2)  Post-procedural complication (2)  Septic shock (2) |
| Serious listed adverse drug reactions | Urticaria (6)  Erythema (2) |
| Non-serious unlisted adverse drug reactions | Chills (10)  Fever (10)  Dyspnoea (6)  Diarrhoea (5)  Nausea (5)  Vomiting (5) |
| Non-serious listed adverse drug reactions | Urticaria (12)  Headache (5)  Rash (5)  Erythema (4) |

A total of 16 case reports were identified during the reporting period, where patients taking laronidase had a fatal outcome. All of these were either thought to be unrelated to treatment (n = 13) or unassessable (n = 3). There were 8 case reports of cardiac disorders during the reporting period, of which 7 were unrelated to laronidase, and in the remaining case, causality could not be assessed (Genzyme 2007).

There were 6 case reports classed as “General Disorders and Administration Site Conditions”, of which 3 were unrelated to laronidase, 1 was unassessable, and 2 were considered related to laronidase. In one of these cases, an 8 year old girl who had been receiving laronidase infusions for 18 months, developed fever, swelling of the lips, shaking, chills and vomiting during a laronidase infusion. The infusion was stopped and the patient was admitted to hospital for two days, where she was treated with antibiotics. The patient was found to have positive IgE and IgG antibodies towards laronidase. Subsequent infusions were uneventful. The second related case was in a 4 year old boy who had been receiving laronidase for 3 years prior to the infusion-related adverse event, in which he had facial urticaria and oedema and malaise for 5 minutes. This was deemed to be serious and related to laronidase. The infusion was stopped, he was treated with epinephrine, and recovered the same day (Genzyme 2007).

Three case reports were classified as “Immune system disorders”, all of which were assessed to be unrelated to laronidase. There were 9 case reports coded as “Infections and infestations”, of which 7 were considered unrelated to treatment, one was unassessed, and one was thought to be related to laronidase. A three year old boy had a normal temperature at the start of infusion, which was raised to 39.4°C on completion of infusion. He was given paracetamol and vomited. The patient was diagnosed with a viral illness and hospitalised overnight. He recovered without sequelae.

There were 6 cases of injury, poisoning, and procedural complications during the reporting period, of which 3 were unassessable, and the remaining 3 were deemed unrelated to laronidase (Genzyme 2007).

There were five serious case reports listed under “Investigations”, of which one was unassessable in relation to laronidase, while the four others, all in one 4 year old boy, were considered related to treatment with laronidase. Infusion-associated reactions occurred on five different occasions over five weeks, including facial urticaria, generalised erythema, oxygen desaturation, and coughing/wheezing, which required the infusion to be stopped. The patient was given medication for the symptoms, and recovered the same day. After the fifth infusion which resulted in adverse events, laronidase treatment was stopped (Genzyme 2007).

Two neoplasms were reported, neither of which were considered related to laronidase. Three nervous system disorders were reported, all considered unrelated to laronidase. One unrelated spontaneous abortion was reported (Genzyme 2007).

Eleven reports of “Respiratory, Thoracic and Mediastinal Disorders” were received during the reporting period, of which 6 were considered unrelated to treatment, 3 were assessed as relating to laronidase, and 2 were unassessable. Of the cases thought related to laronidase, a male patient was hospitalised with difficulty breathing and hives, 29 hours after infusion with laronidase. He was treated with supplemental oxygen and recovered without sequelae. In the second case, the patient had received 90% of his infusion, when he developed generalised oedema, swelling of the face, and peri-oral oedema, with pruritic urticaria on the lower extremities, torso and face. The patient was given epinephrine, which reduced the urticaria and facial oedema. The patient vomited several times. After several hours, the symptoms resolved, and the infusion was re-started with the addition of an antihistamine and hydrocortisone, without incident. In the third case, after an hour of laronidase infusion, the patient had a fever, difficulty breathing, generalised tremor, tachypnoea, generalised cyanosis, vomiting and diarrhoea. The infusion was stopped; the patient was given dipirone and hydrocortisone, and recovered without sequelae. The infusion was re-started at a slower rate (Genzyme 2007).

One surgical adverse event was reported, unrelated to laronidase.

Three cases of vascular disorders were reported, of which one was unassessable, one was considered unrelated to laronidase, and one was considered related. In this case, a 6 year old boy developed facial redness and arterial hypertension during the second half of his infusion, which was described as an allergic reaction.

The conclusion of the PSUR was that the adverse events reported are often indicative of underlying MPS I disease, and the benefit/risk ratio of laronidase is favourable (Genzyme 2007). However, it is also apparent that infusion-related hypersensitivity reactions are not uncommon.

##### MPS II

The reporting period for idursulfase was between July 2010 and July 2011. Information from this reporting period was provided to the LSDP Reference Group. The information is withheld in this draft report at the request of the drug sponsor.

Table 113 Adverse reactions to idursulfase during reporting period (Shire Pharmaceuticals 2011)

| Preferred term | No. of serious events | No. of non-serious events | Total |
| --- | --- | --- | --- |
| Infusion related reaction | ''''''' | '''''' | '''''' |
| Rash (inc. erythematous and papular) | ''' | ''''''' | ''''' |
| Urticaria | ''' | ''''''' | ''''' |
| Dyspnoea | '''' | '''' | ''' |
| Pyrexia | '''' | ''' | '''' |
| Convulsion | '''' | ''' | ''' |
| Cough | '''' | ''' | ''' |
| Erythema / generalised erythema | ''' | ''' | '''' |
| Tremor | ''' | ''' | '''' |
| Cyanosis | '''' | ''' | ''' |
| Anxiety | '''' | '''' | ''' |
| Total | '''''' | ''''''''' | '''''''''' |

'''''''' ''''''''' '''''''''''''''''''' '''''''''''''''' ''''''''''''' ''''''' ''''''''''' '''''''''''''''''' ''''''''' ''''' '''''''''''''''' ''''' ''' '''''''''''''' ''''''''' ''''' '''''''''''''''''''' '''''''''''''''''''''''''''' '''''''''''''''''' '''''''''''''' ''''''''''''''''' ''''''''' ''''''''''''''''''' ''''''''''''''''' ''''''''''''''' '''''''''''''' ''''''''''''''''''''''''' '''''''''''''''''''''''''' ''''''''''''''''''' ''''''''''''''' '''''''''' '''''''' ''''''''''''''''''''' '''''''''''''''' '''''''''''' '''''' ''''''''''''''''' '''' '''''' ''''''''''''''''' ''''''''''''''''''''' '''''''''''''''''''''' '''''''''''' '''''''''''''''''''''''''''' ''''''''''''

''''''' ''''''''' ''''''''''''''''''' ''''' ''''''''''''''''''''''' ''' '''''''''' '''''''''''''' '''' '''''' ''''''''''''''''''''''' '''' '''''''''''' ''''''''''''''''''' ''''''''' '''''''''''''''''''''' '''''''''''''''''''''''''' ''''''''''' ''''' ''''''' ''''''''''' '''' '''''''''''''''''''''' ''''''''' '''''''''''''''''' '''' ''''''''''''' '''' '''''''''''''''''''

''''''''''' ''''''''''' '' '''''''''''''''' ''''''''''''' ''''''' '''''''''''''''''' ''''''''''''' ''''' ''''''''''' '' ''''''''' '''''''''''''''' ''''''''''''''' '''' ''''''''' '' '''''''''''' ''''''''' '''''''''''''''''''''' ''''''' ''''''' ''''''''''''''''''' ''''''''' '''''''''''''''' '''''''''''''''''''' '''''''''''''''''''' '''' ''''''''''' '''' '''''''''' ''''' ''''''''''''''''''''''' ''''' '''''''''''''''' '''''''''' '''''''''''''''''''''''''''''' ''''''''''''

A summary of adverse drug reactions, by system organ class and frequency, is shown in Table 114.

Table 114 Frequency of adverse drug reactions to idursulfase (Shire Pharmaceuticals 2011)

| System Organ Class | Very common adverse drug reactions (>1/10) | Common adverse drug reactions (>1/100, <1/10) | Frequency not known |
| --- | --- | --- | --- |
| Immune System disorders | '''''' | ''''' | '''''' |
| Nervous system disorders | '''' | '''''' | '''''' |
| Cardiac disorders | '''' | '''''' | ''''''' |
| Vascular disorders | '''' | '''' | ''' |
| Respiratory, thoracic and mediastinal disorders | '''' | ''' | '''' |
| Gastrointestinal disorders | '''' | '''' | '''' |
| Skin and subcutaneous tissue disorders | ''' | '''' | '''' |
| Musculoskeletal and connective tissue disorders | '''' | ''' | ''' |
| General disorders and administration site conditions | ''' | '''' | ''' |
| Immune System disorders | ''' | ''' | '''' |
| Nervous system disorders | '''' | '''' | ''' |
| Cardiac disorders | ''''' | ''''''''' | ''''''''' |

##### MPS VI

An extended assessment of harms of galsulfase was made using A Periodic Safety Update Report (PSUR) for the period 1 May 2013 to 1 May 2014 provided by BioMarin Pharmaceutical Inc. The PSUR reported the cumulative global patient exposure to galsulfase from the date of first approval of 01 June 2005 until 31 May 2014. Overall, the serious adverse events (SAEs) from clinical trials and adverse drug reactions (ADRs) from post-marketing sources during the 2013-2014 reporting period showed no change in the characteristics, frequency, or severity of listed events and there was no increased reporting frequency of ADRs. The safety data reviewed for the reporting period and from the cumulative perspective of the non-clinical and clinical data, the Clinical Surveillance Program (CSP), and the post-marketing experience indicates no change in the positive benefit-risk profile of galsulfase.

Unpublished information from the PSUR was provided to the LSDP Reference Group but this has been redacted in this draft report at the request of the drug sponsor.

'''''''''''' ''''''' '''''''''''''''''' ''''''''''''''' ''' ''' '''''''''''''''''' ''''''''' '''''''' ''''''''''''''''' '''''''''''''''''' ''''''''''''''''''''' ''''''''' ''''''' '''''''''' ''''''''' ''''''''''''''' '''''''''' '''''''''' '''''''''' ''''''''''''''' ''''' '''''''''''''' '''''''''''''' '''''''''''''''''' '''''' ''''''''''' ''''' ''''''''''''''''''' ''''''''''''' '''' '''''' '''''''''''''''' '''''''''''' '''''''''''''''''' '''' '''''''''''''''' '''''''''''''''''' '''''''''''''''''''''' ''' ''' ''''''' '''''''''''''' '''''''' '''''''''' '''' '''''' ''''''''''''''' '''''''''''' ''''''''' '''''''''''''''' ''''' '''''''''' '''''''''''' ''''' '''''' ''''''''''''''''''''' '''''''' '''''''' ''''''''''' ''''''''' '''''' '''' '''''' '''''''''''''''''''' '''''''''''''''' ''''''''''''' '''''' ''''''''' '''''''''''''''''' '''''''' '''''' ''''''''''''''''''''' ''''' ''''''''''''''''''' ''''''' '''''''''''''''''''''' '''''''''''''''''''''' '''' '''''''' ''''' '''''''' '''' ''''''''''''''' '''''''''''''''' ''''''' '''''''''' '''''''''''' ''''''' ''''''''''''''''''''''''' '''''''''''''''''' '''''''''''' ''''''''' '''''''''''''''''' ''''''''''''''''''''''''''''''''' '''''' ''''''''''''

Table 115 Summary of important identified and potential risks and missing information for galsulfase (BioMarin Pharmaceuticals Inc. 2014)

| Identified Risks | Hypersensitivity reactions / infusion associated reactions |
| --- | --- |
| Potential Risks | ''''''''''''''''''' ''''''''''''''''  '''''''''''' '''''''''''''''''''''''''''  ''''''''''''''''''''''''''''''''''' '''''''''''''''''''''''''''''''''  '''''''''''''''''''' '''''''''''''''''''''''''''  '''''''''''''''' '''''''''' ''''''''''''''''''''''''''''  '''''''''''''''''''''''''''''''''''''''''''  ''''''''''''''''''''''''' '''''''''''''''''''''' |
| Important Missing Information | '''''''''' '''' ''''''''''''' '''''''''''''''''''''''  '''''''''''''''''''''''''' '''''''''''''''''''''''''' ''''''''''''''''''''''' '''' '''''''''''''''''''' '''''''''''''''' '''''''''' ''''''''''''''''' '''''''''' ''''''''''''''''' ''''' ''''''''''''' ''''''''''''''''''''''''''''''' |

''' ''''''''''''''''''' ''''' '''''''''''''' ''''''''' ''''''''''''''''' ''''''' '''''''''' '''''''''''''''''''' ''' ''''''''''''' '''' ''''''''''' '''''''' '''''''''''''''''''''' '''''''' ''''''''''' ''''''''' '''''''''''' ''''''''''' '''' ''''''''''''''''''''''''''''''''''' '''''''''''' ''''''' ''''''''' ''''''''''' '''''''''''''' '''''''''' '''''''''''''''''''' ''''''''' ''''''''''''''''''' ''''''''''''''''' ''''''''' ''''''''' ''''''''''''''''''''''''''''' ''''''''''''''' ''''''''''''''''''' '''''''''''''''' ''''''''''''''''' ''' ''''''''''''''''''' '''''''''' '''''''''''''' '''''''''''''''' '''''''''''''''''' '''''''''''''''' '''''''''''''''''''' '''''''''''''' '''''' '''''''''''''''' '''''''' '''''''''' ''''''''''''''''' '''''''''''''''' '''''''''''' ''''''''''' '''''''''''''''''' '''''''''''''''''''''''' '''''''''' ''''''''''''''''''''''''''' '''''''''''''''''' ''''''''''''''''' '''''''''''''''''''''''''''' ''''''' '''''''''''

Table 116 Frequency of adverse drug reactions with galsulfase (BioMarin Pharmaceuticals Inc. 2014)

| System Organ Class | Very common adverse drug reactions (>1/10) | Common adverse drug reactions (>1/100, <1/10) | Frequency not known |
| --- | --- | --- | --- |
| Immune system disorders | ''' | ''' | '''''''''''''''''''''''''''''''  '''''''''''''''' |
| Infections and infestations | '''''''''''''''''''''''''  ''''''''''''''''''''''''''''''''' | ''' | '' |
| Nervous system disorders | '''''''''''''''''''''  '''''''''''''''''''''' | '''''''''''''''' | ''''''''''''''''''''''''''''''''' |
| Eye disorders | '''''''''''''''''''''''''''''  '''''''''''''''''''' ''''''''''''''''' | '' | '' |
| Cardiac disorders |  |  | ''''''''''''''''''''''''''''''  '''''''''''''''''''''''''''''''  '''''''''''''''''''' |
| Ear and labyrinth disorders | ''''''' '''''''''''  ''''''''''''''''' '''''''''''''''''''' | ''' | ''' |
| Vascular disorders | '''''''''''''''''''''''''''''' | ''''''''''''''''''''''''''''''' | ''''''''''''' |
| Respiratory, thoracic and mediastinal disorders | '''''''''''''''''''''''  ''''''''''''''' ''''''''''''''''''''''''''' | ''''''''''''''''  '''''''''''''''  ''''''''''''''''''''''''''''' '''''''''''''''''  ''''''''''''''''  ''''''''''''''''''''''''''''''''' | ''''''''''''''''''''''' '''''''''''''''''''''  '''''''''''''''''''  ''''''''''''''''''''''''''''' |
| Gastrointestinal disorders | '''''''''''''''''''''''' '''''''''''  ''''''''''''''''''''' ''''''''''''''  ''''''''''''''''''''  '''''''''''''''''' | ''' | ''' |
| Skin and subcutaneous tissue disorders | ''''''''''''''''''''''''''''''''  '''''''''''  '''''''''''''''''''''  ''''''''''''''''' | '''''''''''''''''''' | ''' |
| General disorders and administration site conditions | ''''''''''  ''''''''''''''' ''''''''''  '''''''''''''''  '''''''''''''''''  ''''''''''''''''' | ''' | '' |
| Musculoskeletal and Connective Tissue Disorders | ''''''''''''''''''''' | '' | ''' |

#### Australian data registry information

Due to the small numbers, the data from the LSDP patient summaries for the three types of MSP (I, II & VI) have been reported together.

As of June 2014, there were 35 patients treated for either MPS I (7 patients), MPS II (15 patients) or MPS VI (13 patients). Dosing data for three additional patients who were initiated on idursulfase for MPS II following the data cut-off were also available.

Figure 1 Sex distribution across MPS Types for patients receiving drugs through the LSDP

Figure 1 Sex distribution across MPS Types for patients receiving drugs through the LSDP

Date of drug commencement was available for 34 patients (97%) in the Department of Health’s register and ranged from 2002 to 2014. Duration on treatment is not a reflection of eligibility for LSDP-funded medication, however, with 70% of patients already on a drug prior to the first recorded consultation in the clinical summary assessment spreadsheet[[17]](#footnote-17), or who are recorded as being on a drug without any subsequent recorded consultation. This could have occurred because patients were receiving a drug prior to reimbursement through the LSDP via a special access arrangement or compassionate program.

Age at commencement varied from 2 months to 55 years for all MPS patients (average 13.6 years). Average age at drug commencement was slightly younger for MPS VI (10 years) than MPS I or II (16.5 years and 15 years, respectively) (Table 117).

Table 117 Characteristics of patients with MPS and treatment through LSDP

| Characteristic of patients or dose | MPS I | MPS II | MPS VI |
| --- | --- | --- | --- |
| % Male | 57% | 100% | 62% |
| Mean age at drug commencementa | 16.5 years | 15.1 years | 10.3 years |
| Mean duration on treatmentb | 4.2 years | 3.8 years | 5.7 years |
| Drug and maximum permitted dose according to LSDP criteria. | Laronidase-Rch  0.58 mg/kg/week | Idursulfase-Rhu  0.5 mg/kg/week | Galsulfase-Rch  1.0 mg/kg/week |
| Most recent dose (mean)c | 0.55 mg/kg/week | 0.54 mg/kg/week | 0.98 mg/kg/week |
| Proportion of patients who exceeded maximum permitted dose at the most recent reviewc | 3/7 (42.9%) | 12/18 (66.7%) | 5/13 (38.5%) |

a Commencement date was explicitly recorded for 31 patients and could be estimated from the disease advisory committee comments for 3 others. It was not available for one patient with MPS II.

b Duration on treatment was calculated from commencement date to the most recently recorded consultation. If no consultation was available, or no consultation was recorded following the commencement of the drug, the data were disregarded. Data were available for 32 patients.

c Three additional patients were included for MPS II who were enrolled after the data cut-off of June 2014 (n=18).

Dosing was commonly reported in the patient spreadsheets used for the registry, as recommending dose was one of the roles of the disease advisory committees. Weight was also commonly reported by the treating clinician, permitting a calculation of dose per kg. The maximum permitted doses according to the current LSDP criteria for MPS varies according to Type, and are consistent with the doses used in the trials (0.58 mg/kg/week for laronidase; 0.5 mg/kg/week or fortnight for idursulfase; and 1.0 mg/kg/week for galsulfase). In a substantial proportion of subjects, drugs were slightly dosed above the maximum permitted dose although it remains unclear why this may have occurred. It is possible that a slightly higher dose than permitted was recommended so that the total dose provided was equal to a whole number of vials (rather than discarding a portion of a vial).

While important outcome measures such as forced vital capacity (FVC) and six minute walk distance (6MWD) were reported in the registry, these were not reported consistently and, in the absence of identified baseline (before treatment) values, analysis is difficult. For 6MWD, a baseline value (a measurement taken prior to initiation of the drug) and at least one follow up value was available for 6 patients (17%). From the baseline value to the most recent value available, 6MWD improved for three patients, although this is impossible to interpret without assessing the individual characteristics (age and comorbidities) that may have influenced performance in a 6 minute walk distance test.

##### Conclusion

It is clear that the data registry has been kept as a record of the disease advisory committee deliberations and populated with some clinical data to enable decision making. However, the data are insufficient to verify the efficacy or safety of the drugs used for MPS or to establish the cost of additional treatments or interventions associated with laronidase, idursulfase, or galsulfase treatment.

#### Impact of findings

A summary of the studies included in the systematic review for the drugs on the LSDP for MPS, and an outline of the evidence that is new (published subsequent to the relevant submissions to the PBAC) is shown in Table 118.

Table 118 Studies included assessing drugs to treat mucopolysaccharidoses (MPS) I, II and VI

| Drug | Results | References | Evidence not included in submissions to the PBAC |
| --- | --- | --- | --- |
| Laronidase | 1 RCT + extension | Wraith et al (2004)  Clarke et al (2009) | Clarke et al (2009) was extension study of Wraith et al (2004) which was included in submission to the PBAC. 100% improved on urinary glycosaminoglycans (GAG), 15% attained normal values.  92% of those with abnormal liver values attained normal values.  % predicted normal FVC slight decline, but improvement on 6MWT, AHI, should range of motion, visual acuity and disability index. |
| Idursulfase | 1 RCT + extension | Muenzer et al (2006)  Muenzer et al (2011) | Muenzer et al (2011) was extension study of Muenzer et al (2006). Muenzer et al (2011) reported that there was a decline on urine GAG levels over 36 months (97% normal at baseline, 33% at follow-up). 6MWT improved slightly. Minimal % predicted FVC change |
| Galsulfase | 1 RCT + extension | Harmatz et al (2006) | No new data could be extracted from new extension studies. |

RCT = randomised controlled trial; PBAC = Pharmaceutical Benefits Advisory Committee; GAG = glycosaminoglycans; FVC = forced vital capacity; 6MWT = 6-minute walk test; AHI = apnoea / hypopnea index

##### Laronidase

There was one key trial used in the submission to the PBAC which assessed laronidase against placebo in patients with MPS I (Wraith et al 2004). The systematic review identified one 3.5 year open-label extension to this trial (where all patients received laronidase) (Clarke et al 2009). This extension study provided longer term data, which showed either improvements or stabilisation on the majority of outcome measures (6 minute walk test, liver volume, apnoea symptoms, shoulder range of motion, visual acuity and disability index). There was a slight decline in the proportion of patients with predicted normal forced vital capacity (FVC). However, the new data were non-comparative, and it is therefore uncertain how the data compare to an untreated population in the longer-term. These results are therefore unlikely to alter the decision regarding funding of laronidase on the LSDP.

##### Idursulfase

There was one trial included in the relevant submission to the PBAC, providing evidence of the effectiveness of 1 year of idursulfase compared to placebo, in patients with MPS II (Muenzer et al 2006). Since being listed on the LSDP, an open-label extension study to this trial has been published, providing data for another 2 years (i.e. 3 years for those who were randomised to idursulfase initially, or 2 years for those who received placebo in the trial). The extension study found that absolute forced vital capacity continued to improve for patients who were 18 years old or less at baseline, over the 3 years of treatment with idursulfase. Adult patients (over 18 years) had a slight decrease in absolute forced vital capacity over 3 years. Results on the 6MWT were reasonably similar between 1 year (the length of the randomised trial) and 3 years. Liver and spleen volume remained stable between 1 and 3 years, and joint flexibility continued to improve between 1 and 3 years. The extension data would therefore be unlikely to alter the decision to fund idursulfase.

##### Galsulfase

The highest level of evidence assessing galsulfase for patients with MPS VI was a trial comparing the drug against placebo, which was included in the submission to the PBAC. A subsequent extension study was identified, which included the sample who participated in the key trial, but the data were combined with results of patients from two other trials, and the study was therefore excluded. Therefore, the systematic review did not include any data in addition to what was included in the relevant submission to the PBAC, and would have no impact on the decision to fund galsulfase.

### Medicine to treat Paroxysmal Nocturnal Haemoglobinuria (PNH)

**Is eculizumab safe and effective compared to supportive care (with/without placebo) for treatment of patients with Paroxysmal Nocturnal Haemoglobinuria?**

The clinical claim submitted to the PBAC was that a patient’s lifespan with classic PNH would be substantially extended as a consequence of taking eculizumab compared to best supportive care. The PBAC considered that published and unpublished data supported this claim.

One double-blinded, randomised, placebo-controlled trial (N = 87) provided high quality evidence that, in the short-term (6 months), eculizumab reduces transfusion requirements and improves quality of life in patients with relatively severe PNH, compared to standard care (GRADE ⨁⨁⨁⨁). A *post-hoc* analysis provided moderate quality evidence that patients treated with eculizumab have, on average, better renal outcomes than those receiving placebo (GRADE ⨁⨁⨁⨀).

The single arm extension study of this trial (N = 195), which also included patients from two other studies, provided low quality evidence that the effectiveness of eculizumab at reducing transfusion requirements appears to be maintained over a median treatment duration of 30 months. Eculizumab also reduced the rate of thromboembolic events.

There is minimal comparative evidence and only one case series addressing the effect of eculizumab on overall survival in patients with PNH.

The only new evidence identified through the systematic review, was a historical control study, which reported on survival. This study reported that eculizumab prolonged overall survival compared to no treatment; however, due to serious flaws in the design of this study, there are concerns regarding the validity of this analysis.

In the randomised trial, adverse events that were more common in the eculizumab group, compared to the placebo group, included headache, back pain and fatigue. Important identified risks associated with eculizumab treatment in patients with PNH include meningococcal infections, sepsis, serious infections and infusion reactions.

**Information withheld from this report at the request of the drug sponsor.**

'''''' ''''''''''''''''''''' '''''''''' '''''''''''' ''''''''''''''''''' ''''''' ''''''''' ''''''''''''''''''''''' ''''''''''''''''''''' ''''''''''''''''''''' '''''''''''''''''''''''''''''' ''''''''''' '''''''''''''' '''' ''''''''''''''''''''' ''''''''''''''''''''''''' '''''''''''''' ''''''''''''''''''''' ''''''' '''''' '''''''''''''''''''''''' '''''''''''''''''''''''''''' ''''''''''''''''''''' ''''''''' ''''''' ''''''''''''' ''''''''''''''''' ''''''''' ''''''''' '''''''''''''''' '''''''''''''''''''''''''''''' '''''' ''''''' ''''''''''' '''''''''''''''' ''''''''''''''''''''' '''''''''' '''''''''''' ''''''''''''''' '''''''' '''''''''''''''' ''''''''''''' ''''''''''''

#### Background

##### Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is an uncommon, life-threatening haematopoietic stem cell disorder, characterised by complement-mediated intravascular haemolysis and a pre-thrombotic state (Hillmen et al. 2013). PNH is caused by an acquired somatic mutation in the X chromosome of a totipotent haemopoietic stem cell (Dmytrijuk et al. 2008). The mutation results in a deficiency of glycosylphosphatidylinositol glycan (GPI) Class A protein, which is critical for the biosynthesis of GPI membrane anchoring proteins (GPI-APs). The mutation results in the reduction or complete absence of the GPI-anchored complement regulatory proteins CD55 and CD59. The absence of these proteins makes PNH cells vulnerable to complement mediated intravascular and extravascular haemolysis, although it is the intravascular haemolysis that contributes the most to the disease morbidity (Pu & Brodsky 2011).

Chronic haemolysis leads to the release of free haemoglobin and the subsequent depletion of nitric oxide. This, in turn, leads to vaso-occlusion and platelet activation and results in the common manifestations of PHN, such as fatigue, dyspnoea, recurrent abdominal pain, dysphagia, chest pain and pulmonary hypertension. In addition, chronic haemolysis increases the risk of thrombotic events (TEs), renal insufficiency and other organ damage, and premature mortality (Hillmen et al. 2013).

In a study of 220 untreated PNH patients diagnosed over a period of 46 years (1950-1995), the Kaplan-Meier survival estimate was 65% at 10 years and 48% at 15 years after diagnosis (Socie et al. 2012). Poor survival was associated with the occurrence of thrombosis as a complication, evolution to pancytopenia, myelodysplastic syndrome or acute leukaemia, age over 55 years at diagnosis and thrombocytopenia at diagnosis; while better survival was shown for patients in whom aplastic anaemia predated the PNH.

##### Pre-eculizumab

Prior to the development of eculizumab, treatment of PNH was based around management of anaemia and thrombotic complications through transfusion of red blood cells, iron and/or folic acid supplementation, steroids and anti-coagulants.

##### Eculizumab

Eculizumab, a genetically-engineered humanised monoclonal antibody, is a terminal complement inhibitor that specifically binds to the complement protein C5, thereby inhibiting the formation of pre-inflammatory, prothrombotic C5a and C5b, and preventing the generation of the terminal membrane attack complex C5b-9 (Hillmen et al. 2013; Therapeutic Goods Administration 2014).

The TGA approved dosing regimen of eculizumab in PNH consists of a 4-week initial phase followed by a maintenance phase:

* Initial phase: 600mg of eculizumab administered via a 25 – 45 minute intravenous infusion every week for the first 4 weeks
* Maintenance phase: 120mg of eculizumab via a 25 – 45 minute intravenous infusion for the fifth week, followed by 900mg of eculizumab administered via a 25 – 45 minute intravenous infusion every 14 ± 2 days.

Due to its mechanism of action, the use of eculizumab increases the patient’s susceptibility to meningococcal infection (*Neisseria meningitides).* Due to this, patients must be administered a meningococcal vaccine at least two weeks prior to initiation of eculizumab therapy and revaccinated according to current medical guidelines for vaccine use (Therapeutic Goods Administration 2014). Eculizumab has been subsidised through the LSDP since 2011.

#### Systematic review inclusion criteria

Table 119 outlines the criteria for choosing studies that assess the safety and effectiveness of eculizumab for the management of paroxysmal nocturnal haemoglobinuria.

Table 119 Criteria for selecting studies to assess the safety and effectiveness of eculizumab

| Characteristic | Inclusion criteria |
| --- | --- |
| Study design | The highest level of evidence available (from Table 2) that addressed the research questions. Case reports would have been included if none of the study designs in Table 2 were available. |
| Population | Patients with Paroxysmal Nocturnal Haemoglobinuria (PNH), with granulocyte clone size ≥10%, and raised lactate dehydrogenase level (≥1.5 times upper limit of normal for reporting laboratory) |
| Intervention | Eculizumab (Soliris®)  plus meningococcal vaccination with a tetravalent vaccine at least two weeks prior to first dose and revaccination as per Australian Immunisation Handbook.  Subgroup analysis: by dose (e.g. doses consistent with TGA listing, as well as experimental dosing regimens) |
| Comparator | Supportive care (with/without placebo) |
| Outcomes | *Safety:* adverse events related to treatment – for example, headaches, nasopharyngitis, fatigue; and compliance with treatment (i.e. treatment withdrawal or suboptimal dosing)  *Primary effectiveness:* survival  *Secondary effectiveness:* quality of life; pain; thrombotic or embolic events; transfusion requirements; pulmonary insufficiency (shortness of breath and/or chest pain); renal function: glomerular filtration rate. |
| Language | Studies in languages other than English would have been translated if it appeared from the abstract that they represented a higher level of evidence than that available in English. |
| Research question | Is eculizumab safe and effective compared to supportive care (with/without placebo) for treating patients with Paroxysmal Nocturnal Haemoglobinuria? |

#### Results of the literature search

The systematic review identified 16 publications fulfilling the study eligibility criteria.

The highest level of evidence assessing the comparative effectiveness and safety of eculizumab for the treatment of PNH was a randomised, double-blind, placebo-controlled trial, TRIUMPH (N = 87) (Hillmen et al. 2006). On completion of the 26-week trial, patients were enrolled in an extension study, which also included patients from two other studies: an open-label phase II pilot study (case series, N = 11) (Hill et al. 2005; Hillmen et al. 2004), and an open-label phase III case series (SHEPHERD, n = 195) (Brodsky et al. 2008). Three publications reported the outcomes of this common 104-week extension study, which was analysed predominantly on a before-and-after treatment basis (Hillmen et al. 2010; Hillmen et al. 2007; Hillmen et al. 2013). While a retrospective analysis of a subgroup of patients enrolled in the TRIUMPH trial (Hill et al. 2010) also fulfilled the study eligibility criteria, the analysis did not present any additional results on outcomes relevant to this review. As the TRIUMPH trial only reported relatively short-term outcomes, the results from the combined extension study are also presented, as this represents the highest level of evidence for the longer-term effectiveness of eculizumab.

The only study which reported the effect of eculizumab treatment on survival, compared to supportive care, was Kelly et al (2011) (Kelly, RJ et al. 2011). This was a single-centre historic control study in which outcomes in eculizumab-treated patients were compared to those of a control group of patients managed at the same centre in the 7 years before the availability of eculizumab.

Six case-series (before-and-after analyses) also fulfilled the eligibility criteria: one performed in Japan (Kanakura et al 2011, 2013: N = 29)(Kanakura et al. 2013; Kanakura et al. 2011), one in Korea (Kim et al 2010; N = 6)(Kim et al. 2010), two in Germany (Roth et al 2011: N = 19; Hochsmann et al 2012: N = 41)(Hochsmann et al. 2012; Roth et al. 2011), and two in the US (DeZern et al 2013, N = 30; Reiss et al 2014, N = 7)(DeZern, Dorr & Brodsky 2013; Reiss et al. 2014). One of the US studies examined the safety and effectiveness of eculizumab in children aged 11-17 years of age (Reiss et al. 2014).

#### Description of the studies included in the report

##### TRIUMPH randomised controlled trial

TRIUMPH was a randomised, double-blind, placebo-controlled trial consisting of a 2-week screening period, an observation period of up to 3 months, and a 26 week treatment period (Hillmen et al. 2006).

Patients who did not require a transfusion during the observation period were considered ineligible. Eligible patients were randomised to receive either eculizumab or placebo within 10 days of the qualifying transfusion. Randomisation was performed centrally, with stratification according to the number of units of packed red blood cells transfused during the previous year. Blinding of participants, investigators and outcome assessors was maintained until the end of the study.

Two of the 43 (4.7%) patients in the eculizumab group did not complete the trial, one due to transport difficulties and the other due to pregnancy; ten out of 44 (22.7%) patients in the placebo group discontinued infusions because of a perceived lack of efficacy, but remained in the study. An intention-to-treat analysis was performed for the primary outcomes, although it is not clear how missing values were dealt with.

Patients were required to have a PNH type III[[18]](#footnote-18) erythrocyte proportion of 10% or more, lactate dehydrogenase (LDH) levels at least 1.5 times the upper limit of the normal range. In addition, they must have received at least four packed red blood cell (RBC) transfusions during the previous 12 months, and a platelet count of at least 100x109/L. While the PNH granulocyte clone size was not stipulated in the inclusion criteria, the median clone size in the 31 patients with baseline values was 95.3% (range: 82.6-99.5%)(Hillmen et al. 2007). Due to the stringent inclusion criteria, especially the requirement of at least four packed RBC transfusion during the previous 12 months, these patients may, on average, have more severe disease than the Australian PNH patient population. Ongoing standard therapy for immunosuppression, bleeding and anaemia was provided for all patients on the condition that the doses were constant before and throughout the study. In addition, all patients were vaccinated against *Neisseria meningitides*.

Patients received intravenous infusions of either eculizumab or placebo at a dose of 600mg every week (±2 days) for 4 weeks, followed 1 week (±2 days) later by 900mg, and then by a maintenance dose of 900mg every 2 weeks (±2 days), through week 26. This dose of eculizumab is consistent with the TGA listing.

A total of 87 patients from 34 sites in the United States, Canada, Europe, and Australia met the eligibility criteria and were randomly assigned to either eculizumab (43 patients) or placebo (44 patients).

A full comparison of baseline characteristic between the two treatment groups is presented in Table 165. While the majority of baseline characteristics were reasonably similar across the two treatment groups, a greater proportion of patients in the placebo group had a history of aplastic anaemia than in the eculizumab group (27.3% and 14.0%, respectively), and the median duration of disease in the placebo group (9.2 years) was longer than in the eculizumab group (4.3 years). These differences may have favoured eculizumab over placebo (Kathula 2006). There was also some disparity in the pre-treatment thromboembolic (TE) event rate between the two treatment groups (5.18 events and 2.34 events per 100 patient-years in the eculizumab and placebo groups, respectively) (Hillmen et al. 2007), while the use of anticoagulants at baseline was correspondingly higher in the eculizumab group compared to the placebo group (49% and 25%, respectively)(Hillmen et al. 2006).

Outcomes of relevance to this review included: transfusion requirements (one of two pre-specified primary outcomes), transfusion independence, and change in level of fatigue from baseline to 26 weeks (FACIT-Fatigue instrument). In addition, quality of life was included as a pre-specified exploratory analysis. The limited sample size and duration of the TRIUMPH trial precluded the determination of the comparative effectiveness of eculizumab in terms of less common outcomes, such as thromboembolic (TE) events and mortality.

##### Open-label, single arm extension study

The long-term effectiveness of eculizumab was assessed in a multicentre 104-week non-comparative extension study (Hillmen et al. 2010; Hillmen et al. 2007; Hillmen et al. 2013) that enrolled patients from three independent parent studies: the TRIUMPH trial (N = 87), an open-label phase II pilot study (Hillmen et al 2004, 2005; N = 11) (Hill et al. 2005; Hillmen et al. 2004), and an open-label phase III case series (SHEPHERD, Brodsky et al 2008; N = 97)(Brodsky et al. 2008). At the end of the parent studies, 187 of the 195 eligible patients (95.9%) enrolled in the extension study (Hillmen et al. 2013). Summaries of the small pilot study and the SHEPHERD study are provided below.

The phase II pilot study was an open-label case-series (before-and-after), consisting of an initial 12-week acute-phase with a 1-year extension study (Hill et al. 2005; Hillmen et al. 2004). The study was conducted in the UK. Patients were eligible for enrolment if they had a detectable GPI-deficient haematopoietic clone and had received at least four RBC transfusions in the preceding 12 months. Baseline PNH granulocyte clone size ranged from 47.8% to 99.9% (Hillmen et al. 2007). All patients were vaccinated against *N. meningitides* before treatment. The dose of eculizumab was the same as that in the TRIUMPH trial, and was consistent with that in the TGA listing. Eleven patients were included in the study, eight of whom had a previous diagnosis of aplastic anaemia. All patients completed both the initial 12-week phase and the 1-year extension study. Relevant effectiveness outcome measures included transfusion requirements and quality of life.

SHEPHERD (Brodsky et al. 2008) was an open-label 52-week prospective open label single arm clinical study, conducted in the US, Europe, Australia and Canada. The eligibility criteria were similar to those in TRIUMPH, with the exception that patients were only required to have received at least one transfusion in the past two years, compared with four or more in the past year in TRIUMPH, and platelet counts of ≥30 x 109/L, compared to ≥100 x 109/L in TRIUMPH. As in the TRIUMPH trial, patients were required to have a PNH type III RBC proportion of 10% or more and LDH levels at least 1.5 times the upper limit of normal. The median PNH granulocyte population size was 96.0% (range: 1.1-99.9%)[[19]](#footnote-19) (Hillmen et al. 2007). As the eligibility criteria were more inclusive than those in the TRIUMPH trial, the study population was probably more representative of the Australian PNH population. Dosing of eculizumab was consistent with the recommendations in the TGA-approved PI for eculizumab. A total of 97 patients were enrolled in the study; 96 completed the 52-week study. Outcomes of interest included change in level of fatigue from baseline (FACIT-Fatigue instrument), quality of life, TE events, and transfusion requirements.

The long-term open-label extension study consisted of a 104-week treatment period and a 16-week post-treatment follow-up period for any patients who terminated treatment early (Hillmen et al. 2013). At the end of the initial parent studies, 187 of the 195 patients (95.9%) enrolled in the extension study. All three parent studies used the same dosing regimen for eculizumab; in the extension study patients continued to receive the maintenance dose of eculizumab (900mg every 14 ± 2 days). Patients who received placebo in the TRIUMPH trial commenced eculizumab therapy using the same dosing regimen as that outlined in the TRIUMPH trial.

Baseline was defined as the pre-eculizumab value collected from the parent study, except for those patients in the TRIUMPH study who received placebo, where baseline was the value collected at the final visit of this study. Nineteen (9.7%) of the original 195 patients discontinued treatment: nine discontinued because of an AE, seven withdrew consent, two were discontinued based on the decision of the investigator, and one was non-compliant with the protocol. Eight of the discontinuations occurred during a parent study.

While the total period of eculizumab administration across the parent and extension studies was 66 months, a 36-month cut-off was used for safety and effectiveness assessments to ensure that there were sufficient numbers of patients for statistical analysis. The median treatment duration for patients included in this 36-month cut-off was 30.3 months (interquartile range: 26.2-33.1 months).

Effectiveness assessments were performed at least every two weeks. Outcome measures included survival (non-comparative), incidence of thrombotic events (TEs), transfusion requirements, transfusion independence and renal function.

##### Kelly et al (2011)

Only one full publication was identified which reported the effect of eculizumab on survival, compared to supportive care, in patients with PNH (Kelly, RJ et al. 2011). In addition, a conference abstract summarising the results of a cohort study, based on data for 1,047 patients enrolled in the international PNH registry, was located (Socie et al. 2012); as full publication for this study could not be located, it was not possible to assess the quality of this study.

Kelly et al (2011)(Kelly, RJ et al. 2011) presented the results of a study which enrolled 79 consecutive PNH patients treated with eculizumab at a single centre, 43% of whom participated in one of the three multicentre studies listed above. Outcomes in the eculizumab-treated patients were compared with those for a group of 30 patients who were cared for at the same centre in the 7 years before the availability of eculizumab.

Patients were eligible for eculizumab treatment if they had transfusion-dependent haemolysis (4 or more transfusions in 12 months) or had a significant PNH-related complication regardless of transfusion history. All patients had a PNH granulocyte clone size ≥10% (range 41.8-100%), and the majority had LDH levels ≥1.5 time the upper limit of normal (range 587-10,3000IU/L). The mean duration of eculizumab treatment was 39 months, with a range of 1-98 months.

The only detail provided regarding the pre-eculizumab control group is that they fulfilled the same criteria for eligibility for eculizumab treatment as those in the treated group. No details are provided regarding baseline characteristics or the mean/median duration of follow-up for this cohort.

While it is not clear in the methods section of the publication, the discussion indicates that once eculizumab became available, surviving control patients commenced eculizumab therapy and were subsequently included in the treatment group, “effectively acting as their own controls”. The number of control patients who received eculizumab once it was available, and who were subsequently included in the treated group, is not reported, although approximately 33% died prior to eculizumab becoming available. Due to the lack of data on the controls, it is not possible to estimate the risk of bias, although there is likely to be a degree of survival bias.

For the pre-eculizumab patients who then proceeded to treatment, this study is essentially a case series, with before-and-after treatment outcomes; however, treatment outcomes are not reported specifically for the sub-group of patients who were included in the pre-eculizumab group. Similarly, it is not possible to compare the sub-group who entered the study after eculizumab became available with the pre-treatment group, i.e. as an historic control analysis. Given the limitations of this study, there are major validity issues regarding the comparative analyses, especially for survival.

#### Results of the included studies

##### Primary effectiveness: Survival

Kelly et al. (Kelly, RJ et al. 2011) used a Cox regression model with time-dependent covariates to assess the effect of eculizumab treatment on overall survival, compared to the untreated pre-eculizumab group. Those who were treated with eculizumab had a significantly higher 5-year survival rate (95.5%; 95%CI 87.6, 98.5) than those with PNH who were untreated (66.8%; 95%CI 41.4, 85.1), with a hazard ratio of 0.21 (95%CI 0.05, 0.88).

As discussed above, there are major concerns regarding the validity of the survival analyses. The results of the survival analyses are summarised in Table 120.

Table 120 The effect of eculizumab on survival in PNH patients

| Study | Eculizumab  % (95%CI) | Control  % (95%CI) | Hazard ratio  (95%CI) | p-value |
| --- | --- | --- | --- | --- |
| **Kelly et al (2011)** | N = 79 | N = 30 |  |  |
| Overall survivala |  |  | 0.21(0.05,0.88) | 0.030 |
| Five year survival | 95.5%  (87.6%, 98.5%) | 66.8%  (41.4%, 85.1%) |  | 0.01 |

CI = confidence interval

a Cox regression model with time-dependent covariates. For the pre-eculizumab cohort, patients were censored at the time they first received eculizumab.

##### Conclusion

The comparative evidence was minimal and only one case series addressed the effect of eculizumab on overall survival in patients with PNH. The available evidence was of very low quality (GRADE ⊕⨀⨀⨀).

##### Secondary effectiveness outcomes

The highest level of evidence for the secondary effectiveness outcomes, as specified in the study eligibility criteria, was the TRIUMPH trial (Hillmen et al. 2006) and the associated extension study (Hillmen et al. 2010; Hillmen et al. 2007; Hillmen et al. 2013).

##### Transfusion requirements

In the TRIUMPH trial (Hillmen et al. 2006), the effect of eculizumab treatment on transfusion requirements, defined as the number of units of packed RBCs transfused during the 26-week treatment period, was reported as a primary outcome, while the proportion of patients who were transfusion independent over the duration of the trial was a prespecified secondary outcome. The trigger for the administration of transfusions was pre-specified: patients received transfusions when they had symptoms resulting from anaemia and their haemoglobin levels reached the individualised, predetermined set point[[20]](#footnote-20). As outlined above, patients were only eligible for enrolment in this trial if they had received at least four packed RBC transfusions during the previous 12 months; as a result, these patients may, on average, have more severe disease than the Australian patient population. Results of these analyses are summarised in Table 121.

Patients receiving eculizumab required significantly fewer units of packed RBCs per patient over the 26-week treatment period than those in the placebo group (median 0 units versus 10 units, p<0.001). This significant reduction in transfusion requirements was evident across all strata of baseline transfusion requirement (Dmytrijuk et al. 2008). Fifty-one percent (22/43) of patients in the eculizumab group did not require a transfusion over the 26-week treatment period, compared with 0% in the placebo group. A reduction in transfusion requirements of this magnitude is likely to be clinically relevant.

Table 121 Effectiveness of eculizumab on transfusion requirements in the TRIUMPH trial

| Outcome | Eculizumab (n = 43) | Placebo (n = 44) | P-value |
| --- | --- | --- | --- |
| Transfusion requirements, units of packed RBCs |  |  |  |
| Before treatmenta |  |  |  |
| Median (interquartile range)  Mean (SE) | 9.0 (6-12)  9.6 (0.6) | 8.5 (7-12.5)  9.7 (0.7) |  |
| During treatment |  |  |  |
| Median (interquartile range)  Mean (SE) | 0 (0-6)  3.0 (0.7) | 10 (6-16)  11.0 (0.8) | <0.001b |
| Stratified by baseline transfusion requirement, medianc |  |  |  |
| 4-14 units  15-25 units  >25 units | 0.0  2.0  3.0 | 6.0  10.0  18.0 | <0.0001  0.0007  0.0003 |
| Transfusion independence, n (%) | 22 (52.1) | 0 (0.0) | <0.0001d |

RBCs = red blood cells; SE = standard error

a Transfusion data were obtained during 12 months before treatment were normalised to a value equivalent to the value for a 6-month period

b Comparison between treatment groups duringtreatment, Wilcoxon rank-sum test

c Source: (Dmytrijuk et al. 2008)

d Comparison between treatment groups duringtreatment, Fisher’s exact test

In the extension study, approximately 50% of the patients were recruited from SHEPHERD (Hillmen et al. 2013). In contrast to the TRIUMPH trial, in which the trigger for transfusion was clearly and objectively defined, in the SHEPHERD study, patients received transfusions if medically indicated (Brodsky et al. 2008). It is also not clear what criteria for transfusion were used during the extension study. In addition, in SHEPHERD, patients were only required to have at least one transfusion in the previous two years, while in both TRIUMPH and the pilot study they were only eligible if they had four transfusions in the previous 12 months.

The change from baseline in the number of units of packed RBCs administered to patients receiving transfusions over the course of the study is presented in Table 122 (Hillmen et al. 2013). A reduction in the number of packed RBCs transfused was evident within three months of starting treatment, and this effect appeared to be maintained over the duration of the study; the clinical relevance of an effect of this magnitude was not addressed. Hillmen et al (2013) (Hillmen et al. 2013) reports that by weeks 30-36, the percentage of patients achieving transfusion independence[[21]](#footnote-21) was 82.1% (64/78), compared with 8.2% (16/195) in the 6 months prior to the start of treatment (risk difference: 73.8%; 95%CI: 64.5, 83.2%[[22]](#footnote-22)).

Table 122 Mean number of packed red blood cells administered to patients receiving transfusions over the course of the study

| Study Period (months)a | n | Mean (SE) | Mean change form baseline (SE) | P-valueb |
| --- | --- | --- | --- | --- |
| Baselinec | 164 | 5.3 (0.22) |  |  |
| 0-3 | 74 | 4.4 (3.33) | -1.5 (0.38) | 0.0001 |
| 3-6 | 76 | 4.7 (0.37) | -1.5 (0.42) | 0.0007 |
| 6-9 | 61 | 4.8 (0.40) | -1.1 (0.50) | 0.0293 |
| 9-12 | 58 | 4.6 (0.41 | -1.7 (0.54) | 0.0025 |
| 12-15 | 62 | 3.6 (0.29) | -2.5 (0.49) | 0.0001 |
| 15-18 | 50 | 4.2 (0.32) | -2.0 (0.55) | 0.0006 |
| 18-21 | 50 | 4.3 (0.51) | -2.1 (0.65) | 0.0022 |
| 21-24 | 42 | 4.6 (0.61) | -1.4 (0.64) | 0.0333 |
| 24-27 | 37 | 4.0 (0.49) | -2.9 (0.65) | <0.0001 |
| 27-30 | 30 | 4.4 (0.95) | -1.5 (0.98) | 0.1298 |
| 30-33 | 10 | 3.1 (0.55) | -3.0 (0.65) | 0.0013 |
| 33-36 | 7 | 2.4 (0.30) | -3.6 (1.13) | 0.0196 |

SE = standard error

a The overall median duration of treatment of patients included in the 36-month efficacy analysis cut-off was 30.3 months (interquartile range: 26.2-33.1 months)

b The method of statistical analysis was not reported. It is not clear whether any statistical adjustment was made for multiple analyses.

c The period over which the baseline was measured was not reported

Source: (Hillmen et al. 2013)

##### Conclusion

One double-blinded, randomised, placebo-controlled trial (N = 87) provided high quality evidence (GRADE ⊕⊕⊕⊕) that, in the short-term (6 months), eculizumab reduces transfusion requirements in patients with relatively severe PNH, compared to standard care.

The extension study of this trial (N = 195), which also included patients from two other studies, provided low quality evidence (GRADE ⊕⊕⨀⨀) that the effectiveness of eculizumab in reducing transfusion requirements appears to be maintained over a median duration of treatment of 30 months.

##### Quality of life

In the TRIUMPH trial, quality of life was assessed using two instruments: the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) instrument and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) instrument, although the latter was designated as a pre-specified exploratory analysis. The FACIT-F scale has not been validated in PNH patients (Dmytrijuk et al. 2008).

For the change in fatigue scores from baseline[[23]](#footnote-23), an improvement in the eculizumab group compared to the placebo group was evident from week two of treatment onwards (Figure 3) (Hillmen et al. 2006). Patients in the eculizumab treatment group had a mean increase in scores on the FACIT-F instrument of 6.4 ± 1.2 points from baseline to week 26 (¬12%), indicating an improvement in fatigue, while the mean score in the placebo group decreased by 4.0 ± 1.7 points. A mixed-model analysis of covariance showed a significant difference between the groups (p<0.001), with the absolute difference of 10 points (¬19%) likely to be patient-relevant (Table 123).

The results using the EORTC QLQ-C30 instrument indicated that patients on eculizumab had a significant improvement in scores on the scale for global health status, and for the majority of sub-scales, compared with the placebo group (Table 123)(Hillmen et al. 2006).

Table 123 The effect of eculizumab on quality of life in the TRIUMPH trial

| Scale | Mean change form baseline to Week 26a | Mean change form baseline to Week 26a | Absolute difference | P-Valueb |
| --- | --- | --- | --- | --- |
| - | **Eculizumab** | **Placebo** | - | - |
| FACIT-Fatigue scorec  Mean ± SE | N = 41d  6.4 ± 1.2 | N = 39d  - 4.0 ± 1.7 | 10.4 | P<0.001 |
| Quality of life (EORTC QLQ-C30)e | N = 43 | N = 44 |  |  |
| Global health status scale | 10.9 | -8.5 | 19.4 | <0.001 |
| **Functioning scales**  Role  Social  Cognitive  Physical  Emotional | 17.9  16.7  7.9  9.4  7.5 | -6.9  2.0  -6.1  -3.5  -3.7 | 24.8  14.7  14.0  12.9  11.2 | <0.001  0.003  0.002  <0.001  0.008 |
| **Symptom scales**  Fatigue  Pain  Nausea and vomiting | -16.9  -12.3  -0.4 | 10.0  5.3  2.8 | 26.9  17.6  3.2 | <0.001  0.002  0.06 |
| **Single-item measures**  Dyspnoea  Loss of appetite  Insomnia  Financial difficulties  Constipation  Diarrhoea | -7.9  -10.3  -7.9  -10.3  -6.3  4.8 | 8.9  3.3  4.9  0.0  0.0  5.7 | 16.8  13.6  12.8  10.3  6.3  0.9 | <0.001  <0.001  0.01  0.19  0.20  0.15 |

EORTC QLQ-C30 = European Organisation for research and treatment of Cancer Quality of Life Questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy –Fatigue; SE = standard error

a Values represent least-square means.

b From a mixed analysis-of-covariance model, with baseline scores as the covariate, treatment and time as fixed effects, and the patient identifier as a random effect.

c FACIT-Fatigue instrument: scores can range from 0 to 52. A positive change from baseline indicates an improvement in fatigue and a negative change indicates a worsening in fatigue.

d Source: Dmytrijuk 2008

e Positive change indicates improvement of Global Health status and Functional scales, and negative change indicates improvement on symptom scales

Source: (Hillmen et al. 2006)

##### Conclusion

There is high quality evidence (GRADE ⨁⨁⨁⨁) that eculizumab improves quality of life, compared to standard care, over a 6 month treatment period in patients with relatively severe PNH.

##### Thrombotic events

While thrombotic events were recorded during the TRIUMPH trial, the duration of the trial was not long enough to determine any difference between treatment groups for this relatively uncommon outcome. Only one thrombotic event occurred during the treatment period, in the placebo group.

The rate of thrombotic events was a prespecified outcome in the common extension trial. As these events are potentially fatal (Hillmen et al. 1995), any reduction in the rate of thrombotic events is clinically relevant.

Thrombotic events were defined by the same major adverse vascular event (MAVE) criteria in all studies. Because of the diverse anatomic locations of thrombosis in patients with PNH, multiple diagnostic techniques were used. The most common methods were ultrasound, computed tomography scan, magnetic resonance imaging, and angiogram. At least 73% of pre-treatment MAVEs were objectively identified (Hillmen et al. 2007).

In the extension study, a before-and-after treatment analysis was performed, including all 195 patients who enrolled in the three parent studies (ITT analysis). The eculizumab treatment TEs included all events during the period from the first eculizumab dose in the parent studies until the earlier of the follow-up after the last dose of eculizumab or the database lock (Hillmen et al. 2007).

A time-matched analysis, in which the duration of exposure before and during treatment was equalised for each patient, showed that in the 467.1 patient-years prior to eculizumab treatment, there were a total of 52 thrombotic events in 25 patients. The administration of eculizumab reduced the event incidence rate from 11.13 events per 100 patient-years to 2.14 events per 100 patient-years, a relative reduction of 81.8% (p<0.0005) (Table 124) (Hillmen et al. 2013). In a sub-group analysis of patients receiving antithrombotic agents (N = 103), the thrombotic event incidence rate reduced from 10.61 events per 100 patient-years (40 events over 377.1 patient-years) to 0.62 events per 100 patient-years (1 event over 161.9 patient-years) (p<0.0001) (Hillmen et al. 2007).

Prior to eculizumab treatment, 63/195 patients (32.3%) experienced 124 thrombotic events, both venous (85%) and arterial (15%), over a total of 1,683 patient-years (Hillmen et al. 2007). The most common sites of venous thrombosis were the lower limb deep veins (18.5%), mesenteric/splenic veins (18.5%), and hepatic/portal veins (16.9%); the most common type of arterial thrombosis was cerebrovascular accident/transient ischaemic attack (13.7%).

The percentage of patients free from thrombotic events increased from 67.7% before treatment to 96.4% during treatment. While on eculizumab, seven patients reported a total of 10 thrombotic events over 467.1 patient-years (Hillmen et al. 2013): five thrombophlebitis/deep vein thrombosis (three events occurred in one patient), one deep vein thrombosis, one retinal vein thrombosis, one possible thrombosis in a fistula, and a combination of portal vein thrombosis and splenic infarcts in the final patient. There are insufficient data to determine whether the treatment effect is consistent across all types of thrombotic events.

Table 124 Thromboembolism events in patients with and without eculizumaba

| TE events | Time-matched before treatment | During treatment |
| --- | --- | --- |
| Patients, no. | 195 | 195 |
| Thrombotic events | 52 (25 patients) | 10 (7 patients) |
| Patient-years | 467.1 | 467.1 |
| Thrombotic event rate n/100 patient-years | 11.1 | 2.14b |

a includes TRIUMPH placebo-treated patients who transitioned to eculizumab treatment

b p<0.0005 for comparisons of eculizumab treatment versus before treatment, ITT analysis, Wilcoxon signed rank test.

Source: (Hillmen et al. 2013)

##### Conclusion

There is low quality evidence that eculizumab reduces the rate of thrombotic events; there are insufficient data to determine if this effect is consistent across all types of thrombotic events (GRADE ⨁⨁⨀⨀).

##### Renal function

While renal function was not specified as an outcome in the TRIUMPH trial, a *post hoc* analysis was presented in Hillmen et al. (2010), which also presented a before-and-after analysis using 18-month treatment data from the extension study.

Renal function was measured by chronic kidney disease (CKD) stage, defined using the Kidney Disease Outcomes Quality Initiative (Table 166, Appendix E). An improvement in renal function was defined as a categorical documented reduction in CKD stage level (e.g. a change from Stage 4 to Stage 3, or Stage 3 to Stage 1) or fulfilling the criteria of no CKD, while a worsening in renal function was defined as a categorical increase in CCKD state level.

The results of the *post hoc* analysis of the effect of eculizumab treatment on renal function in the TRIUMPH trial are presented in Table 125. The subgroup analyses, based on baseline CKD stage, should be interpreted with caution due to the small number of patients included in each sub-group. The results indicate that, on average, patients on eculizumab treatment had better renal function outcomes than those receiving placebo over the 26-week treatment period.

Table 125 Effect of 6-month eculizumab treatment on renal function (change in stage of CKD with treatment)\*

| Baseline stage | Improvement (%) | No change (%) | Worsening (%) | p-valuea |
| --- | --- | --- | --- | --- |
| Eculizumab |  |  |  |  |
| All patients (n = 41) | 29.3 | 65.9 | 4.9 | 0.005 |
| Stages 3-5 (n = 9) | 11.1 | 88.9 | 0.0 | 0.30 |
| Stages 1-2 (n = 17) | 64.7 | 23.5 | 11.8 | 0.006 |
| Placebo |  |  |  |  |
| All patients (n = 42) | 16.7 | 69.0 | 14.3 | 0.78 |
| Stages 3-5 (n = 9) | 22.2 | 66.7 | 11.1 | 0.56 |
| Stages 1-2 (n = 14) | 35.7 | 50.0 | 14.3 | 0.25 |
| Eculizumab vs placebo |  |  |  | 0.04b |

CKD = chronic kidney disease

a The comparison (except for eculizumab vs placebo) performed for each group or for all patients, tested the null hypothesis that patients are as likely to improve as they are to worsen (Chi-square analysis)

b The comparison of eculizumab vs placebo tests the null hypothesis that the probability of patients improving or worsening with eculizumab is equal to the same probabilities with placebo (Chi-square analysis).

\* Source: (Hillmen et al. 2010)

The changes in stage of CKD over 18 months of eculizumab treatment, as reported for the extension trial, are summarised in Table 126. There are no equivalent pre-treatment data for the majority of patients in the study. While these results suggest that renal function is maintained over 18 months in the majority of patients, as the results are non-comparative, it is not possible to determine to what extent this outcome is attributable solely to eculizumab treatment.

Hillmen et al (2013) (Hillmen et al. 2013) reported that the percentage of patients showing improvement, worsening or whom had no change in CKD was 25.4%, 6.1% and 68.5% respectively at 6 months, compared with 44.8%, 6.9% and 48.3% respectively at 36 months. It is not clear why the 6 month results differ from those in Table 126, which were sourced from Hillmen et al (2010) (Hillmen et al. 2010). Overall, following 36 months of treatment, 93.1% of patients showed either an improvement or stabilisation in CKD, and patients were significantly more likely to experience an improvement than a worsening in renal function (p = 0.015) (Hillmen et al. 2013).

Table 126 Effect of long-term eculizumab treatment on renal function

| Baseline stage | Improvement in stage of CKD (%) | No change in stage of CKD (%) | Worsening in stage of CKD (%) | P-valuea |
| --- | --- | --- | --- | --- |
| 6 months |  |  |  |  |
| All patients (n = 189) | 31.7% | 60.3% | 7.9% | <0.001 |
| Stages 3-5 (n = 40) (mean change in GFRb) | 20.0% (+10.3) | 75.0% (-0.3) | 5.0% (-2.9) | 0.05 |
| Stages 1-2 (n = 81) | 64.2% | 24.7% | 11.1% | <0.001 |
| 12 months |  |  |  |  |
| All patients (n = 179) | 35.2% | 58.1% | 6.7% | <0.001 |
| Stages 3-5 (n = 39) (mean change in GFRb) | 20.5% (12.8) | 76.9% (-0.6) | 2.6% (-4.2) | 0.02 |
| Stages 1-2 (n = 77) | 71.4% | 23.4% | 5.2% | <0.001 |
| 18 months |  |  |  |  |
| All patients (n = 166) | 34.3% | 60.2% | 5.4% | <0.001 |
| Stages 3-5 (n = 35) (mean change in GFRb) | 22.9% (11.5) | 71.4% (0.3) | 5.7% (-6.3) | 0.05 |
| Stages 1-2 (n = 73) | 67.1% | 30.1% | 2.7% | <0.001 |
| 36 monthsc |  |  |  |  |
| All patients | 44.8% | 48.3% | 6.9% | 0.015 |

CKD = chronic kidney disease; GFR = glomerular filtration rate

a The comparison (except for eculizumab vs placebo) performed for each group or for all patients, tested the null hypothesis that patients are as likely to improve as they are to worsen (Chi-square analysis)

b Glomerular filtration rate measured in mL/min/1.73m2

Source: Data for 6 months, 12 months and 18 months were sourced from Hillmen et al (2010)(Hillmen et al. 2010), while those for 36 months were sourced from Hillmen et al (2013)(Hillmen et al. 2013).

##### Conclusion

The *post hoc* analysis of change in CKD stage for the TRIUMPH trial provides moderate quality evidence that patients treated with eculizumab have, on average, better renal outcomes than those receiving placebo over a 26-week treatment period (GRADE ⨁⨁⨁⨀).

#### Summary of comparative effectiveness

There are serious methodological issues in the only study addressing the effect of eculizumab on overall survival in patients with PNH (Kelly, RJ et al. 2011). The study provides very low quality evidence and the results should be interpreted with caution.

A randomised, double-blinded, placebo-controlled trial provides high quality evidence supporting the effectiveness of eculizumab, compared to placebo, in reducing transfusion requirements and improving quality of life, and moderate quality evidence that it results in better renal outcomes in PNH patients, over 26 weeks of treatment (Hillmen et al. 2006).

A single-arm extension study, combining patients from three parent studies, provides low quality evidence that the effectiveness of eculizumab in reducing transfusion requirements is maintained over a median duration of treatment of 30 months, and that, compared to standard treatment, eculizumab reduces the rate of thromboembolic events in PNH patients over a total of 467 patient-years (Hillmen et al. 2010; Hillmen et al. 2007; Hillmen et al. 2013).

#### Safety of eculizumab in the treatment of PNH

##### Comparative safety of eculizumab

The only study reporting the comparative safety of eculizumab compared to placebo in the treatment of PNH is the 26-week TRIUMPH randomised controlled trial (Hillmen et al. 2006).

No patients died during the trial. Two patients in the eculizumab treatment group discontinued prematurely, one because of patient choice and the other because of pregnancy (who went on to deliver a normal infant) (Dmytrijuk et al. 2008; Hillmen et al. 2006).

Serious adverse events were reported in 13 patients: 4 in the eculizumab group and 9 in the placebo group (Table 127); none of these events were considered to be treatment-related. Adverse events that were more common in the eculizumab group were headache, back pain and fatigue. After the first two weeks of treatment, the number of headaches that occurred in the two groups was similar. A single thrombosis occurred in a patient in the placebo group (Hillmen et al. 2006).

One patient in each treatment group had detectable levels of antibodies against eculizumab. The levels were low, were detected at a single visit, and did not affect complement inhibition in the patient receiving eculizumab (Hillmen et al. 2006).

Table 127 Adverse events in the TRIUMPH trial

| Adverse eventa | Eculizumab Group  (N = 43) | Placebo group  (N = 44) |
| --- | --- | --- |
| - | n (%) | n (%) |
| **Total no. of serious adverse events** | 4 (9) | 9 (20) |
| Exacerbation of PNH | 1 (2) | 3 (7) |
| Renal colic | 1 (2) | 0 |
| Lumbar- or sacral-disk prolapse | 1 (2) | 0 |
| Α-haemolytic streptococcal bacteraemia | 1 (2) | 0 |
| Central-line and urinary infection | 0 | 1 (2) |
| Upper respiratory tract infection | 0 | 1 (2) |
| Probable viral infection | 0 | 1 (2) |
| Neutropenia | 0 | 1 (2) |
| Cellulitis, folliculitis, and neutropenia | 0 | 1 (2) |
| Anaemia and pyrexia | 0 | 1 (2) |
| **Most frequent adverse eventsb** | - | - |
| Headachec | 19 (44) | 12 (27) |
| Nasopharyngitis | 10 (23) | 8 (18) |
| Back pain | 8 (19) | 4 (9) |
| Nausea | 7 (16) | 5 (11) |
| Upper respiratory tract infection | 6 (14) | 10 (23) |
| Fatigue | 5 (12) | 1 (2) |
| Cough | 5 (12) | 4 (9) |
| Diarrhoea | 4 (9) | 5 (11) |
| Arthralgia | 3 (7) | 5 (11) |
| Abdominal pain | 2 (5) | 5 (11) |
| Dizziness | 2 (5) | 5 (11) |
| Vomiting | 2 (5) | 5 (11) |
| Viral infection | 1 (2) | 5 (11) |

PNH = paroxysmal nocturnal haemoglobinuria

a Adverse events were coded with the use of preferred terms from the MedDRA

b The event occurred in at least 10% of patients in either group

c After the first 2 weeks of treatment, 10 patients (23%) receiving placebo and 9 patients (21%) receiving eculizumab had headache

Source: (Hillmen et al. 2006)

##### Non-comparative clinical data

A summary of the United States Food and Drug Administration (FDA) report for eculizumab for the treatment of patients with PNH, reported safety data from a total of 236 eculizumab treated patients, including the 43 patients from the TRIUMPH trial and 193 patients from uncontrolled PNH clinical studies (Dmytrijuk et al. 2008). Serious adverse events occurring in two or more patients included viral infection (2.6%), headache (2.1%), anaemia (1.6%), pyrexia (1.6%), and haemolysis (1.0%). Across the studies, infections did not seem to be more frequent with eculizumab than in those who received placebo in the randomised trial, although the incidence of herpes simplex infection in eculizumab treated patients was 5.7%, compared with none in the placebo control group (Dmytrijuk et al. 2008).

There were three cases of *Neisseria* meningitis in patients, one of whom was unvaccinated. None of the patients died, but the unvaccinated patient had complications including amputation of parts of some digits because of gangrene, pulmonary embolus, and pneumonia (Dmytrijuk et al. 2008).

A total of four eculizumab treated patients died. One patient with PNH and haemosiderosis suffered a pulmonary embolus and a haemorrhagic cerebral infarction 31 days after the last eculizumab dose; one patient with cholecystitis became septic and died from a cerebrovascular accident approximately 2 months after the last dose of eculizumab; one patient with myelodysplastic syndrome (MDS) developed cellulitis, sepsis, and acute renal failure after a fish hook infection and died from worsening of MDS; and one patient died of metastatic adenocarcinoma after 13 months on eculizumab (Dmytrijuk et al. 2008).

##### Safety in special populations

In a small case series Reiss et al (2014) assessed the safety of eculizumab in seven PNH patients aged 11-17 years, over a 12 week treatment period(Reiss et al. 2014). All seven patients experienced at least one treatment-emergent AE. Two AEs were considered to be probably drug-related: one case of severe upper abdominal pain and one patient with mild hypertension; both resolved with standard clinical or no intervention. Twelve serious AEs (SAEs) occurred in two patients; all were due to hospitalisation or prolongation of hospitalisation, and included acute sinusitis, anaemia, aplastic anaemia, catheter-site cellulitis, headache, menorrhagia, acute otitis media, thrombocytopenia and vaginal haemorrhage. The only severe SAE was in a patient with underlying aplastic anaemia who was hospitalised due to severe anaemia; this SAE was classified as unrelated to study drug.

There are limited data on the safety of eculizumab in pregnancy. Kelly et al (2010) reported the outcome in seven patients with PNH who received eculizumab at some stage during pregnancy (Kelly, R et al. 2010). One patient had an elective termination. Of the remaining patients, two received eculizumab up to 4-5 weeks gestation, one from week 27 gestation and during the postpartum period, and two throughout gestation and postpartum. While four of the six patients experienced complications in pregnancy, including breakthrough haemolysis, pre-eclampsia, postpartum haemorrhage and postpartum pyrexia of unknown origin, all had healthy babies.

##### Extended assessment of safety

The following data are extracted from the most recent Periodic Safety Update Report (PSUR) for eculizumab (Soliris®), dated 30 May 2013. These results are currently considered confidential, and have been redacted.

''''' '''' '''''' ''''''''' '''''''''' '''''''''''''' '''''''' '''''''''''''''''' ''' ''''' '''''''''''''''''''' '''''''''''''''' ''''' '''''''''''''''''' ''''''' ''''''' '''''' '''''''''''' ''''''''''''''' '''''''''''''''' '''' ''''''''''' ''''''''' '''''' ''''''''''''''''' '''' '''''' '''''''''''''''''''''''''' '''' ''''''''''''''''''''''' '''''' ''''''''''''''''' '''''''''''''''' '''' '''''''''''''''' ''''''''''''''''' '''' ''''''' ''''''''' '''' '''''''''''' ''''''''' ''' '''''''''''' ''''''''''' '''''' ''''''''''''''''' '''''''''''''''' ''''' ''''''''''''''''' '''''''''''''''' '''' '''''''''''''''''''' '''''''''' ''''''' ''''''' '''''''''''''''''' '''''''''''''''''''''''' '''' ''''''''' ''' ''''''''' '''''''''''''''''''''''' '''''''''''''''''''''''''''' '''''''' ''''' ''''''''''''''' ''''''''''''' '''''''''' ''''''''''''''''''''' '''''' '''''''' '''''''''''''' '''''''' ''''''''' ''''''' '''''''''''''''' '''''''''''''''''''''' ''''''''''''''' '''''''''''''''''''' '''''''''''''' '''''''''''''''''

''''''''''''''''''''' '''''''''''''''''' ''''''''' '''' ''''''''' ''''''''''''''' '''''''''''''''' '''''''''''''''''''''''''''''' '''''''''''''''''' '''''''''''' ''''''''''''''' '''''''''''''''''' '''''''' '''''''''''''' '''''''''''''''''' ''''' ''''''''''''''''' '''''''''''''' ''''''''''''''''''' '''''''''' '''''''''' ''''''''''''''''''''''''''''''' '''''''''''''''''''''''' ''''''' '''''''''''''''''''''''''''''' '''''''''''''''''''''''''''' '''''''' '''''''''''''''''''''''''''''''' '''''''''' ''''''''''' ''''' '''''''''''''''''''' ''''''''''''''''' ''''''''' ''''''''''''''' '''''''''''''' '''''''''''' ''''''' '''''''''''''''''''''' ''''''''''''''''''' '''' '''''' '''''''''' '''''''''''' '''''''''' '''''' ''''''''' ''''' '''''''''' '''''''' ''' ''''''''''''''''''''''''' ''''''''''''

##### ''''''''''''' '''''''''''''''''

''' '''''''''' '''' ''''''' ''''''''' ''''' ''''''''''''''' '''''''''''''''''' ''''''''''' '''''''''''''''''' '''' '''''''' '''' ''''''' ''''''''''' '''' ''''''''''' '''''''' ''''''''''''''''' '''' ''''''''' '''''''''''''''''' '''''' ''''''''''''''' '''''''' ''''''''''''''''''' ''''''''''''''' ''''''''''''''' ''''' ''''''''''''' ''''''''''''''' '''''''''''''' ''''' '''''''''''''''''''' ''''' ''''''' ''''''' '''''''''''''''''''''''''''''''''''' '''''''''''' ''''' ''''''''''' '''''''''''''''''''''''''''''' ''''''''''''''''''' ''''''' ''' ''''''''''' ''''''''''''''''''''' ''''''''''''' ''''''' ''''''''''''''''' '''''''''''''''' '''' ''''''''''''' '''''''''''''' ''''''' ''''''''''' ''''' '''''''''''''''''''''' ''''''''''''

'''''''' ''''''''''' ''''''''' '''''''''''''''''''''' ''''''''''''''' ''''''''''''''''''' ''''''' '''''''' '''' '''''' ''''''''''''''''''''''' '''''''''' ''''''''''''' '''''' '''''''''''''' ''''''''''' ''''''''''''''''''''' '''''''''''''''''' ''''''''''''' ''''''''' '''''''''''''''''' '''''''' ''''''''''''''''''' '''''''''''''''''' '''''''''''''''''''''''''''' '''''''''''''''' '''''''''''' ''''''''''''''' ''''''' ''''''''''''''' ''''''''''' ''''''''''''''''' '''''''''' '''''''' '''''''''''''''''' '''''' '''''' '''''''''' '''''''''' ''''' '''''''''''''''''''' ''''''''''' '''''''''''''''''''''''' ''''''''' ''''' ''''''''' '''''''''' '''''' '''' ''''''''''''''' '''' ''''''' ''''' ''''''''''''''''''''''''''''''''''' ''''''''''''''''''' '''' '''''' '''''''''''''''' '''' ''''''''''''''''''''''''''''''' '''''''''' '''''''''''''''''''''''''''''''''' ''''''''''''''' ''''''''''''

###### ''''''''''''''''''''''''''''' '''''''''''''''''''

'''' '''''' '''''''''''''' ''''''''''' '''''' '''''''' '''''''' '''''''''''''''' ''''''''''''''''''''' '''''''''''''' ''''''''''''''''''' '''''' ''''''''''''''''''' '''' '''''''''''''''''''''''''''' '''''''''''''''''' '''''''' '''''''''' ''''''''''''' '''''' '''''' ''''''''''''''''''''''' '''''''''''''''''''''''''' ''''''''''''''''''' ''''''' ''''''''''''''''''' ''''''''' ''''' ''''''''''''''''''''''''''''' ''''''''''''''''' ''' ''''''''''''''''''' ''''' ''''' ''''''''' ''''''' '''''''' ''''''''''''''''''''''''' '''''''' '''''''' '''''''''''''''''''''''''''''' '''''''''''''''' '''''''' ''' ''''''' ''''''''' '''''''' ''''''' ''''''' ''''''''''''''''''''''''''' '''''''''''''''' '''''' '''''''''''''''''''''''''''' '''''''''''''''''' ''''''''''''''''''' ''''' ''''''''''''''''''''''''' ''''''''''''''' ''''''' ''''''''''''''''''' ''''''''' '''''''''''''''''' '''' ''''''''''''''''''''''''''''' '''''' ''''''' '''''''' '''''''''''''''''''''''''''' '''''''''''''' ''''' '''''''''''''''''' ''''''''''''''''''''''' '''''''''''''''''' ''''''''''''''''' '''''''''''' '''''''''''''

###### ''''''''''''''' ''''''''''''''''

''' ''''''''' '''' '''''' ''''''''''' ''''' ''''''''''''''''' ''''''''''''''' '''''''''' '''''''''''''''''''' ''''' ''''' '''''''''''' '''''' ''''''''''''''''' '''''''' '''''''''''''''''''' '''' '''''''''''''''' ''''''''''''' ''''' ''''''''''''''''''''' '''''''''''''''''''' ''''' '''''''''''''''''''' '''''''''''''''' ''''''''''''' ''''' ''''''''''''''''''''' '''''''' '''''' '''''''' '''' ''''''''''''''''' '''' ''''' ''''''''''' ''''''' ''''''''''''''''' ''''''' ''''''''''''''''''' '''' '''''''''''''''''' ''''''''''''''''''' '''''''''''''''' ''''''' '''' '' '''''''''' '''''''''''''' ''''''''''''''''' '''''''''''''''' ''''''''''''''' ''''''''''''''' ''''''''''''''''''' '''''''''''''''''' '''''''''''''''''''''''''''''' '''' '''''''''''''' ''''''' ''''''''''''''''''''' ''''''''''' ''''''''''''' '''''''''' '''''''''' ''' '''''''''''''' '''''''' ''''' ''''''''''' '''' ''''''''''''' '''''''''''' ''''' '''''''''' ''''' '''''''' '''''''' ''''''''''''''' ''''''' '''''''''''''''''''' '''' ''''' ''''''''''''''''''''''' '''''''''''

''''''''''''' '''''''''''''''' ''''' ''''''''''''''' ''''''''''''' ''''''''''''''''' ''''''''''''''''' '''''''''' ''''' '''''''''''''''' ''''''''''''''''' '''''''' '''''''''''''''' '''''''''''''''''''' '''''''''''''''''''''''''''' ''''''''''''''''''''' ''''''''''''''''''' '''''''''''''''''' '''''''''' ''''''''''' '''' '''''''''''''' ''''''''''''''''''' ''''''''' ''''' ''''''''''''''''''''''' '''''''''''''''' ''''' '''''''''''' ''''''''''' ''''''''''''''''' ''''''''''''''''''' ''''''''''''''''''''''''''' ''''''''''' ''''''''''''''''''''''' '''''''''''' '''''''''''''''''''' ''''''''''''''''''' ''''''''' ''''''''''''''''' ''''''''''''''' '''''''''''''''''''''''' ''''''''''''''''''''' '''''''''''''' '''''''''''''''''' '''''''''' ''''''' ''''''''''''' ''''' '''''''' ''''''''' ''''''''''''''' '''''''''''''' ''''''''''''

###### ''''''''''''' '''''''''''''''''''''' ''''''''' ''''''''''''''''''''''''''''' '''' '''''''''''''''''''' ''''''''''''''''''''

''' ''''''''' ''''' ''''' ''''''''''' '''' ''''''''''''''' '''''''''''''''''''' '''''''''' '''''''''''''''''''''''''''' '''' '''''''''''''''''''' '''''''''' '''''''''''''''' '''''''''''' '''''''''' '''''''' '''''''''''''' '''''''''''''''''''''''' ''''' '''''' ''''''''''''''''''' ''''' '''''''''' '''''''' '' '''''''''' '''''''''''''''''''''' '''' ''''''''''''''''' '''''''''''''' ''''' ''''''''''''''''''' ''''' '''''''''' '''''''''''''''''' '''' '''''''' '''''''''''''''' ''''''''' '''''''''''''''' ''''' '''''''' '''''' ''''''''''' '''''''''''' ''''' '''''' '''''''''' ''''''''''''''''' '''''''' ''' '''''''''''' '''' ''''''' ''''''''''''' '''''''''' '''''' '''''' ''''''''' ''''' '''''''''''''''''''' '''''''''' ''''''' ''''''''' ''''' ''''''''''' ''' '''''' '''''''''''' '''''''' ''''''''' '''''''' '''''' ''''''''''''' '''''''' '''''''''' ''''''''''''''''''' ''''''''' '''''''''' '''' '''''''''' '''''''''' '''' ''''''''' '''''''''''''''' ''''''''''''' ''''''' '''''''''''''''' '''' ''''''''''''''' '''''''''''''''''''' ''''''''' ''''''''''''''''''''''''''' ''''''''''''''''' '''''''''''' ''''''''''''

###### '''''''''''''''''''''' '''''''' '''''''''''''''''''''''''''''' ''''''''''''''''''''''''''

''' '''''''' '''' ''''''' '''''''''''''''''''''''''' ''''''''''' ''''''''''''''''''' '''' '''''''''''' '''''' ''''''''''' ''''''''' ''' '''''''' '''''''''''''''' ''''''''''''''''''' '''''''''' ''''''' ''''''''''''''' ''''''''''''''''''''''' '''' ''''' ''''''''''' '''''' ''''''''''''''' ''''''' '''''''''''''''''''''' '''' ''''' ''''''''''''''' ''''''''''''' '''' '''''''''''''''''''' '''' '''''' ''''''''''' '''''' '''''''''''''''' '''''''' '''''''''''''''''''''' ''''' ''''''' '''''''''''''' '''''''' ''' ''''''' ''''''''' '''''' ''''''''''''''' '''''''' '''''''''''''''''''' '''''''''''''' ''''''''''''''' '''' '''''''''''''''''''''' '''''''''''''''''''' ''''''''''''''''''''''' '''''''''''''' '''''' ''''''''''''''''''''' '''''''''''''''' ''' ''''''''''' '''''''''''''''''''' '''''' '''''''''' ''''''''''''' '''''''' ''''''' '''''''''' ''''''''''''''''''''' ''''' ''''''' '''''''''''''''''''' '''''''''''''''''' '''''' ''''''''' '''''''''' '''''''''''''''' '''''''' ''''' ''''''''' '''''''''''''''''''''''''

''''''''''''''''''''''''' ''''''''''''''''''''''''''' ''''''''''' '''''''''''''''' ''''''' '''''''' ''''''''''''''''' ''''''' ''''''''' '''''''''''''' ''''''''''' ''''''''' '''' ''''''''''' ''''''''''''''''''' '''''''' ''''''''''' ''''''''''' ''''' ''''''''''''''''''' '''''''''''''''' '''''''''' '''''''' '''''''' '''''''''''''''''''' ''''''''''''''''''' ''''''''' ''''''' '''''''''''''''' '''''''' '''''' ''''''''' '''''''''''''' '''''''''''''''''' '''''''' '''''''''''' '''''''' '''''''''''''' ''''' '''''''''''''''''''' ''''''''''''''''''' ''''''''''''' ''''' '''''' ''''''''''''''''''''''' '''' '''''''' '''''''''''''''''''''''''''' '''''''''''' '''''''''''''''''''' ''''' '''''''''' ''''''''' ''''''''''''''''''' '''''''''' ''''''' '''''''''''' '''' ''''''''''''''' '''' ''''' ''''''''''''' ''''' ''''''''''''''''''''' '''''''''''''''''''' '''''''''''''''' ''''''''''''' '''''''''''

###### '''''''''''''''''''''''''''''

''' ''''''''' '''' ''''''''' ''''''''' ''''''''' '''''''''''''''''''' ''''' '''' '''''''''''' '''''''' '''''''''''''' ''''''''''''''''''''''' '''' ''''' ''''''''' ''''''' ''''''' '''''''''''''''' '''''''''''''''''''''' ''''' '''''''''''''''' ''''''''''''''''' ''''' ''''''''''''' ''''''''''''''''' ''''''''''''''' ''''' '''''''''''''''''''''' ''''''' '''''''''''''''''''''''''''' '''' '''''' '''''''''''''' '''''''''' '''''''' '''''' '''''''''''''''' '''''''''' ''''''''' ''''''''''''''''' '''' '''''''''''''' '''''''''''''''''''''''' ''''''''''''''''''' ''''''''''''''''' ''''''''''''' '''''''' '''''''''''''''''''''' ''''''' '''''''''' ''''''' '''''''''' ''''' ''''''''''''''''''' '''''''''''''''''''' ''''' '''''''''''''''''' ''''''''''''''''''''''''''' '''' '''''''''''' '''''''''''''''' ''''' '''''''''''''''' '''''''''''''' ''''''''''''''' '''''''''''''' ''''''''''''

###### ''''''''''''' '''' ''''''''''''''''''' '''''''''''''''''''

''''' ''''''''''''''''''' ''''''''' ''''''' '''''''''''''''''''

''''''''''''''''''' ''''''''''''''' ''''''''''''''''''''' '''''''''''''''' '''' ''''''' '''''''''' '''''''''''''''' '''''' '''''''''''' '''' '''''''''''''''''''' '''' '''''' '''''''''''''''''' '''''''''''''' '''''''''''''''''''''' ''''''''''''''''''' '''''''' '''''''''''''''' ''''''''''''''' '''''''''''''' '''''''''' ''''''''''''' ''''''''''''''''''''''''' '''''''''''''''' ''''''' '''''''''''''' ''''''''' ''''''''' '''''''''''''''''''''''

'''''''' ''''''''''' ''''''''''''' ''''''''''''''''''' '''''''' '''''' '''''''''''''''''''''' '''''''''''''' ''''' ''''''''''''''''''''''' '''''''''''''''' '''''''''''''' ''''''''''''''''' '''''''''''''' '''''''''''

#### Australian data registry information

Currently, there is one drug, eculizumab, listed for the treatment of Paroxysmal Nocturnal Haemoglobinuria (PNH) on the LSDP.

As part of managing patient eligibility on the LSDP, patient summaries were kept in a spreadsheet format. This enabled the disease advisory committee to see the results for individual patients and advise on the treatment and dose. However, these data are not in a format that it can be easily aggregated (even within individual patient records). A registry has been kept by the drug sponsor for eculizumab and these data (non-identifiable) were made available. The Alexion registry contained '''''' patients at the time of data cut-off. Most of these patients (if not all) are likely to be enrolled onto the LSDP but were not linked to the LSDP patient summaries. '''''''' ''''''''''''' ''''''''''''''' '''''' '''''' ''''''''''''' '''''''' '''''''''''''''' '''''''''''''''''''''''''''' '''''''' ''''' ''''''' ''''''''''''' '''''' '''''''''' '''' '''''''''''''''' '''''''' ''''''''''' '''''' '''''''''''''''''''''' ''''''' '''''''''''''' '''' ''''''''''''''''''''''' '''''''' ''''''''''''''''' ''' ''''''''''' '''''''''''' ''''' '''''''''' '''''''''''''''' '''''''' '''''''''''''' '''''''' '''''''''''''''''' '''''' ''''''''''''''' ''''''''''' '''''''''''''''' ''''''''''''''''' '''' ''''''' '''''''''''''''''''''''''' ''''''''''''''' '''''''''''' ''''''''''''''''''

##### Results

A comparison of the baseline characteristics of patients with LSDP patient summaries with those on the Alexion database and the Alexion PNH report was provided.

Table 128 Baseline characteristics across the data sources for patients receiving eculizumab

| **Characteristic** | LSDP patient sheets | Alexion database | Alexion PNH report |
| --- | --- | --- | --- |
| Number of patients | 85 (start dates and data available for 75) | '''''' | '''''' |
| Median age at disease diagnosis | NR | '''''''''' ''''''''''''' | ''''''''''' '''''''''''''' |
| Median age at start of drug | 40.0 years | '''''''''' ''''''''''''' | ''''''''''' '''''''''''''' |
| Female | NR | ''''''''' | ''''''''''''''''' |

NR = not reported; PNH = paroxysmal nocturnal haemoglobinuria

'''' '''''''''' '''' '''''''' '''' '''''' ''''''''''''''''''''''''''''''''' '''' '''''''' '''''''''''''''''''' ''''''' ''''''''''' '''''''' '''''''''''''' ''''''' '''''''''''''' ''''''' ''''''' ''''''''' '''''''''''''' '''''''' '''' ''''''''''''''' '''''''' ''''''' ''''''''''''''' ''''''''' ''''''' ''''''''''''''' ''''''''''''''''''' '''''' '''''''' ''''''''''''''''' ''''''''''''''''''''' ''''''''''''''''' '''''' ''''''''''' '''''''''''' '''''''''

The maximum permitted (ongoing) dose according to the LSDP criteria is 900mg/fortnight, which is consistent with what was used in the key trial for eculizumab (Hillmen et al 2006). The LSDP Reference Group was provided with information from the sponsor’s registry but this is considered confidential and has been redacted. ''''' '''''' '''''''''' '''''''''''' '''''''' ''''''''' '''' '''''' '''''''''''''' '''''''''''''''''''''' '''''''' ''' ''''''''''''''' ''''''''' '''''''''' '''''''''''''''''' ''' '''''''''' '''' '''''''''''' '''' '''''''''''''''''''''''''''''''' '''' '''''''' ''''''''''' ''''''' '''''''' ''''''' '''' ''' ''''''''''''' ''''''''''''''''' '''' ''''''''''''' '''''''' ''''''''''''' '''''''''''' ''''' '''''''''' ''''''' '''' '''''''' ''''''''' ''''''' '''''''' ''''''' ''''' '' ''''''''''''''' ''''''''''''''''''''' ''''''''' '''''''''''''''''' ''''''''''''''''' '''''' ''''''''''''' ''''''''''''''''''' '''''''''''''''' ''''''' '''''''''''' ''''''''''''' ''''''''' '''''''''''''''''''''''''''''''''' ''''''''' '''''' '''''''''''''''''''''' '''''''' ''''''''' ''''''''' ''''' ''''''''''''''' '''''''''''''''' ''' ''''''''' '''''''''''' '''''''' '''''''' ''''' ''''''' '''''''''' ''''''''''' '''''''''' '''''''' '''''''''' ''''''' ''''''''''''''''''' ''''''''''''''''''''''' ''''''' ''''''''''''''''''' ''''''''''''' '''''''''''''' '''''''' ''''' ''' '''''''' ''''''''''''' '''''' '''''''''''' ''''''''' ''''''''''''''''''' '''' ''''''''''''''''''''' '''''''''''''''' '''''''''''''''''''''''''''' '''''''''''''''''' ''''''' ''''''''''''''''''''' '''' '''''''''''''''' ''''''''' ''' '''''''''' ''''''''''''''''' '''''''''''''''''''''''''''''' '''' '''''''''''' ''''''' ''''''''' ''''''''''''' ''''''''''''''''''''''''' ''''' '''''''''' ''''''''''''''''' '''''' ''''''' '''''''' '''' '''''''''''' ''''''''''''''''' '''''''''''''''''''''' '''''''''''''' ''''''' ''''''''' '''''''''''''''''''''''' ''' ''' '''''''''''''' '''''''' '''''''''' ''''''''' '''''' ''''''''''''''''' '''' ''''''' ''''''''''' ''''''''''''' '''''''''''''''' ''''''''''

Table 129 Dosing across the data sources for patients receiving eculizumab

| Dose characteristic | LSDP patient sheets | Alexion database | Alexion PNH report |
| --- | --- | --- | --- |
| Median dose at last administration | 900mg/fortnight | 900mg/fortnight | 900mg/fortnight |
| Proportion of patients exceeding 900 mg/fortnight at any time | NE | '''''''''''''' ''''''''''''''''''' | ''''''''' |
| Proportion of patients exceeding 900mg/fortnight at the most recent administration | 4% (3/75) | '''''''''''''' '''''''''''''''''' | ''''''''' |
| Proportion of patients exceeding 900mg/fortnight (excluding in the first year of treatment) | NE | '''''''' ''''''''''''' | ''''''''' |

NE = not extractable (the data may be available but is in a format that cannot be queried, or would be onerous to extract). Note that the LDH data were extracted from the patient summary although the process was lengthy and replicating it for other variables would be equally as lengthy.

PNH patients often presented with lactate dehydrogenase (LDH) levels greater than 1.5 x the upper limit of normal (ULN). Lee et al (2013) reported that an LDH level of ≥ 1.5ULN was associated with a significantly higher risk of thromboembolism (Lee et al. 2013). The vast majority (98.6%) of patients in the LSDP patient summaries had a baseline value of LDH greater than 1.5 x ULN (average was 7.69xULN). By the most recent laboratory measurement, this had reduced to about 21% and '''''''''' in the LSDP patient summaries ''''''' ''''''' '''''''''''''' ''''''''''''''''' '''''''''''''''''''''''. Average LDH levels as a proportion of the ULN reduced from 7.7 to 1.4 in the LSDP patient summaries (Table 130).

''''' ''''''''''''''' ''''''''''' '''''' ''''''''''''''''''''''' ''' ''''''''''''''''' '''''' '''''''''''' '''''' ''''''''''''''''''' '''''''' ''''''' ''''''''' ''''''''''''' ''''''''''''''''''''''' ''''''''''''''''''''''''' '''''''''''''''''' '''''' '''''' '''''''' ''''''''''''''''' ''''''''' ''''''' '''''''''''''' '''''' '''''' '''''' '''''''''' ''''''''''''' '''''''''''''''''' '''''''' ''''''''''' '''''''''''''''''' '''''''''''''''''' '''''' ''''''' '''''''' ''''' '''''''''''''''''''' ''''''''' '''' '''''''''''''' ''''''' ''' ''''''''''''''''''''''''' '''''''''' '''' ''''''' '''''''' '''''''''''''' ''''''''''''' '''''''' ''''' '''''''''''' '''''' '''''''''''''''' '''''''' ''''' ''''''''''''''''' ''''''''''''''' '' ''''''''''''''''''''''' ''''''''''' '''''' ''''''''''''''''''''' ''''''''' '''''''''''''''''''' '''''''' ''''''''''''''''' '''''''''''''''' ''''' '''''''''''''''' ''''' '''''''' '''''''''' ''''''''' ''''' ''''''''''''''' ''''' '''''' ''''''''' ''''' '''''''''''''''''''''' ''''''''''''' '''''''''

''''''''''''''''' ''''''''' ''''''''''''''''''' ''''''''' ''''''''''' '''''''''''''''''''' '''''''''''''' '''''' ''''''''''''''''' '''''''''''''' ''''''''''' '''''''' ''''''''''''''''''' ''''''''''''''''' ''''''''''''''''''''''''''''' ''' '''''''''''''''' ''''' '''''''''''''''' '''''''''''''''' '''''''''''' '''''''''''' '''' '''''''' ''''''''' ''''''''''' '''''''''''''''''''''''''''' ''''''''''''' '''''''''''

''''''''''''''''''''' '''''''''''''' ''''''''' ''''''''''''''''''''' ''''' '''''''''''''' ''''''''''' '''''''''' '''''' ''''''''' '''''' ''' '''''''''''' '''' ''''''''''' ''' ''''''''' '''''''''''' '''''''''

##### Conclusion

As part of the administration of the LSDP, patients consented to participate in the “evaluation of effectiveness of the drug by periodic assessment”. The data captured by the LSDP patient sheets are broad and include baseline characteristics and ongoing laboratory findings, instances of transfusions, narrative quality of life and committee comments regarding ongoing eligibility and recommended dose. The patient sheets represent individual records of patients and would be valuable for establishing patient response and ongoing eligibility. '''''''''''''''''' ''''''' '''''''' '''''' '''''' '''''''''''''''''' '''' ''' '''''''''''' ''''''' '''''''''''''' ''''''''''''' '''''''''''''''''''''''' '''''''''''' ''''''''' ''''''''''''''' '''''''''''' ''''''''''''''''''' '''''''''''''''' ''''' '''''' ''''''''''''''''''''' ''''' ''''''''' '''''''''''' '''''''''''''''''

At the time of assessment, the claimed benefit of eculizumab was in terms of avoided transfusions and haemoglobin stabilisation (other outcomes were not adequately demonstrated). A *post hoc* analysis of severe morbidity events using a before treatment – after treatment comparison showed a reduction in severe morbidity events occurring in multiple organs. The LSDP patient summary sheets do not permit a comparison of pre-treatment transfusion requirements although may have adequate data to inform a change in haemolysis (as measured by LDH) and haemoglobin. The format in which this information is stored limits the scope of any analyses. It is apparent that the level of transfusion-independence obtained in the Hillman et al (2013) extension study (82% at 30-36 weeks) may not have been realised in the Australian community setting (65% within an unknown time period).

'''''''' ''''''''''''''''' ''''''' ''''''''''''''''' '''''''''''''''' ''''''''' '''''' ''''''''''''''''' ''''''''' ''''''''''' '''' ''' '''''''''''' '''''''' ''' '''''''''''''''''''' ''''' ''''''''''''''' ''' '''''''''''' '''''''''''''''' '' '''''''''''''''''''''''''' ''''''''''''' '''''''' ''''''''''' ''''' '''''''''''''''''' '''' ''''''''''''''''' ''''''''''''''''''' ''''''''''''''''

Baseline LDH levels (as a multiple of the ULN) were extracted from the LSDP patient summaries. Compared to the most recent LDH measurements, the proportion of patients experiencing an LDH level ≥ 1.5 times the ULN is markedly reduced (98.6% at baseline compared with 21.3% at most recent measurement). This may indicate that eculizumab is reducing haemolysis.

The assessment of other outcomes, such as hospitalisations, transfusions and quality of life, are limited by the lack of pre-treatment data. If future data collections are established to verify the effects of a drug, adequate pre-treatment data will be required ''''''' ''' ''''''''''' ''''' '''''''''''''' ''' '''''' '''''''''''''' '''''''' ''''''''' '''' ''' '''''''''''''' ''''''''' '''''''''''''''' ''''''''''''''''''''''' ''''''' '''''''''''''''''

Table 130 Laboratory outcomes: LDH and Haemoglobin

| Laboratory outcome | LSDP patient sheets | Alexion database | Alexion PNH report |
| --- | --- | --- | --- |
| Proportion of patients with LDH ≥ 1.5ULN at baseline | ''''''''''''''' ''''''''''''''''  ''''''''''''''''''' '''' ''''''''''''''''''''''  '''''''''''''' '''' ''''''''''''''''''''''''' | '''''''' | '''''''  ''''''''''''''''' '''' ''''''''''''''''''''  ''''''''''''' '''' '''''''''''''''''''''' |
| Proportion of patients with LDH ≥1.5ULN at most recent measure | '''''''''''''''' ''''''''''''''''  ''''''''''''''''' '''' '''''''''''''''''''''''  '''''''''''''' '''' '''''''''''''''''''''''' | '''''''''' '''''''''''''''  '''''''''''''''''' '''' '''''''''''''''''''''''  ''''''''''''''' '''' ''''''''''''''''''''''' | '''''''' |
| Proportion of patients experiencing an LDH ≥ 1.5 ULN while on treatment | ''''''''' | ''''''''''''''' ''''''''''''''''' | ''''''''' |
| Median haemoglobin for all tests on the registry (on treatment) | '''''''' | ''''''''''''''' '''''''''''''''''''''' '''''''''' '''''''''' | '''''''' |
| Median haemoglobin at most recent test | '''''''' | ''''''''''''''''''' | '''''''''''''''' |
| Proportion of patients whose average Hb (while on treatment) is lower than 120g/L (LLN for women) | ''''''' | '''''''''' '''''''''''''''''' | '''''''' |
| Proportion of patients whose average Hb (while on treatment) is lower than 120g/L excluding measurements taken within the first year of treatment. | ''''''' | '''''''''' '''''''''''''''' |  |
| Proportion of patients who had transfusions while on treatment | ''''''''' | '''''''''''''' '''''''''''''''''' | ''''''' |
| Average number of units for those who received transfusions | ''''''' | ''''''''''''''''''''''''''''''' '''''''' ''''''''''''' '''''''' '''''''''' ''''''' '''''''''''''''''' '''''''''' '''''''''''''''''' '''' ''''''''''''''''''''''''''' ''''''''''''''''''''' ''''''''''''' '''''' '''' ''''''''' ''''''''''''''''''''' | ''''''' |

LDH = lactase dehydrogenase; LLN = lower limit of normal; NEb = not extractable; NR = not reported; PNH = paroxysmal nocturnal haemoglobinuria; ULN = upper limit of normal

a Follow up is measured from treatment start to final recorded transfusion in patients who experienced at least one transfusion.

b (the data may be available but is in a format that cannot be queried, or would be onerous to extract). Note that the LDH data were extracted from the patient summary although the process was lengthy and replicating it for other variables would be equally as lengthy.

General note: proportions, means and medians reported for laboratory outcomes may exaggerate the severity and likelihood of adverse findings as it is likely that clinicians would more likely order laboratory tests in those who they suspect as having a negative finding (low haemoglobin, high LDH).

Table 131 Fatigue and hospitalisations

| Outcome measure | LSDP patient sheets | Alexion database | Alexion PNH report |
| --- | --- | --- | --- |
| Proportion of patients who experienced severe fatigue while on treatment (FACIT Fatigue score of less than 30) | '''''''' | ''''''''''''''' ''''''''''''''''' | '''''''' |
| Proportion of patients who experienced severe fatigue at the most recent QoL questionnaire. | ''''''' | ''''''''''''''' '''''''''''''''''' | ''''''' |
| Median FACIT Fatigue score at final QoL entry (of a possible 52 – higher is better) | '''''''' | ''''''''''' '''''''''''''''' '''' ''''''' '''''''''''' '''''' ''''''''''''''''''''''' | '''''' '''''''''''''' ''''' ''''''''' ''''''''''''' ''''' ''''''''''''''''''''''' |
| Hospitalisationsa | ''''''' | ''''''' ''''''''''''''' ''''''''''' '''''''''''''''''''''''''''' '''''' '''''' ''''''''''''''''''' '''' '''''' '''''''''''' '''''''''''' '''''' '''''''''''''''''''''''' ''''''''''''''''''''''''''''''''''''' '''''''' ''''''''''' '''''''' '''''''''''' ''''''''' ''''''''''''''''''' | '''''''' |

NEb = not extractable; NR = not reportable

a Admission duration is calculated from the difference between the discharge date and the admission date inclusively (i.e., the admission day is calculated as 1 day). In the absence of a discharge date (occurred only once) a same day admission was assumed.

bThe data may be available but is in a format that cannot be queried, or would be onerous to extract. Note that the LDH data were extracted from the patient summary although the process was lengthy and replicating it for other variables would be equally as lengthy.

Table 132 Studies included assessing drugs to treat paroxysmal nocturnal haemoglobinuria (PNH)

| Drug | Results | References | Evidence not included in submission to the PBAC |
| --- | --- | --- | --- |
| Eculizumab | 1 RCT + extensions  1 historical control study | Hillmen et al (2006)  Hill et al (2005), Hillmen et al (2004), Brodsky (2008)  Kelly et al (2011) | The historical control study, Kelly et al (2011) reported that survival was improved with eculizumab:  5-year survival HR 0.21 (95%CI 0.05, 0.88) |

RCT = randomised controlled trial; HR = hazard ratio

# Horizon scanning

A horizon scan has been performed to address ToR 2:

1. **Review the emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future**

## What is horizon scanning?

Horizon Scanning is a process by which new and emerging health technologies are identified, rapidly assessed, and prioritised according to their potential impact on the public health care system. Potentially significant new health technologies are assessed briefly, usually in terms of their safety, effectiveness, cost, health system impact and ethical considerations.

For the LSDP technical assessment, the horizon scanning section has considered what interventions could potentially be relevant to the LSDP in the near future, based on:

a) a rare disease or condition defined as having a prevalence of 5 in 10,000 people (International Conference on Rare Disease, ICORD, Definition) and fulfilling the current eligibility criteria for the LSDP[[24]](#footnote-24). This includes consideration of drugs addressing patients with subclassifications of the more common diseases, as well as of drug chaperones and gene therapies; or

b) a rare disease or condition with a prevalence rate consistent with the drugs currently listed on the LSDP (≤1 in 100 000 people) and fulfilling the current eligibility criteria for the LSDP.

The analysis sought to consider the potential ramifications associated with each of the above options, in regards to the number of drugs potentially eligible, the size of the populations that could be eligible for these drugs, and the potential cost impact (incorporating dosage requirements).

## Topic eligibility

### Rarity

Different definitions of ‘rare’ diseases/conditions have been assessed under ToR 3 (International Comparison). For the purposes of Horizon Scanning, the implication of different definitions of ‘rare’ has been assessed in terms of the likely number of drugs eligible for the LSDP in the future, i.e. the potential number of eligible conditions, and the number of Australians with these conditions. Two definitions of ‘rare’ are compared. The use of the ICORD definition with ‘rare’ defined as an estimated prevalence of 5 in 10 000 (or 1 in 2 000) has been compared against the rarity of the diseases and conditions for which drugs are currently listed on the LSDP (i.e. ≤1 in 100 000) - these latter treatments have been predominantly enzyme replacement therapies.

Providing a definition of ‘rare’ has the potential to have a major impact on the number of individuals considered eligible for the LSDP. This is illustrated by using incidence data for some well-known diseases in Australia.

If a definition of <1 per 100,000 is used to define rare, then most of the major cancers in Australia would not be considered rare. However when considering an incidence of <1 in 2000 as rare, only the major cancers (bowel, breast, prostate) do not qualify; every other cancer has an incidence less than one in 2000. Table 133 shows some conditions that may be considered common and rare, and depending on the definition used, they can be classified as either all rare (using a definition of <1 per 2000) or all not rare (using a definition of <1 per 100 000).

Table 133 Incidence of conditions that could be considered rare

| Condition | Incidence per 100,000 | Incidence per 2000 |
| --- | --- | --- |
| Melanoma(Australian Institute of Health and Welfare and Australasian Association of Cancer Registries 2012) | 49.80 | 0.996 |
| Lung cancer(Australian Institute of Health and Welfare and Australasian Association of Cancer Registries 2012) | 43.20 | 0.864 |
| Lymphoid cancers(Australian Institute of Health and Welfare and Australasian Association of Cancer Registries 2012) | 28.10 | 0.562 |
| Cystic fibrosis(Cystic Fibrosis Australia 2014) | 40.00 | 0.800 |
| Huntington’s disease(Australian Huntington's Disease Association (NSW) Inc 2014) | 6-12 (prevalence) | 0.120-0.240 (prevalence) |
| Motor neurone disease(Motor Neurone Disease Australia 2014) | 2.65 | 0.053 |
| Tuberculosis(Bareja, Waring & Stapledon 2014) | 6.1 | 0.122 |

### Disease/condition

Although patients considered for the LSDP to date have had distinct rare diseases, not particular subclassifications of more common diseases, this latter possibility is not explicitly excluded. The implications of “salami-slicing” diseases into smaller sub-groups have been discussed in regards to the potential impact on the LSDP (see ‘Rare phenotypes / genotypes of common diseases’ section on page 219).

### Drugs

Different definitions of drugs has also been explored, allowing the Reference Group to consider the implications of using different definitions of “drug” or “pharmaceutical”, i.e. gene therapies and biologics.

## Method

A search of the literature for new and emerging pharmaceuticals relevant to rare diseases was conducted using:

1. the bibliographic databases PubMed (Pre-Medline only) and Embase.com. The search terms are given in Table 134 (based on Embase.com). The databases were searched, as per standard practice, using Boolean logic and the syntax unique to each database;
2. the selected sources given in APPENDIX F were also canvassed for new medicines or molecules suggested for rare diseases and conditions. These sources are suggested by the LSDP Reference Group, the EuroScan Toolkit, the AHTA Horizon Scanning Operations Manual, regulatory agencies, sources used by EuroScan, the Agency for Healthcare Research and Quality (AHRQ) horizon scanning agency (Emergency Care Research Institute, ECRI) and the Canadian Agency for Drugs and Technology in Health (CADTH) in their horizon scanning for drugs.

Table 134 Search terms for horizon scanning

| Element | Search terms and limits |
| --- | --- |
| Search terms | 'orphan drug'/exp OR 'orphan drug' OR (orphan NEAR/5 ('disease' OR 'drug' OR 'medicine')) OR (orphan AND ('diseases'/exp OR condition\* OR 'drug'/exp OR 'medicine'/exp)) OR (('rare disease'/exp OR 'rare disease' OR ‘rare condition’ OR chaperone\*) AND ('drug'/exp OR 'drug' OR 'medicine'/exp OR 'medicine'))) OR “clever molecular therapies” |
| Limits | [english]/lim AND [humans]/lim |
| Search period | 2013-2014 |

The sources shown in APPENDIX F were searched using the same terms with the caveat that single terms, phrases, or combinations of these may need to be varied according to the type of searching that each literature source permits. In other words, a more generalised approach was required for sources that used a search engine platform; however, an advanced search was used where that option was available. Given that horizon scanning seeks to determine the impact of technologies that are rapidly diffusing or likely to emerge within the next 3 years, the search was conducted for the period of one calendar year preceding the search date.

Broad categories of disease are discussed, with detail provided on a small number of key conditions. The key examples were selected based on diversity of type, as well as the likelihood of emergence in the near future. Particular types of new/emerging pharmaceutical treatments for rare diseases are reviewed briefly (≤ 5 pages) using an “Impact summary” format. The aim of the “Impact summary” is to provide sufficient detail to determine whether the medicine is targeting a rare disease, whether it affects life expectancy, and whether there are alternative treatments available which are cost-effective. Only those likely to emerge in the Australian health system within the next three years are discussed. Any drugs that cannot be legitimately expected to emerge within this time frame (e.g. drugs for which only animal studies are available) were not reviewed.

## Results

The biggest potential impact to the LSDP on the horizon is the move towards personalised medicine, and the way that common diseases are now being divided into rare phenotypes/genotypes, which could individually meet the criteria for the LSDP. The United States Food and Drug Administration allow orphan designation for “orphan subtypes” of common diseases, and in 2013, over a third of drug applications sought orphan designation.

The horizon scanning search revealed many different drugs in many different classes that could have potential relevance to the LSDP. However, in most cases, there is too little information available about the patient population (i.e. specific mutation or indication) to enable a thorough analysis of the likelihood of eligibility. There do seem to be areas of growing importance, including the use of monoclonal antibodies and gene therapies. The majority of developments on orphan drugs are in the oncology field, and this will raise questions as to whether specific, rare mutations of relatively common diseases will be eligible for the programme. In addition, many of the identified drugs that could potentially emerge as standard treatments for rare conditions are already used for the treatment of different clinical indications; and this could have implications for the public funding of these treatments.

A large number of potential treatments for many rare conditions were identified, predominantly identified through Orphanet (a reference portal for information on rare diseases and orphan drugs). This includes personalised or stratified medicine approaches, whereby genetic biomarkers are used to better target drugs for specific conditions, as well as novel treatments. These latter treatments include cell therapy, antisense RNA interference therapy, monoclonal antibodies and gene therapy. In many cases, particularly with relation to the oncology field, it was difficult to ascertain whether the drug would be eligible for the LSDP as there was a lack of detail about the specifics of the condition or the particular patient indications. Thus, whilst much of the work in orphan drugs is in the oncology field, it is difficult to predict the possible ramifications for the LSDP. Further information on this issue is given in the section on “Rare phenotypes” below.

Emerging treatments for other conditions are potentially relevant in terms of impacting on the LSDP. In particular, work on monoclonal antibodies (and their delivery systems) is likely to affect autoimmune disorders, and stem cell treatments are likely to become increasingly important in the treatment of neurological conditions.

Although our search for new and emerging drugs revealed many different drugs in many classes for many conditions, the list is not exhaustive. Given the commercial nature of most drug development, it is to be expected that much of the research into treatments for rare diseases is not in the public domain. Within the constraints of our literature search, what follows is a list of treatments identified that may be relevant to the LSDP in the future. Each of the diseases or conditions presented below have been identified as being treated with a novel drug and meets one of the definitions pre-specified as “rare”. Table 171 provides a snapshot of the prevalence of the condition and the emerging treatments. More detailed discussion of some of these treatments is given below including, where relevant, the results of recent research.

### Rare phenotypes / genotypes of common diseases

There is currently no clear definition of a “disease” or “condition”, and it is possible that common diseases or conditions may be divided into subsets of diseases, which could then be interpreted to meet the definition of a “rare disease”. In the United States, the Food and Drug Administration can grant orphan designation for a drug to be used in an “orphan subset” of a common disease (Reese 2014). For example, a common disease is non-small cell lung cancer, whereas an orphan subset may be non-small cell lung cancer with an EGFR mutation. To meet the criteria of an orphan subset, evidence is required that the proposed treatment only targets the specific rare subset of the disease, and is not effective at treating those who have the broader condition (Reese 2014). If an application is seen to be artificially ‘salami-slicing’ an indication in order to meet the rules for prevalence of an orphan drug, the orphan designation application will be rejected. However, scientific advances can provide plausible evidence to support claims of the uniqueness of subtypes. Geneticists are able to identify mutations to rare syndromes, virologists have been able to track the evolution of receptors on the surface of flu viruses, and biochemists have discovered particular misfolded proteins that appear responsible for diseases such as Alzheimer’s (Reardon 2014).

There are important implications if subgroups of common diseases are considered as potentially eligible targets for drugs listed on the LSDP. In 2010, a survey of Biopharmaceutical companies by the Tufts Center for the Study of Drug Development found that 94% of companies were investing in personalised medicine research, with 12 – 50% of drugs in the development pipeline, being described as personalised medicine (Long & Works, 2013). The companies estimated they would increase their spending on personalised medicine by 50% between 2010 and 2015. Another estimate is that orphan drugs will constitute 15.9% of worldwide prescription sales by 2018 (White 2013).

In the United States, the definition of lymphoma has been dividing into different subtypes, which are being classed as ‘orphan diseases’. In 2013, the FDA granted orphan designation to 21 different types of lymphoma treatment, and the Office of Orphan Product Development (OOPD) designated 260 drug applications as orphans, which is up 38% from 190 in 2012 (Reardon 2014). This equates to more than one-third of new drugs approved by the FDA in 2013, being designated as orphan drugs. A previous director of the OOPD, Timothy Coté, speculated that it is conceivable that orphan drugs may one day account for most of the FDA’s drug approvals (Reardon, 2014). With the completion of the Human Genome project, the mechanisms of over 5,000 diseases is now known, which has increasingly allowed subgroups within traditionally common illnesses to be identified.

The FDA currently waives their fees for orphan drug applications. These fees provide the majority of the FDA’s funding, and have risen from $573,500 to $2.17 million in the last decade. It is likely that the increasing proportion of drug applications which have had their fees waived is responsible for the increase in fee for the remaining applications (predominantly generic drugs and equipment manufacturers) (Bisset 2014).

It is suggested that the incentives in place for pharmaceutical and biotechnology companies to develop orphan drugs are now outdated, as the future is dominated by ‘orphan’ drugs for small patient populations (Bisset 2014). With the proliferation of subtype targeted drugs for conditions such as cancer, one option may be to limit orphan designation to the development of drugs with little established data behind them, where companies take more of a risk to treat diseases which are not fully understood (Bisset 2014).

In terms of eligibility for the LSDP, if these “orphan subsets” of common conditions meet the ‘rare’ eligibility criterion, it is unclear whether the criterion of ‘lack of availability of existing lifesaving treatments’ would also be judged according to the broader disease classification (including, for example, cancer staging) or whether it would apply at the molecular level. For example, if currently available cancer treatments are not biomarker-targeted, it could be construed that there are no effective treatments currently available for particular “orphan subset” cancers and thus the drug might be eligible for the LSDP if a survival benefit is demonstrated.

Areas of focus for targeting treatment to particular subtypes have been cancer, cardiovascular disease, infectious diseases and respiratory disease. Some examples of treatments that target rare subtypes of common diseases are given in the ‘Drugs for rare subtypes of common diseases’ section on page 229.

### Rare-diseases in the era of next-generation sequencing

Defining a rare disease as occurring in less than 1 in 2000 people, it is estimated that there are between 6000 and 7000 rare diseases, which are caused by single gene mutations. In the last 25 years, the molecular aetiology of approximately half of these has been identified through linkage mapping and candidate gene analysis. With the advent of next-generation sequencing, the identification of causative genes is accelerating, and it is predicted that the remaining disease-causing genes will be identified by the year 2020 (Boycott et al. 2013). Understanding the underlying biological mechanism behind different diseases allows the potential for new therapeutics to be considered. One example of this is the identification of SLC18A2 through whole exon sequencing; it is the causative gene behind infantile-onset movement disorder. The gene encodes VMAT2, which is a translocator of dopamine, and serotonin. This suggested that dopamine could be used to treat the disease. Consistent with this hypothesis, dopamine agonists were found to reduce symptoms and allow more normal development (Boycott et al. 2013). Despite a better understanding of disease aetiology, it is predicted that in the next 20 years there will only be approximately 75 new approvals for orphan drug products in Europe (Boycott et al. 2013).

Genetic disorders of high penetrance are usually related to: i) loss-of-function mutations, which lead to a reduction in the level or activity of a particular protein; or ii) gain-of-function mutations, which lead to an increase in protein level or activity (Beaulieu et al. 2012). Therapy can be directed at normalising the imbalance, by enhancing mRNA, protein or protein activity in loss-of-function disorders, or by moderating the mRNA, protein, protein function or pathway activity in gain-of-function mutations (Beaulieu et al. 2012). A table of possible forms of therapy for loss-of-function and gain-of-function disorders is listed in Table 135. Although using genetic mutations as a target for treatment is credible and feasible, the development of effective therapeutics may take time. One of the most “common” rare diseases, Duchenne’s muscular dystrophy, has been the subject of many years and millions of dollars of research, and there is currently still not an effective therapy in use for the disorder (Beaulieu et al. 2012). On the other hand, another “common” rare disease, cystic fibrosis, has recently seen the development of ivacaftor (Kalydeco), the only drug in its class (a potentiator) currently licensed for use in clinical practice. Known investigationally as VX770, it directly affects the CFTR mutation G551D by enhancing gating at the cell surface. Its effectiveness has been validated in several randomised controlled trials. Combination therapy with lumacaftor (a corrector) is now being trialled (Kumar, Tana & Shankar 2014).

Table 135 Direct therapeutic approaches to treat rare genetic diseases

| Approach | Intervention | Disease examples |
| --- | --- | --- |
| **Loss-of-function, usually recessive disorders** | **-** | **-** |
| DNA replacement | Gene therapy | Severe combined immunodeficiency |
| -- | Bone marrow transplantation | Mucopolysaccharidoses |
| Splicing correction | Antisense oligonucleotides | Duchenne muscular dystrophy (preclinical) |
| -- | Small molecules | Familial dysautonomia (preclinical) |
| mRNA increase | Small molecules | Spinal muscular atrophy (preclinical) |
| Protein replacement | Enzyme replacement therapy | Lysosomal storage diseases |
| Increase in protein activity, stability or level | Translational read through | Duchenne muscular dystrophy (preclinical) |
| - | Chaperonin therapy | Cystic fibrosis  Transthyretin amyloidosis |
| - | Proteasome inhibition | Pompe disease (preclinical) |
| **Gain-of-function, usually dominant disorders** | **-** | **-** |
| Transcriptional downregulation | Antisense oligonucleotides | Myotonic dystrophy (preclinical) |
| -- | RNA interference | Huntingdon disease (preclinical) |
| Protein inhibition | Small molecules | Noonan syndrome (preclinical) |

Source: (Boycott et al. 2013)

### Autoimmune disorders

Monoclonal antibodies are potential new treatments for autoimmune disorders. These antibodies bind to specific, targeted disease-causing entities. In 2013, the FDA approved more than 30 monoclonal antibodies for immunological disease and different cancers (Long & Works 2013). Gevokizumab, which is not yet listed on the ARTG, is a potential new treatment for Behcet’s disease uveitis. Two RCTs are currently underway to test its efficacy (NCT01965145, NCT02258867).

Another monoclonal antibody identified was tocilizumab for systemic sclerosis, which is currently listed on the ARTG for a different indication. This drug has only been reported in the literature for individual cases, and there is one trial underway (NCT01532869). Caplacizumab for thrombotic thrombocytopenic purpura is not yet listed on the ARTG, and was not identified in any reported or ongoing trials. Rituximab has been widely used in observational studies to treat refractory myasthenia gravis, but not yet in controlled trials. Further information is available in APPENDIX F.

Other identified drugs include apremilast for Behcet’s disease. Apremilast has been FDA approved for psoriatic arthritis but is not currently approved for Behcet’s disease. One completed clinical trial of this drug was identified (NCT00866359) but it has not been published. The trial found a statistically significant reduction in oral ulcers in the apremilast group.

Fingolimod is listed on the ARTG for multiple sclerosis and is a potential treatment for chronic inflammatory demyelinating polyneuropathy. There are no published studies but one trial is underway (NCT01625182).

Amifampridine is a potential treatment for Lambert-Eaton myasthenic syndrome (LEMS). It is a phosphate salt version of 3,4- Diaminopyridine (3,4-DAP). A review identified in the published literature reported a meta-analysis of four studies trialling 3,4-DAP in 54 LEMS patients, and concluded that whilst it significantly improved muscle strength score, the clinical implications of the improvement were unclear. This report concluded that 3,4-DAP remained the ‘drug of choice’ for patients with LEMS. (Sedehizadeh, Keogh & Maddison 2012). It was also considered the ‘treatment of choice’ by another review (Lindquist & Stangel 2011). Amifampridine has orphan designation by the EMA but was not located on the FDA-approved drugs list and it is not currently listed on the ARTG.

Pomalidomide is a potential treatment for systemic sclerosis. It is currently listed on the ARTG for a different indication. There are no published studies of pomalidomide, although one multi-centre trial is underway (NCT01559129).

### Brain and nervous system diseases, including neurodegenerative disorders

There is currently a PBS listed treatment for amyotrophic lateral sclerosis (ALS), known as riluzole. There has been considerable research into alternative treatments for ALS as riluzole has been shown to only marginally increase survival without improving quality of life (Srivastava 2014) and several authors still consider that there is no effective treatment for ALS (Srivastava 2014), (Mitsumoto, Brooks & Silani 2014). Several new, alternative treatments for ALS, with differing mechanisms, have been identified. These include three specific stem cell treatments - autologous bone-marrow derived mesenchymal stem cells, human spinal cord-derived neural stem cells and glial cell-derived neurotrophic factor (GDNF)-produced stem cell therapy. These therapies are in early stages of safety and efficacy studies, with some complete and many listed in trial registers (i.e. clinicaltrials.gov) as ongoing. Arimoclomol is a hydroxylamine derivative and is undergoing assessment in a double blind placebo controlled trial (NCT00706147). Ozanezumab is a monoclonal antibody that has been tested in a small placebo-controlled study (Meininger et al. 2014) and in an ongoing RCT (NCT01753076). Tirasemtiv has also been used in early trials. Arimoclomol, ozanezumab and tirasemtiv are not yet listed on the ARTG. Stem cell treatments are biologics and subject to specific TGA regulations. These treatments have the potential to be eligible for the LSPD, not only due to being advancements in stem cell technologies, but also due to the limited benefit of the only listed drug for this rare condition.

Three new drugs for Huntington’s disease were identified, none of which have been considered by the TGA for this indication. Pridopidine has been trialled in people with Huntington’s disease in a multicentre study in the US and Canada. A small but not statistically significant positive treatment effect on motor function was found (Huntington Study Group HART Investigators 2013). A European multicentre RCT of similar design also found no evidence of treatment efficacy (de Yebenes et al. 2011). One further ongoing trial of pridopidine is listed on clinicaltrials.gov (NCT02006472), and an extension study of a previous RCT is also ongoing (NCT01306929). It is unclear whether a therapeutic effect from this drug will be unequivocally demonstrated. Cysteamine is listed on the ARTG for nephropathic cystinosis. This drug was mentioned with reference to Huntington’s as early as 1986 and tested in a dose-finding and tolerability study in the mid 2000s; however, no further trials were identified other than one that is ongoing (NCT02101957). SIRT-1 inhibitors have been posited as possible treatments for Huntington’s disease but they are not listed on the ARTG and no studies were located on their use as a treatment for Huntington’s.

Rufinamide is an adjunctive treatment for the prevention of seizures in Lennox-Gestaut (LG) epilepsy. It is approved by the FDA and has orphan designation by the EMA. Guidelines from NICE in the UK recommend rufinamide as an adjunctive treatment (National Institute for Health and Clinical Excellence 2012). It is not listed on the ARTG but has been used as an adjunct treatment for LG epilepsy for several years. A meta-analysis of RCTs that compared adjunctive rufinamide to placebo in patients with LG and other types of drug resistant epilepsy was published in 2011 (Verrotti et al. 2011). It found rufinamide reduced the number of seizures in adult and paediatric patients. Another meta-analysis that examined adverse events found rufinamide to be associated with a significant increase in somnolence, dizziness, fatigue and headache, and with discontinuation rates (Alsaad & Koren 2014). An RCT conducted in 2014 in Japan of rufinamide versus placebo in patients with LG epilepsy also found a significant reduction in seizures (Ohtsuka et al. 2014). There are two studies of interest on clinicaltrials.gov, including a European registry study (NCT01991041) and a randomised controlled trial in children (NCT01405053). Given that this syndrome usually begins in children aged less than four years, and that controlling seizures usually requires combinations of medications, rufinamide is likely to come under consideration by the TGA as a treatment, but it is unclear if it will fit the criteria for the LSDP as there is no suggestion to date that it extends survival. An impact summary is available at APPENDIX F.

### Blood, bone marrow and immune system diseases

Numerous coagulation factors were identified as potential treatments for bleeding disorders. These include: afamelanotide for congenital erthropoietic porphyria, anagrelide hydrochloride for essential thrombocythemia, catridecacog for congenital factor XIII deficiency and rFIXFC for haemophilia B are all approved by the TGA and have orphan designation (along with several other coagulation factors). One other coagulation factor is approved by the TGA but is not an orphan drug: recombinant factor IX fusion protein for haemophilia B. It is unclear if these drugs would be eligible for the LSDP, as in most cases insufficient information about the new drug, and its specific indication or unique features, is available. It is thought that most of these drugs would be available via the public hospital system, with costs borne by the states and jurisdictions.

ACE-536 fusion protein is in phase 2 clinical trials for the treatment of beta-thalassemia (NCT01749540), and there are several other drugs that were identified as potential treatments for bleeding disorders for which little information is available. Gantotinib is a suggested treatment for essential thrombocythemia, myelofibrosis and poylcythemia but no studies using this drug were located in PubMed or in clinical trials registries. Fedratinib for myelofibrosis and ruxolitinib for polycythemia vera also have orphan drug status.

Three C1 esterase inhibitors were identified for the treatment of hereditary angioedema, of which two are approved by the TGA and are on the orphan drugs list (both are plasma derived); a third transgenic C1 esterase inhibitor has not been considered by the TGA. Additionally, icatibant, a selective competitive antagonist at the B2 receptor, is an orphan drug approved by the TGA. Again, it is unclear if these treatments would meet eligibility criteria for LSDP, given the availability of multiple treatments.

Gene therapy is a potential treatment for blood disorders. LentiGlobin gene therapy is currently being trialled to treat beta-thalassemia (NCT01745120, NCT01206075). Gene therapy is also a suggested treatment for haemophilia B; however a recent Cochrane review identified no trials of gene therapy in haemophilia A or B (Sharma et al. 2014), nor for sickle cell disease (Olowoyeye & Okwundu Charles 2014). There are several phase 1 and 2 studies underway for this new treatment, and given the advances in this area of molecular biology, there is likely to be a number of new treatments on the horizon for bleeding disorders.

A recombinant von Willebrand factor drug (BAX 111) was identified for the treatment of von Willebrand disease, however it is not clear how this differs from existing treatments including von Willebrand factor.

There are a few new treatments on the horizon for sickle cell anaemia and malaria. Purified poloxamer 188, which was first trialled in the early 2000s for sickle cell anaemia, is currently being investigated in a multi-centre trial (NCT01737814), and rivipansel is also currently being trialled (NCT02187003). Artesunate has orphan drug status as a treatment for malaria, while early trials are underway for the use of tafenoquine to treat the condition. Neither sickle cell disease or malaria are significant problems in Australia, although there is a growing African and Indian immigrant subpopulation whom may carry the HbS sickling mutation which protects against malaria.

### Cardiovascular diseases

One stem cell treatment, ixmyelocel-T, was identified for the treatment of familial isolated dilated cardiomyopathy. This treatment is not listed on the ARTG, and was not located on the FDA or EMA databases. It has been investigated for safety and efficacy in phase I and II clinical trials and is currently being assessed in a RCT (NCT01670981). A recent systematic review of stem cell therapies for dilated cardiomyopathy indicated that there was considerable heterogeneity in the studies to date, and suggested that further studies were necessary before the safety and efficacy could be adequately determined (Gho et al. 2013). This treatment is likely to be one of many stem cell treatments for rare diseases that emerges in the near future, and could come under consideration for the LSDP.

### Cancers

Many emerging treatments were identified for different cancers. A report by America’s pharmaceutical research companies published in 2013, entitled “Rare Diseases: A report on orphan drugs in the pipeline” indicated that in the United States, cancer drugs formed the largest category of medicines in development (Swinney & Xia 2014). In Europe, nearly half of orphan drug approvals between 2001 and 2012 were for oncology, with nearly a third of these for leukaemia (Norman 2013).

For some very rare cancers for which there is no or limited clinical or therapeutic experience, it has been suggested that molecular profiling and trialling different treatments to address the molecular profile of the cancer may be the best option. One case report of an individual with metastatic cancer of Cowper’s Gland (the 9th case in the medical literature) reports the successful use of this approach over a seven year period (Myers et al. 2014).

In general, the potential new treatments fall into several broad categories: monoclonal antibodies, immunoconjugates (combining antibodies and cytotoxins), vaccines, antineoplastics and protein kinase inhibitors.

Blood, bone marrow and immune system

Two main categories of emerging oncology drugs target the blood, bone marrow and immune system. These are monoclonal antibodies and protein-tyrosine kinase inhibitors. There is a very large body of published work on monoclonal antibodies and cancers, with many early trials, and it should be expected that this type of treatment will continue to develop and come to market. Current example monoclonal antibodies for common cancers include cetuximab and panitumumab for KRAS wild type metastatic colorectal cancer.

Tyrosine kinase inhibitors (TKIs) are already used to treat several common cancers, for example targeting endothelial growth factor receptors (EGFR) in non-small cell lung cancer (erlotinib, gefitinib, afatinib, and crizotinib), BCR-abl in Philadelphia chromosome-positive chronic myeloid leukemia (imatinib, nilotinib), HER2 in breast cancer (lapatinib), and multiple kinases in metastatic renal cancer (pazopanib). A new class of TKI has recently emerged. Lenvatinib received orphan drug designation for the treatment of follicular and papillary thyroid cancer from the European Commission in April 2013 and the EMA has recently approved accelerated assessment of this multiple kinase inhibitor for the treatment of patients with progressive radioiodine-refractory, differentiated thyroid cancer.[[25]](#footnote-25) It is therefore likely that existing TKIs and TKIs in development will be used to treat rare cancers and potentially be eligible for the LSDP if the existing treatments do not currently extend survival.

Liver

Several novel second-line treatments for metastatic hepatocellular carcinoma were identified: pexastimogene devacirepv (Pexa Vec), a thymidine kinase-deleted vaccinia virus; lyso-thermosensitive liposomal doxorubicin (ThermoDox), a temperature-sensitive liposomal formulation of the anthracycline antibiotic doxorubicin with potential antineoplastic activity; and G-202, a ‘prodrug’, which when used with sorafenib, is able to achieve higher concentrations of the active agents at the tumour site while avoiding systemic toxicity (National Cancer Institute 2014). None of these drugs are as yet listed on the ARTG.

Pexastimogene devacirepvec has had limited early safety and dose-finding trials, but is not currently being trialled for this indication. ThermoDox is currently being trialled (NCT02112656), as is G-202 (NCT01777594).

Skin

Many new treatments for skin cancer are on the horizon; as with other cancers, it is not clear in which particular patients (e.g. with specific mutations or stage of cancer) or under which treatment conditions (e.g. refractory conditions) these treatments may be used, and thus it is difficult to ascertain individual relevance to the LSDP. These treatments are diverse and include vaccines (POL-103A/ polyvalent melanoma vaccine, melapuldencil-T/autologous dendritic cell vaccine and FANG autologous tumour cell vaccine), a nanoparticle albumin-bound paclitaxel (Abraxane, on the ARTG for different indication), monoclonal antibodies (lambrolizumab, nivolumab), immunoconjugates (talimogene laherparapvec), protein kinases (trametinib+dabrafenib, both on the ARTG), poly(ADP-ribose) polymerase (PARP) -1 and -2 inhibitor (veliparib), an arginine-degrading enzyme (pegylated arginine deiminase) and various other antineoplastics (vincristine liposomal, coxsackievirus A21).

Hepatic circulation diseases

Defibrotide is on the orphan drug list and is the only drug approved in the EU for use in patients with hepatic veno-occlusive disease secondary to hematopoietic stem cell transplants (Keating 2014). Guidelines by the British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) recommend defibrotide for prevention of hepatic veno-occlusive disease in children and adults with certain risk factors who are undergoing allogeneic stem cell transplants, and for treatment of hepatic veno-occlusive disease (Dignan et al. 2013). No prevalence data are available for this condition, but as it is mainly seen as a side effect of the chemotherapy associated with stem cell transplants, the growth of this therapy could see this side effect become more common.

Lysosomal storage diseases

Unsurprisingly most identified treatments for these disorders involve enzymes (recombinant human lysosomal acid lipase, recombinant human alpha-mannosidase, cerebroside sulfatase, elsulfase alfa and sulfamidase enzyme replacement therapy), but treatments also include haematopoietic stem cell gene therapy and glucosylceramide synthase inhibitors (miglustat). Miglustat is listed on the TGA orphan drugs list for both Gaucher and Niemann-Pick disease, whilst elsulfase alfa, for Morquio A syndrome, is also on the orphan list. Recombinant human alpha-mannosidase (Lamazyn) is a potential new treatment for alpha-mannosidosis, and has undergone early trials and is being further researched.

### Metabolic and enzyme deficiency disorders, excluding lysosomal storage diseases

Several other metabolic and enzyme deficiency disorder treatments were identified, including gene therapies. Treatments for hereditary tyrosinaemia type 1 (nitisinone) and hypophosphatasia (asfotase alfa) are already on the TGA orphan drug list, whilst a treatment for homocystinuria (betaine anhydrous) is listed on the ARTG. A gene therapy for familial chylomicronaemia syndrome (alipogene tiparvovec gene therapy, Glybera) is likely to be submitted to the ARTG in late 2015 or early 2016, and an alternative treatment for this condition (diacylglycerol acytransferase-1 inhibitor, Pradigastat) is also on the horizon; both are designated orphan drugs by the EMA.

### Musculoskeletal diseases

Several new treatments were identified for Duchenne muscular dystrophy (DMD) that could be considered for the LSDP in the future, including two that have orphan drug designation in Europe for this indication (idebenone, halofuginone hydrobromide). Drisapersen and eteplirsen have been trialled in DMD patients but neither are approved in the US, Australia or Europe as yet. A gene therapy-delivered myostatin inhibitor is also a potential treatment for DMD, and was granted orphan designation by the FDA; however it is only in early trial stages.

### Respiratory system diseases and pulmonary circulation disorders

The common infection experienced by people with cystic fibrosis, *pseudomonas aeruginosa*, has several potential new treatments. All are antibiotics with varying mechanisms, and delivered by inhalation; aztreonam is already listed as an orphan drug on the ARTG, whilst levofloxacin has orphan designation by the EMA; both have been used in RCTs. A third antibiotic is liposomal amikacin for inhalation which is not approved in Australia, the US or Europe, but is also undergoing trials.

For chronic thromboembolic pulmonary hypertension (CTEPH) which is inoperable, there is one treatment already on the orphan drug list in Australia, riociguat. One other identified drug, ambrisentan, is on the PBS for a different, albeit related, indication: pulmonary arterial hypertension. In observational studies of ambrisentan, patients with chronic thromboembolic pulmonary hypertension have been included in the population of patients with various types of pulmonary hypertension, indicating that treatments are similar for these conditions and as such, ambrisentan is unlikely to be eligible for the LSDP (Badesch et al. 2012; Condliffe et al. 2014). A further identified treatment, beraprost 314dlung, not listed on the ARTG, has been trialled in other pulmonary arterial hypertension conditions, but not for CTEPH. It was originally approved as an orphan drug for this indication in Europe, but has since been withdrawn by the sponsor.

Numerous treatments for idiopathic pulmonary fibrosis were identified, none of which are listed on the ARTG. These include the monoclonal antibodies simtuzumab and tralokinumab, neither of which are approved in the US; although tralokinumab has orphan designation for this indication in Europe (simtuzumab is not approved in Europe). Simtuzumab has been used in trials of liver fibrosis and a current safety and efficacy trial is underway (NCT01769196). Likewise, tralokinumab has been used in trials for treating asthma, and an efficacy study is also underway for idiopathic pulmonary fibrosis (NCT01629667). Pirfenidone was very recently approved for this indication in the US and has orphan designation in Europe; a systematic review of studies found it to be beneficial for the treatment of idiopathic pulmonary fibrosis (Loveman et al. 2014). Nintedanib is also approved in the US and Europe and has EMA orphan designation, and is also being considered in Europe as an adenocarcinoma treatment. Two related trials (analysed together) found the treatment to be successful in slowing disease progression (Richeldi et al. 2014). Recombinant human pentraxin-2 protein also has orphan designation in Europe, but does not have approval in the US. No relevant studies were identified with this treatment.

### Drugs for rare subtypes of common diseases

### Cancers

Breast

A search of the TGA website identified pertuzumab as an orphan drug for the treatment of *HER2*-positive metastatic breast cancer patients who have undergone no prior anti-*HER2* therapy or chemotherapy for metastatic disease. It is unlikely that this therapy could be assessed as appropriate for the LSDP as a previous submission to the PBAC has sought Section 100 listing (Efficient Funding of Chemotherapy Drugs). The PBAC has deferred a decision on listing until further evidence is available on *all* anti-*HER2* medicines for first-line treatment of metastatic breast cancer.

Gastrointestinal tract

The literature search identified two drugs for the treatment of gastrointestinal cancers that are currently registered by the FDA: lapatinib and the first-in-class bispecific antibody MM-111.

Lapatinib is being trialled (phase 3) for the treatment of *ErbB2*-positive oesophageal cancer; however, no published study for this particular indication was identified. A randomised controlled trial of lapatinib versus placebo reported that among 32 patients with a variety of *HER2-*amplified solid tumours (gastroesophageal, bladder, ovarian and uterine), complete response was achieved in only one patient (while 9 patients had stable disease, 20 had progressive disease, and data was unavailable for the remaining 2 patients) (Galsky et al. 2012). The study was discontinued due to the low response rate.

No published studies on the use of MM-111 for the treatment of *HER2-*postive advanced adenocarcinoma of the stomach and gastroesophageal junction were identified.

Skin

In addition to the various drugs identified above for melanoma of differing stages, two treatments purposed for melanoma treatment in patients with specific mutations were identified: astuprotimut-R and vemurafenib.

Astuprotimut-R was registered with the FDA in 2013 as undergoing phase 3 investigation for the treatment of MAGE-A3-positive melanoma in stages IIB to IV. No studies of astuprotimut-R for this indication could be identified, however, phase 3 trial results will be available in 2016 (NCT00796445).

Vemurafenib for the treatment of melanoma in patients with the *BRAF* gene mutation V600 was recently considered by the PBAC and found to have unacceptably high costs on the basis of information currently available from the sponsor. It is noteworthy that dabrafenib, which the PBAC concluded to be non-inferior to vemurafenib for the relevant indication, is PBS-listed. Therefore, the clinical need for listing of vemurafenib on the LSDP appears tenuous.

Urinary system

Three medicinal products were identified which are intended for the treatment of renal cell carcinoma, each for a different patient indication.

Axitinib, intended for the second-line treatment of advanced renal cancer (i.e. patients have failed one prior systemic therapy), is not further discussed here given the PBS-availability of sorafenib, the comparator used in phase 3 trials (Escudier & Albiges 2014) supporting the application for TGA approval of axitinib.

The peptide vaccine “IMA901” (immatics Biotechnologies GmbH, Tübingen, Germany) is currently being investigated for the treatment of HLA-A\*2 positive renal cell carcinoma patients in a phase 3 clinical trial (NCT01265901). The expected completion date for this study is July 2015. One identified publication which reported on phase 2 results of IMA901 among the 96 patients with the relevant clinical indication concluded that immune responses to the vaccine were associated with longer overall survival (Walter et al. 2012).

A randomised, placebo-controlled phase 3 trial investigated the effect of vaccination with modified vaccinia Anakara encoding tumour antigen 5T4 (MVA-5T4) in 733 metastatic renal cancer patients (Amato et al. 2010). No significant difference was observed in overall survival (median 20.1 versus 19.2 months in the active treatment and placebo groups, respectively). The authors noted that exploratory analyses suggests subsets of patients with metastatic renal cell carcinoma may gain significant benefit from MVA-5T4, but this is yet to be investigated in randomised controlled trials.

# International systems comparison

A review was performed to assess how pharmaceuticals that treat rare diseases are subsidised across countries. This addresses ToR 3:

1. **Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.**

## International comparison objective

The purpose of this section of the technical assessment is to provide insight into the variety of mechanisms that govern the reimbursement of drugs for rare diseases internationally and to identify any research and/or policy approaches that could potentially improve the operations and administration of the LSDP in Australia. To do this we:

* Identified countries where drugs for rare/ultra-rare diseases are subsidised by Governments or third party providers of health care (*e.g.* HMOs in the USA); and
* Compared and contrasted the different mechanisms for subsidy and the basis of the decision to list drug-disease combinations for subsidy. These mechanisms are compared to the current eligibility criteria defined for the LSDP[[26]](#footnote-26).

## Research questions

The research questions have been developed through a consideration of the elements involved in the process of deciding to reimburse (e.g. publicly fund; insurance coverage) drugs for rare diseases.

### Payer characteristics

* What are the characteristics of the funding body (e.g. government or other third-party payer)?
* To which population is the reimbursement programme accessible (e.g.universal coverage, targeted/selected coverage)?
* What is the level of reimbursement (full / partial)?

### Mechanisms for subsidy

* What is the definition of rare/ultra-rare disease?
* Is there a separate review process for drugs for rare diseases? If yes, how does this differ from the regular review process?
* What are the programme details / eligibility criteria?

### Basis of the decision

* Who makes the decision?
* What is the basis for a positive or negative recommendation (e.g. cost-effectiveness or budget impact considerations or other)?
* What aspects are different in the consideration of the reimbursement of a drug for a rare disease (e.g. lower level of clinical evidence and high cost-effectiveness ratio)?

### Monitoring Outcomes of the Decision

* Is there monitoring of areas of uncertainty in drug funding decisions concerning rare/ultra-rare conditions?
* If so, what methods are used?
* Is there a timetabled programme for the review of decisions or is it *ad hoc*?

## Method

Information was gathered from various sources and triangulated to provide the most up-to-date summary of approaches used in programmes that are analogous to the LSDP internationally.

### Survey of INAHTA members

Members of the International Network of Agencies for Health Technology Assessment (INAHTA) were approached via email, seeking their input on the questions posed in section 4.2 above.

### Grey literature

Websites of payers in different health systems were canvassed for descriptions of reimbursement processes for pharmaceuticals targeting rare diseases. Websites dedicated to rare diseases and orphan drugs were also be canvassed, including EURORDIS (http://www.eurordis.org/eu-rare-disease-policy), and Orphanet (www.orpha.net). In addition, reimbursement dossiers of orphan drugs were searched for any potentially relevant information.

Materials from recent key conferences in the field of HTA (HTAi[[27]](#footnote-27) and ISPOR[[28]](#footnote-28)) were examined to identify prolific authors in the field and to isolate descriptions of current reimbursement processes in different countries/settings.

### Published literature

A review of the international literature was conducted. Papers were identified by searching databases including, but not limited to, Embase.com (including both Embase and MEDLINE), Health Systems Evidence (http://www.mcmasterhealthforum.org/hse), Google Scholar and Health Technology Assessment Databases. The bibliographies of included papers were checked for other relevant papers.

Table 136 contains search terms for the identification of international systems where the drugs for rare diseases are reimbursed. Key words and Emtree terms were developed using an Embase.com platform. The same text words and relevant alternatives were used for the other bibliographic databases, where applicable. The literature review for this chapter of the technical report was non-systematic. Therefore these search terms are only indicative of the approaches that were used and selection criteria were not be pre-formulated (other than that the material addresses the research questions). The information obtained was extracted in a standardised format (Appendix H), synthesised and presented narratively.

Table 136 Search terms to identify policy approaches by international systems (Embase.com example)

| Elements | Suggested search terms |
| --- | --- |
| Topics | ('reimbursement'/exp OR 'reimbursement' OR reimburs\* OR 'funding' OR 'funding'/exp OR funding)  AND  ('orphan drug'/exp OR 'orphan drug' OR (orphan AND ('disease' OR 'disease'/exp OR disease OR 'drug'/exp OR drug OR 'medicine'/exp OR medicine)) OR 'rare disease'/exp OR 'rare disease' OR (rare AND (‘condition’ OR 'disease' OR 'disease'/exp)) |
| Limits | NOT [animals]/lim |
| Search period | 2000 - 2014 |

## International comparison results

Information was sought from the literature on how different countries address the evaluation and funding mechanisms for orphan drugs for rare and ultra-rare diseases and conditions. In addition, members of the International Network of Agencies for Health Technology Assessment were surveyed.

The definition of rare and ultra-rare diseases was most commonly defined by legislation, designed to provide incentives to industry for developing and marketing drugs to treat or prevent the conditions. These incentives are in the form of substantial fee waivers, tax credits, market exclusivity for 7 – 10 years, and less stringent requirements to prove the cost-effectiveness of the drug. The definition of a rare disease varied from being the equivalent of less than one in 1,500 (definition used by the United States Food and Drug Administration for orphan designation, or orphan subtype designation), to a prevalence of less than 1 in 500,000 in China. For the purpose of orphan drug registration, the Australian Therapeutic Goods Act defines a rare disease as one that has fewer than 2,000 patients, which is approximated as a prevalence of 1 in 10,000 persons. The TGA have a narrower definition of rare disease than most of the countries.

A separate review process is used for subsidisation decisions concerning drugs targeting rare diseases in Italy (funding access to drugs for rare diseases before market authorisation); England and Wales (through the Highly specialised technologies programme); Canada (through a Rare Disease Drug Program and Alberta’s Short Term Exceptional Drug Therapy programme), and Japan (through the Specified Diseases Treatment Research Program).

Australia has no specific evaluation programme for drugs for rare diseases (DRDs). However, a DRD can be considered to be reimbursed through the LSDP if the PBAC accepts its clinical effectiveness but rejects its listing on the PBS as the DRD does not meet the cost-effectiveness criterion. In Germany and France, the review processes for drugs targeting rare diseases are also not separate from usual drug subsidisation processes. However, in Germany, when drugs target conditions without alternative therapeutic options, they will generally be granted reimbursement without price limit. In France, the clinical evidence required for orphan drugs reflects the limitations associated with gathering evidence on rare conditions.

Many countries allow special consideration of orphan drugs, allowing funding without pharmacoeconomic evaluations, higher cost-effectiveness thresholds, a broader societal perspective, allowing lower levels of evidence, and placing greater weight on the lack of alternative treatments.

Funding decisions for orphan drugs are re-evaluated after 1.5 – 5 years in Belgium, the Netherlands, France and the United Kingdom.

Managed entry schemes for DRDs are used in Belgium, England and Wales, Italy, the Netherlands and Sweden, using either performance-based risk sharing or financial-based schemes.

### Introduction

This section of the report discusses the results of a literature review on the funding arrangements for drugs to treat rare and ultra-rare diseases. The results of this literature review have been supplemented by a survey of INAHTA members as described above.

The literature review identified a number of funding bodies that reimbursed drugs for the treatment of rare and ultra-rare diseases. The report predominately focuses on funding bodies in the following regions; Canada (Ontario and Alberta), Europe (England, Wales and Scotland, Belgium, Austria, Netherlands, Sweden, Spain, Italy, Germany and France), and selected Asian countries (Japan, South Korea and China). Information regarding the reimbursement of DRDs in Australia is also presented in this section for the purpose of comparison.

### Payer characteristics

Funding bodies and coverage

Health care in the Netherlands is covered by two forms of insurance: obligatory health insurance where private health insurance companies cover short-term medical treatment; whilst long-term treatments (*e.g.* semi-permanent hospitalisation) are covered by a state-controlled mandatory insurance scheme (Schafer et al. 2010).

Canada is the only country with a universal (publicly funded) health care system that does not include coverage of prescription medications, except for drugs administered in hospitals and for certain special populations (*e.g.* elderly or indigent) in some provinces. The majority of the population obtains drug coverage through private insurers, either through their employers or purchased individually (ISPOR 2011).

In other counties, including Australia, health care is primarily public, financed mainly from national health insurance and/or general taxation (Appendix I, Table 173).

Level of reimbursement for pharmaceutical products

The level of reimbursement varies across countries. For example, Austrian social insurance covers the drug price, less a fixed sum of patient contribution of 5.4 Euro per pack. In Spain and France, however, a percentage of the overall drug cost is covered by the respective national health care insurance agency. In Spain, the level of reimbursement relies on health care settings and disease conditions: 100% reimbursement for hospital pharmaceuticals, 90% reimbursement for pharmaceuticals for the management of chronic illnesses (*e.g.* diabetes, asthma and epilepsy), and 60% reimbursement for the majority of prescription-only pharmaceuticals (ISPOR 2009d). The degree of patient co-payment in France ranges from 35% to 100% of its retail price, depending on the product’s medical value classification (Garau & Mestre-Ferrandiz 2009; ISPOR 2009b).

## Mechanisms for subsidy

Definition of rare and ultra-rare diseases

The definition of rare diseases varied between the identified funding bodies. In most cases this definition was defined by legislative activity that was often designed to provide incentives for industry for developing and marketing drugs to diagnose, treat, or prevent rare conditions.

In the European Union (EU), orphan drug legislation (Regulation (EC) No 141/2000) came into effect in the year 2000 and defined rare diseases as those with a prevalence of not more than 5 in 10,000 (i.e. 1:2,000) (Canadian Agency for Drugs and Technologies in Health 2013). While orphan designation and authorisation is processed at the EU level, it is the responsibility of individual EU member states to fund orphan drugs for their various indications. The vast majority of the member states identified during this review employ the EU definition of a rare disease for this purpose.

Although there is no explicit definition of a ‘rare disease’ used for determining eligibility for the LSDP, one criterion for the funding of a drug via the LSPD is that the drug should be approved by the TGA for treatment of a rare but clinically definable disease. According to the Therapeutic Goods Regulations 1990, a rare disease is defined as “a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time” (Australian Government 1990). This corresponds to a prevalence of about <1 in 10,000, a stricter definition of rare disease than most of the other countries included in the review. The TGA Orphan Drugs[[29]](#footnote-29) Program was established in 1998 with the purpose of helping make medicines available to sufferers of rare diseases. It is noted that the TGA Orphan Drugs Program is currently under review. The January 2015 discussion paper : 1) highlighted three areas of consideration for possible reform, including the definition of orphan drugs, the patient threshold and possible charging models; 2) put forward possible reform options for each of the areas of consideration; and 3) suggested several combinations of reform options for further consultation (Therapeutic Goods Administration 2015).

Table 137 contains a summary of the definitions of rare diseases employed by various funding bodies identified during the review.

Table 137 Definition of rare and/or ultra-rare diseases

| Organisation / Region | Definition of rare diseases |
| --- | --- |
| Australia: Therapeutic Goods Administration (Australian Government 1990) | Affects ≤2,000 Australians, *i.e.* prevalence of about < 1 in 10,000 |
| Ontario, Canada (Ontario Public Drug Programs) (Canadian Agency for Drugs and Technologies in Health 2013) | Incidence rate of < 1:150,000 live births or new diagnoses per year |
| Alberta, Canada: Alberta Human Services (Alberta Health and Wellness 2008; Canadian Agency for Drugs and Technologies in Health 2013) | Genetic lysosomal storage disorders occurring < 1 in 50,000 Canadians |
| European Medicines Agency (Canadian Agency for Drugs and Technologies in Health 2013) | Prevalence of < 5 in 10,000 |
| Sweden: Swedish National Health Service (Visschers, van Gemert & Olde Damink 2011) | Prevalence of < 1 in 10,000 |
| United Kingdom: National Institute for Clinical Excellence (Picavet, Cassiman & Simoens 2013) | Affects < 1000 people in England and Wales, *i.e.* prevalence of < 1 in 50,000a |
| United States: Food and Drug Administration (Visschers, van Gemert & Olde Damink 2011) | Affects < 200,000 Americans, *i.e.* prevalence of < 1 in 1,500 |
| Japan: Ministry of Health, Labour and Welfare (MHLW) (Gao, Song & Tang 2013) | Affects <50,000 people in Japan, *i.e.* prevalence of < 4 in 10,000 |
| South Korea: Ministry of Food and Drug Safety (MFDS), formerly known as the Korean Food and Drug Administration \*(KFDA) (Gao, Song & Tang 2013) | Affects <20,000 people in Korea, *i.e.* prevalence of < 4 in 10,000 |
| China (Ma et al. 2011; Song et al. 2012) | Rare diseases not been clearly defined by legislation.  Consensus on the definition of rare disease: prevalent of < 1 in 500,000 or neonatal incidence of < 1 in 10,000 |

a Definition of ultra-rare disease

Incentives to seek orphan designation

As well as reimbursement processes (discussed below) there are other forms of regulatory incentives to encourage drug companies to seek orphan designation for their products (see Table 138).

Incentives put in place in Australia and by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) are shown in Table 138. In the United States, companies usually apply for orphan-drug designation during the early drug development process. If the drug is marketed, the FDA waivers the $2.17 million “user fee” that companies must normally pay for new drugs under the Prescription Drug User Fee Act (Reardon 2014; Woodcock 2012). The company also receives tax credits for costs incurred with clinical trials, and has market exclusivity for 7 years, which means that approvals for similar drugs are blocked.

Table 138 Incentives to seek orphan drug designation in Australia, the EU and USA

| Location | Incentives |
| --- | --- |
| Australia | 5-year market exclusivity (under consideration by the Australian jurisdiction)  Waiver of application and evaluation fees by the Therapeutic Goods Administration and no annual registration fees  Distinct evaluation pathway (close collaboration with the Food and Drug Administration in the USA) |
| EU | 10 year market exclusivity  Free or discounted scientific advice (“protocol assistance”)  Fee waivers/ reductions for initial marketing authorisation applications and post-authorisation activities  Authorisation via the centralised system  Additional incentives for small and medium sized enterprises |
| USA | 7 year market exclusivity  Free waivers  Grants  50% tax credit on cost of US trials  Fast-track procedure to evaluate file |

Source: (Hetherington 2013); (Reardon 2014) (Orphanet 2015) EU = European Union, USA = United States of America

Funding mechanisms specific to orphan drugs

In Australia, DRDs are subject to the same application and evaluation processes for PBAC consideration as the drugs for common diseases. However, it is possible to fund a DRD via the LSDP if the PBAC rejects the PBS listing of this drug on cost-effectiveness grounds and if the DRD meets LSDP criteria and conditions as described in Appendix I, Table 174 (The Department of Health 2015). Of the funding bodies in other countries, only a few used separate review processes for the evaluation of orphan drugs for reimbursement purposes. A summary of the funding mechanisms for orphan drugs is given in Appendix I, Table 174.

In the Netherlands hospital system, drugs for rare diseases may be provisionally listed via a policy rule if no case-mix category exits for the orphan condition (DBC, Dutch: *Diagnosebehandelcombinatie, a* casemix classification system analogous to Australia’s DRG system used for activity based funding of hospital activities). This listing is made on the condition of collecting further evidence and having a re-appraisal in no more than 3 years’ time (Garau & Mestre-Ferrandiz 2009).

Similarly, the Italian Pharmaceutical Agency (Agenzia Italiana del Farmaco – AIFA) has two mechanisms that assist with the early access and reimbursement of drugs for rare diseases. Law 648/96 supports the provision of treatments for conditions that have no valid alternative therapy available. To be eligible for funding by the National Health Service, results of Phase II trials must be available, in addition to one of the following: i ) the medicines are authorised in other countries; ii) they are being tested in a Phase III clinical trial; or iii) they are marketed for another therapeutic indication (Garau & Mestre-Ferrandiz 2009). An alternative mechanism for funding in Italy relates to the ‘orphan drug specific process’ (Garau & Mestre-Ferrandiz 2009). A 5% AIFA special fund is made up of a contribution paid by pharmaceutical companies to be reinvested. According to the regulation, half of this fund should be devoted to providing access to drugs for rare diseases before marketing authorisation, with the other half being used to promote independent research and other similar activities (Garau & Mestre-Ferrandiz 2009).

In England and Wales, the Advisory Group for National Specialised Services (AGNSS) evaluated ultra-orphan drugs before April 2013. The AGNSS followed a multi-criteria decision analysis framework that used a broad range of criteria beyond cost-effectiveness and a holistic view across all of the criteria. The two-step procedure involved an initial assessment of nine entry criteria relating to the rarity of the condition and the complexity of its care. Once accepted, the application was assessed based on 12 core criteria in terms of the following four perspectives: i) health gain; ii) societal value; iii) reasonable cost; and iv) best practice (National Institute for Health and Care Excellence 2013). The National Institute for Health and Clinical Excellence (NICE) has been responsible for evaluating highly specialised health technologies for people in England with ultra-orphan diseases since April 2013. An interim process has been developed by NICE, building on the decision making framework developed by the AGNSS. The evaluation of technologies by the “highly specialised technologies programme” engages a specific evaluation committee that is an independent advisory body. The committee, comprising individuals who work in the National Health Service, pharmaceutical and medical devices industries, patient and caregiver organisations, and relevant academic disciplines, makes recommendations to NICE for, or against, the use of a technology based on its costs and benefits (Canadian Agency for Drugs and Technologies in Health 2013).

Evidence of orphan-disease specific evaluation processes were found in two Canadian Provinces. In Ontario, the Drugs for Rare Diseases (DRDs) program is open to diseases with an incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year, and a lack of availability or feasibility of adequately powered randomised controlled trials detecting clinically relevant outcomes given the rarity of the disease (Canadian Agency for Drugs and Technologies in Health 2013). There is no restriction on the types of rare diseases considered for evaluation. The evaluation is conducted by a separate 5-member DRD Working Group and reports directly to the Executive Officer of the Ontario Public Drug Programs. The evaluation framework uses an evidence-based process and consists of five steps:

* Assesses whether a submitted disease meets the framework’s criteria of “rare”
* Gains an understanding of the natural history of the disease
* Assesses the potential effectiveness of the drug, based on the best available evidence
* Evaluates budget and cost impact
* Identifies whether any additional follow-up data is needed (Canadian Agency for Drugs and Technologies in Health 2013).

Alberta’s Rare Disease Drug Program (started in April 2009) is restricted to genetic lysosomal storage disorders occurring in less than 1 in 50,000 Canadians, as determined by Alberta Health. Drugs currently eligible for coverage in Alberta include Gaucher disease, Fabry Disease, MPS-I (Hurler/Hurler Scheie), Hunter disease and Pompe disease (Alberta Health and Wellness 2008; Canadian Agency for Drugs and Technologies in Health 2013). Patients to be treated under this program must consent to a number of conditions including:

* Conditional initial and continued coverage are dependent upon clinical outcomes,
* Ongoing clinical outcome monitoring is mandatory, and
* Inadequate patient response or deterioration, as defined by pre-established withdrawal criteria for a specific drug and/or as assessed by the program’s clinical review panel, will dictate coverage discontinuation.

Note that the presence of a significant illness likely to affect life expectancy, outside of the rare disease itself, is considered a contraindication to drug funding.

Submitted applications are reviewed by Alberta’s Rare Disease Clinical Review Panel, which is a Ministry-appointed panel consisting of rare-disease-treating specialists and other health care professionals with related clinical expertise. Final coverage decisions for rare disease drug funding are made by Alberta’s Minister of Health (Alberta Health and Wellness 2008; Canadian Agency for Drugs and Technologies in Health 2013). The process used by Alberta’s Rare Disease Drug Program is very similar to the manner in which the LSDP operates[[30]](#footnote-30).

In March 2012, Alberta launched a new Short Term Exceptional Drug Therapy Program. This program is limited to therapies without current public or private funding options. Some restriction on expected drug therapy costs apply:

* For inpatients, drug therapy (oncology drugs included) costs are expected to be between $1,500 and $50,000; and
* For outpatients with rare clinical conditions (excluding oncology indications) if the total drug cost is expected to be <$100,000 a year (Canadian Agency for Drugs and Technologies in Health 2013).

In Japan, the Specified Diseases Treatment Research program, has specified 56 diseases that are covered by public funding (Japan Intractable Diseases Information Center 2014). Information regarding the decision making processes on which diseases are covered were not identified by the literature review.

### Basis of the decision to fund

Many funding bodies do not have a separate review process for orphan drugs but do allow special consideration in their evaluation of drugs to treat rare diseases. In comparison to non-orphan drugs, these funding bodies relax the requirement for a full pharmacoeconomic evaluation (Belgium, the Netherlands and Germany) (Denis et al. 2011; Garau & Mestre-Ferrandiz 2009; Vegter et al. 2010). Others accept higher incremental cost-effectiveness ratios to take into account other social and equity considerations, such as Sweden’s differing cost-effectiveness thresholds for different characteristics of disease-linked severity, NICE’s consideration of the broader societal perspective, and the waiving of the cost-effectiveness criterion when the PBAC considers the reimbursement of a DRD through the LSDP (Canadian Agency for Drugs and Technologies in Health 2013; Garau & Mestre-Ferrandiz 2009; National Institute for Health and Care Excellence 2013; The Department of Health 2015). In Belgium, Sweden and France, a lower level of evidence for orphan drugs may be accepted; however, in Belgium drug sponsors are required to provide a revised dossier 1.5 – 3 years after initial reimbursement approval (Denis et al. 2011; Garau & Mestre-Ferrandiz 2009).

For pricing and reimbursement systems that do not treat orphan drugs any different relative to non-orphan drugs, many have criteria that would be likely to result in a positive listing. For example, the reimbursement and funding bodies in Germany, Italy and France placed a greater weight on the lack of available treatments (comparator) (Garau & Mestre-Ferrandiz 2009). In these countries, a full pharmacoeconomic evaluation is not required, nor is it an official criterion in the decision making process for orphan drugs. In Germany, drugs that are classified as innovative or those without any therapeutic equivalent are exempt from classification in Germany’s reference pricing system and are generally reimbursed. In France, the medical value (Service Médical Rendu – SMR) is assessed in terms of efficacy and disease severity considerations, in addition to the incremental medical value (Amélioration du Service Médical Rendu – ASMR). The ASMR is assessed based on the degree of innovation of a new drug relative to existing treatments. In Italy, one criterion used to assess drugs for reimbursement is whether the new product is indicated for a disease with no alternative or whether there is an existing adequate therapy.

A summary of the decision-making processes as they relate to the reimbursement of orphan drugs by country is given in Appendix I, Table 175.

### Monitoring outcomes of the decision

In Australia, the LSDP does not require a re-assessment of the decision on a listing following its initial approval (The Department of Health 2015), although this can occur on an ad hoc basis. Limited information was found on the processes by which outcomes of the decision are monitored by pricing and funding bodies in other countries (Appendix I, Table 176).

In Belgium, pharmaceutical companies are required to submit a revised dossier to the DRC (the drug reimbursement committee) approximately 1.5-3 years following initial approval (Denis et al. 2011). In the Netherlands, the policy rule on orphan drugs for hospital treatments requires the funding body to reappraise evidence that has been collected after a maximum of 3 years and reviews its decisions on the product listing (Garau & Mestre-Ferrandiz 2009). In France the registration on the reimbursable list is only valid for 5 years. At the end of this period, the Commission d’Evaluation des Médicaments (HAS) re-evaluates the medical value (SMR) and incremental medical value (ASMR) of the drug. The price may also be reviewed by the Comité Economique des Produits de Santé (CEPS) based on the outcomes of the decision by HAS (ISPOR 2009b).

Given the difficulty of collecting data for ultra-rare diseases, the AGNSS in the United Kingdom assumes that a further data collection will occur in 5 years following recommendation and assesses the ability of the applicant to do this (Canadian Agency for Drugs and Technologies in Health 2013).

Managed Entry Schemes

Due to the inherent nature of rare diseases, clinical evidence considered during the reimbursement process tends to be limited relative to drugs for common diseases. Some of this uncertainty stems from a lack of evidence owing to the difficulty of recruiting a sufficient number of patients for a trial or from ethical considerations surrounding the use of certain trial designs (*e.g.* randomised controlled trial when no alternative treatment exists). Uncertainty surrounding the clinical effectiveness of orphan drugs is often higher as a result of the small sample sizes, reliance on surrogate outcomes and often heterogeneous patient populations. Moreover, treatments for rare diseases can have relatively high treatment costs, which add to the budgetary uncertainty and financial risk to the payer in the event that the drug does not work as well as expected. To mitigate risk, some funding bodies have employed manage entry schemes for orphan drugs.

In January 2011, the Australian Department of Health introduced a managed entry scheme “whereby the PBAC may recommend PBS coverage at a price justified by the existing evidence, pending submission of more conclusive evidence of cost-effectiveness to support listing of the drug at a higher price” (The Pharmaceutical Benefits Scheme 2011). None of the drugs currently listed on the LSDP have been introduced using a managed entry scheme approach.

A recent review of managed entry schemes for orphan drugs in Europe (Morel et al. 2013) found evidence of 42 managed entry schemes specific to 26 drugs implemented between 2006 and 2012 in five European countries (Belgium: n = 4; England and Wales: n = 8; Italy: n = 15; the Netherlands: n = 10; and Sweden: n = 5). The review found that performance-based risk-sharing arrangements (55%; n = 23) were slightly more prevalent than financial-based schemes (n = 19) and that performance-based risk sharing arrangements were relatively more common in Italy, the Netherlands and Sweden. Financial-based schemes were mainly found in Belgium, England and Wales, and Italy. A summary of managed entry schemes is given in Table 139 (sourced from Morel et al 2013 (Morel et al. 2013)).

Table 139 Overview of Managed Entry Arrangements (MEAs) identified across five European countries, described by country and design

| Types of MEAs | Country | | | | | Number of |
| --- | --- | --- | --- | --- | --- | --- |
| - | B | E | I | NL | S | MEAs |
| Performance-based arrangements |  |  |  |  |  | 23 |
| Performance-linked reimbursement schemes |  |  |  |  |  |  |
| Money-back guarantees |  |  | x |  |  | 8 |
| Coverage with evidence development (CED) |  |  |  |  |  |  |
| CED ‘only with research’ |  |  |  | x | x | 15 |
| Financial-based arrangements |  |  |  |  |  | 19 |
| Patient-level financial schemes |  |  |  |  |  | 10 |
| Discounted treatment initiation |  |  | x |  |  | 6 |
| Patient utilisation cap |  | x |  |  |  | 2 |
| Patient cost cap | x | x |  |  |  | 2 |
| Population-level financial schemes |  |  |  |  |  | 9 |
| Discount | x | x | x |  |  | 7 |
| Price-volume agreement with budget cap | x |  |  |  |  | 2 |
| Grand total | 4 | 8 | 15 | 10 | 5 | 42 |

B = Belgium; E = England & Wales; I = Italy; NL= Netherlands; S = Sweden; CED = coverage with evidence development; MEA = managed entry arrangement

Source: Morel *et al* 2013 (Morel et al. 2013)

# Appraisal of value metrics

## Purpose

The fifth ToR relates to the appraisal of value metrics, and analysis of current registry data:

1. **Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug’s treatment outcomes, including in terms of quality of life achieved through the programme and their cost.**

With regard to ToR 5, AHTA was advised by the Department and the LSDP Reference Group that this should be addressed by identifying published literature reporting on cost effectiveness and quality of life measures or other metrics for determining ‘value’. In addition, literature (from ToR1) reporting quality of life or similar patient-related outcomes was reviewed and considered in terms of the ‘value’ of the treatment to patients and/or the broader society. Alternative potentially useful metrics to measure ’value’ are considered. Implications are explored for re-determining the ‘value for money’ of the medicines currently subsided on the LSDP for rare and ultra-rare conditions.However, it is beyond the scope of the Review to construct a full economic model for each drug listed on the LSDP in order to quantify the value of the drug using the ‘value metric’ decided upon by the Reference Group.

The analysis of current registry data has been threaded throughout this report by appending relevant analyses to the different systematic review ‘disease’ chapters.

## Background: Principles of value in the PBS and the LSDP

The Pharmaceutical Benefits Advisory Committee (PBAC) is required to advise on ‘value-for money’ of proposed medicines (Pharmactical Benefits Advisory Committee 2013), section 1.1). As part of the consideration of value, a quantitative estimate of cost-effectiveness is sought, incorporating information relating to costs associated with utilisation of the proposed drug (and associated drugs, medical and other related health care resources) and an estimate of associated outcomes valued in terms of overall quality and length of life; for example, ‘quality-adjusted life-years (QALY) gained’. This information enables a cost-utility (CU) analysis to be undertaken ((Pharmactical Benefits Advisory Committee 2013) section 3.1).

A CU analysis results in a single value metric called an incremental cost effectiveness ratio (ICER), expressed as costs/QALY, which directly estimates the additional cost of each unit of health outcome (QALY) that use of the proposed drug is estimated to provide. Interpretation of the ICER is logical - the lower the cost of a QALY (health benefit), the increased ‘value for money’ of the treatment. In theory, any and all patient-relevant health/health-related outcomes can be transformed to QALYs, thus enabling a consistent comparison of value (the ICER in $/additional QALYs) across all drugs proposed for funding. The PBAC does not publish a specific threshold ICER to which it considers drugs as offering reasonable value (Harris et al. 2008); however, expenditure on drugs with extremely high ICERs is not considered to represent good value for money, relative to funding drugs with low ICERs.

There is currently no formal adjustment to the methodology to prepare or interpret an ICER (cost/QALY) value metric within different contexts. The PBAC does allow for consideration of factors not captured in the ICER estimate as part of the decision-making process. Submission Guidelines advise that where appropriate, any equity assumptions and considerations should be described and examined in sensitivity analyses. Also a ‘Rule of Rescue’ (ROR) applies when the following criteria are all met:

1. no alternative intervention exists in Australia;
2. the medical condition is severe, progressive and expected to lead to premature death;
3. the condition applies to a small number of patients, and
4. the medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition ((Pharmactical Benefits Advisory Committee 2013) section F.3).

A positive recommendation for drug listing on the Pharmaceutical Benefits Schedule (PBS) may be favoured under these conditions, irrespective of a relatively high ICER or quantitative assessment of ‘value’. This is an acknowledgment by the PBAC of the additional aspects of societal value and distributional preferences that are not currently captured in the ICER metric. The extent to which these factors ultimately influence decision-making may be considered subjective and lacking transparency, yet equity-based adjustments are invariably subjective to some extent.

Currently, drugs not recommended for PBS listing on cost-effectiveness grounds may potentially be recommended for consideration of funding through the Life Saving Drugs Program (LSDP) if they meet all of the following criteria:

1. There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration.
2. The disease is identifiable with reasonable diagnostic precision.
3. Epidemiological and other studies provide evidence acceptable to the PBAC that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease.
4. There is evidence acceptable to the PBAC to predict that a patient’s lifespan will be substantially extended as a direct consequence of the use of the drug.
5. The drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme (PBS) listing because it fails to meet the required cost effectiveness criteria.
6. There is no alternative drug listed on the PBS or available for public hospital in-patients, which can be used as lifesaving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for the LSDP.
7. There is no alternative non-drug therapeutic modality (e.g. surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost effective treatment for this condition.
8. The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.

LSDP Criteria 1, 4 and 5 relate to effectiveness as required in the ROR criterion (iv). LSDP criterion 3 regarding reduced life-expectancy is similar to the ROR criterion (ii). The LSDP criteria 6 and 7 regarding lack of alternative interventions is essentially equivalent to the ROR criterion (i).

Differences between the two potential funding requirements are: The LSDP specifically requires:

* the disease to be identified with precision; and
* that it is unreasonable to expect the patient/carer to meet the financial costs privately (LSDP criteria 2 and 8),

whereas these are not specific considerations for listing on the PBS. The PBS ROR consideration has an additional requirement:

* that the population who may receive funding is small (ROR criteria iii),

and this is not a specified LSDP criterion, although all drugs currently funded through the LSDP are for ‘rare or ultra-rare’ conditions with small patient populations.

Perhaps the most significant difference between the two funding schemes is that when the PBAC considers a drug as meeting ROR criteria, the consideration is still in conjunction with the routine assessment of effectiveness, safety, cost-effectiveness and financial impacts. Therefore ‘value for money’ is always considered by the PBAC, albeit how value is interpreted in the context of a submission addressing ROR criteria may not be obvious. The LSDP funding criteria do not consider ‘value for money’ at all; rather it is implicit that any demonstration of clinical effectiveness may potentially be considered of value.

## Method of assessing alternative value metrics

Four different approaches were identified, which could be considered as alternative metrics for defining the value of orphan drugs:

1) Cost-utility evaluation, broadened to include the impact of the disease or condition on family and carers, not just patients. Taking into account the broader impact of a severe and rare disease would favour orphan drugs over traditional cost-utility evaluations, but this is unlikely to be significant enough for the drugs on the LSDP to be considered cost-effective under traditional criteria and the equity concerns would not be resolved.

2) Equity-weighted cost-utility evaluation that incorporates societal preferences for equity and social justice, and places greater preference on treatments which are: life-saving, treat more severe diseases, affect the socio-economically disadvantaged, children, people with dependents etc. There was contradictory information on whether rarity *per se* should be considered a cause for preference weighting. Equity weights can be applied either to change (increase) the relative QALY gain or to adjust the interpretation of the ICER (i.e. raise the threshold ICER) – but mathematically both approaches are equivalent.

3) Multi-Criteria Decision Analysis (MCDA), is an alternative ‘scoring’ framework which includes assessments of treatment impacts across all domains that are pre-determined as relevant. These could incorporate, for example, the effectiveness and safety of the drug, the economic impact, and other considerations, such as severity of the disease, the equity / ethical and social implications of the drug, or current health policy goals. Deriving scores to weight different elements can be complex but could potentially involve committees or surveying the broader community. MCDA scores could be used to give indication of value or directly with respect to a decision rule.

4) Input-based costing does not take into account the health benefit of the drug but considers only the costs associated with the development and production of the drug. In practice it is difficult to externally verify the validity of the production cost estimates.

Combinations of methods could be utilised with careful consideration to avoiding duplication.

Analysis of the data on existing LSDP drugs indicates that many of the drugs have insufficient evidence to support a cost-utility analysis. Calculation of alternative values cannot be undertaken without consensus on the nature and magnitude of equity weights or an MCDA framework that would apply. Lack of effectiveness data is of concern when attempting to quantify value; therefore uncertainty may need to be explicitly included in assessments of value.

A search was undertaken for potential alternative metric methodologies to estimate the value of orphan drugs. Papers were identified by searching databases including, but not limited to, Econlit, HEED, Embase.com (including both Embase and Medline), Google Scholar, and the Health Technology Assessment database. The bibliographies of included papers were checked for other relevant papers. Materials from recent key conferences in the field of HTA and economics (IHEA[[31]](#footnote-31), SMDM[[32]](#footnote-32), HTAi[[33]](#footnote-33), ISPOR[[34]](#footnote-34)) were also examined to identify recent research in the area and key authors in the field.

Qualitative evaluation methods were not included. A limited number of alternative metric approaches to the assessment of value for health interventions, beyond the existing cost-utility approach, that are potentially applicable to orphan drugs, were identified. These include:

1. Broadened cost-utility evaluation (with improved sensitivity and a broader perspective),
2. Equity-weighted cost-utility evaluation using various weighting criteria, e.g. disease severity (non-specific to orphan drugs) or disease rarity (specific to orphan drugs),
3. Multi-Criteria Decision Analysis (MCDA), and
4. Input-based costing.

Only the last two methodologies depart from cost-utility analysis approach and the use of QALYs in some form.

While the identified methodologies are not necessarily specific to orphan drugs (although some aspects may specifically relate to orphan status) each has been proposed as useful in the orphan drug setting because, broadly speaking, if assessed using these alternative methodologies, many orphan drugs would be identified as having greater ‘value’ than they would otherwise be the case using a mainstream (e.g. PBAC) economic evaluation. Whether or not the additional value identified would be sufficient to justify public-funding under a mainstream pharmaceutical funding scheme (e.g. the PBS) remains uncertain.

The methods of assessing value are presented in the order of the extent to which they vary (from least to most) from the existing economic evaluation approaches currently applied in a routine PBAC assessment of drug value.

The protocol for this technical assessment required that the findings on ‘value’ metrics be considered and applied at a high level to the results obtained from the systematic review of the drugs currently funded by the LSDP (Section 3). Evidence of health outcomes, as identified in the systematic review (TOR 1), and also a wider search to identify any health economic assessments was undertaken for these drugs.

The issue of attempting to identify ‘value’ when there is a limited evidence base is another problematic issue regarding valuing (and funding decisions) for orphan drugs. This is demonstrated in the review of the existing LSDP drugs and discussed further there.

## Cost-utility evaluation using QALYs with improved measurement tools and incorporating a broader (societal) perspective

There is criticism in the literature that generic *methods to measure change in quality of life* and determine health state utilities (and QALYs) are not adequately sensitive to capture all patient-relevant outcomes, particularly for some rare diseases. Disease-specific quality of life (QoL) measures, where available, tend to indicate additional QoL changes may exist beyond those captured by generic tools (Mulla et al. 2014) (Basch & Bennett 2014). Therefore cost-utility analysis using QALY differences estimated by generic QoL tools that are not well-suited to the particular rare or ultra-rare disease or condition may underestimate the cost-effectiveness of an orphan drug. However the onus to develop or utilise appropriate QoL measurement tools to obtain effectiveness data for orphan drugs is in the realm of primary research, rather than at the technology assessment or decision-making level. Beyond acknowledging the potential use of disease-specific QoL instruments and their potential use in cost-utility analyses, further research into improved and /or disease-specific QoL assessment tools is beyond the scope of this review. While use of more sensitive QoL measures may impact individual cost-effectiveness analyses favourably for orphan drugs, this is not specifically an orphan drug issue, nor does it constitute a fundamental change to current assessment or reimbursement decision-making approaches.

With respect to *perspective*, the existing PBAC guidelines specify the preferred economic evaluation method is a cost-utility analysis (p177) intended to identify incremental *health* outcomes and *healthcare* resource costs *for the population for which listing is sought* (p 173-5). The Guidelines acknowledge that occasionally the patient may incur non-health care resource use or gain non-health benefits, and with adequate justification, inclusion of these may also be relevant ((Pharmactical Benefits Advisory Committee 2013) Appendix 9).

There is a view that the tendency to exclude non-health related costs/outcomes, and the restriction of outcomes to those achieved directly in the patient receiving treatment, is not appropriate where a true societal perspective on value is sought. Davidson and Levin (Davidson & Levin 2010), and then Al-Janabi (2011) (Al-Janabi, Flynn & Coast 2011), detail the relevance of undertaking a broader economic evaluation which includes relatives (and caregivers) costs and QoL outcomes. They present a strong case that maximisation of population health requires consideration of the effects on carers in addition to the patient receiving the drug. This is particularly relevant where drug treatments are for conditions where there are heavy carer burdens or long-term family care is involved, and where the intervention will affect the carer’s role or responsibilities.

Tsuchiya (2012) further extends this concept, suggesting that a patient’s treatment may have QoL effects on their dependent family members i.e. where the person receiving treatment is a caregiver to a dependent person/s. This can be illustrated with an extreme case scenario such as where failure to access treatment in a parent results in children being orphaned or fostered. Tsuchiya argues that a truly societal perspective should also include these impacts (Tsuchiya 2012).

The justification of a revised perspective – invariably requiring increasingly complex economic analysis and modelling – to including broader cost and outcome considerations is neither restricted to orphan drugs alone, nor necessarily applicable to all orphan drugs. In any disease where family care is a significant factor, this methodology may influence decisions; it is likely to decrease ICERs, irrespective of the issue of disease rarity.

The “Social economic burden and health-related quality of life in patients with rare diseases in Europe” (BURQOL-RD project) is a European project intended to develop disease-based models capable of quantifying the socio-economic burden and health related quality of life (HRQOL) of patients suffering from specific Rare Diseases and their caregivers. It is considered that this could serve as the basis for an approach to assess new interventions for rare diseases in the EU (Linertova et al. 2012). As yet, results of this project appear only available for cystic fibrosis and these findings are published in Hungarian, so at this time, findings from the project are not able to be considered in the Australian setting - although it is evident that the use of non-professional caregivers is identified and considered (Pentek et al. 2014).

Adoption of a more inclusive CU analytic methodology represents an evolving sophistication in the methodology of cost-utility analysis, but does not constitute any fundamental change in the concepts of cost-effectiveness evaluation. The interpretation of these analyses or methods of application of societal preferences relating to drug treatments (orphan or otherwise) is consistent with a traditional health economics perspective.

A more inclusive modelling methodology (as described) is likely to increase the apparent cost-effectiveness of many orphan drugs, if evidence is available that it can be calculated. However, for drugs on the LSDP, estimated ICERs are many times greater than those seen in common drug assessments. Therefore, the likelihood that the above-described revisions would impact the ICER to the extent that orphan drugs meet mainstream cost-effective criteria or thresholds in health economic decision-making is unlikely. Further, an increase in the scope and complexity of an economic assessment will not be a viable solution for identifying ‘value’ if there is inadequate evidence available to formulate even a basic cost-utility analysis.

## Adjusted Cost-utility analysis: Equity weighted cost-effectiveness

Aside from the ‘internal validity’ of cost-utility analyses with respect to inclusiveness of all aspects of health impact and cost, there is a broad range of published literature to suggest that the ranking or selection of treatments based on raw ICERs in a QALY maximisation (utilitarian) approach, will not reflect societal preferences for public health expenditure in all circumstances (Dolan et al. 2005).

Rather, evidence suggests that when faced with a choice between health interventions of equivalent ICERs and budget impacts, there may be strong public preferences for funding of one intervention over another on the basis of societal values of equity and social justice. Likewise, even where ICERs and budget impacts are not equivalent, these social values may also direct preferences away from the most efficient utilitarian approach to a less efficient but preferred distribution, based on social values.

Preference weighting of various social value criteria (excluding rarity)

Reported circumstances or characteristics of patients or treatments which have been proposed as warranting preference-weighting include:

1. treatments which are life-saving (rather than life prolonging or life enhancing) (Donaldson, C et al. 2011);
2. treatment for populations of patients with more severe disease (Nord & Johansen 2014);
3. treatment for particular populations of social concern e.g. – socio-economically disadvantaged, children, people with dependents, etc. (Norheim et al. 2014);
4. treatments which provide considerable rather than marginal benefit (Mentzakis, Stefanowska & Hurley 2011);
5. treatments which will aid large numbers of people; (Bobinac, A. et al. 2012) and
6. treatments which will have economic productivity benefits (Norheim et al. 2014).

As data are available to support the notion that society has a preference to fund interventions which arise in these six circumstances above other health intervention funding, it is commonly proposed that application of an equity weighting for funding treatment (either when generating or interpreting QALYs), that is based on societal preferences, should occur. In practice the quantification of this type of weighting proves difficult. Where quantitative data on preferences exists there is significant variability between studies. For example, Nord and Johansen (2014) reviewed available data on the preferences for severity grading in preference allocation. Although consistently identifying a positive weighting and strong concern on the basis of disease severity (17 out of 20 studies) the quantification of the weighting had large variation, with estimated severity coefficients from 0 to 88 to be applied to a severity scale (Nord & Johansen 2014). For many other proposed ‘weight deserving’ attributes (preference to children, preference to the socially disadvantaged etc.), despite strong in-principle agreement on the domains, there is little quantitative data available to estimate the extent to which a social preference should be applied. This is particularly the case for data reflecting Australian societal values.

If the adoption of social preference weightings (applied on the basis of disease severity and/or the other patient characteristics described above) was considered both worthwhile and feasible, then there would be no reason to limit this to the assessment of orphan drugs for reimbursement decisions; although it might be expected to apply more often in orphan disease conditions (McCabe, Edlin & Round 2010). Rather, equity-adjustments on the basis of disease severity, or other social justice criteria, could be applicable to all pharmacoeconomic assessment processes.

Preference weighting specifically on the basis of ‘disease rarity’

It is contentious whether there is a societal preference for increased spending of health resources specifically on ‘orphan’ disease conditions.

The view and supporting argument that ‘rarity’ *per se* is not an ethically relevant value is expressed clearly by Norheim et al (2014) and McCabe et al (2010) (Norheim et al. 2014) (McCabe, Edlin & Round 2010). This is supported by findings in the following social research:

* A survey of 2,767 Norwegians aged 40-67 found that the majority (76.8%) did not, in principle, support preferential funding of rare diseases i.e. at the expense of the health of the majority of the population (Desser, A. S., Olsen & Grepperud 2013);
* This was broadly consistent with the author’s findings in a previous trade-off study which indicated little evidence for a societal preference of rare disease treatments at the expense of common disease treatments (Desser, A. S. et al. 2010), and a survey of Norwegian doctors that found no stated preference to prioritise on the basis of disease rarity (Desser, Arna S. 2013);
* A study of American University students indicated that they did not have a preference that increased funding for the same level of health outcome was justified in rare diseases over a common disease (Mentzakis, Stefanowska & Hurley 2011); and
* A NICE Citizens Council (2004), convened specifically to discuss whether or not a premium should be paid on orphan drugs, had a clear majority that considered “rarity in itself should not be a reason for paying premium prices” (unanimous) and “The treatment an individual receives from the NHS should not be affected in any way by the number of patients suffering or likely to suffer from their condition” (>75% agreement). However, this report concluded that premiums for orphan drugs may be warranted for *reasons other than rarity* (e.g. disease severity) (NICE Citizens Council 2004).

A lesser amount of evidence exists to support the contrary suggestion that society does support ‘special consideration’ of funding for orphan drugs. This includes:

* A different NICE Citizens Council (2008) where 20 out 29 Council members voted to support departing from the established NICE ICER threshold in circumstances where the illness is rare (NICE Citizens Council 2008);, and
* Despite the quantitative trade-off study failing to particularly support preferential orphan drug funding, it was identified (somewhat contradictorily) that there was strong support for the statement “rare disease patients should have the right to treatment even if more expensive” (mean score 4.5/5 on Likert scale) and a preference for doctors to ‘keep some money aside for treatment of rare diseases’ (Desser, Arna S. 2013).

Following a theoretical experiment, it was concluded that “…distributional preferences depend on the size of the health gain. Participants preferred programmes which distributed the total gain as long as they provided a *sufficiently* big individual gain, but they preferred to concentrate the gain rather than give *insignificant* gains to many people” (Rodriguez-Miguez & Pinto-Prades 2002). Under this function, the extent to which orphan drugs would receive preferential treatment would depend on the relative size of the *health gain per individual* provided by the orphan drug compared to the size of the health gain per individual associated with alternative treatments (which would constitute the opportunity cost). Application of these findings suggests that a minimum effect size would be warranted with any preferential allocation of funding to orphan drugs.

Preference weighting to ‘reward and further stimulate scientific innovation’

It has been suggested that novel orphan drugs may warrant preferential value weighting because society values the scientific knowledge and technological innovation they are associated with. Supporting the ‘innovation’ may bring indirect and long-term benefits not immediately associated with the product and indirectly return substantial value (Rollet, Lemoine & Dunoyer 2013). It is not possible to determine whether this argument is applicable or whether in the long-term this approach is efficient and would maximise health outcomes. However the argument is also supported from an equity standpoint, in that patients with rare conditions should be able to access quality treatments like other patients and therefore it is necessary to provide incentives for industry to continue to produce treatments for as yet untreatable conditions (BIA UK BioIndustry Association 2014). There is various information and discussion on other mechanisms to incentivise research in rare disease in the literature (Groft & Rubinstein 2013; Maurer 2006; Rollet, Lemoine & Dunoyer 2013).

Methodology to apply preference (equity) weighting

Adaptation of an equity-adjusted approach to assessing cost-effectiveness requires a multi-stage approach.

1. Identification of the relevant equity criteria
2. Quantification of the relative value (importance) of the associated equity criteria.
3. Application of equity weights to the cost-utility analyses; either by
   1. Adjusting QALYs as appropriate before calculation of the ICER; or by
   2. Adjusting the ICER threshold which is considered cost-effective.

(a. and/or b. yield mathematically equivalent results. (Bobinac, A. et al. 2012)

Quantification of the relative value (importance) of the associated equity criteria can be undertaken using numerous methods. Approaches to determine equity weights include: elicitation of social preferences through various exercises (e.g. willingness to pay, person trade-off, bi/multi-variate choice or conjoint analysis) (Bobinac, A. et al. 2012). Examples of mathematical techniques for transformation of the QALY (or ICER) on the basis of preferences have been published (Bleichrodt, Diecidue & Quiggin 2004) (Nord & Johansen 2014). Alternatively, multi-criteria decision analysis (MCDA) – discussed below as a method of obtaining an alternative value metric - can be used as a technique for determining equity weights (Bobinac, A. et al. 2012).

Existing data on social preferences is available for some criteria but this has been shown to vary widely within and across populations. Nord and Johansen (2014) state that the relationship between an equity criterion and a QALY or Willingness-To-Pay (WTP) weighting “needs to be determined through a careful procedure of value judgements by policy-makers”. They ultimately conclude that deciding the extent of the adjustment factor is a political choice (Nord & Johansen 2014).

Application of an equity weighting to the cost-utility metric can be undertaken for a specific analysis. For example, by applying an equity weighting to the estimated QALY gain associated with the intervention being considered which would effectively reduce the ICER for that intervention. A broader policy application could be to adjust the threshold, considered to be acceptably cost-effective, that is applicable to any intervention where equity-weighting is justified. Mathematically these approaches yield identical results as the ICER is a direct function of the QALYs gained (Bobinac, A. et al. 2012).

## Multi-Criteria Decision Analysis (MCDA)

MCDA is a methodology in which decision-makers score and rank alternatives in a systematic manner, based on explicit criteria, to obtain a transparent decision (Goetghebeur et al. 2012). The philosophy of the approach is that the multiple criteria included in the assessment are grounded in substantive values (ethics) and collectively generate a holistic definition of ‘value’ (Wagner 2014). These criteria can include dimensions of value such as: burden of disease, socioeconomic parameters and other considerations relevant to society’s distributional preferences (including costs, effectiveness and other factors discussed under ‘equity-weighting’).

The criterion may involve either quantitative and/or qualitative information, and there are various alternative ‘decision support methods’ which may be applied to construct the final MCDA model (Diaby & Goeree 2014).

Simple MCDA methodology (summarised from (Angelis & Kanavos 2014), (Diaby & Goeree 2014)) includes the following steps:

1. Define the decision context and the boundaries of the problem
2. Identify criteria and attributes against which alternatives will be compared
3. Identify alternatives
4. Score options (assessed against criteria)
5. Weight criteria to reflect relative importance
6. Aggregate scores and weights, and
7. Examine results and conduct sensitivity analyses.

Criteria

Best-practice use of MCDA specifies that the decision-making criteria should include all *essential* aspects of the assessment and decision. Further, the criteria should have certain properties; they need to *understandable* to all participants; a *measurable* performance of the alternatives against the criteria needs to be possible; criteria should be *non-redundant* (i.e. with no overlap between other criteria), *independent* of other criteria (i.e. preferences orderings for each criteria should not depend on performance of other criteria) and *concise* ((Goetghebeur et al. 2008) (Angelis & Kanavos 2014)). The selected criteria can be arranged in levels with broader top-level criteria being broken down into sub-criteria for scoring or weighting purposes, as required.

MCDA frameworks that detail criteria for health technology assessments of drugs include: EVIDEM, a Canadian developed model (Goetghebeur et al. 2008) and other multi-attribute scoring tools developed in Malaysia (Ramli et al. 2013) and Thailand (Youngkong et al. 2012). Potentially the HTA framework developed by a collaboration of European HTA organisations (EUnetHTA 2013) could be applied to MCDA. The broad domains of evidence criteria included in these published or proposed HTA MCDA frameworks are given in Table 140.

Table 140 Example of different domains included in published MCDA applicable to drug evaluations.

| **EVIDEM (Goetghebeur et al. 2008)** | **EUnetHTA Core Model**  **(EUnetHTA 2013)** | **(Ramli et al. 2013)** | **(Youngkong et al. 2012)** |
| --- | --- | --- | --- |
| * Disease Information * Epidemiology * Treatment patterns and guidelines * Impact of intervention on therapy * Characteristics of intervention * Clinical data * Effectiveness data * Patient reported outcomes * Comparator data * Price information/ justification * Economic evaluation * Budget Impact | * Health problem and current use of technology * Description and technical characteristics of technology * Clinical effectiveness * Safety * Costs and economic evaluation * Ethical analysis * Organisational aspects * Social aspects * Legal aspects | * Drug applicability * Efficacy * Safety * Economics | * Size of population affected by disease * Severity of disease * Effectiveness of health intervention * Economic impact on household expenditure * Equity/ethical and social implication |

In most cases there are further specific sub-criteria (possibly extending to a number of levels) within the broad criteria. The EUnetHTA HTA model describes these as ‘topics’ within the domain, and within the topics are specific ‘issues’ of interest. Graphically this concept can be presented as a ‘value tree’ (Angelis & Kanavos 2014) and utilised for multi-level MCDA scoring.

Scoring and weighting

Generally scoring and weighting is applied specifically at the most detailed (e.g. topic) level associated with criteria and aggregated to higher levels. Ultimately aggregation of all weighted scores results in a single value metric, the ‘MCDA estimate’ on which a decision for funding or not is made.

Aggregation of the scores associated with the decision criteria can be undertaken as a simple linear addition (for example the methodology in (Tony et al. 2011)) or with a simple criteria weighting matrix (examples can be found in Ramli et al. 2013 and Youngkong et al. 2012) More sophisticated methods based on quantification of preference curves obtained through survey or experiment (rather than simple committee voting) and complex score allocation and aggregation methods have also been developed. Depending on the context of use alternative weighting/scoring/aggregation methods may include; value-based measurement methods; goal programming/reference methods and outranking methods (Diaby & Goeree 2014) and computer software (such as M-MACBETH) may be useful (Angelis & Kanavos 2014).

The EVIDEM framework (Goetghebeur et al. 2008, 2012) and EUnetHTA (EUnetHTA 2013) have been developed (and are undergoing ongoing development) with the intention that they may be used as formal decision-making tools across reimbursement decisions in their relative jurisdictions. The detailed methodology of these too extensive to reproduce in detail (but can be accessed publically).

Application to orphan drugs

MCDA is an alternative value assessment tool that is used broadly beyond healthcare. It is not specific to health or health technology assessment. Development of a specific MCDA framework to identify the value associated with orphan drugs has been proposed as a practical application (Hutchings et al. 2012), (Sussex, J, Rollet, P., Garau, M., Schmitt, C., Kent, A. and Hutchings, A 2013; Sussex, J et al. 2013). (Wagner 2014) Wagner (2014) describes a method, based on an adaptation of the EVIDEM framework, which notes that criteria such as disease severity (and sub-criteria: effect of disease on life-expectancy/disability/patient QoL/care) and system capacity (i.e. appropriate monitoring, registries, labs) may be particularly relevant to orphan drugs (Wagner 2014). A simple criteria model specifically for valuing orphan drugs has also been presented (Sussex, J et al. 2013).

## Input-based pricing

An alternative conceptual method of the valuation of cost-effective orphan drugs is to base value (represented by price) on supply input costs (Fellows & Hollis 2013). This proposed method acknowledges that orphan drugs do not meet previously established cost-effective criteria determined from a ‘health outputs’ perspective, but assumes that access to the orphan drug is desirable on other grounds. The proposed methodology is to cost the development and production of drugs and then estimate a regulated but fair price. This methodology detaches ‘health value’ from price, but links the rarity of the disease to the price function. The authors concede this methodology requires further investigation before it is applied (Fellows & Hollis 2013).

## Combined Methods

The alternative methods of obtaining value metrics described above - with the exception of input-based pricing which necessarily is a singular method - can be combined. For example, a broader perspective cost-utility analysis may also be subject to an equity weighting adjustment; or an MCDA may potentially include a broader and/or an equity-weighted CU analysis. Alternatively, MCDA methods may be employed to determine equity weights with which to make CU QALY/threshold adjustments. Where multiple methods are utilised within or alongside each other, care must be taken to ensure that adjustment factors are not double-counted.

## Summary of advantages and disadvantages of alternative value metrics

The various advantages and limitations associated with the alternative approaches to identifying a value metric for orphan drugs are presented in Table 141.

Table 141 Advantages and disadvantages of alternative value metrics for the assessment of orphan drugs for reimbursement decisions

|  | **Advantages** | **Disadvantages** |
| --- | --- | --- |
| Broadened cost-utility perspective | The ICER is a more accurate reflection of the complete value a drug may offer to society.  Relatively easy to incorporate into existing assessment process.  Produces an objective, reproducible value metric. | Fails to reflect social preferences where allocation on an equity basis (i.e. non-utilitarian) is preferred.  In practice, lack of data may limit the scope and accuracy of the economic model.  Would generally increase the cost-effectiveness of many drugs but the magnitude of effect may rarely be decision-altering. |
| Equity-weighted CU analysis (equity-adjusted QALYS or ICER threshold)  *broad equity criteria*  *‘rarity’ as a criteria* | Once criteria are defined and weightings determined, then application to a conventional economic assessment (ICER) or an adjusted benchmark ICER is straightforward and easy to interpret.  Weightings favour non-utilitarian social distribution preferences which are not apparent on conventional ICER calculations. | Selection criteria may be contentious.  Arbitrarily allocated weightings are subjective and yet mathematically determined weightings are highly variable and would require further social research.  Difficult to apply a weighting where the patient population is highly heterogeneous with respect to the weighting factor. |
| MCDA | Can potentially incorporate all identified social concerns and values associated with a drug into a value metric.  Can be set-up with inclusion of fluid or contextual criteria (e.g. ‘current priorities’) allowing for change in health strategy or policy, without change in the process. | Selection criteria may be contentious.  Although intended to be transparent, may become highly complex with reduced transparency.  May have subjective components.  Would require significant planning and set-up to implement. |
| Value-based pricing | Objective determination of (input) value.  Potentially provides incentive for research and investment in drugs for rare diseases with less financial risk to industry. | No consideration of ‘output’ value.  Financial risk to funding body.  Requires sensitive commercial operating cost information which is difficult to verify.  No practical experience. |
| Combined methods  (broad CU perspective / equity adjusted CU / MCDA) | Likely to capture all aspects of a drug’s potential value to society. | Risk of double-counting value elements  High level of complexity  Potentially reduced transparency |

Also, if adopting a new or alternative value metric for decision-making purposes, consideration as to whether this valuation metric could, or should, be limited to orphan drugs may be contentious. The alternative value metrics vary in the extent to which they lend themselves to restricted or defined use in the orphan drug context. An assessment of the extent to which an alternative value metric should be applied to all drugs, or could be limited to orphan drug, is presented in Table 142 although this assessment is necessarily subjective.

Table 142 Summary of the value metrics discussed

| **Value metric** | **Potentially applicable to any drug assessment** | **Justifiable as an approach to orphan drug assessments specifically, without impact on other general drug assessment.** |
| --- | --- | --- |
| Broadened cost-utility perspective | ✓ | 🗶 |
| Equity-weighted QALYS (or equity-adjusted ICER threshold) | - | - |
| Disease/population-based equity criteria  ‘rarity’ as a criteria | ✓  🗶 | 🗶  ✓ |
| MCDA | ✓ | ✓ possibly, but may be contentious |
| Input cost -based pricing | ✓/🗶 theoretically, but not practically | ✓ possibly, but unlikely to be relevant as input cost/patient treated generally substantially lower for drugs with a large market |
| Combined methods | ✓ | ✓ possibly |

As described previously, the alternative methods that have been identified tend to increase the recognised value of the drug by broadening the value base, and manufacturers of other pharmaceuticals may, understandably, also desire formal recognition of greater value in their products as well. A system that utilises different approaches for different products may not be considered fair potentially by either the societal recipients or the industry seeking funding (McCabe, Claxton & Tsuchiya 2005; McCabe, Edlin & Round 2010)). As described in (Wailoo, Tsuchiya & McCabe 2009), an integral aspect of any economic decision considers alternatives forgone (opportunity cost) and any additional identification of value in the assessed product – either through equity weights or increased valuation of certain criteria using an MCDA approach – should also be recognised in the consideration of opportunity cost. Therefore in any single funding/distribution system, attempting to concurrently value different products with different valuation methods may be controversial and have problems of inconsistency.

## Application of value metrics to LSDP drugs

A summary of considerations potentially relevant to the quantification of value using an alternative or adjusted value metric and a description of their relevance to the drugs currently funded by the LSDP is presented in Table 143

Table 143 Relevant considerations of alternative value methodologies for existing LSDP drugs

| **Alternative value metrics: relevant considerations** | **Imiglucerase**  **Velaglucerase**  **Miglustat for Type 1 Gaucher disease** | **Agalsidase alfa**  **Agalsidase beta for Fabry disease** | **Alglucosidase alfa for Infantile Onset Pompe Disease** | **Laronidase for MPS I** | **Idursulfase for MPS II** | **Galsulfase for MPS VI** | **Eculizumab for PNH** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Improved CU analysis: Improved &**  **Broadened capture QoL impact** | No data available | No data available | No data available; however severity and childhood nature of disease is suggestive of high levels parent care and parent QoL impacts. | Childhood symptoms with substantial parent care and parent QoL impacts. | Childhood symptoms with substantial parent care and parent QoL impacts. Detailed in (Raluy-Callado et al. 2013). | Childhood symptoms with substantial parent care and parent QoL impacts. | Diagnosis of PNH in pregnancy: high potential for impact on dependent children. |
| **Equity-weighted CU analysis**  **Or**  **equity considerations incorporated into MCDA:**  **Severity of disease**  **(e.g. reduction of life-expectancy or reduced functional capacity).** | Severity of disease and impact on life expectancy is highly variable. In many cases older age is reached with life expectancy into 60s. (Average of 9 years reduction in life expectancy vs overall population).(Weinreb et al. 2008) | US life expectancy data; males 58.2 years (vs 74.7 years in the general population) and for females: 75.4 years (vs 80.0 years in the general population.) (Waldek et al. 2009) | The classic form is a severe disease with life expectancy in untreated infants <1 year. (A variant form has a slower progression).(Bhengu et al. 2014) | Life expectancy in severe form is less than 10 years. Patients with least severe form can live into early adulthood.  Severe symptoms include restricted movement, breathing and feeding. (Wraith, J. E. & Jones 2014) | Variable severity. Severe cases with significant mental handicap and life expectancy 10-20 years. In less severe cases patients often live into 30s, and occasionally 60s. (Wraith, J. Edmond et al. 2008) | Variable severe symptoms including pain, restricted movement, hearing and sight issues and heart disease. In severe cases death around 20 years, but with slower forms, life expectancy into 40-50s. (Valayannopoulos et al. 2010) | Median survival untreated is 10-20 years. (Parker et al. 2005) |
| **Population of social concern**  **e.g. children** | Not confined to specific population (LSDP age range~ 2-84 years, average of 45 years) | Not confined to specific population.  LSDP mean age at first treatment ~42 years. | Generally diagnosed within first few months of life.  (LSDP population age 1.9-10.5 years, average 5.9 years) | Diagnosed in childhood  (LSDP current age range~ 7-58 years, average start age 16.5 years) | Often diagnosed in teenage years (LSDP current age range~ 1-57 years, average start age 15.1 years) | Often diagnosed in pre-teenage years (LSDP age range~ 4-35 years, average start age 10 years) | Often diagnosed in early adulthood (median age 28 years) (10% in children <21 years). 25% of females diagnosed in pregnancy (Parker et al. 2005). |
| **Rarity as an adjustment factor or MCDA criteria: e.g. Number of patients in Australia** | 62 patients registered on LSDP in 2014. | 78 patients registered on LSDP in 2014 | 3 patients registered on LSDP in 2014 | 6 patients registered on LSDP in 2014 | 15 patients registered on LSDP in 2014. | 12 patients registered on LSDP in 2014. | 78 patients registered on LSDP in 2014. |
| **Input costs** | unknown | unknown | unknown | unknown | unknown | unknown | unknown |

CU = cost utility analysis; MCDA = multi-criteria decision analysis; LSDP = Life Saving Drugs Programme; QoL = quality of life; MPS = mucopolysaccharidoses; PNH = paroxysmal nocturnal haemoglobinuria

It is not possible to indicate the quantitative adjustment that these considerations would have on the ICER, or the interpretation of the ICER, or an MCDA score, or an acceptable price structure, until a quantitative adjustment factor or scoring methodology is decided upon.

For the drugs currently listed on the LSDP a review of the evidence identified in the systematic review which would also be relevant to an alternative value is presented in Table 144. For each drug class a summary of how the evidence could conceptually be translated to a utility based metric is described in the table, as well as the limitations of the evidence with respect to its transformability to a utility-based value metric. In addition, the results from existing practical attempts to measure the value of the LSDP drugs which have been made (e.g. in the literature, submission to the PBAC) are reported. Analyses from other jurisdictions are not directly applicable to the Australian setting; however their existence may be indicative of the practicality of such an assessment, and in very broad terms suggestive of the expected magnitude of an ICER.

Table 144 Identification of outcomes identified in the systematic review of clinical evidence, their applicability to quantitative value assessment and other available economic analyses for existing drugs on the LSDP

| **Orphan Drug and condition** | **TOR 1 outcomes identified** | **Potential application of outcomes in cost-utility analysis** | **Limitations of data available for value assessments**  **(excluding equity considerations)** | **Existing economic analyses** |
| --- | --- | --- | --- | --- |
| Imiglucerase  Velaglucerase  Miglustat for Type 1 Gaucher disease | No survival data.  Some direct QoL data Oliveira, 2013, 31-7) Elstein, 2007, 2296-301,  Surrogate outcome measures (e.g. haematological/ biochemical values, organ size).  Some event data (e.g. bleeding rates). | Event data could potentially be translated and modelled to estimate incremental QALYs associated with disease/treatment events; however accuracy of transformation may be uncertain. | Inability to reliably transform surrogate measures to relevant outcomes/utility measures.  Use of limited selective outcomes to estimate QALYs will introduce bias and unreliability into any ICER estimate. | An Dutch CU analysis of ERT in GD 1 (van Dussen, Biegstraaten, Hollak, et al. 2014) estimated an ICER of €884,994/QALY or €434,416/YFEOD.  A cost minimisation of velaglucerase (vs imiglucerase) was submitted to the PBAC. |
| Agalsidase alfa  Agalsidase beta for Fabry disease | Survival data available but not statistically significant.  No direct QoL data.  Some clinically relevant outcome data available (e.g. pain, events).  Other outcome evidence related to surrogate measures (e.g. biochemical values). | Clinically relevant outcomes (e.g. pain, events) could potentially be translated to incremental QALY changes. | Use of limited and selective outcomes to estimate QALYs will potentially introduce bias and unreliability into any ICER estimate.  Inability to reliably transform surrogate measures to relevant outcomes/utility measures. | A Dutch cost-utility assessment of ERT (agalsidase alfa or agalsidase beta) (Rombach et al. 2013): identified an ICER range of €5.5 - €7.5 million/QALY.  (Connock, Juarez-Garcia, et al. 2006) an English CU assessment estimated an ICER for agalsidase beta of £252,000/QALY.  '''''''''''''''''''''' ''''''''''''''' ''''''''''''''''''''''''' '''' '''''''''''''''' '''''''''''''''' ''''''''''''''' '''''''''''''''''''''''''''' '''''''''''''''''''''''''' '''''''''' '''''''' ''''''''''' '''''''''''''''''''''''' '''' '''' ''''''''''' ''''' ''''''''''''''''''''''''''' ''''''''''''''''''''''''''  '''''''''''''''''''''' '''''''''''''''' ''''''''''''''''''''' '''' ''''''''''''' ''''''''''''''' '''''''''''''''' '''''''''''''' ''''''''''''''''''''''' '''' ''''''''''''''''''''''''''''''''''' |
| Alglucosidase alfa for Infantile Onset Pompe Disease | Relevant survival data and ‘ventilator-free survival’ data available. | Survival, ventilator-free survival data could be modelled and transformed to QALYs to estimate ICER. | Clinical data requires extrapolation to life-time time horizon and transformation to QALYs. (QoL not assessed directly and utility values may be uncertain). Potential utility benefits beyond the patient (i.e. for parents) not captured in trial data. Inherent uncertainty with respect to evidence quality. | A Dutch cost-utility analysis (Kanters et al. 2014) estimated incremental costs/QALY were €1.0 million and incremental cost/LYG were € 0.5 million.  ''''''''' ''''''''''''''''''''''''' ''''''''''''''''''''' '''''''''''''''''''''''''' ''''' ''''''''' '''''''''''''' '''''''''''''''' ''''''''''''''''''' '''''' ''''''''''''''''''''''''''''' '''''''''' '''' ''''''''''''''''''''''''''''''''''''''''''' ''''''''''''''' '''''''''''' '''' '''''' ''''''''''''''' |
| Laronidase for MPS I | No survival data or direct QoL data.  Data on exercise tolerance, sleep apnoea and joint movement available. | Clinically relevant outcomes (e.g. exercise tolerance, sleep apnoea and joint movement) could potentially be translated to incremental QALY changes. | Transformation of limited clinical outcome data to QALYs uncertain and unlikely to accurately capture true QALY effects. | (Connock, Juarez-Garcia, et al. 2006) was unable to estimate an ICER in QALYs for Laronidase.  ''''''''' '''''''''''''''''''''''''' '''' ''''''''' '''''''''''''' '''''''''''''' '''''''''''''''''''''' '''''''''' ''' '''''''''''''''''''''''' '''''''' '''''''''' ''''''''''''' ''''''''''''''''''' |
| Idursulfase for MPS II | No survival data or direct QoL data.  Data on physical functioning and respiratory function available.  Other outcome evidence related to surrogate measures (e.g. biochemical values). | Clinically relevant outcomes (e.g. physical functioning and respiratory function) could potentially be translated to incremental QALY changes. | Transformation of clinical event data to QALYs uncertain and unlikely to accurately reflect incremental QALYs.  Inability to reliably transform surrogate measures to relevant utility measures. | No published economic analyses of idursulfase were identified.  '''''''''' ''''''''''''''''''''''''' '''' '''''''' '''''''''''''' ''''''''''''''' '''''''''''''''''''''''''' '''''' ''''''''''''''''''' '''''''''''''''''''''' '''''' '''''''''''''''''''''''''' '''''''''''' ''''''''''''''''''''''' ''''''''''''''' ''''''''''''''' '''' ''''''''''''''''''''' |
| Galsulfase for MPS VI | No survival data or direct QoL data.  Clinical outcome data (physical functioning capacity) available but not statistically significant.  Other outcome evidence related to surrogate measures (e.g. biochemical values). | Outcome data could potentially be translated to QALYs, however this may be considered highly uncertain given the lack of statistical significance. | Use of non-statistically significant data and limited selective outcomes will produce unreliable and biased estimate of ICER.  Surrogate measures unable to be transformed to relevant utility measures. | No published economic analyses of galsulfase were identified.  '''''''''' ''''''''''''''''''''''''''' '''' ''''''''' ''''''''''''''' '''''''''''''''' '''''''''''''''''''''' '''' ''''''''''''''''''''''''''''''''''''''''''''' ''''''''''''''''' '''''''''''''''''''''''''' ''''''''''''''''''''''''' '''''''''''''''''''''' ''''''''''''' ''''''''''''''''''''''''''''''''' ''''''''''''''''''''''' ''''''''' '''''''''''''''''''''''''' '''''''''''''''' '''''''''''''''''''''''' '''' ''' ''''''''''' '''' '''''''''''''''''''''' '''''''' ''''' '''''''''''''''' |
| Eculizumab for PNH | Survival data available but of poor quality. Quality of life and event data available. | Survival, QoL and event data could be modelled and transformed to QALYs to estimate ICER. | Nature of clinical evidence suitable for CU analysis, however unreliability of survival data (due to study design) compromises validity of claim.  Broader utility implications for carers (family) not identified. | A Canadian CU analysis (Coyle, Cheung & Evans 2014) estimated ICERs of CAN$4.62 million/LYG and CAN$2.13 million/QALY.  ''''''''' ''''''''''''' ''''''''''''''' ''''''''''''''''''''''''''''' ''''' ''''''''''''' '''''''''''''' ''''''''''''''''''''' '''''''''''''''' '''' ''''''''''''''''''''''''''''''''''''''''' ''''''''' '''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''''' |

CU = cost utility; ERT = enzyme replacement therapy; GD 1 = Gaucher disease Type 1; ICER = incremental cost-effectiveness ratio; LYG = life years gained; PBAC = Pharmaceutical Benefits Advisory Committee; QoL = quality of life; QALY = quality adjusted life year; YFEOD = year free of end organ damage

In addition to the analyses included in the table above, a broad economic analysis of enzyme and substrate replacement therapies in people with lysosomal storage disorders was undertaken in England (Wyatt et al. 2012a). This analysis considered Gaucher disease, Fabry disease, MPS I, MPS II, Pompe or Niemann-Pick C disease. Assessments of quality of life and, in some cases, carer burden were examined. Although associations of treatment and outcomes were identified, the authors decided that they could not undertake valid cost-effectiveness analysis given the paucity of evidence of effectiveness and quality of life outcomes.

Of the drugs currently listed on the LSDP, three had minimal survival or quality of life data. None had high quality survival data and high quality of life or event data. While assessment of cost-utility could be undertaken, the accuracy is likely to be uncertain. Incomplete data on all aspects of treatment effect (survival and extensive information on quality of life – potentially including carer/parent/dependent quality of life) is likely to result in an underestimate of the drug’s value (unless unreported harms are greater than unreported benefits).

Furthermore numerous drugs lacked any valid comparative data or statistically significant effectiveness data or relied on surrogate outcome measures with poor ability to translate into patient-relevant outcomes; where this is the case, any estimate of value - irrespective of the methodology or value metric selected for use – is essentially unreliable. An attempt to finalise the ‘value’ a drug without knowledge of whether or not it does anything is futile and no value metric should be calculable or meaningful where there is no evidence of clinical effectiveness.

The limited clinical data on treatment outcomes and the difficulty of identifying the extent that real health benefits are reflected in single-dimensional or surrogate outcomes is clearly a complicating factor in a quantitative assessment of value for many orphan drugs which ideally should be addressed at the primary research level, rather than at a policy or funding decision level.

## Adjustment to value on basis of uncertainty or risk

The difficulty of obtaining good quality evidence with respect to orphan drugs is commonly described in the literature; small disease populations result in smaller clinical trials with less certain and more variable results; trials are expensive given the drug cost and the dispersed nature of the population; ethical complications exist around use of placebos and obligations around continuation of treatment and affordability. Uncertainty with respect to expected health outcome returns is inherent with any expenditure on health technology, at the individual and population level but given the particularly high costs of orphan drugs and the limited clinical outcome data available, funding orphan drugs from a limited budget is risky. The countering argument; that because populations are small there is limited overall budget impact is suggested as a mitigating factor to the risk. However as the number of orphan conditions and treatments increases (as can be seen from the Horizon Scanning section) the collective impact increases.

Uncertainty is currently described as a consideration with respect to cost-effectiveness assessment by the PBAC however an explicit quantifiable relationship is not described (Pharmactical Benefits Advisory Committee 2013). Consumer preference theory states that, *ceterus parabus*, increased consumer risk is naturally associated with decreased consumer value (Maier, Wilken & Dost 2014). A research study by (Bobinac, Ana et al. 2014) explores how willingness to pay (WTP) for a QALY gain (a quantitative indication of value) changes where outcomes are uncertain and proposes that a probability weighting improves the validity of WTP per QALY estimates. Specific quantitative probability weightings for the study population are derived. It is concluded that further research to quantify probability weightings as they apply to valuations of the QALY would be required before they can be applied in a decision-making context; however the results of this study highlight that an adjustment of this nature may be relevant when assessing value metrics in health and this would be particularly relevant in the context of high uncertainty when reimbursing orphan drugs.

# Framework for data collection on rare diseases in Australia

Conditions that are treated by drugs listed on the LSDP are rare and, consequently, the claims concerning the effectiveness of the drugs listed on the LSDP are likely uncertain. One mechanism to monitor the effect and cost of these drugs in the Australian setting is to establish a data collection that contain disease and drug information, health outcome measures and costing data.

The seventh ToR for the LSDP review was, therefore, to:

1. **Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.**

The intended outcome of this section of the technical assessment is a high level summary of key concepts related to data collection for rare diseases in Australia and methods for addressing the goals of such a data collection.

## Purpose

To establish the components of a dataset, methods of data capture and considerations of privacy required for future databases that are set up for the purpose of auditing the efficacy and cost of drugs listed on the LSDP (or other such reimbursement programme).

The following issues have been addressed:

* The purposes for which a drug surveillance registry would be required;
* The processes for determining whether data collection will be necessary;
* The types of data that will be required for achieving the purposes of the drug surveillance registry;
* Key considerations when creating a drug surveillance registry (methods of data collection, quality assurance, ethics and privacy, registry governance and funding);
* Methods of data collection; and
* Methods of quality assurance.

## Method

As part of the overall review of the LSDP, a review of the current Australian data registries was undertaken. Successful components and limitations of the current registry process were identified and used to inform the discussion for ToR 7.

Input was sought from consultants for this ToR, including a data management expert with responsibility for a population registry, an ethicist and a statistician.

The approach taken for this section of the technical assessment was to:

* Identify relevant privacy acts and confidentiality legislation governing the collection, storage and use of patient level health data in Australia.
* Review the literature to inform discussion and direction in the following areas:
  1. Types of data required to audit or assess the efficacy and cost of a drug in the community (and processes for establishing what data are required);
  2. Methods of data collection and storage that are efficient and low cost and will ensure accuracy and compliance among data providers;
  3. Methods of testing data completeness and accuracy (quality assurance);
  4. Mechanisms to ensure appropriate levels of patient privacy that abides by Australian legislation including the completion, transmission and storage of data and rules governing access to data for analysis; and
  5. Appropriate data structures for storing health related data to enable linking of multiple data forms and the periodic reporting of outcomes for auditing or policy purposes.

## Results

Due to the small number of patients with rare diseases in Australia, it is suggested that Australian physicians and patients be encouraged to participate in international registries, where they exist.

Elements which should be considered in developing a registry include:

● Define the purpose of the registry i.e. to evaluate eligibility for ongoing access to drugs, measure costs of the drug and management of the condition, evaluate the safety and effectiveness of a drug; use cost, safety and effectiveness measures to facilitate risk-share agreements between sponsors and Government; and to ensure access to data by key stakeholders

● The best method for the collection of data that balances ease of use, and the amount of detail required, so that the data collected fits the purpose and is not an unreasonable burden on the patient, their families or the treating physician. Questions need to be clear and unambiguous, with explicit definitions for each data item.

● Incorporating quality assurance processes to ensure completeness of data and compliance, through the use of prompts, clear instructions, data dictionaries, automated reminders, cross-checking with external sources, clarification with data provider to correct spurious or missing data, an audit trail of changes, and reporting of common errors to enable ongoing improvements.

● Governance structures, including key stakeholders who are involved in the development, and maintenance of the registry, delivering reports to Government and public, and funders of the registry.

● Ensure that the privacy of patients is maintained and appropriate consent or assent is achieved for the collection of data. Due to the small number of patients, even aggregated de-identified data may be able to be identified, so careful decisions need to be made regarding who can access the data.

● Consider how the registry should be resourced and funded, both the high initial set-up costs, plus the ongoing costs of running the registry, both in terms of the data management and information technology, as well as the steering committee costs.

### Background

As can be seen from the systematic literature review that has been undertaken, the evidence base for drugs listed on the LSDP is often scant. Consequently, the claims of efficacy and safety that are made as part of a public funding submission can be uncertain. A drug surveillance registry with the purpose of collecting data to address these uncertainties would likely support the functions of a program that reimburses drugs for rare diseases (McNeil et al. 2010).

This type of drug surveillance registry is different from a rare diseases registry. Gliklich et al 2014 (Gliklich, Dreyer & Leavy 2014) indicated that there are four key purposes of a rare diseases registry:

1. to connect affected patients, families and clinicians;
2. to study the natural history of a disease;
3. to support research; and,
4. to establish a patient base for evaluating drugs.

Given the size of the Australian population and the rarity of these conditions, if the aim is to address all of these objectives, one approach may be to encourage or facilitate participation of Australian clinicians in international data collection for already established rare disease registries (Genzyme (Fabry Registry) ; Genzyme (MPS I Registry) ; Genzyme (Pompe Registry) ; International Collaborative Gaucher Group & Genzyme).

International rare disease registries that provide data addressing point 2 above might help inform an initial regulatory decision to enable access to a drug for a rare condition. Reimbursement decisions, however, rely on an assessment of *comparative drug* *performance*, and often in patients with specific characteristics. These data may not be obtainable from international rare disease registries as they serve a broader purpose.

If data *are* obtainable from a rare diseases registry there are challenges associated with interpreting the findings within a drug reimbursement context. The analysis of registry data is problematic due to the lack of a comparator and inherent biases associated with patient selection and identification, losses to follow up, missing data on key variables, differences in methods for measuring outcomes and the impact on patient prognosis of varying treatment decisions. Due to these limitations, a rare diseases registry is not likely to facilitate a robust evaluation of either the effectiveness or cost-effectiveness of an intervention (Simoens 2011; Wyatt et al. 2012b).

A drug surveillance registry may enable reimbursement agencies to pay for a drug and collect data to improve certainty around the effect a drug may have (such as a ‘coverage with evidence development’ approach). However, such registries have predictable deficiencies in terms of the answers they can provide. Furthermore, there is a risk that the trial data required to more completely support the decision to reimburse a drug may not be forthcoming if conditional drug reimbursement is provided. The experience of early marketing authorisation of oncology drugs by the FDA reveals that drugs given conditional approval may not generate the evidence required to enable full marketing approval(Johnson et al. 2011). Chalkidou (2008) has noted that once public funding has been granted, sponsors of a drug are unlikely to fund research which may reveal a reduction in therapeutic efficacy or narrow the population in which the treatment can be used (Chalkidou et al. 2008). Therefore, the decision to reimburse on the proviso that data on drug effectiveness be captured in a registry may substitute for further clinical trials; and the benefits of earlier reimbursement with some data capture should be balanced against the potential loss of future certainty. It is important to recognise that, in a global sense, the Australian population represents a relatively small market and refusal of the Australian Government to reimburse may not provide adequate incentive to perform an expensive clinical trial.

In the Australian context, a drug surveillance registry for patients with rare diseases might have several important roles. The current chapter seeks to establish the design of a registry to support reimbursement decisions for drugs for rare diseases. The core purposes for such a registry are outlined in Section 8.4, page 270.

For the purposes of this report, a drug surveillance registry is defined as both the database that holds the data, the governance of the database and the systematic process of collection, storage and reporting of register data. The proposed registry for the collection of data relating to drugs that are reimbursed by the Australian Government for rare diseases has been referred to in this chapter as a *drug surveillance registry for rare diseases*. It is important that this chapter is not misconstrued as a proposal for a registry for rare diseases to capture patient data outside of the context of a reimbursed drug.

It is proposed that the design of the registry (including the method of data collection) will be based upon the successes of the current registry process, the current capacity of the program to collect data, the registry purpose, analyses of other successful, local and international registries and reference to local and international guidelines on registry formation.

### Current LSDP Registries

Registers for each of the drugs currently covered by the LSDP have been set up to capture patient data. The primary purpose of these registers has been to record the Disease Advisory Committees’ deliberations on the initial and ongoing eligibility of an individual patient for a drug. The DACs’ decisions were based upon extensive patient information comprising of clinical records, imaging and pathology reports but not all of these data were transferred fully to the registers. As the purpose of these registers was not to *audit* patient eligibility or determine drug effectiveness, the data entry requirements to create and sustain a complete register were not warranted. Further affecting the completeness of the registers was the concomitant use of drug industry registries to capture patient outcome data for much of the life of the LSDP.

The current registers adequately report on the deliberations of the DACs, but are unable, in most cases, to provide robust data to test the effectiveness of the drugs reimbursed through the LSDP (a purpose for which the registers were never designed).

A description of the current registers, as well as the data from Australian patients captured by industry based registers, has been addressed alongside the systematic literature review results in Section 4.

## Proposed Registry Framework

In establishing a framework upon which a drug surveillance registry may be designed, specific information is required on current data capture systems, data transfer methods, linking processes and the capacity for the development and maintenance of a registry system. As some of this information may be contingent upon the agreed scope of the registry following the review of the LSDP, the framework proposed below seeks only to outline principles to guide the development of the registry and provide possible examples for its implementation.

In addition to information derived from answering the other Terms of Reference, as well as reflections on the operation of the current registries, additional following sources have been consulted when describing a framework for data collection in Australia (Australian Commission on Safety and Quality in Health Care 2009; Bellgard et al. 2012; Gliklich & Dreyer (Eds) 2010; Herzog, Scheuren & Winkler 2007; Rare Diseases Task Force 2011).

The Australian Commission on Safety and Quality in Health Care (ACSQHC) is a government agency that coordinates national improvements in safety and quality in health care. The agency has developed several useful documents describing the design requirements of a quality registry. The report most relevant to the design of a registry for the LSDP is *“Operating principles and technical standards for Australian clinical quality registries”*, which was endorsed by the Health Minister in November 2010. The considerations outlined in this document have been used to inform the structure of this chapter.

In proposing a framework for a drug surveillance registry, this chapter addresses the following areas, adapted from those proposed by the ACSQHC (Australian Commission on Safety and Quality in Health Care 2009):

* Purpose of the registry
* Data collection
* Quality assurance
* Governance and custodianship
* Ethics, privacy and data security
* Information output and reporting
* Resources and Funding

The data elements to be collected may vary according to the rare condition being treated by the reimbursed drug.

### Purpose of a registry for surveillance of drugs treating rare conditions

The design of a registry must be closely aligned with the explicit purposes for which it is built. Although drug surveillance registries are primarily used to monitor the safety of a drug, they can have other purposes. The likely purposes of the proposed registry for the collection of data on drugs that are reimbursed by the Australian Government to treat rare diseases are:

* To verify the initial and ongoing eligibility of patients receiving subsidised drugs against the eligibility criteria proposed for the subsidisation;
* To measure the costs of the drug, as well as the management of the drug subsidy program;
* To evaluate the safety and effectiveness of a drug, particularly against the claims that were made during the process by which the drug was initially approved for subsidisation;
* To use cost, and measures of safety and effectiveness, to provide mechanisms to support outcome-based risk-share arrangements between sponsors and Government that may facilitate the reimbursement of drugs when precise estimates of value are unavailable at the time of ‘listing’;

In summary, the above purposes are proposed to ensure that the value of the drug claimed at the time of the drug’s evaluation is realised when it is used in the Australian population.

Not all drugs that are reimbursed to treat rare diseases will require the same extent of data capture. If the use of certain drugs is well established and supported by evidence, the additional burden of capturing health outcome data may have limited utility for informing reimbursement policy. Under these circumstances the collection of a core dataset may be sufficient to establish patient eligibility - and, if required, ongoing eligibility. Decisions about the extent of data capture and the purposes of a disease registry must be determined by the steering committee prior to subsidisation of the drug.

Table 145 Questions to consider regarding the necessity of a registry

| ***A drug that will be or is likely to be reimbursed through a rare diseases funding pathway is submitted for evaluation. The rare diseases registry steering committee must determine:*** |
| --- |
| * Are there eligibility criteria that may exclude some patients with the disease from receiving the drug, and if so, is a registry necessary to ensure eligibility criteria are observed? |
| * Are the claims regarding the magnitude of effectiveness (or safety) difficult to determine from the evidence? If so, would the decision to reimburse the drug at the proposed price be reversed if the drug was found to be less effective or less safe? Alternatively, would the sponsor accept a lower price for earlier listing on the basis that, once outcomes can be verified, a higher price would be granted? Can the claims of effectiveness be measured in a registry (in a relatively short period of time)? |
| * Are the claims regarding the cost offsets achieved with treatment or the costs associated with the drug reliable? Could these costs vary enough in the Australian setting to alter the estimate of value of the drug? If so, could these costs be captured in a registry? |
| * Would the likely benefits of data collection outweigh the costs? Could a price for the drug be negotiated that would negate the need for ongoing data collection? |
| * If a registry is required, engage with stakeholders. |

#### Review of eligibility

Patients who currently wish to receive a drug through the LSDP must meet certain eligibility criteria[[35]](#footnote-35):

##### Initial eligibility

A patient must meet the following conditions to receive subsidised drugs through the LSDP:

1. Satisfy the relevant criteria for treatment with the drug, as detailed in the relevant drug/condition LSDP Guidelines
2. Participate in the evaluation of effectiveness of the drug by periodic assessment, as directed by the relevant LSDP drug/condition Guidelines, or have an acceptable reason not to participate.
3. Not be suffering from any other medical condition, including complications or sequelae of the primary condition that might compromise the effectiveness of the drug treatment.
4. Be a permanent Australian resident who qualifies for Medicare.

##### Ongoing eligibility

Patient eligibility is reviewed in accordance with the frequency set out in the relevant drug/condition LSDP Guidelines, but generally 12 months after commencing therapy and every 12 months thereafter. Continued eligibility is subject to the assessment of evidence, as outlined in the relevant drug/condition LSDP Guidelines, which demonstrates:

1. Clinical improvement in the patient, or
2. Stabilisation of the patient’s condition.

The assessment of eligibility is made with regard to the natural course and stage of the disease, as described in the relevant drug/condition LSDP Guidelines, and any exceptional circumstances that may apply.

The proposed registry must capture relevant data to enable the determination of initial and (if relevant) ongoing patient eligibility. As the benefit of a drug is drug and disease specific, the eligibility criteria will need to be tailored to each drug and therefore the registry must capture drug / condition specific fields to establish eligibility. The assessment of ongoing eligibility must be made at intervals that are also drug / condition specific.

Table 146 Questions to consider regarding the collection of eligibility data

| Questions to consider |
| --- |
| * Has the sponsor identified ongoing drug eligibility criteria or stopping criteria? |
| * Are these criteria justified? |
| * Can patients who are no longer eligible for the drug be clearly identified using objective criteria? |
| * Will continued treatment beyond stopping criteria be of harm to patients? |
| * Will continued treatment be of benefit? |
| * Could a reduction in the cost of the drug offset the loss of value in patients who are treated beyond the stopping criteria? (i.e., can stopping criteria be avoided?) |
| * If stopping criteria are required, does ongoing patient eligibility need to be recorded? Can the treating physician manage the decision of when to stop treatment? |
| * If stopping criteria need to be monitored, what are the steps to be taken when a patient meets the stopping criteria? |
| * Will the patient information included in the registry highlight the loss of benefit or possible harms associated with ongoing treatment subsequent to stopping criteria being met? |

#### Cost of drug and management of condition

Drugs currently provided through the LSDP are not considered to be cost-effective by the PBAC. The Government must therefore ensure that the overall financial impact of the drug as well as the realised return for investment (in terms of health gained and costs avoided) are in line with what was proposed at the time of listing. When drugs are listed on the LSDP, the Government considers the cost of the drug in comparable overseas markets as well as the cost of other drugs already funded through the LSDP for the same condition. Substantial deviations from the effectiveness or cost of the drug proposed at the time of listing could, in the absence of a pricing mechanism linked to effectiveness or overall cost, pose a risk to the sustainability of a program for reimbursing drugs for rare diseases.

To monitor the impact of reimbursing drugs for rare diseases, a registry must capture parameters that enable estimation of the cost of the drug as well as the cost of the additional monitoring required for a patient on the drug. Substantial departures from the financial impacts as originally presented by the sponsor may necessitate a review of the proposed price of the drug in order to ensure the funding program remains a viable mechanism for the provision of drugs for rare diseases.

The variables designed to capture data for the cost of the drug will likely involve the following:

* Dose and frequency of drug delivery
* Patient compliance with medication
* Concurrent medications
* Imaging / pathology to monitor progress
* Additional therapeutic interventions
* Hospitalisations
* Professional attendances/consultations

Due to the often high cost of these drugs, variables would only be selected if it is plausible that their occurrence is likely to impact on the overall cost of the management of the disease. Specific variables will need to be selected on the basis that they are claimed as cost-offsets at the time of the submission to the PBAC. Mechanisms for containing cost or maintaining value for a drug are discussed in the following section.

Table 147 Questions to consider regarding the collection of cost data

| Questions to consider |
| --- |
| * Is the dosing of the drug likely to differ from that proposed in the submission? |
| * Would a difference in dosing result in change in the estimate of value of the drug of sufficient magnitude to alter the decision to reimburse? |
| * Can an agreement be reached that would mitigate the risk to the Government if dosing is different in the Australian population than is presented in the submission? |
| * Are other substantial costs involved with monitoring patients who receive the drug? |
| * Are any substantial cost offsets claimed in the submission? |
| * Could variations in the monitoring costs or cost offsets change the estimate of the value of the drug sufficiently to alter the decision to reimburse? |
| * Can these costs be captured? |
| * Could a managed entry agreement help mitigate the risk of reimbursing a drug that may have a higher cost, higher management costs or fewer cost offsets than claimed in the submission? |

#### Evaluation of effectiveness and safety

Registers have long been used to help detect safety signals for a drug after it has been marketed. This is because important adverse events may occur more frequently than can be observed in a clinical trial setting(Andrade et al. 1995) as clinical trials may select patients less likely to experience adverse events(Rothwell 2005), the reporting of adverse events may be poor(Ioannidis, J. P. & Contopoulos-Ioannidis 1998; McPherson & Hemminki 2004), or the trial may be underpowered to detect differences in adverse events across arms(Ioannidis, John PA 2009; Tsang, Colley & Lynd 2009)). A register based in Australia is unlikely to provide additional insight to drug safety in people with rare diseases because of the small number of locally treated patients. Data that are already captured by industry through periodic safety update reports (PSURs) or post-market trials or registries (often mandated by regulatory bodies(Food and Drug Administration (FDA) April 2011)), would be more comprehensive.

Evidence of the therapeutic effectiveness of drugs that treat rare diseases can similarly be of poor quality due to the rarity of the disease, variability of the disease and often lengthy course with uncertain late effects (Kruer & Steiner 2008; Wilcken 2001). While it is a criterion of the current LSDP that drugs be clinically effective, in some instances the evidence base cannot assist in the determination of the magnitude of therapeutic effect. A registry will not assist with this determination but the collection of post-market data may be able to verify that the therapeutic effectiveness and safety that is *claimed* at the time of listing is realised when the drug is used in the general population.

When comparing the data compiled by the registry with the data suggested in the funding submission, a lower than expected response rate or higher than expected rates of adverse events may impact on the assessment of the value of the funded drug. It is not uncommon for effectiveness or cost-effectiveness of interventions to differ markedly in real world situations when compared to clinical trials (MacIntyre et al. 2000; Wennberg et al. 1998). This may be of limited interest to regulatory bodies if the direction of effect is preserved and the balance of benefits and harms is maintained; however, it is likely to be important to payers if the magnitude of the benefits that were proposed are not being realised. Use of registry data to verify some of the claimed benefits and harms would be particularly important if these clinical outcomes are linked to an agreement between Government and Industry at the time of reimbursing the drug e.g. a managed entry arrangement.

The linking of an ongoing level of reimbursement with the achievement of a defined level of clinical benefit has been previously used for an orphan drug in the Australian setting (Owen et al. 2008). The success of this approach was untested as the sponsor accepted a price reduction due to a lower priced competitor rather than participating in the alternative risk-share agreement (Wlodarczyk, Reid & Pater 2011), negating the need for re-negotiation of price to achieve a pre-agreed ICER. This type of managed entry arrangement is not dissimilar to ‘coverage with evidence development’ or managed entry/exit arrangements that have been used in Australia (Wlodarczyk, Reid & Pater 2011) and internationally (Morel et al. 2013).

To facilitate managed entry agreements based on the performance of the drug, a registry must capture sufficient data to measure patient response and record adverse events. The required variables need to be drug and condition specific and should include patient baseline characteristics and ongoing outcome measures. These outcome measures would include validated surrogate outcomes, as well as clinically-relevant and patient-relevant endpoints (as determined by patient representatives and clinical experts). The registry should continue to capture data on patients until death or until consent for data collection is withdrawn and should be designed to capture death or other important outcomes (hospitalisation, medical intervention) from other sources(Australian Commission on Safety and Quality in Health Care 2009) when patients are lost to follow up (e.g. ceases treatment or dies).

If the disease or drug is particularly new and an international registry does not yet exist, there may be some utility in designing registry fields and patient consent to facilitate the future linking of Australian data with international data to assist in the understanding of rare diseases. This may be done by ensuring adequate scope of data collection and that data definitions utilised in a drug surveillance registry are consistent with those in the international setting.

Table 148 Questions to consider regarding the collection of efficacy data

| Questions to consider |
| --- |
| * Are the claimed benefits of the drug derived from robust sources? |
| * Are there concerns that benefits observed in the sponsor’s submission may not be realised in the Australian setting? |
| * Would a reduction in benefits substantially affect the value to society of the drug? |
| * Can the benefits of the drug be objectively measured and recorded in a registry? |
| * If surrogate outcomes are preferred to infer therapeutic effectiveness, then have these surrogate outcomes been previously validated? |
| * Are the costs associated with the treatment of the disease (including drug costs or adverse events) likely to vary from those presented in the submission? |
| * Can the cost items and frequency of resource use that were used in the submission be feasibly captured in a registry? |
| * Could a managed entry agreement help mitigate the risk of reimbursing a drug that does not achieve the benefits claimed in the submission, is substantially more costly than claimed in the submission, or does not achieve the cost-offsets claimed in the submission? |
| * Could collection of data into a registry help capture the actual outcomes and costs of reimbursing a drug to enable a comparison with the expected (submission based) claims of outcomes and costs? |

### Data collection and security

The method of data collection will be contingent upon the types of data elements captured by the registry. The scope and type of data will be condition-specific. For the purpose of outlining the method of data collection, the following types of data are considered:

* Scheduled data collection (3 to 12 monthly) from a single physician
* Data collection from patients or guardians
* Data collection from external sources (Births, Deaths and Marriages registry)

The aim of designing methods of data capture is to enable capture close to the time of the event, ensure quality and completeness of data, ensure that data collected from different providers are consistent (data definitions are explicit), to minimise the time and complexity associated with data entry and to minimise ‘double-handling’ of data.

### Timing of data capture

One of the key purposes of a drug surveillance registry could be to enable an ongoing assessment of eligibility of the patient receiving drugs through a drug reimbursement program. Currently, the frequency of these assessments is approximately 12 monthly but the committee may request an eligibility review more frequently[[36]](#footnote-36). To prevent ‘creeping’ of scheduled encounters (which may occur if each encounter is slightly late, and the encounters are scheduled to be 6 months from the previous one), the eligibility review schedule should be established at the time of entry into the reimbursement program. The use of pre-scheduled visits would simplify data reporting and if the schedule is shared centrally it could be used to prompt physicians when data is overdue, or to remind physicians of an impending consultation. A manual or automated reminder mechanism that is linked to the patient eligibility review schedule could help to reduce missing data (Brandt et al. 2006). These methods are more aligned with those used in clinical trials, and would ordinarily be difficult to apply to registries. However, as the proposed registry may be less of a passive data collection process and more like data collection in a trial, standardisation of follow up visits may be reasonable.

The schedule could be built into the data capture tool but would need to commence from the first day of drug administration.

### Data quality and completeness

The quality of the data captured by a registry is related to:

* The ease of completing data forms (by improving compliance);
* The careful choice of relevant data fields;
* Clear and unambiguous questions;
* Data validation methods inbuilt in the data collection method to limit the scope of answers and to force responses in fields that should not be left empty (Brandt et al. 2006; Cole et al. 2006);
* Clear and explicit definitions for data (Australian Commission on Safety and Quality in Health Care 2009); and
* Prompts and reminders to complete data (Welker 2007).

The utility of a data registry is limited by the quality, appropriateness and completeness of the data captured (Arts, De Keizer & Scheffer 2002; Gliklich & Dreyer (Eds) 2010). The types of data to be captured should reflect the key purposes of the registry. In addition, the design of the registry should aim to ensure that data are complete and auditable. Complete data collection may be achieved by linking ongoing provision of the subsidised drug to the complete collection of data.

While high quality data can be generated using paper based data capture forms, missing fields or ambiguous answers will require manual intervention to correct. There are added costs associated with data management (Day, Fayers & Harvey 1998) and the possibility of introducing errors at the point of transcription (Arts, De Keizer & Scheffer 2002; Reynolds-Haertle & McBride 1992).

Another approach to data capture would be through a dedicated web-based system connected to a secure database. This approach would be costly to implement and would require ongoing technological support to maintain the security of the system. In registries where the number of patients is small, the initial costs of developing the system may be greater than the savings associated with processing of paper based data collection methods (Gliklich & Dreyer (Eds) 2010; Le Jeannic et al. 2014). As such a system would likely be built using specialised software and stored on centralised servers, access to - and manipulation of - the data would require knowledge of databases and querying language, which may require staff training. Changes to a specialised data collection system may be expensive to implement and require a testing period. Given the likely small number of patients that may be captured by a future registry, the cost of implementing such a system would be an important consideration. However, this system would permit real-time data queries and data validation tools that would improve the quality of data collected into the register. While the initial cost may be substantial, if designed appropriately, modular additions to the system for new drugs may be less expensive and this may represent value for money in the longer term – even if patient numbers are smaller. While less of a consideration, the implementation of such a system may increase the capacity of the Department to undertake similar projects in related areas.

A hybrid approach to the capture of data would involve the design of a data form using commonly available software such as a spreadsheet or word processor software. Designed effectively, such forms can have much of the functionality of a purpose built web-based entry form, although the data are not automatically entered into a centralised database. Reporting functions within either of these programs could enable the transmission (via email) of temporarily de-identified (and possibly encrypted) data to a central location where the data from the report could be re-identified and uploaded into a repository. This method would lack some of the important functionality of a more powerful web-based solution but may be more cost-effective.

The costs involved with each of the methods of data capture may vary depending upon the current systems and capacities of the Department. Therefore, a costing process may be appropriate prior to the decision to implement one system instead of another.

Regardless of the method of data capture, the definitions of data and variables must be published in a data dictionary (or incorporated into the data capture forms) to ensure that information from different physicians is consistent, and that data collected into the register are compatible with data held in international registers.

### Quality assurance

Quality assurance processes in a registry are related to the scope of the data collection and the purpose for the registry. As a drug surveillance register for rare diseases is likely to capture a relatively small number of patients, and the timing of assessments are either predictable or pre-specified, it may be feasible to quality assure using the processes commonly undertaken in clinical trials. If, however, the register grows substantially, most quality assurance measures would likely need to become automated.

Quality assurance processes can occur prior to, during, or after the data collection and involve the following aspects (Gassman et al. 1995; Sariyar et al. 2013), some of which have been addressed previously:

* A data collection form with built in data verification;
* Clear instructions for completing data forms;
* A data dictionary with clearly defined variables;
* Pre-specified timing of data collection;
* Automated reminders before scheduled visits or when data capture has not taken place;
* Automated or manual checking for likely errors of data based on previous responses;
* Cross-checking with external sources of data;
* Clarification with the data provider to correct spurious or missing data;
* An automated audit trail to track changes to data within the database;
* Logging of quality assurance activities; and
* Reporting of common data errors and quality assurance activities to enable ongoing improvement of data collection processes.

In some cases, the types of data and methods of data capture may be novel. In these situations, a pilot phase encompassing the first few patients enrolled into the scheme, or alternatively, in which data providers are asked to report on ‘dummy’ patients, may be valuable to ensure adequate and accurate data are being captured.

To a large extent the quality of data entered into a drug surveillance register can be maintained by careful design of data collection methods. However, while quality assurance using data forms can avoid missing data or implausible data, it cannot prevent erroneous data entry. In many cases this may be difficult to avoid without auditing medical records. For some outcomes, it may be valuable to require data providers to send copies of selected source documents to the central repository. In many cases, these sources may be pathology or radiology reports and could be stored as attachments to the patient record in the register. Verifying data that has been entered against the source documents would likely be an intensive process, although could be organised to occur only at times when a patient’s record requires scrutiny.

The scope for using data-linkage across systems to cross-check data accuracy will likely be limited. As most source data, with the exception of date (and possibly cause) of death, is likely to be medical in nature, it will be stored in disparate systems across state-based and private pathology databases. Furthermore, many of the source documents will not be structured in such a way that permits automated data extraction thereby limiting the usefulness of an automated process. Given the relatively small number of patients and the high technology and cost barriers, an automated solution is not likely to be acceptable. If access to source data from pathology providers is required, this requirement and the scope of such access could be made explicit at the time of patient consent.

The quality of the information regarding a patient’s death will be variable, if provided by the physician responsible for the patient’s access to subsidised treatment. It is possible that physicians who care for patients enrolled onto the LSDP or similar funding programs will not be notified of a patient’s death if it has occurred from another cause or if the patient has ceased to receive treatment. Periodic requests to state death registers would assist with determining the precise date of death, a description of the primary cause and associated factors relating to the death of a patient.

A dedicated versioning process may be required to capture all changes made to data tables, particularly if the method of data entry is via a web-service. This functionality would increase the complexity and cost of the registry.

All quality assurance activities should be adequately recorded (Sariyar et al. 2013). For example, details relating to the identification of data errors, timeliness of data collection, phone calls to verify data, queries made by data providers, technology failures (such as errors in data transmission or data storage) need to be captured. A simple quality assurance data form, capturing details concerning the data provider and the nature of the error should be completed for each data quality issue. Collated reports of quality assurance activities will enable commonly occurring errors to be addressed and data collection methods to be improved. An example is provided in Appendix J, Table 177.

It may be appropriate for data management staff to develop standard operating procedures to describe their work procedures to ensure that data is handled consistently across staff and tenures.

### Registry governance, staff and data custodianship

The governance of a drug surveillance registry for rare diseases should include key stakeholders who are responsible for establishing the registry, determining data elements, developing and maintaining the technical systems, delivering reports to Government and the public, and the funders of the registry. This group, which may also include registry staff (e.g. data management or computing support), would assume the role of a steering committee and be responsible for the day to day activities of the registry. The scope of these activities, as well as the role of individual members of the committee, would ordinarily be established within a constitution or ordinances to which the committee must abide.

Some decision making may require additional input involving other stakeholders such as clinical experts, patient representatives, a statistician or industry representatives.

The question of who has access to the data within the registry should be considered carefully. Ordinarily, data registers contain vast numbers of patients, meaning that identification of patients in the absence of key identifiers (name, date of birth) would be difficult. However, in the case of a drug surveillance registry for rare diseases, the risk of identification of patients is high as there are very few patients with the condition who would be eligible for the drug. The governance of the registry must clearly define the level of data access, as well as the type of data that are accessible. Data management and technical staff will necessarily have access to identified data, and appropriate confidentiality agreements should be agreed upon with these staff. Other staff involved in the registry might require access to aggregated data in reports. The procedures around data access are important, and will be required at the time of application to Human Research Ethics Committees.

A proposed governance structure diagram is shown in Figure 2.

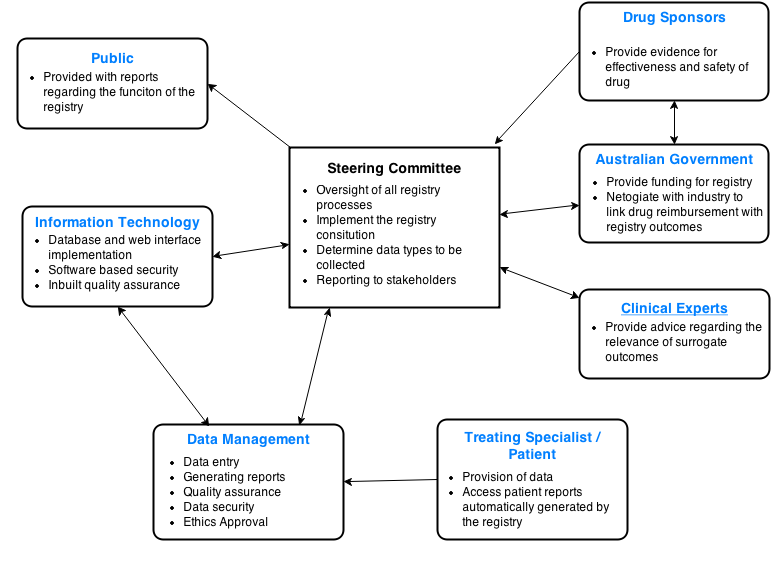


Figure 2 Governance structure and direction of information flow

### Ethics, Privacy and Data Security

Personal information collected on individuals must be transmitted and stored in a secure manner to abide by the Privacy Act 1988.

#### Data security

Achieving data security requires several systems to be in place. Data storage, access and transfer must all be addressed and compliant with Federal and State privacy laws.

Data must be kept in a safe and secure storage place. For the most part, records are likely to be electronic and stored in a central Government repository. The characteristics of such storage are described by current Government privacy policies[[37]](#footnote-37) which comply with the Privacy Act 1988, Australian Privacy Principles and the Australian Government Protective Security Policy[[38]](#footnote-38). If some records are paper-based, these will need to be stored in a locked cabinet to which there is restricted access (access is described by the governance of the registry, details of which are submitted to the HREC).

Protocols for accessing the data should be made explicit and described by the steering committee. This access should be restricted by using an adequate authentication process and access should be recorded so that changes to the data can be attributed to individual users of the system.

If data are not entered directly through a secure web-interface, transfer of data should be performed via a secure government file transfer service.

As a drug surveillance registry for rare diseases may pursue the collection of quality of life or other patient relevant metrics directly from the patient, it may be necessary to use paper-based forms. The security of these forms may be bolstered by sending the forms with a random identifier generated at the time the questionnaire forms are created, such as a barcode, rather than using the patient’s name. This will ensure that the questionnaire, when returned to the registry data managers, will have no identifying information except for the code that links the questionnaire back to the patient once it is scanned or entered.

#### Privacy Legislation

Privacy legislation varies across Australia and compatibility of activities undertaken in the course of running a drug surveillance registry for rare diseases will need to be verified against these standards. A list of these different standards is provided in Table 149. However, in cases where patients are able to be consented, or a legal guardian is able to give consent on behalf of a patient, the collection of identified information is more straightforward from a privacy point of view. The relevant sections of the Privacy Act (1988) and the Guidelines approved under Section 95A of the Privacy Act (1988) are primarily concerned with the collection of data from patients for who it is impractical to attain consent. More relevant to the conduct of a rare diseases registry is the National Statement on Ethical Conduct in Human Research (2007).

Ethics approval will need to be sought from an appropriate HREC (such as the Department of Health HREC). The HREC will require an overview of the purpose of the register, a description of its governance, who has access to data and how data will be published, details regarding data security, and a copy of all forms to be given to the patient / guardian (patient / guardian consent form, quality of life forms). If there are substantive changes to the registry that may be of patient interest (such as the use of the data or the types of data that are being collected), a new consent form may need to be generated for patients to sign. Each change to the consent form must be approved by the HREC.

A registry funded by the Department of Health, or governed by Departmental staff, will require approval from the Department of Health Human Research Ethics Committee[[39]](#footnote-39). Whether separate applications need to be made to State or Territory HRECs may depend upon the type of data being sought from patients. If data are provided directly from the clinician caring for the patient, or the patient, and does not require linkage with any hospital systems, the Departmental HREC approval may suffice.

Table 149 Commonwealth and State privacy legislation

| Jurisdiction | Relevant documents |
| --- | --- |
| Commonwealth | Privacy Act (1988)  Guidelines approved under Section 95A of the Privacy Act (1988)  Australian Privacy Principles (previously the National Privacy Principles)  National Statement on Ethical Conduct in Human Research (2007)  Australian code for the responsible conduct of research (2007) |
| NSW | Privacy and Personal Information Protection Act (1998)  Health Records and Information Privacy Act (2002) |
| Victoria | Privacy and Data Protection Act (2014)  Health Records Act (2001) |
| Queensland | Information Privacy Act (2009) |
| Australian Capital Territory | Health Records Act (1997) |
| Tasmania | Personal Information Protection Act (2004) |
| South Australia | Health Care Act (2008) |
| Northern Territory | Information Act (2002) |
| Western Australia | None specific. |

#### Patient consent

Patient consent to enable collection of data for the purpose of the registry is a requirement for access to drugs through the current reimbursement process. The current eligibility criteria may enable a patient to not consent to collection of their health data if they have an acceptable reason. For future data collections, acceptable reasons to withhold or withdraw consent for the collection of health data should be explicitly agreed upon by the proposed registry steering committee.

Consent may be ‘specific’, ‘extended’ or ‘unspecified’. Specific consent would be limited to the purposes outlined for the specific project. This type of consent is limiting and will almost always be inappropriate for a drug surveillance registry which seeks to collect data over an extended period during which time patients may die and research questions may evolve. It may be more appropriate to seek extended consent (data can be used for the original project, an extension of the original project, or in a new project for the same general area), or unspecified consent which would permit use of the data in any future research area. While the latter is the most attractive option to researchers, it is the least palatable to patients and ethics committees. In most cases, extended consent is sufficient. Updates relating to the use of the data, or type of data that is being collected, will need to be submitted to the HREC. The committee may decide that the changes are minor, or may decide that the program or data collection has changed enough to warrant re-consenting patients.

Children under 16 years of age cannot give legal consent, and this must be given by a parent or guardian[[40]](#footnote-40). However, if possible, children should be involved in the decision and their assent should be sought. Children who are under 18 years of age usually cannot provide legal consent to participate in research; however data collection for the purposes of the registry would likely be regarded as very low risk by a HREC, who may ask that a mature child, as well as the guardian, provide consent.

Note that this consenting process is relevant only to the collection of data and does not incorporate the consenting process for treatment. A sample consent form has been provided in Appendix K. The sample consent form was adapted from an NHMRC template and may be excessively long in its current form. Consideration should be made when devising a patient consent form to balance the length of the form against the need to fully inform a patient of the risks and benefits of the data collection.

### Data reporting

It is important that data from the registry can be accessed in a timely manner by stakeholders, including the clinicians overseeing the care of patients receiving the reimbursed drug. For the administration of a reimbursement program for drugs for rare diseases, a key stakeholder is the Australian Government. Timely access to the data by the Government to enable auditing of a reimbursement program is important and provides one argument against being reliant on industry based registries.

Due to the very small number of patients who may be on a drug surveillance register for rare diseases or conditions, reporting of information must carefully balance the granularity of information for particular audiences. For example, reports for the public should be careful not to contain adequate information that someone could be identified. This may require very limited data to be provided for some rare conditions (for example, when there are fewer than 5 or 10 patients represented in the registry).

Data reporting is important to enable improvements in the registry design and to assess the overall success of a program for reimbursing drugs for rare diseases. These reports should be available at meetings of the registry steering committee.

In some circumstances, data custodians or researchers may discover information that impacts on the wellbeing of a patient. These circumstances and the methods to communicate to the patient (or more likely the physician responsible for their care) should be discussed and agreed upon by the steering committee at the inception of the registry.

### Registry funding

The funding required for a registry will be dependent upon the type of registry required. A central database with web-based data entry will have a high initial set up cost although running costs may be less than the management of systems requiring manual data entry.

When determining the funding source for the registry, the following should be considered:

1. The funding source is sustainable;
2. The ongoing costs include maintenance and upgrading of the registry software;
3. Costs involve staffing of the registry (data management and computing technical support);
4. Costs associated with the oversight of the registry (steering committee costs); and
5. The initial set up cost.

The most reasonable source for funding may be a combination of the Department (particularly for the initial costs) and drug sponsors. The yearly running costs of the registry could be calculated and a proportion of that could be divided among the sponsors whose listing is contingent upon ongoing data collection.

Given the nature of the proposed registry, alternative methods of cost-recovery are unlikely.

#### Proposed data elements

The proposed data elements to be captured by the registry will need to be determined at the time of listing the drug. These will be contingent upon the purpose of the registry for that particular drug, and may be informed by the steering committee questions posed in Table 145 to Table 148.

The categories of data elements are listed in Table 150 with a description of when their collection would be of value.

Table 150 Proposed data elements for a drug surveillance register

| Data category | When it should be collected | When not necessary |
| --- | --- | --- |
| Patient / guardian consent | Always. The extent of the consent (whether the patient / guardian opted out of any data collection) and the currency of the consent (a history of all of the versions of consent forms that have been signed) should be stored. | Ongoing consent forms may not be necessary if data collection ceases after initial eligibility or the nature of the data collection or use of the data remains unchanged. |
| Initial eligibility | Initial eligibility should always be ascertained for each patient at application. Supporting documentation should be provided however the collection of specific data points will only be necessary if required to establish ongoing eligibility or the effect of the drug. | - |
| Ongoing eligibility | The disease can progress to a point where treatment is no longer effective or there is no evidence or clinical plausibility for ongoing benefit. Supporting documentation may be required to establish that the disease has not progressed to a ‘no treatment’ stage. Ongoing eligibility must always be captured if there is a risk that the disease could progress such that the treatment has a negative benefit/risk balance. | The drug has established adequate efficacy regardless of stage of disease.  Negotiations with the sponsor have resulted in a price commensurate with the drop in efficacy in patients who progress. |
| Baseline and follow up surrogate measures of effectiveness / safety | Disease improvement or stability is determined by comparing with baseline markers (i.e. haematological, biochemical, organ size, neurological function etc.).  The agreed price of a drug is linked to outcomes achieved in patients taking the drug through a managed entry arrangement. | No ongoing eligibility criteria are required and no managed entry scheme requiring the measurement of effectiveness has been entered into. |
| Dose and frequency | This should routinely be provided by the treating clinician for all patients who require any other data to be collected.  If no other data is captured, dose and frequency could be sought from another source. | - |
| Monitoring and major intervention costs | The cost of monitoring patients (i.e., scans, biopsies, specialist visits) receiving the drug is expected to be high (relative to the cost of the drug), these additional costs are unknown or not been accounted for at the time of the decision to reimburse the drug and the Department would seek to renegotiate with the drug sponsor if these costs are greater than expected. This may form part of a managed entry arrangement.  Interventions (hospitalisation, transfusions, organ transplants, medications) that are expected to be avoided or reduce in frequency while on the drug and the Department would seek to renegotiate if costs associated with these interventions are greater than expected. This may form part of a managed entry arrangement. | The cost of monitoring the use of the drug is unlikely to be substantial.  The reduction in interventions claimed at the time of the decision to reimburse the drug is likely to be met, or unlikely to impact on the overall cost of treatment.  The ongoing price of the drug to the Government is not linked to other costs or will not be renegotiated on this basis. |
| Baseline and follow up patient / carer reported wellbeing | Improvement of quality of life or pain is an important outcome for the drug, and the agreed price of the drug is linked to a stabilisation or improvement in these outcomes. | Patient reported outcomes do not make up the claim of effectiveness for the drug. Price is not linked to establishing an improvement or stabilisation for this outcome. |
| Death | This should be sought for all patients. However, while this may be requested from the data provider, this may prove difficult to capture reliably. Alternative sources for date and cause of death should be sought. | - |

# Conclusion

During the conduct of this technical assessment new evidence was obtained on the safety and effectiveness of the drugs currently funded through the LSDP. The systematic literature review determined that the findings presented in the new evidence were largely consistent with the original recommendations to subsidise these drugs. Specifically,

* One new trial demonstrated that imiglucerase was superior to vitamin D alone at reducing the risk of bleeding and indicators of bone disease in patients with Type 1 Gaucher disease. Post-market data collected on patients receiving subsidised imiglucerase through the LSDP indicated that, on average, these patients had improvements in their haemoglobin levels, platelet counts and spleen and liver volumes.
* No new trial evidence was identified on patients receiving velaglucerase alfa to treat Type 1 Gaucher disease. Post-market data obtained on patients receiving subsidised velaglucerase alfa indicated that, on average, these patients had improvements in their haemoglobin levels, platelet counts and spleen and liver volumes.
* No new studies were identified concerning miglustat treatment in patients with Type 1 Gaucher disease. However, information was obtained that was not provided in the original miglustat submission to the PBAC. These new data indicated there were higher chitotriosidase levels in patients receiving miglustat than in those being treated with imiglucerase. No further data were identified to change the original finding that miglustat improved patient quality of life, relative to imiglucerase, as a consequence of the mode of administration of the drug.
* No new trial evidence was identified on patients receiving agalsidase alfa to treat Fabry disease. Post-market data collected on patients receiving subsidised agalsidase alfa through the LSDP indicated that the average patient glomerular filtration rate (GFR) was slightly reduced. This was contrary to the claim made in the submission to the PBAC that GFR would improve or remain stable. These results need to be considered in the context of the small number of patients providing data and the varying follow-up times for each patient.
* One new trial in six patients with Fabry disease found that patients who received agalsidase beta had better cardiac function than those who received a placebo, although the study was too small to determine whether this difference was due to chance or the impact of the drug. Post-market data collected on patients receiving subsidised agalsidase beta through the LSDP indicated that, on average, there was a small absolute improvement in GFR.
* No new studies were identified on patients receiving alglucosidase alfa to treat infantile onset Pompe Disease. However, longer term data were obtained for one of the historical control studies provided in the original submission to the PBAC. These new data supported the conclusion that alglucosidase alfa prolongs the survival of patients with infantile onset Pompe Disease. This was further supported by the post-market data collected on patients receiving the drug through the LSDP. ''''''''' '''''''''''''' ''''''''''''''''' ''''''''''''''''''''''' ''''''' ''''''''''''''' ''''''' ''''''''''' '''''''' ''''''''''''' ''''''''' '''''''''' ''' '''''''''''''''' '''' ''''''''''''''''''''' '''''''''' ''''' ''''''''''''''''' '''''''' ''''''''''' ''' ''''''''''''''''' ''''''''' '''''''''' '''' ''''''''''' '''''''''''''''''' '''' '''''''''' ''''' '''''''''''''' ''' '''''''''' ''''''' ''''' '''''''''''' ''''''''''''''''''''''
* The original submission for the use of alglucosidase alfa to treat juvenile onset Pompe Disease did not have data stratified according to whether the onset of Pompe Disease occurred as a juvenile or adult. The literature searches for this technical assessment identified one case series and 15 case reports of patients with juvenile onset Pompe Disease who have received the drug. Patients improved from baseline when treated with alglucosidase alfa, in terms of respiratory outcomes and muscle functioning. There was a large amount of heterogeneity in terms of the extent of patient response, as well as differences in the health outcomes that were mentioned. Only one patient in Australia is currently receiving subsidised alglucosidase alfa for juvenile onset Pompe disease.
* In the treatment of mucopolysaccharidosis I (MPS I) with laronidase, one new extension to a trial was identified. These longer term data, of a placebo-controlled trial included in the original submission to the PBAC, were not as favourable to laronidase, indicating that the majority of the improvement occurs in the first 6 months. Additional distance walked on the 6 minute walk test (6MWT) after 3.5 – 4 years was less than after 6 months. Forced vital capacity (FVC) was reduced from baseline after 3.5 - 4 years. Other outcomes (liver volume, apnoea symptoms, shoulder range of motion, visual acuity and disability index) were improved from baseline. These new published data were non-comparative, and so it was uncertain how the results would compare to an untreated population over the longer-term. The format of the individual data collected on patients receiving laronidase through the LSDP prevented analysis to determine the clinical benefit of the drug.
* In the treatment of mucopolysaccharidosis II (MPS II) with idursulfase, one new extension to a placebo-controlled trial was identified. These longer term data indicated that absolute forced vital capacity continued to improve for patients aged ≤18 years with 3 years of treatment with idursulfase. Adult patients (over 18 years) had a slight decrease in absolute forced vital capacity over 3 years. Results on the 6MWT were reasonably similar between 1 year (the length of the trial) and 3 years. Liver and spleen volume remained stable between 1 and 3 years, and joint flexibility continued to improve between 1 and 3 years. The extension data are therefore consistent with the evidence that informed the original recommendation to fund idursulfase. The format of the individual data collected on patients receiving idursulfase through the LSDP prevented analysis to determine the clinical benefit of the drug.
* One new extension to a placebo-controlled trial was identified for the treatment of mucopolysaccharidosis VI (MPS VI) with galsulfase; however, no new data could be extracted from the publication. The format of the individual data collected on patients receiving galsulfase through the LSDP prevented analysis to determine the clinical benefit of the drug.
* One new historical control study was identified that assessed the effect of eculizumab on the health of patients with paroxysmal nocturnal haemoglobinuria. Survival was improved with eculizumab compared to placebo, with a 5-year survival HR of 0.21 (95%CI 0.05, 0.88). Although there were methodological problems with the study, the results support the clinical claim and the short term data provided in the submission to the PBAC, that eculizumab extends survival in patients with paroxysmal nocturnal haemoglobinuria. The format of the individual data collected on patients receiving eculizumab through the LSDP prevented analysis to determine the clinical benefit of the drug.

Although the drugs currently subsidised through the LSDP appear to be clinically effective and with an acceptable safety profile, they have been previously determined to be cost-ineffective or the data available were insufficient to estimate the cost-effectiveness. The LSDP was created to allow compassionate access to drugs that would improve the survival of patients with very rare diseases. There are, however, indications that the LSDP may not be sustainable in its current form.

With an increase in knowledge regarding the genetic causes of many conditions, diseases which have previously been considered common are now being divided into many different ‘rare’ subtypes. These subtypes can be individually targeted with drugs given ‘orphan’ designation by regulatory agencies and may be considered eligible for the LSDP according to the current eligibility criteria. It may therefore not be financially viable in the long term to determine the eligibility of drugs for subsidisation through the LSDP according to the criterion of disease ‘rarity’.

Lessons learned from international experience in the public funding of orphan drugs for rare diseases show a range of approaches that might be adopted to work towards a sustainable LSDP. Several countries have evaluation and funding mechanisms that are specific to orphan drugs. Some countries allow special consideration of orphan drugs as part of their usual reimbursement processes, including through relaxed requirements for pharmacoeconomic evaluation, a higher cost-effectiveness threshold, an acceptance of poorer quality evidence, consideration of a broader societal perspective or the placement of a greater weight in decision-making on the lack of alternative treatments. Several health systems require that initial funding decisions of orphan drugs are re-assessed over the longer term. Managed entry schemes and risk-share arrangements have also been implemented to monitor the performance of orphan drugs.

In terms of determining the value for money of orphan drugs, there are a number of methods that might be considered. In addition to routine cost-utility analyses, alternative approaches might include:

* Broadened cost-utility evaluation, with improved sensitivity and broadened perspective;
* Equity-weighted cost-utility evaluation, using various weighting criteria, e.g. disease severity (non-specific to orphan drugs), or rarity (specific to orphan drugs);
* Multi-Criteria Decision Analysis (MCDA); or
* Input-based costing.

There is evidence that societal preferences do not always follow a utilitarian approach of maximising quality adjusted life years (QALYs). Principles such as equity and social justice may cause a preference for non-utilitarian allocation. Preferences have been proposed that place greater value on: i) treatments that are life-saving; ii) treatment for patients with more severe disease; and iii) treatments for populations of social concern such as the socio-economically disadvantaged, children, or people with dependents. The cost-utility methods mentioned above incorporate societal preferences as part of the ‘value’ metric that is used. One of the methods (MCDA), however, incorporates these societal preferences through the public funding decision-making process itself.

Consideration of the limitations of the available evidence to measure the *clinical effectiveness* of existing drugs on the LSDP – to inform a value assessment – presents a difficulty, irrespective of the metric used. The level of uncertainty, or risk, itself may be relevant to incorporate into an alternative value metric.

In cases where there are uncertainties regarding aspects of the safety, clinical effectiveness and cost-offsets of the drugs considered eligible for the LSDP, the development of a drug surveillance registry tailored to address these uncertainties would be valuable. This type of data collection would support managed entry or performance-based risk share arrangements. Claims that are made with regard to the safety and clinical effectiveness of these orphan drugs, in terms of individual patients’ responses to the treatments, could be verified.

Registry data are not appropriate for determining the comparative clinical effectiveness of different drug treatments – that is the role of randomised controlled trials. However, in cases where there are no alternative treatments that improve patient survival and where there is good information on the natural history of the condition, a drug surveillance registry may be a viable option for confirming the safety and clinical effectiveness of a subsidised drug treatment. It would be important to ensure that the drug surveillance registry is developed to answer a specific question and that the appropriate governance, technical arrangements and resourcing are in place before commencing data collection.

# REFERENCES

Actelion Pharmaceuticals Australia Pty Ltd. 2007, *Economic evidence supporting the inclusion of Zavesca(R) on the Pharmaceutical Benefits Scheme*.

Actelion Pharmaceuticals Ltd. 2012, *Product Monograph: Zavesca(R), miglustat, capsule 100 mg, professed standard, glucosylceramide synthase inhibitor*.

Actelion Pharmaceuticals Ltd. 2013, *Periodic benefit-risk evaluation report for miglustat (Zavesca(R) / Brazaves (R))*.

Al-Janabi, H, Flynn, TN & Coast, J 2011, 'QALYs and carers', *PharmacoEconomics*, vol. 29, no. 12, Dec, pp. 1015-1023.

Alberta Health and Wellness 2008, 'Alberta Rare Diseases Drug Program: Fact Sheet', p. 1, viewed 3 July 2014, <http://www.health.alberta.ca/documents/Pharma-Strategy-2008-rare-disease.pdf>.

Alegra T, Vairo F, de Souza M V, Krug B C & Schwartz I V D 2012, 'Enzyme replacement therapy for Fabry disease: A systematic review and meta-analysis<p>', *Genet Mol Biol<p>*, vol. 35<p>, no. 4 (suppl)<p>, pp. 947-954<p>.

Alexion Europe 2013, *Periodic safety update reort no. 9 for eculizumab*.

All Wales Medicines Strategy Group 2007, 'Idursulfase (Elaprase®) (Structured abstract)', *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000454/frame.html>.

Alsaad, AM & Koren, G 2014, 'Exposure to rufinamide and risks of CNS adverse events in drug-resistant epilepsy: a meta-analysis of randomized, placebo-controlled trials', *Br J Clin Pharmacol*, vol. 78, no. 6, Dec, pp. 1264-1271.

Amato, RJ, Hawkins, RE, Kaufman, HL, Thompson, JA, Tomczak, P, Szczylik, C, McDonald, M, Eastty, S, Shingler, WH, de Belin, J, Goonewardena, M, Naylor, S & Harrop, R 2010, 'Vaccination of metastatic renal cancer patients with MVA-5T4: a randomized, double-blind, placebo-controlled phase III study', *Clin Cancer Res*, vol. 16, no. 22, Nov 15, pp. 5539-5547.

Andrade, SE, Walker, AM, Gottlieb, LK, Hollenberg, NK, Testa, MA, Saperia, GM & Platt, R 1995, 'Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings?', *N Engl J Med*, vol. 332, no. 17, Apr 27, pp. 1125-1131.

Angelini, C, Semplicini, C, Tonin, P, Filosto, M, Pegoraro, E, Soraru, G & Fanin, M 2009, 'Progress in enzyme replacement therapy in glycogen storage disease type II', *Therapeutic Advances in Neurological Disorders*, vol. 2, no. 3, pp. 143-153.

Angelis, A & Kanavos, P 2014, 'A conceptual and methodological framework for value assessment of medical technologies using MCDA', paper presented at Health Technology Assessment international, Washington DC, USA, June

Arts, DG, De Keizer, NF & Scheffer, GJ 2002, 'Defining and improving data quality in medical registries: a literature review, case study, and generic framework', *J Am Med Inform Assoc*, vol. 9, no. 6, Nov-Dec, pp. 600-611.

Australian Commission on Safety and Quality in Health Care 2009, *Operating Principles and Technical Standards for Australian Clinical Quality Registries*, <http://www.med.monash.edu.au/sphpm/creps/docs/operating-principals-and-technical-standards-nov-2008.pdf>.

Australian Government 1990, 'Therapeutic Goods Regulations 1990', <http://www.comlaw.gov.au/Details/F2012C00121>.

Australian Huntington's Disease Association (NSW) Inc 2014, *How common is Huntington's Disease?*, Australian Huntington's Disease Association (NSW) Inc, New South Wales, Australia., viewed 3 Nov 2014, <http://www.huntingtonsnsw.org.au/information/hd-facts/how-common>.

Australian Institute of Health and Welfare and Australasian Association of Cancer Registries 2012, *Cancer in Australia: an overview 2012.*, AIHW, Canberra, Australia.

Badesch, DB, Feldman, J, Keogh, A, Mathier, MA, Oudiz, RJ, Shapiro, S, Farber, HW, McGoon, M, Frost, A, Allard, M, Despain, D, Dufton, C & Rubin, LJ 2012, 'ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension', *Cardiovasc Ther*, vol. 30, no. 2, Apr, pp. 93-99.

Banikazemi, M, Bultas, J, Waldek, S, Wilcox, WR, Whitley, CB, McDonald, M, Finkel, R, Packman, S, Bichet, DG, Warnock, DG & Desnick, RJ 2007, 'Agalsidase-beta therapy for advanced Fabry disease: a randomized trial<p>', *Ann Intern Med<p>*, vol. 146<p>, no. 2<p>, pp. 77-86<p>.

Banikazemi, M, Bultas, J, Waldek, S, Wilcox, WR, Whitley, CB, McDonald, M, Finkel, R, Packman, S, Bichet, DG, Warnock, DG, Desnick, RJ & Fabry Disease Clinical Trial Study, G 2007, 'Agalsidase-beta therapy for advanced Fabry disease: a randomized trial', Journal

Research Support, Non-U.S. Gov't, *Ann Intern Med.*, vol. 146, no. 2, pp. 77-86<http://annals.org/data/Journals/AIM/20129/0000605-200701160-00148.pdf>.

Banugaria, SG, Prater, SN, Ng, YK, Kobori, JA, Finkel, RS, Ladda, RL, Chen, YT, Rosenberg, AS & Kishnani, PS 2011, 'The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease', *Genet Med*, vol. 13, no. 8, Aug, pp. 729-736.

Banugaria, SG, Prater, SN, Patel, TT, DeArmey, SM, Milleson, C, Sheets, KB, Bali, DS, Rehder, CW, Raiman, JAJ, Wang, RA, Labarthe, F, Charrow, J, Harmatz, P, Chakraborty, P, Rosenberg, AS & Kishnani, PS 2013, 'Algorithm for the Early Diagnosis and Treatment of Patients with Cross Reactive Immunologic Material-Negative Classic Infantile Pompe Disease: A Step towards Improving the Efficacy of ERT', *PLoS ONE*, vol. 8, no. 6.

Bareja, C, Waring, J & Stapledon, R 2014, 'Tuberculosis notifications in Australia, 2010', *Commun Dis Intell Q Rep*, vol. 38, no. 1, pp. E36-48.

Basch, E & Bennett, AV 2014, 'Patient-reported outcomes in clinical trials of rare diseases', *J Gen Intern Med*, vol. 29 Suppl 3, Aug, pp. S801-803.

Beaulieu, CL, Samuels, ME, Ekins, S, McMaster, CR, Edwards, AM, Krainer, AR, Hicks, GG, Frey, BJ, Boycott, KM & Mackenzie, AE 2012, 'A generalizable pre-clinical research approach for orphan disease therapy', *Orphanet J Rare Dis*, vol. 7, p. 39.

Bellgard, MI, Macgregor, A, Janon, F, Harvey, A, O'Leary, P, Hunter, A & Dawkins, H 2012, 'A modular approach to disease registry design: successful adoption of an internet-based rare disease registry', *Hum Mutat*, vol. 33, no. 10, Oct, pp. E2356-2366.

Bembi, B, Pisa, FE, Confalonieri, M, Ciana, G, Fiumara, A, Parini, R, Rigoldi, M, Moglia, A, Costa, A, Carlucci, A, Danesino, C, Pittis, MG, Dardis, A & Ravaglia, S 2010, 'Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II', *Journal of Inherited Metabolic Disease*, vol. 33, no. 6, Dec, pp. 727-735.

Ben Turkia, H, Gonzalez, DE, Barton, NW, Zimran, A, Kabra, M, Lukina, EA, Giraldo, P, Kisinovsky, I, Bavdekar, A, Ben, D, M, F, Gupta, N, Kishnani, PS, Sureshkumar, EK, Wang, N, Crombez, E, Bhirangi, K & Mehta, A 2013, 'Velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease', *Am J Hematol*, vol. 88, pp. 179-184.

Bernstein, DL, Bialer, MG, Mehta, L & Desnick, RJ 2010, 'Pompe disease: Dramatic improvement in gastrointestinal function following enzyme replacement therapy. A report of three later-onset patients', *Molecular Genetics and Metabolism*, vol. 101, no. 2-3, Oct-Nov, pp. 130-133.

Better Health Channel 2014, *Myasthenia gravis*, Government of Victoria., viewed 5 November 2014, <http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Myasthenia\_gravis>.

Bhengu, L, Davidson, A, du Toit, P, Els, C, Gerntholtz, T, Govendrageloo, K, Henderson, B, Mubaiwa, L & Varughese, S 2014, 'Diagnosis and management of Pompe disease', *S Afr Med J*, vol. 104, no. 4, Apr, pp. 273-274.

BIA UK BioIndustry Association 2014, *Very rare diseases, complex issues: Future evaluation of ultra-orphan medicines in the UK*.

Bierer, G, Balfe, D, Wilcox, WR & Mosenifar, Z 2006, 'Improvement in serial cardiopulmonary exercise testing following enzyme replacement therapy in Fabry disease', *Journal of Inherited Metabolic Disease*, vol. 29, no. 4, pp. 572-579.

BioMarin Pharmaceuticals Inc. 2014, 'Periodic benefit risk evaluation report for Naglazyme (galsulfase) Report Period 01 Jun 2013 - 31 May 2014'.

Bisset, C 2014, *Too much of a good thing: is the orphan drug act sustainable?*, Total Orphan Drugs, viewed 23rd November 2014, <http://www.orphan-drugs.org/2014/04/03/breaking-point-cost-increasing-orphan-drug-designations/>.

Bleichrodt, H, Diecidue, E & Quiggin, J 2004, 'Equity weights in the allocation of health care: the rank-dependent QALY model', *J Health Econ*, vol. 23, no. 1, Jan, pp. 157-171.

Bobinac, A, van Exel, J, Rutten, FH & Brouwer, WF 2014, 'The Value of a QALY: Individual Willingness to Pay for Health Gains Under Risk', *PharmacoEconomics*, vol. 32, no. 1, 2014/01/01, pp. 75-86.

Bobinac, A, van Exel, NJ, Rutten, FF & Brouwer, WB 2012, 'Inquiry into the relationship between equity weights and the value of the QALY', *Value Health*, vol. 15, no. 8, Dec, pp. 1119-1126.

Boycott, KM, Vanstone, MR, Bulman, DE & MacKenzie, AE 2013, 'Rare-disease genetics in the era of next-generation sequencing: discovery to translation', *Nat Rev Genet*, vol. 14, no. 10, Oct, pp. 681-691.

Brandt, CA, Argraves, S, Money, R, Ananth, G, Trocky, NM & Nadkarni, PM 2006, 'Informatics tools to improve clinical research study implementation', *Contemp Clin Trials*, vol. 27, no. 2, Apr, pp. 112-122.

Braunlin, E, Rosenfeld, H, Kampmann, C, Johnson, J, Beck, M & Giugliani, R 2013, 'Enzyme replacement therapy for mucopolysaccharidosis VI: long-term cardiac effects of galsulfase (Naglazyme(R)) therapy', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, pp. 385-394, DOI 10.1007/s10545-012-9481-2, <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/180/CN-00973180/frame.html>.

Brodsky, RA, Young, NS, Antonioli, E, Risitano, AM, Schrezenmeier, H, Schubert, J, Gaya, A, Coyle, L, de Castro, C, Fu, CL, Maciejewski, JP, Bessler, M, Kroon, HA, Rother, RP & Hillmen, P 2008, 'Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria', *Blood*, vol. 111, no. 4, Feb 15, pp. 1840-1847.

CADTH 2011, *Eliglustat tartrate, miglustat, imiglucerase, velaglucerase or a combination of these for the treatment of gaucher disease: a review of clinical effectiveness and safety (Structured abstract)*, Health Technology Assessment Database, Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa.

Canadian Agency for Drugs and Technologies in Health 2013, 'Drugs for rare diseases: evolving trends in regulatory and health technology assessment perspectives', pp. 1-40, viewed 3 July 2014, <http://www.cadth.ca/products/environmental-scanning/environmental-scans/environmental-scan-42>.

Casal, JA, Lacerda, L, Perez, LF, Pinto, RA, Miranda, MCS & Tutor, JC 2002, 'Relationship between serum markers on monocyte/macrophage activation in type 1 Gaucher disease', *Clinical Chemistry and Laboratory Medicine*, vol. 40, pp. 52-55.

Centre for Drug Evaluation and Research 2010, *VPRIV(R) (velaglucerase alfa, Gene-Activated(R) Glucocerebrosidase [GA-GCB]) 60 Units/lg Intravenous Every Other Week*, Statistical Reviews and Evaluation, Clinical Studies, Food and Drug Administration.

Chakrapani, A, Vellodi, A, Robinson, P, Jones, S & Wraith, JE 2010, 'Treatment of infantile Pompe disease with alglucosidase alpha: The UK experience', *Journal of Inherited Metabolic Disease*, vol. 33, no. 6, pp. 747-750.

Chalkidou, K, Lord, J, Fischer, A & Littlejohns, P 2008, 'Evidence-based decision making: when should we wait for more information?', *Health Aff (Millwood)*, vol. 27, no. 6, Nov-Dec, pp. 1642-1653.

Chen, LR, Chen, CA, Chiu, SN, Chien, YH, Lee, NC, Lin, MT, Hwu, WL, Wang, JK & Wu, MH 2009, 'Reversal of Cardiac Dysfunction after Enzyme Replacement in Patients with Infantile-Onset Pompe Disease', *Journal of Pediatrics*, vol. 155, no. 2, pp. 271-275.e272.

Cheng-Hakimian, A, Anderson, GD & Miller, JW 2006, 'Rufinamide: Pharmacology, clinical trials, and role in clinical practice', *Int J Clin Pract*, vol. 60, no. 11, Nov, pp. 1497-1501.

Chien, YH, Lee, NC, Thurberg, BL, Chiang, SC, Zhang, XK, Keutzer, J, Huang, AC, Wu, MH, Huang, PH, Tsai, FJ, Chen, YT & Hwu, WL 2009, 'Pompe disease in infants: improving the prognosis by newborn screening and early treatment', *Pediatrics*, vol. 124, no. 6, Dec, pp. e1116-1125.

Clarke, LA, Wraith, JE, Beck, M, Kolodny, EH, Pastores, GM, Muenzer, J, Rapoport, DM, Berger, KI, Sidman, M, Kakkis, ED & Cox, GF 2009, 'Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I', *Pediatrics*, vol. 123, no. 1, pp. 229-240, DOI 10.1542/peds.2007-3847, <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/004/CN-00666004/frame.html

http://pediatrics.aappublications.org/content/123/1/229.full.pdf>.

Cole, E, Pisano, ED, Clary, GJ, Zeng, D, Koomen, M, Kuzmiak, CM, Seo, BK, Lee, Y & Pavic, D 2006, 'A comparative study of mobile electronic data entry systems for clinical trials data collection', *Int J Med Inform*, vol. 75, no. 10-11, Oct-Nov, pp. 722-729.

Condliffe, R, Elliot, CA, Hurdman, J, Sabroe, I, Billings, C, Kiely, DG & Hamilton, N 2014, 'Ambrisentan therapy in pulmonary hypertension: clinical use and tolerability in a referral centre', *Ther Adv Respir Dis*, vol. 8, no. 3, Apr 30, pp. 71-77.

Connock, M, Burls, A, Frew, E, Fry-Smith, A, Juarez-Garcia, A, McCabe, C, Wailoo, A, Abrams, K, Cooper, N, Sutton, A, O'Hagan, A & Moore, D 2006, 'The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher disease: a systematic review', *Health Technology Assessment*, pp. 1-152.

Connock, M, Juarez-Garcia, A, Frew, E, Mans, A, Dretzke, J, Fry-Smith, A & Moore, D 2006, 'A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1', *Health Technol Assess*, vol. 10, no. 20, Jun, pp. iii-iv, ix-113.

Connock, M, Wang, D, Fry-Smith, A & Moore, D 2008, 'Prevalence and prognosis of paroxysmal nocturnal haemoglobinurea and the clinical and cost-effectiveness of eculizumab (Structured abstract)', *Health Technology Assessment Database*, no. 4, p. 1, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32008100046/frame.html>.

Coyle, D, Cheung, MC & Evans, GA 2014, 'Opportunity cost of funding drugs for rare diseases: the cost-effectiveness of eculizumab in paroxysmal nocturnal hemoglobinuria', *Med Decis Making*, vol. 34, no. 8, Nov, pp. 1016-1029.

Cystic Fibrosis Australia 2014, *About cystic fibrosis.*, Cystic Fibrosis Australia, viewed Nov 3 2014, <http://www.cysticfibrosis.org.au/all/learn/>.

da Silva, EMK, Strufaldi, MWL, Andriolo, RB & Silva, LA 2014, 'Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome)', *Cochrane Database Syst Rev*, vol. 1, //, p. CD008185.

Davidson, T & Levin, L-A 2010, 'Is the Societal Approach Wide Enough to Include Relatives? Incorporating Relatives' Costs and Effects in a Cost-Effectiveness Analysis', *Applied Health Economics and Health Policy*, vol. 8, no. 1, pp. 25-35.

Day, S, Fayers, P & Harvey, D 1998, 'Double data entry: what value, what price?', *Control Clin Trials*, vol. 19, no. 1, Feb, pp. 15-24.

de Fost, M, Aerts, JM, Groener, JE, Maas, M, Akkerman, EM, Wiersma, MG & Hollak, CE 2007, 'Low frequency maintenance therapy with imiglucerase in adult type I Gaucher disease: a prospective randomized controlled trial', *Haematologica*, vol. 92, pp. 215-221.

de Yebenes, JG, Landwehrmeyer, B, Squitieri, F, Reilmann, R, Rosser, A, Barker, RA, Saft, C, Magnet, MK, Sword, A, Rembratt, A & Tedroff, J 2011, 'Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial', *Lancet Neurol*, vol. 10, no. 12, Dec, pp. 1049-1057.

Dechelotte, P 2003, *Gastrointestinal and nutritional adverse effects of Zavesca (miglustat)*, Expert Report, Rouen.

Denis, A, Mergaert, L, Fostier, C, Cleemput, I, Hulstaert, F & Simoens, S 2011, 'Critical assessment of Belgian reimbursement dossiers of orphan drugs', *PharmacoEconomics*, vol. 29, no. 10, pp. 883-893.

Department of Health & The Rt Hon Earl Howe 2012, 'NICE to assess high cost low volume drugs', p. 1, viewed 1 October 2014, <https://www.gov.uk/government/news/nice-to-assess-high-cost-low-volume-drugs>.

Deroma, L, Guerra, M, Sechi, A, Ciana, G, Cisilino, G, Dardis, A & Bembi, B 2014, 'Enzyme replacement therapy in juvenile glycogenosis type II: a longitudinal study', *European Journal of Pediatrics*, vol. 173, no. 6, Jun, pp. 805-813.

Desnick, RJ 2004, 'Enzyme replacement therapy for Fabry disease: lessons from two alpha-galactosidase A orphan products and one FDA approval', *Expert Opin Biol Ther*, vol. 4, no. 7, //, pp. 1167-1176.

Desser, AS 2013, 'Prioritizing treatment of rare diseases: A survey of preferences of Norwegian doctors', *Social Science & Medicine*, vol. 94, no. 0, 10//, pp. 56-62.

Desser, AS, Gyrd-Hansen, D, Olsen, JA, Grepperud, S & Kristiansen, IS 2010, 'Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67', *British Medical Journal*, vol. 341, p. c4715.

Desser, AS, Olsen, JA & Grepperud, S 2013, 'Eliciting preferences for prioritizing treatment of rare diseases: the role of opportunity costs and framing effects', *PharmacoEconomics*, vol. 31, no. 11, Nov, pp. 1051-1061.

DeZern, AE, Dorr, D & Brodsky, RA 2013, 'Predictors of hemoglobin response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria', *Eur J Haematol*, vol. 90, no. 1, Jan, pp. 16-24.

Diaby, V & Goeree, R 2014, 'How to use multi-criteria decision analysis methods for reimbursement decision-making in healthcare: a step-by-step guide', *Expert Rev Pharmacoecon Outcomes Res*, vol. 14, no. 1, Feb, pp. 81-99.

Dignan, FL, Wynn, RF, Hadzic, N, Karani, J, Quaglia, A, Pagliuca, A, Veys, P, Potter, MN, The Haemato-oncology Task Force of the British Committee for Standards in, H, the British Society for, B & Marrow, T 2013, 'BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation', *Br J Haematol*, vol. 163, no. 4, pp. 444-457.

Dmytrijuk, A, Robie-Suh, K, Cohen, MH, Rieves, D, Weiss, K & Pazdur, R 2008, 'FDA report: eculizumab (Soliris) for the treatment of patients with paroxysmal nocturnal hemoglobinuria', *Oncologist*, vol. 13, no. 9, Sep, pp. 993-1000.

Dolan, P, Shaw, R, Tsuchiya, A & Williams, A 2005, 'QALY maximisation and people's preferences: a methodological review of the literature', *Health Econ*, vol. 14, no. 2, Feb, pp. 197-208.

Donaldson, C, Baker, R, Mason, H, Jones-Lee, M, Lancsar, E, Wildman, J, Bateman, I, Loomes, G, Robinson, A, Sugden, R, Prades, J, Ryan, M, Shackley, P & Smith, R 2011, 'The social value of a QALY: raising the bar or barring the raise?', *BMC Health Services Research*, vol. 11, no. 1, p. 8.

Donaldson, J, Khan, WS, Tailor, H, Hughes, DA, Mehta, AB & Maruthainar, N 2011, 'Gaucher disease: Outcome following total hip replacements and effect of enzyme replacement therapy in a cohort of UK Patients', *HIP International*, vol. 21, no. 6, pp. 665-671.

El Dib, RP, Nascimento, P & Pastores, GM 2013, 'Enzyme replacement therapy for Anderson-Fabry disease', *Cochrane Database of Systematic Reviews*, no. 2<p>.

El Dib, RP & Pastores, GM 2007, 'Laronidase for treating mucopolysaccharidosis type I', *Genetics and Molecular Research*, vol. 6, no. 3, pp. 667-674.

El Dib, RP & Pastores, GM 2009, 'A systematic review of new advances in the management of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): focus on galsulfase', *Biologics*, vol. 3, //, pp. 459-468.

Elder, ME, Nayak, S, Collins, SW, Lawson, LA, Kelley, JS, Herzog, RW, Modica, RF, Lew, J, Lawrence, RM & Byrne, BJ 2013, 'B-Cell depletion and immunomodulation before initiation of enzyme replacement therapy blocks the immune response to acid alpha-glucosidase in infantile-onset Pompe disease', *J Pediatr*, vol. 163, no. 3, Sep, pp. 847-854 e841.

Elstein, D, Dweck, A, Attias, D, Hadas-Halpern, I, Zevin, S, Altarescu, G, Aerts, JF, van, W & Zimran, A 2007, 'Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement', *Blood*, vol. 110, pp. 2296-2301.

Elstein, Y, Eisenberg, V, Granovsky-Grisaru, S, Rabinowitz, R, Samueloff, A, Zimran, A & Elstein, D 2004, 'Pregnancies in Gaucher disease: A 5-year study', *American Journal of Obstetrics and Gynecology*, vol. 190, no. 2, Feb, pp. 435-441.

Eng, CM, Guffon, N, Wilcox, WR, Germain, DP, Lee, P, Waldek, S, Caplan, L, Linthorst, GE & Desnick, RJ 2001, 'Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease', *New England Journal of Medicine*, vol. 345, no. 1, pp. 9-16.

Epilepsy Action Australia 2014, *About epilepsy*, Epilepsy Action Australia, NSW, Australia, viewed 4 Dec 2014, <http://www.epilepsy.org.au/about-epilepsy>.

Escudier, B & Albiges, L 2014, 'Pazopanib for the treatment of advanced renal cell cancer', *Expert Opinion on Orphan Drugs*, vol. 2, no. 6, pp. 605-616.

EUnetHTA 2013, *HTA Core Model Application for Pharmaceuticals (2.1) - PUBLIC DRAFT*, National Institute for Health and Welfare, viewed 19/11/2014, <http://meka.thl.fi/htacore/ViewApplication.aspx?id=17128>.

European Medicines Agency 2003, 'Scientific Discussion', *European Public Assessment Report (EPAR)*, <http://www.ema.europa.eu/docs/en\_GB/document\_library/EPAR\_-\_Scientific\_Discussion/human/000435/WC500046721.pdf >.

Fecarotta, S, Ascione, S, Montefusco, G, Della, CR, Villari, P, Romano, A, Del, GE, Andria, G & Parenti, G 2013, 'Improvement of dysphagia in a child affected by Pompe disease treated with enzyme replacement therapy', *Ital J Pediatr*, vol. 39, //, p. 30.

Fellows, GK & Hollis, A 2013, 'Funding innovation for treatment for rare diseases: adopting a cost-based yardstick approach', *Orphanet J Rare Dis*, vol. 8, p. 180.

Fernandez, C, Legido, A, Jethva, R & Marks, HG 2012, 'Correction of a short cardiac PR interval in a 12-year-old girl with late-onset Pompe disease following enzyme replacement therapy', *Genetics in Medicine*, vol. 14, no. 8, Aug, pp. 757-758.

Food and Drug Administration (FDA) April 2011, *Guidance for Industry - Postmarketing Studies and Clinical Trial - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf>.

Furusawa, Y, Mitsuhashi, S, Mori-Yoshimura, M, Shimada, Y, Yamamoto, T, Shibuya, M, Shimizu, J, Ohashi, T, Saito, Y, Nishino, I, Oya, Y & Murata, M 2014, 'Late-onset Pompe disease after 4 years of enzyme replacement therapy: An autopsy case', *Neurology and Clinical Neuroscience*, vol. 2, no. 1, pp. 7-9.

Furusawa, Y, Mori-Yoshimura, M, Yamamoto, T, Sakamoto, C, Wakita, M, Kobayashi, Y, Fukumoto, Y, Oya, Y, Fukuda, T, Sugie, H, Hayashi, YK, Nishino, I, Nonaka, I & Murata, M 2012, 'Effects of enzyme replacement therapy on five patients with advanced late-onset glycogen storage disease type II: a 2-year follow-up study', *J Inherit Metab Dis*, vol. 35, no. 2, Mar, pp. 301-310.

Galsky, MD, Von Hoff, DD, Neubauer, M, Anderson, T, Fleming, M, Nagarwala, Y, Mahoney, JM, Midwinter, D, Vocila, L & Zaks, TZ 2012, 'Target-specific, histology-independent, randomized discontinuation study of lapatinib in patients with HER2-amplified solid tumors', *Invest New Drugs*, vol. 30, no. 2, Apr, pp. 695-701.

Gao, JJ, Song, PP & Tang, W 2013, 'Rare disease patients in China anticipate the sunlight of legislation', *Drug Discov Ther*, vol. 7, no. 3, Jun, pp. 126-128.

Garau, M & Mestre-Ferrandiz, J 2009, 'Access mechanisms for orphan drugs: A comparative study of selected European countries', pp. 1-32, viewed 3 October 2014, <www.raredisease.org.uk/documents/OHEBriefingOrphanDrugs.pdf>.

Gassman, JJ, Owen, WW, Kuntz, TE, Martin, JP & Amoroso, WP 1995, 'Data quality assurance, monitoring, and reporting', *Control Clin Trials*, vol. 16, no. 2 Suppl, Apr, pp. 104S-136S.

Genzyme 2006, *Fabrazyme(R) (agalsidase beta) Global Periodic Safety Update (PSUR)*.

Genzyme 2007, 'Periodic safety update report, 1 May 06 - 30 April 07 for Aldurazyme(R) 500U (laronidase-rch)'.

Genzyme (Fabry Registry), *Fabry Registry*, viewed 18/11/2014, <http://www.fabrycommunity.com/Healthcare/Registry.aspx>.

Genzyme (MPS I Registry), *MPS I Registry*, viewed 18/11/2014, <http://www.mps1disease.com/patients/mpsi-registry.aspx>.

Genzyme (Pompe Registry), *Pompe Registry*, viewed 18/11/2014, <http://www.pompe.com/healthcare-professionals/pompe-registry.aspx>.

Genzyme Australasia Pty Ltd 2011, *Periodic safety update report: Myozyme (alglucosidase alfa-rch)*.

Gho, JM, Kummeling, GJ, Koudstaal, S, Jansen Of Lorkeers, SJ, Doevendans, PA, Asselbergs, FW & Chamuleau, SA 2013, 'Cell therapy, a novel remedy for dilated cardiomyopathy? A systematic review', *J Card Fail*, vol. 19, no. 7, Jul, pp. 494-502.

Giraldo, P, Irun, P, Alfonso, P, Dalmau, J, Fernandez-Galan, MA, Figueredo, A, Hernandez-Rivas, JM, Julia, A, Luno, E, Marin-Jimenez, F, Martin-Nunez, G, Montserrat, JL, de la, S, Vidaller, A, Villalon, L & Pocovi, M 2011, 'Evaluation of Spanish Gaucher disease patients after a 6-month imiglucerase shortage', *Blood Cells Mol Dis*, vol. 46, pp. 115-118.

Glauser, T, Kluger, G, Sachdeo, R, Krauss, G, Perdomo, C & Arroyo, S 2008, 'Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome', *Neurology*, vol. 70, no. 21, May 20, pp. 1950-1958.

Gliklich, RE & Dreyer (Eds), NA 2010, *Registries for evaluating patient outcomes: a user's guide (2nd Ed)*, Agency for Healthcare Research and Quality,, <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1897&pageaction=displayproduct>.

Gliklich, RE, Dreyer, NA & Leavy, MB 2014, 'Rare Disease Registries'.

Goetghebeur, MM, Wagner, M, Khoury, H, Levitt, RJ, Erickson, LJ & Rindress, D 2008, 'Evidence and Value: Impact on DEcisionMaking--the EVIDEM framework and potential applications', *BMC Health Serv Res*, vol. 8, p. 270.

Goetghebeur, MM, Wagner, M, Khoury, H, Levitt, RJ, Erickson, LJ & Rindress, D 2012, 'Bridging health technology assessment (HTA) and efficient health care decision making with multicriteria decision analysis (MCDA): applying the EVIDEM framework to medicines appraisal', *Med Decis Making*, vol. 32, no. 2, Mar-Apr, pp. 376-388.

Gong, S & Jin, S 2012, 'Current progress in the management of rare diseases and orphan drugs in China', *Intractable & Rare Disease Research*, vol. 1, no. 2, pp. 45-52.

Gonzalez, DE, Turkia, HB, Lukina, EA, Kisinovsky, I, Dridi, MF, Elstein, D, Zahrieh, D, Crombez, E, Bhirangi, K, Barton, NW & Zimran, A 2013, 'Enzyme replacement therapy with velaglucerase alfa in Gaucher disease: Results from a randomized, double-blind, multinational, Phase 3 study', *Am J Hematol*, vol. 88, pp. 166-171.

Grigorescu-Sido, P, Drugan, C, Alkhzouz, C, Zimmermann, A, Coldea, C, Denes, C, Grigorescu, MD, Cret, V & Bucerzan, S 2010, 'Baseline characteristics and outcome in Romanian patients with Gaucher disease type 1', *Eur J Intern Med*, vol. 21, pp. 104-113.

Groft, SC & Rubinstein, YR 2013, 'New and evolving rare diseases research programs at the National Institutes of Health', *Public Health Genomics*, vol. 16, no. 6, pp. 259-267.

Guyatt, G, Oxman, AD, Akl, EA, Kunz, R, Vist, G, Brozek, J, Norris, S, Falck-Ytter, Y, Glasziou, P, DeBeer, H, Jaeschke, R, Rind, D, Meerpohl, J, Dahm, P & Schunemann, HJ 2011, 'GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables', *J Clin Epidemiol*, vol. 64, no. 4, Apr, pp. 383-394.

Guyatt, G, Oxman, AD, Sultan, S, Brozek, J, Glasziou, P, Alonso-Coello, P, Atkins, D, Kunz, R, Montori, V, Jaeschke, R, Rind, D, Dahm, P, Akl, EA, Meerpohl, J, Vist, G, Berliner, E, Norris, S, Falck-Ytter, Y & Schunemann, HJ 2013, 'GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes', *J Clin Epidemiol*, vol. 66, no. 2, Feb, pp. 151-157.

Harmatz, P, Giugliani, R, Schwartz, I, Guffon, N, Teles, EL, Miranda, MC, Wraith, JE, Beck, M, Arash, L, Scarpa, M, Yu, ZF, Wittes, J, Berger, KI, Newman, MS, Lowe, AM, Kakkis, E & Swiedler, SJ 2006, 'Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study', *J Pediatr*, vol. 148, no. 4, Apr, pp. 533-539.

Harmatz, P, Yu, ZF, Giugliani, R, Schwartz, IVD, Guffon, N, Teles, EL, Miranda, MCS, Wraith, JE, Beck, M, Arash, L, Scarpa, M, Ketteridge, D, Hopwood, JJ, Plecko, B, Steiner, R, Whitley, CB, Kaplan, P, Swiedler, SJ, Hardy, K, Berger, KI & Decker, C 2010, 'Enzyme replacement therapy for mucopolysaccharidosis VI: Evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase', *Journal of Inherited Metabolic Disease*, vol. 33, no. 1, pp. 51-60.

Harris, AH, Hill, SR, Chin, G, Li, JJ & Walkom, E 2008, 'The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994-2004', *Med Decis Making*, vol. 28, no. 5, Sep-Oct, pp. 713-722.

HAYES & Inc 2013, *VPRIV (Velaglucerase Alfa for Injection; Shire Human Genetic Therapies Inc.) for type 1 gaucher disease*, HAYES, Inc, Lansdale, PA.

Hayes, RP, Grinzaid, KA, Duffey, EB & Elsas, ILJ 1998, 'The impact of Gaucher disease and its treatment on quality of life', *Quality of Life Research*, vol. 7, no. 6, pp. 521-534.

Herzog, TN, Scheuren, FJ & Winkler, WE 2007, *Data quality and record linkage techniques*, vol. 1, Springer.

Hetherington, A 2013, 'Avoiding the most common pitfalls with orphan applications', *GFA Insight*, no. 4, pp. 2-4.

Hill, A, Hillmen, P, Richards, SJ, Elebute, D, Marsh, JC, Chan, J, Mojcik, CF & Rother, RP 2005, 'Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria', *Blood*, vol. 106, no. 7, Oct 1, pp. 2559-2565.

Hill, A, Rother, RP, Wang, X, Morris, SM, Jr., Quinn-Senger, K, Kelly, R, Richards, SJ, Bessler, M, Bell, L, Hillmen, P & Gladwin, MT 2010, 'Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria', *Br J Haematol*, vol. 149, no. 3, May, pp. 414-425.

Hillmen, P, Elebute, M, Kelly, R, Urbano-Ispizua, A, Hill, A, Rother, RP, Khursigara, G, Fu, CL, Omine, M, Browne, P & Rosse, W 2010, 'Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria', *Am J Hematol*, vol. 85, no. 8, Aug, pp. 553-559.

Hillmen, P, Hall, C, Marsh, JC, Elebute, M, Bombara, MP, Petro, BE, Cullen, MJ, Richards, SJ, Rollins, SA, Mojcik, CF & Rother, RP 2004, 'Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria', *N Engl J Med*, vol. 350, no. 6, Feb 5, pp. 552-559.

Hillmen, P, Lewis, SM, Bessler, M, Luzzatto, L & Dacie, JV 1995, 'Natural history of paroxysmal nocturnal hemoglobinuria', *N Engl J Med*, vol. 333, no. 19, Nov 9, pp. 1253-1258.

Hillmen, P, Muus, P, Duhrsen, U, Risitano, AM, Schubert, J, Luzzatto, L, Schrezenmeier, H, Szer, J, Brodsky, RA, Hill, A, Socie, G, Bessler, M, Rollins, SA, Bell, L, Rother, RP & Young, NS 2007, 'Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria', *Blood*, vol. 110, no. 12, Dec 1, pp. 4123-4128.

Hillmen, P, Muus, P, Roth, A, Elebute, MO, Risitano, AM, Schrezenmeier, H, Szer, J, Browne, P, Maciejewski, JP, Schubert, J, Urbano-Ispizua, A, de Castro, C, Socie, G & Brodsky, RA 2013, 'Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria', *Br J Haematol*, vol. 162, no. 1, Jul, pp. 62-73.

Hillmen, P, Young, NS, Schubert, J, Brodsky, RA, Socie, G, Muus, P, Roth, A, Szer, J, Elebute, MO, Nakamura, R, Browne, P, Risitano, AM, Hill, A, Schrezenmeier, H, Fu, CL, Maciejewski, J, Rollins, SA, Mojcik, CF, Rother, RP & Luzzatto, L 2006, 'The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria', *N Engl J Med*, vol. 355, no. 12, Sep 21, pp. 1233-1243.

Hochsmann, B, Leichtle, R, von Zabern, I, Kaiser, S, Flegel, WA & Schrezenmeier, H 2012, 'Paroxysmal nocturnal haemoglobinuria treatment with eculizumab is associated with a positive direct antiglobulin test', *Vox Sang*, vol. 102, no. 2, Feb, pp. 159-166.

Hollak, C, Maas, M, Akkerman, E, den, H & Aerts, H 2001, 'Dixon quantitative chemical shift imaging is a sensitive tool for the evaluation of bone marrow responses to individualized doses of enzyme supplementation therapy in type 1 Gaucher disease', *Blood Cells Mol Dis*, vol. 27, pp. 1005-1012.

Hong, JM, Jang, S, Yang, BM, Lee, HJ, Kwon, HY, Park, MH & Bae, EY 2014, 'The analysis of the drug reimbursement decisions before and after the positive list system in South Korea', *Value in Health*, vol. 17, no. 3, pp. A12-A13.

Hughes, DA, Elliott, PM, Shah, J, Zuckerman, J, Coghlan, G, Brookes, J & Mehta, AB 2008, 'Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa', *Heart*, vol. 94, no. 2, //, pp. 153-158.

Huntington Study Group HART Investigators 2013, 'A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease', *Mov Disord*, vol. 28, no. 10, Sep, pp. 1407-1415.

Hutchings, A, Ethgen, O, Schmitt, C & Rollet, P 2012, 'PHP100 Defining Elements of Value for Rare Disease Treatments', *Value in Health*, vol. 15, no. 4, 6//, p. A31.

International Collaborative Gaucher Group & Genzyme, *Gaucher Registry*, viewed 18/11/2014, <http://www.gauchercare.com/healthcare/registry.aspx>.

Ioannidis, JP 2009, 'Adverse events in randomized trials: neglected, restricted, distorted, and silenced', *Archives of internal medicine*, vol. 169, no. 19, pp. 1737-1739.

Ioannidis, JP & Contopoulos-Ioannidis, DG 1998, 'Reporting of safety data from randomised trials', *Lancet*, vol. 352, no. 9142, Nov 28, pp. 1752-1753.

Iorio, R, Damato, V, Alboini, PE & Evoli, A 2014, 'Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis', *J Neurol*, Oct 12.

Ishigaki, K, Murakami, T, Nakanishi, T, Oda, E, Sato, T & Osawa, M 2012, 'Close monitoring of initial enzyme replacement therapy in a patient with childhood-onset Pompe disease', *Brain & Development*, vol. 34, no. 2, Feb, pp. 98-102.

ISPOR 2007, 'ISPOR Global Health Care Systems Road Map: Scotland - Reimbursement process', p. 8, viewed 1 October 2014, <http://www.ispor.org/htaroadmaps/scotland.asp>.

ISPOR 2008, 'ISPOR Global Health Care Systems Road Map: Italy - Pharmaceuticals', p. 5, viewed 7 October 2014, <http://www.ispor.org/htaroadmaps/italy.asp>.

ISPOR 2009a, 'ISPOR Global Health Care Systems Road Map: Austria - Pharmaceuticals', viewed 13 November 2014, <http://www.ispor.org/HTARoadMaps/Austria.asp>.

ISPOR 2009b, 'ISPOR Global Health Care Systems Road Map: France - Pharmaceuticals', viewed 3 October 2014, <http://www.ispor.org/htaroadmaps/France.asp>.

ISPOR 2009c, 'ISPOR Global Health Care Systems Road Map: Germany - Pharmaceuticals', viewed 3 October 2014, <http://www.ispor.org/htaroadmaps/germany.asp#2>.

ISPOR 2009d, 'ISPOR Global Health Care Systems Road Map: Spain - Pharmaceutical', viewed 7 October 2014, <http://www.ispor.org/htaroadmaps/spain.asp>.

ISPOR 2009e, 'ISPOR Global Health Care Systems Road Map: Sweden - Pharmaceutical', viewed 7 October 2014, <http://www.ispor.org/htaroadmaps/sweden.asp>.

ISPOR 2011, 'ISPOR Global Health Care Systems Road Map: Canada - Pharmaceutical', p. 1, viewed 3 July 2014, <http://www.ispor.org/htaroadmaps/canadapharm.asp>.

Jameson, E, Jones, S & Wraith, JE 2013, 'Enzyme replacement therapy with laronidase (Aldurazyme (R)) for treating mucopolysaccharidosis type I', *Cochrane Database of Systematic Reviews*, no. 9, pp. 1-20.

Jansson, S 2007, 'Implementing accountability for reasonableness--the case of pharmaceutical reimbursement in Sweden', *Health Econ Policy Law*, vol. 2, no. Pt 2, Apr, pp. 153-171.

Japan Intractable Diseases Information Center 2014, 'What is an intractable disease? ', p. 1, viewed 7 July 2014,

Johnson, JR, Ning, YM, Farrell, A, Justice, R, Keegan, P & Pazdur, R 2011, 'Accelerated approval of oncology products: the food and drug administration experience', *J Natl Cancer Inst*, vol. 103, no. 8, Apr 20, pp. 636-644.

Kanakura, Y, Ohyashiki, K, Shichishima, T, Okamoto, S, Ando, K, Ninomiya, H, Kawaguchi, T, Nakao, S, Nakakuma, H, Nishimura, J, Kinoshita, T, Bedrosian, CL, Ozawa, K & Omine, M 2013, 'Long-term efficacy and safety of eculizumab in Japanese patients with PNH: AEGIS trial', *Int J Hematol*, vol. 98, no. 4, Oct, pp. 406-416.

Kanakura, Y, Ohyashiki, K, Shichishima, T, Okamoto, S, Ando, K, Ninomiya, H, Kawaguchi, T, Nakao, S, Nakakuma, H, Nishimura, J, Kinoshita, T, Bedrosian, CL, Valentine, ME, Khursigara, G, Ozawa, K & Omine, M 2011, 'Safety and efficacy of the terminal complement inhibitor eculizumab in Japanese patients with paroxysmal nocturnal hemoglobinuria: the AEGIS clinical trial', *Int J Hematol*, vol. 93, no. 1, Jan, pp. 36-46.

Kanters, TA, Hoogenboom-Plug, I, Rutten-Van Molken, MP, Redekop, WK, van der Ploeg, AT & Hakkaart, L 2014, 'Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease', *Orphanet J Rare Dis*, vol. 9, p. 75.

Kathula, SK 2006, 'Eculizumab in Paroxysmal Nocturnal Hemoglobinuria', *New England Journal of Medicine*, vol. 355, no. 26, pp. 2786-2788.

Keating, GM 2014, 'Defibrotide: a review of its use in severe hepatic veno-occlusive disease following haematopoietic stem cell transplantation', *Clin Drug Investig*, vol. 34, no. 12, Dec, pp. 895-904.

Kelly, R, Arnold, L, Richards, S, Hill, A, Bomken, C, Hanley, J, Loughney, A, Beauchamp, J, Khursigara, G, Rother, RP, Chalmers, E, Fyfe, A, Fitzsimons, E, Nakamura, R, Gaya, A, Risitano, AM, Schubert, J, Norfolk, D, Simpson, N & Hillmen, P 2010, 'The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab', *Br J Haematol*, vol. 149, no. 3, May, pp. 446-450.

Kelly, RJ, Hill, A, Arnold, LM, Brooksbank, GL, Richards, SJ, Cullen, M, Mitchell, LD, Cohen, DR, Gregory, WM & Hillmen, P 2011, 'Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival', *Blood*, vol. 117, no. 25, Jun 23, pp. 6786-6792.

Khan, KS, Ter Riet, G, Glanville, JM, Sowden, AJ & Kleijnen, J 2001, *Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews*, CRD Report, no. CRD Report Number 4 (second edition), NHS Centre for Reviews and Dissemination, University of York, York.

Kim, JS, Lee, JW, Kim, BK, Lee, JH & Chung, J 2010, 'The use of the complement inhibitor eculizumab (Soliris(R)) for treating Korean patients with paroxysmal nocturnal hemoglobinuria', *Korean J Hematol*, vol. 45, no. 4, Dec, pp. 269-274.

Kishnani, P, Byrne, B, Hwu, WL, Leslie, N, Mandel, H, Wraith, J & Nicolino, M 2008, 'Alglucosidase alfa in infants and children with advanced pompe disease', *Molecular Genetics and Metabolism*, vol. 93, no. 3, Mar, pp. 254-254.

Kishnani, PS, Corzo, D, Leslie, ND, Gruskin, D, Van der Ploeg, A, Clancy, JP, Parini, R, Morin, G, Beck, M, Bauer, MS, Jokic, M, Tsai, CE, Tsai, BW, Morgan, C, O'Meara, T, Richards, S, Tsao, EC & Mandel, H 2009, 'Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease', *Pediatr Res*, vol. 66, no. 3, Sep, pp. 329-335.

Kishnani, PS, Corzo, D, Nicolino, M, Byrne, B, Mandel, H, Hwu, WL, Leslie, N, Levine, J, Spencer, C, McDonald, M, Li, J, Dumontier, J, Halberthal, M, Chien, YH, Hopkin, R, Vijayaraghavan, S, Gruskin, D, Bartholomew, D, van der Ploeg, A, Clancy, JP, Parini, R, Morin, G, Beck, M, De la Gastine, GS, Jokic, M, Thurberg, B, Richards, S, Bali, D, Davison, M, Worden, MA, Chen, YT & Wraith, JE 2007, 'Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease', *Neurology*, vol. 68, no. 2, Jan 9, pp. 99-109.

Kishnani, PS, DiRocco, M, Kaplan, P, Mehta, A, Pastores, GM, Smith, SE, Puga, AC, Lemay, RM & Weinreb, NJ 2009, 'A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1', *Mol Genet Metab*, vol. 96, pp. 164-170.

Kishnani, PS, Goldenberg, PC, DeArmey, SL, Heller, J, Benjamin, D, Young, S, Bali, D, Smith, SA, Li, JS, Mandel, H, Koeberl, D, Rosenberg, A & Chen, YT 2010, 'Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants', *Molecular Genetics and Metabolism*, vol. 99, no. 1, pp. 26-33.

Kishnani, PS, Hwu, WL, Mandel, H, Nicolino, M, Yong, F, Corzo, D & Infantile-Onset Pompe Disease Natural History Study, G 2006, 'A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease', *J Pediatr*, vol. 148, no. 5, May, pp. 671-676.

Kishnani, PS, Nicolino, M, Voit, T, Rogers, RC, Tsai, AC, Waterson, J, Herman, GE, Amalfitano, A, Thurberg, BL, Richards, S, Davison, M, Corzo, D & Chen, YT 2006, 'Chinese hamster ovary cell-derived recombinant human acid alpha-glucosidase in infantile-onset Pompe disease', *J Pediatr*, vol. 149, no. 1, Jul, pp. 89-97.

Kobayashi, H, Shimada, Y, Ikegami, M, Kawai, T, Sakurai, K, Urashima, T, Ijima, M, Fujiwara, M, Kaneshiro, E, Ohashi, T, Eto, Y, Ishigaki, K, Osawa, M, Kyosen, SO & Ida, H 2010, 'Prognostic factors for the late onset Pompe disease with enzyme replacement therapy: From our experience of 4 cases including an autopsy case', *Molecular Genetics and Metabolism*, vol. 100, no. 1, May, pp. 14-19.

Korpela, MP, Paetau, A, Lofberg, MI, Timonen, MH, Lamminen, AE & Kiuru-Enari, SM 2009, 'A novel mutation of the GAA gene in a Finnish late-onset Pompe disease patient: clinical phenotype and follow-up with enzyme replacement therapy', *Muscle Nerve*, vol. 40, no. 1, Jul, pp. 143-148.

Kruer, MC & Steiner, RD 2008, 'The role of evidence-based medicine and clinical trials in rare genetic disorders', *Clin Genet*, vol. 74, no. 3, Sep, pp. 197-207.

Kumar, S, Tana, A & Shankar, A 2014, 'Cystic fibrosis - What are the prospects for a cure?', *Eur J Intern Med*, vol. 25, no. 9, Oct 18, pp. 803-807.

Lachmann, R & Schoser, B 2013, 'The clinical relevance of outcomes used in late-onset Pompe disease: can we do better?', *Orphanet J Rare Dis*, vol. 8, p. 160.

Le Jeannic, A, Quelen, C, Alberti, C, Durand-Zaleski, I & CompaRec, I 2014, 'Comparison of two data collection processes in clinical studies: electronic and paper case report forms', *BMC Med Res Methodol*, vol. 14, p. 7.

Lee, JW, Jang, JH, Kim, JS, Yoon, SS, Lee, JH, Kim, YK, Jo, DY, Chung, J & Sohn, SK 2013, 'Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry', *Int J Hematol*, vol. 97, no. 6, Jun, pp. 749-757.

Liberati, A, Altman, DG, Tetzlaff, J, Mulrow, C, Gotzsche, PC, Ioannidis, JP, Clarke, M, Devereaux, PJ, Kleijnen, J & Moher, D 2009, 'The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration', *PLoS Med*, vol. 6, no. 7, Jul 21, p. e1000100.

Lindquist, S & Stangel, M 2011, 'Update on treatment options for Lambert-Eaton myasthenic syndrome: focus on use of amifampridine', *Neuropsychiatr Dis Treat*, vol. 7, pp. 341-349.

Linertova, R, Serrano-Aguilar, P, Posada-de-la-Paz, M, Hens-Perez, M, Kanavos, P, Taruscio, D, Schieppati, A, Stefanov, R, Pentek, M, Delgado, C, von der Schulenburg, JM, Persson, U, Chevreul, K, Fattore, G, Worbes-Cerezo, M, Sefton, M & Lopez-Bastida, J 2012, 'Delphi approach to select rare diseases for a European representative survey. The BURQOL-RD study', *Health Policy*, vol. 108, no. 1, Nov, pp. 19-26.

Long, G & Works, J 2013, *Innovation in the Biopharmaceutical Pipeline: a multidimensional view*, Analysis Group.

Loveman, E, Copley, VR, Colquitt, JL, Scott, DA, Clegg, AJ, Jones, J, O'Reilly, KM, Singh, S, Bausewein, C & Wells, A 2014, 'The effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: systematic review, network meta-analysis and health economic evaluation', *BMC Pharmacol Toxicol*, vol. 15, p. 63.

Ma, D, Li, D, Zhang, X & He, L 2011, 'Opportunities and challenges of rare diseases treatments in China', *Chin J Evid Based Pediatr*, vol. 6, no. 2, pp. 81-82.

MacIntyre, K, Capewell, S, Stewart, S, Chalmers, JW, Boyd, J, Finlayson, A, Redpath, A, Pell, JP & McMurray, JJ 2000, 'Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995', *Circulation*, vol. 102, no. 10, Sep 5, pp. 1126-1131.

Maier, E, Wilken, R & Dost, F 2014, 'The double benefits of consumer certainty: combining risk and range effects', *Marketing Letters*, 2014/02/13, pp. 1-16.

Maurer, SM 2006, 'Choosing the right incentive strategy for research and development in neglected diseases', *Bull World Health Organ*, vol. 84, no. 5, May, pp. 376-381.

McCabe, C, Claxton, K & Tsuchiya, A 2005, 'Orphan drugs and the NHS: should we value rarity?', *British Medical Journal*, vol. 331, no. 7523, Oct 29, pp. 1016-1019.

McCabe, C, Edlin, R & Round, J 2010, 'Economic considerations in the provision of treatments for rare diseases', *Adv Exp Med Biol*, vol. 686, pp. 211-222.

McMaster University and Evidence Prime Inc., 2014, *GRADEpro Guideline Development Tool*,

McNeil, JJ, Piccenna, L, Ronaldson, K & Ioannides-Demos, LL 2010, 'The value of patient-centred registries in phase IV drug surveillance', *Pharmaceutical Medicine*, vol. 24, no. 5, pp. 281-288.

McPherson, K & Hemminki, E 2004, 'Synthesising licensing data to assess drug safety', *British Medical Journal*, vol. 328, no. 7438, Feb 28, pp. 518-520.

Meininger, V, Pradat, PF, Corse, A, Al-Sarraj, S, Rix Brooks, B, Caress, JB, Cudkowicz, M, Kolb, SJ, Lange, D, Leigh, PN, Meyer, T, Milleri, S, Morrison, KE, Orrell, RW, Peters, G, Rothstein, JD, Shefner, J, Lavrov, A, Williams, N, Overend, P, Price, J, Bates, S, Bullman, J, Krull, D, Berges, A, Abila, B, Meno-Tetang, G & Wurthner, J 2014, 'Safety, pharmacokinetic, and functional effects of the nogo-a monoclonal antibody in amyotrophic lateral sclerosis: a randomized, first-in-human clinical trial', *PLoS ONE*, vol. 9, no. 5, p. e97803.

Mentzakis, E, Stefanowska, P & Hurley, J 2011, 'A Discrete Choice Experiment Investigating Preferences for Funding Drugs Used to Treat Orphan Diseases: An Exploratory Study', *Health Economics, Policy and Law*, vol. 6, no. 3, pp. 405-433.

Merk, T, Wibmer, T, Schumann, C & Kruger, S 2009, 'Glycogen storage disease type II (Pompe disease)--influence of enzyme replacement therapy in adults', *Eur J Neurol*, vol. 16, no. 2, Feb, pp. 274-277.

Merlin, T, Weston, A & Tooher, R 2009, 'Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'', *BMC Med Res Methodol*, vol. 9, p. 34.

Messinger, YH, Mendelsohn, NJ, Rhead, W, Dimmock, D, Hershkovitz, E, Champion, M, Jones, SA, Olson, R, White, A, Wells, C, Bali, D, Case, LE, Young, SP, Rosenberg, AS & Kishnani, PS 2012, 'Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease', *Genetics in Medicine*, vol. 14, no. 1, pp. 135-142.

Mistry, PK, Sirrs, S, Chan, A, Pritzker, MR, Duffy, TP, Grace, ME, Meeker, DP & Goldman, ME 2002, 'Pulmonary hypertension in type 1 Gaucher disease: genetic and epigenetic determinants of phenotype and response to therapy', *Mol Genet Metab*, vol. 77, pp. 91-98.

Mitsumoto, H, Brooks, BR & Silani, V 2014, 'Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved?', *The Lancet Neurology*, vol. 13, no. 11, 11//, pp. 1127-1138.

Moore, DF, Altarescu, G, Herscovitch, P & Schiffmann, R 2002, 'Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease', *BMC Neurol.*, vol. 2, pp. 1-10.

Moore, DF, Scott, LT, Gladwin, MT, Altarescu, G, Kaneski, C, Suzuki, K, Pease-Fye, M, Ferri, R, Brady, RO, Herscovitch, P & Schiffmann, R 2001, 'Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy', *Circulation*, vol. 104, no. 13, Sep 25, pp. 1506-1512.

Morel, T, Arickx, F, Befrits, G, Siviero, P, van der Meijden, C, Xoxi, E & Simoens, S 2013, 'Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries', *Orphanet J Rare Dis*, vol. 8, p. 198.

Morris, JL 2012, 'Velaglucerase alfa for the management of type 1 Gaucher disease', *Clin Ther*, vol. 34, pp. 259-271.

Motor Neurone Disease Australia 2014, *Overview: motor neurone disease.*, MND Australia, viewed 3 Nov 2014, <http://www.mndcare.net.au/Overview/Motor-neurone-disease.aspx>.

Muenzer, J, Beck, M, Eng, CM, Giugliani, R, Harmatz, P, Martin, R, Ramaswami, U, Vellodi, A, Wraith, JE, Cleary, M, Gucsavas-Calikoglu, M, Puga, AC, Shinawi, M, Ulbrich, B, Vijayaraghavan, S, Wendt, S, Conway, AM, Rossi, A, Whiteman, DA & Kimura, A 2011, 'Long-term, open-labeled extension study of idursulfase in the treatment of Hunter syndrome', *Genet Med*, vol. 13, no. 2, Feb, pp. 95-101.

Muenzer, J, Wraith, JE, Beck, M, Giugliani, R, Harmatz, P, Eng, CM, Vellodi, A, Martin, R, Ramaswami, U, Gucsavas-Calikoglu, M, Vijayaraghavan, S, Wendt, S, Puga, AC, Ulbrich, B, Shinawi, M, Cleary, M, Piper, D, Conway, AM & Kimura, A 2006, 'A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome)', *Genet Med*, vol. 8, no. 8, Aug, pp. 465-473.

Mulla, SM, Miller, P, Agarwal, A, Khokhar, R, Mohiuddin, M, Sadeghi, B, Adams-Webber, T, Guyatt, G & Johnston, B 2014, 'Patient-reported outcomes in studies of patients with rare lysosomal storage diseases: a systematic survey', paper presented at Health Technology Assessment International, Washington DC, USA.

Myers, CE, Gatalica, Z, Spinelli, A, Castro, M, Linden, E, Sartor, O & Sargent, M 2014, 'Metastatic Cancer of Cowper's Gland: A Rare Cancer Managed Successfully by Molecular Profiling', *Case Rep Oncol*, vol. 7, no. 1, Jan, pp. 52-57.

National Cancer Institute 2014, *NCI Drug Dictionary*, National Institutes of Health, viewed 20 Nov 2014, <http://www.cancer.gov/drugdictionary>.

National Institute for Health and Care Excellence 2013, 'Interim process and methods of the highly specialised technologies programme', pp. 1-12, viewed 1 October 2014, <http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf>.

National Institute for Health and Clinical Excellence 2012, *The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care*, National Institute for Health and Clinical Excellence (NICE), London, UK.

National Institute of Neurological Disorders and Stroke 2014, *Lennox-Gastaut Syndrome Information Page*, NINDS, Maryland, US., viewed 4 Dec 2014, <http://www.ninds.nih.gov/disorders/lennoxgastautsyndrome/lennoxgastautsyndrome.htm>.

Ngorsuraches, S, Meng, W, Kim, BY & Kulsomboon, V 2012, 'Drug reimbursement decision-making in Thailand, China, and South Korea', *Value Health*, vol. 15, no. 1 Suppl, Jan-Feb, pp. S120-125.

NICE Citizens Council 2004, *Ultra Orphan Drugs*, NICE Citizens Council Reports, no. 4, National Institute for Clinical Excellence.

NICE Citizens Council 2008, *Departing from the threshold*, NICE Citizens Council Reports, NIfHaC Excellence.

Nicolino, M, Byrne, B, Wraith, JE, Leslie, N, Mandel, H, Freyer, DR, Arnold, GL, Pivnick, EK, Ottinger, CJ, Robinson, PH, Loo, JC, Smitka, M, Jardine, P, Tat•, L, Chabrol, B, McCandless, S, Kimura, S, Mehta, L, Bali, D, Skrinar, A, Morgan, C, Rangachari, L, Corzo, D & Kishnani, PS 2009, 'Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease', *Genet Med.*, vol. 11, no. 3, Mar, pp. 210-219. [Genetics in medicine : official journal of the American College of Medical Genetics].

Nicolino, M, Byrne, B, Wraith, JE, Leslie, N, Mandel, H, Freyer, DR, Arnold, GL, Pivnick, EK, Ottinger, CJ, Robinson, PH, Loo, JC, Smitka, M, Jardine, P, Tato, L, Chabrol, B, McCandless, S, Kimura, S, Mehta, L, Bali, D, Skrinar, A, Morgan, C, Rangachari, L, Corzo, D & Kishnani, PS 2009, 'Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease', *Genet Med*, vol. 11, no. 3, Mar, pp. 210-219.

Nord, E & Johansen, R 2014, 'Concerns for severity in priority setting in health care: A review of trade-off data in preference studies and implications for societal willingness to pay for a QALY', *Health Policy*, Feb 28.

Norheim, O, Baltussen, R, Johri, M, Chisholm, D, Nord, E, Brock, D, Carlsson, P, Cookson, R, Daniels, N, Danis, M, Fleurbaey, M, Johansson, K, Kapiriri, L, Littlejohns, P, Mbeeli, T, Rao, K, Edejer, TT-T & Wikler, D 2014, 'Guidance on priority setting in health care (GPS-Health): the inclusion of equity criteria not captured by cost-effectiveness analysis', *Cost Effectiveness and Resource Allocation*, vol. 12, no. 1, p. 18.

Norman, P 2013, 'Orphan drug approvals in Europe since 2001: An analysis by indication', *Expert Opinion on Orphan Drugs*, vol. 1, no. 2, pp. 131-139.

Ohtsuka, Y, Yoshinaga, H, Shirasaka, Y, Takayama, R, Takano, H & Iyoda, K 2014, 'Rufinamide as an adjunctive therapy for Lennox-Gastaut syndrome: A randomized double-blind placebo-controlled trial in Japan', *Epilepsy Res*, vol. 108, no. 9, Nov, pp. 1627-1636.

Oliveira, FL, Alegra, T, Dornelles, A, Krug, BC, Netto, CB, da, R, N, S, Picon, PD & Schwartz, IV 2013, 'Quality of life of brazilian patients with Gaucher disease and fabry disease', *JIMD Rep*, vol. 7, pp. 31-37.

Olowoyeye, A & Okwundu Charles, I 2014, 'Gene therapy for sickle cell disease', *Cochrane Database of Systematic Reviews*, no. 10, DOI 10.1002/14651858.CD007652.pub4, <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007652.pub4/abstract>.

Orlikowski, D, Pellegrini, N, Prigent, H, Laforet, P, Carlier, R, Carlier, P, Eymard, B, Lofaso, F & Annane, D 2011, 'Recombinant human acid alpha-glucosidase (rhGAA) in adult patients with severe respiratory failure due to Pompe disease', *Neuromuscular Disorders*, vol. 21, no. 7, Jul, pp. 477-482.

Orphanet 2015, *Orphan drugs in Australia*, viewed 10th February 2015, <http://www.orpha.net/consor/cgi-bin/Education\_AboutOrphanDrugs.php?lng=EN&stapage=ST\_EDUCATION\_EDUCATION\_ABOUTORPHANDRUGS\_AUS >.

Owen, A, Spinks, J, Meehan, A, Robb, T, Hardy, M, Kwasha, D, Wlodarczyk, J & Reid, C 2008, 'A new model to evaluate the long-term cost effectiveness of orphan and highly specialised drugs following listing on the Australian Pharmaceutical Benefits Scheme: the Bosentan Patient Registry', *J Med Econ*, vol. 11, no. 2, pp. 235-243.

Oxford Glycosciences 2002, *Research Update 2*, viewed 7th November 2014, <http://www.investegate.co.uk/article.aspx?id=200205021430154345V >.

Papadimas, GK, Spengos, K, Konstantinopoulou, A, Vassilopoulou, S, Vontzalidis, A, Papadopoulos, C, Michelakakis, H & Manta, P 2011, 'Adult Pompe disease: Clinical manifestations and outcome of the first Greek patients receiving enzyme replacement therapy', *Clinical Neurology and Neurosurgery*, vol. 113, no. 4, May, pp. 303-307.

Park, JS, Kim, HG, Shin, JH, Choi, YC & Kim, DS 2014, 'Effect of enzyme replacement therapy in late onset Pompe disease: open pilot study of 48 weeks follow-up', *Neurological Sciences*.

Parker, C, Omine, M, Richards, S, Nishimura, J-i, Bessler, M, Ware, R, Hillmen, P, Luzzatto, L, Young, N, Kinoshita, T, Rosse, W & Socié, G 2005, *Diagnosis and management of paroxysmal nocturnal hemoglobinuria*, vol. 106.

Pentek, M, Kosztolanyi, G, Melegh, B, Halasz, A, Pogany, G, Baji, P, Brodszky, V, Vartokne Hever, N, Boncz, I & Gulacsi, L 2014, '[Health related quality of life and disease burden of patients with cystic fibrosis and their caregivers: Results of the European BURQOL-RD survey in Hungary]', *Orv Hetil*, vol. 155, no. 42, Oct 1, pp. 1673-1684.

Pharmactical Benefits Advisory Committee 2013, *Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee*, Version 4.4 edn, Australian Government, Canberra.

Picavet, E, Cassiman, D & Simoens, S 2013, 'Do ultra-orphan medicinal products warrant ultra-high prices? A review', *Orphan Drugs: Research and Reviews*, vol. 3, pp. 23-31.

Prater, SN, Banugaria, SG, DeArmey, SM, Botha, EG, Stege, EM, Case, LE, Jones, HN, Phornphutkul, C, Wang, RY, Young, SP & Kishnani, PS 2012, 'The emerging phenotype of long-term survivors with infantile Pompe disease', *Genet Med*, vol. 14, no. 9, Sep, pp. 800-810.

Prater, SN, Patel, TT, Buckley, AF, Mandel, H, Vlodavski, E, Banugaria, SG, Feeney, EJ, Raben, N & Kishnani, PS 2013, 'Skeletal muscle pathology of infantile Pompe disease during long-term enzyme replacement therapy', *Orphanet Journal of Rare Diseases*, vol. 8, no. 1.

Pu, JJ & Brodsky, RA 2011, 'Paroxysmal nocturnal hemoglobinuria from bench to bedside', *Clin Transl Sci*, vol. 4, no. 3, Jun, pp. 219-224.

QML Pathology 2009, *Reference Manual*.

Raluy-Callado, M, Chen, W-H, Whiteman, DAH, Fang, J & Wiklund, I 2013, 'The impact of Hunter syndrome (mucopolysaccharidosis type II) on health-related quality of life', *Orphanet Journal of Rare Diseases*, vol. 8, 07/10

03/08/received

07/08/accepted, pp. 101-101.

Ramli, A, Aljunid, SM, Sulong, S & Md Yusof, FA 2013, 'National Drug Formulary review of statin therapeutic group using the multiattribute scoring tool', *Ther Clin Risk Manag*, vol. 9, pp. 491-504.

Rare Diseases Task Force 2011, *Patient registries in the Field of rare diseases. Overview of the issues surrounding the establishment, managment, governance and financing of academic registries.*, viewed 30/10/2014, <http://www.eucerd.eu/upload/file/RDTFRegistriesrev2011.pdf>.

Reardon, S 2014, 'Regulators adopt more orphan drugs', *Nature*, vol. 508, no. 7494, pp. 16-17.

Reese, JH 2014, 'Orphan Drug Designation 101', paper presented at Worldwide Orphan Medicinal Designation Workshop.

Reiss, UM, Schwartz, J, Sakamoto, KM, Puthenveetil, G, Ogawa, M, Bedrosian, CL & Ware, RE 2014, 'Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria', *Pediatr Blood Cancer*, vol. 61, Apr 29, pp. 1544-1550.

Resnick, T, Arzimanoglou, A, Brown, LW, Flamini, R, Kerr, M, Kluger, G, Kothare, S, Philip, S, Harrison, M & Narurkar, M 2011, 'Rufinamide from clinical trials to clinical practice in the United States and Europe', *Epileptic Disord*, vol. 13 Suppl 1, May, pp. S27-43.

Reynolds-Haertle, RA & McBride, R 1992, 'Single vs. double data entry in CAST', *Control Clin Trials*, vol. 13, no. 6, Dec, pp. 487-494.

Richeldi, L, du Bois, RM, Raghu, G, Azuma, A, Brown, KK, Costabel, U, Cottin, V, Flaherty, KR, Hansell, DM, Inoue, Y, Kim, DS, Kolb, M, Nicholson, AG, Noble, PW, Selman, M, Taniguchi, H, Brun, M, Le Maulf, F, Girard, M, Stowasser, S, Schlenker-Herceg, R, Disse, B & Collard, HR 2014, 'Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis', *N Engl J Med*, vol. 370, no. 22, May 29, pp. 2071-2082.

Rodriguez-Miguez, E & Pinto-Prades, JL 2002, 'Measuring the social importance of concentration or dispersion of individual health benefits', *Health Econ*, vol. 11, no. 1, Jan, pp. 43-53.

Rollet, P, Lemoine, A & Dunoyer, M 2013, 'Sustainable rare diseases business and drug access: no time for misconceptions', *Orphanet J Rare Dis*, vol. 8, p. 109.

Rombach, SM, Hollak, CE, Linthorst, GE & Dijkgraaf, MG 2013, 'Cost-effectiveness of enzyme replacement therapy for Fabry disease', *Orphanet J Rare Dis*, vol. 8, p. 29.

Rossi, M, Parenti, G, Della Casa, R, Romano, A, Mansi, G, Agovino, T, Rosapepe, F, Vosa, C, Del Giudice, E & Andria, G 2007, 'Long-term enzyme replacement therapy for pompe disease with recombinant human alpha-glucosidase derived from Chinese hamster ovary cells', *Journal of Child Neurology*, vol. 22, no. 5, pp. 565-573.

Roth, A, Hock, C, Konik, A, Christoph, S & Duhrsen, U 2011, 'Chronic treatment of paroxysmal nocturnal hemoglobinuria patients with eculizumab: safety, efficacy, and unexpected laboratory phenomena', *Int J Hematol*, vol. 93, no. 6, Jun, pp. 704-714.

Rothwell, PM 2005, 'External validity of randomised controlled trials: "to whom do the results of this trial apply?"', *Lancet*, vol. 365, no. 9453, Jan 1-7, pp. 82-93.

Sariyar, M, Borg, A, Heidinger, O & Pommerening, K 2013, 'A practical framework for data management processes and their evaluation in population-based medical registries', *Inform Health Soc Care*, vol. 38, no. 2, Mar, pp. 104-119.

Schaefer, RM, Tylki-Szymanska, A & Hilz, MJ 2009, 'Enzyme replacement therapy for Fabry disease: a systematic review of available evidence', *Drugs*, vol. 69, no. 16, pp. 2179-2205.

Schafer, W, Kroneman, M, Boerma, W, van den Berg, M, Westert, G, Deville, W & van Ginneken, E 2010, 'The Netherlands: health system review', *Health Syst Transit*, vol. 12, no. 1, pp. v-xxvii, 1-228.

Schiffmann, R, Hauer, P, Freeman, B, Ries, M, Scott, LJC, Polydefkis, M, Brady, RO, McArthur, JC & Wagner, K 2006, 'Enzyme replacement therapy and intraepidermal innervation density in fabry disease', *Muscle Nerve*, vol. 34, no. 1, pp. 53-56.

Schiffmann, R, Kopp, JB, Austin, HAr, Sabnis, S, Moore, DF, Weibel, T, Balow, JE & Brady, RO 2001, 'Enzyme replacement therapy in Fabry disease: a randomized controlled trial', *JAMA*, vol. 285, no. 21, Jun 6, pp. 2743-2749.

Schiffmann, R, Mankin, H, Dambrosia, JM, Xavier, RJ, Kreps, C, Hill, SC, Barton, NW & Rosenthal, DI 2002, 'Decreased bone density in splenectomized Gaucher patients receiving enzyme replacement therapy', *Blood Cells Mol Dis*, vol. 28, pp. 288-296.

Schubert, J, Hillmen, P, Roth, A, Young, NS, Elebute, MO, Szer, J, Gianfaldoni, G, Socie, G, Browne, P, Geller, R, Rother, RP & Muus, P 2008, 'Eculizumab, a terminal complement inhibitor, improves anaemia in patients with paroxysmal nocturnal haemoglobinuria', *Br J Haematol*, vol. 142, no. 2, Jun, pp. 263-272.

Sedehizadeh, S, Keogh, M & Maddison, P 2012, 'The use of aminopyridines in neurological disorders', *Clin Neuropharmacol*, vol. 35, no. 4, Jul-Aug, pp. 191-200.

Sharma, A, Easow Mathew, M, Sriganesh, V, Neely, JA & Kalipatnapu, S 2014, 'Gene therapy for haemophilia', *Cochrane Database Syst Rev*, vol. 11, Nov 14, p. CD010822.

Shea, BJ, Hamel, C, Wells, GA, Bouter, LM, Kristjansson, E, Grimshaw, J, Henry, DA & Boers, M 2009, 'AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews', *J Clin Epidemiol*, vol. 62, no. 10, Oct, pp. 1013-1020.

Shire Pharmaceuticals 2011, 'Elaprase(R) (idursulfase) and idursulfase-IT Periodic safety update report'.

Shire Pharmaceuticals 2013, *Periodic safety update report for Agalsidase Alfa (Replagal(R))*.

Shire Pharmaceuticals Ireland Ltd. 2014, *Periodic Safety Update Report (PSUR) for Velaglucerase alfa (VPRIV(R))*.

Simoens, S 2011, 'Pricing and reimbursement of orphan drugs: the need for more transparency', *Orphanet J Rare Dis*, vol. 6, p. 42.

Smid, BE, Rombach, SM, Aerts, JM, Kuiper, S, Mirzaian, M, Overkleeft, HS, Poorthuis, BJ, Hollak, CE, Groener, JE & Linthorst, GE 2011, 'Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients', *Orphanet J Rare Dis*, vol. 6, p. 69.

Socie, G, Schrezenmeier, H, Muus, P, Szer, J, Urbano-Ispizua, A, Maciejewski, JP, Brodsky, RA, Bessler, M, Kanakura, Y, Rosse, WF, Khursigara, G, Bedrosian, CL & Hillmen, P 2012, 'Eculizumab protects against te and prolongs survival in patients with paroxysmal nocturnal hemoglobinuria: An international PNH registry study', *Blood*, vol. 120, no. 21.

Song, P, Gao, J, Inagaki, Y, Kokudo, N & Tang, W 2012, 'Intractable and rare diseases research in Asia', *Biosci Trends*, vol. 6, no. 2, Apr, pp. 48-51.

Soo, M 2014, 'Pharmaceutical reimbursement environment in Korea: current and future', pp. 1-8, viewed 29 September 2014, <http://www.diahome.org/~/media/1F48DEEBD5A24C64B02803805C4C099F.ashx>.

Srivastava, AK 2014, 'Clinical relevance of stem cell therapies in amyotrophic lateral sclerosis', *Neurol India*, vol. 62, no. 3, May-Jun, pp. 239-248.

Starzyk, K, Richards, S, Yee, J, Smith, SE & Kingma, W 2007, 'The long-term international safety experience of imiglucerase therapy for Gaucher disease', *Mol Genet Metab*, vol. 90, pp. 157-163.

Stirnemann, J, Belmatoug, N, Vincent, C, Fain, O, Fantin, B & Mentre, F 2010, 'Bone events and evolution of biologic markers in Gaucher disease before and during treatment', *Arthritis Research and Therapy*, vol. 12, no. 4.

Stirnemann, J, Vigan, M, Hamroun, D, Heraoui, D, Rossi-Semerano, L, Berger, MG, Rose, C, Camou, F, de, R-S, Grosbois, B, Kaminsky, P, Robert, A, Caillaud, C, Froissart, R, Levade, T, Masseau, A, Mignot, C, Sedel, F, Dobbelaere, D, Vanier, MT, Valayanopoulos, V, Fain, O, Fantin, B, de, V, T, B, Mentre, F & Belmatoug, N 2012, 'The French Gaucher disease registry: clinical characteristics, complications and treatment of 562 patients', *Orphanet J Rare Dis*, vol. 7, p. 77.

Sugai, F, Kokunai, Y, Yamamoto, Y, Hashida, G, Shimazu, K, Mihara, M, Inoue, S & Sakoda, S 2010, 'Use of the muscle volume analyzer to evaluate enzyme replacement therapy in late-onset Pompe disease', *Journal of Neurology*, vol. 257, no. 3, Mar, pp. 461-463.

Sussex, J, Rollet, P, Garau, M, Schmitt, C, Kent, A & Hutchings, A 2013, 'A pilot study of multicriteria decision analysis for valuing orphan medicines', *Value Health*, vol. 16, no. 8, Dec, pp. 1163-1169.

Sussex, J, Rollet, P., Garau, M., Schmitt, C., Kent, A. and Hutchings, A 2013, 'Multi-criteria decision analysis to value orphan medicines. ', Office of Health Economics., London.

Swinney, DC & Xia, S 2014, 'The discovery of medicines for rare diseases', *Future Medicinal Chemistry*, vol. 6, no. 9, pp. 987-1002.

Terk, MR, Dardashti, S & Liebman, HA 2000, 'Bone marrow response in treated patients with Gaucher disease: evaluation by T1-weighted magnetic resonance images and correlation with reduction in liver and spleen volume', *Skeletal Radiol*, vol. 29, pp. 563-571.

The Department of Health 2015, 'Other supply arrangements outside the Pharmaceutical Benefits Scheme (PBS)', <http://www.health.gov.au/LSDP>.

The Pharmaceutical Benefits Scheme 2011, 'Framework for the introduction of a Managed Entry Scheme for submissions to the Pharmaceutical Benefits Advisory Committee', <http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-PBAC-submissions>.

Therapeutic Goods Administration 2010a, *Product Information: Cerezyme*.

Therapeutic Goods Administration 2010b, 'Product Information: Fabrazyme(R)', <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04342-3>.

Therapeutic Goods Administration 2010c, *Product Information: Replagal(R) (agalsidase alfa ghu)*.

Therapeutic Goods Administration 2012a, *Myozyme Product Information*, Canberra.

Therapeutic Goods Administration 2012b, *Product Information: VPRIV(R) (velaglucerase alfa ghu)*.

Therapeutic Goods Administration 2014, *Solaris Product Information*, Canberra.

Therapeutic Goods Administration 2015, *TGA Orphan Drugs Program discussion paper*, DoH Therapeutic Goods Administration, Australian Government.

Thurberg, BL, Byers, HR, Granter, SR, Phelps, RG, Gordon, RE & O'Callaghan, M 2004, 'Monitoring the 3-year efficacy of enzyme replacement therapy in Fabry disease by repeated skin biopsies<p>', *J. Invest. Dermatol.*, vol. 122, no. 4, pp. 900-908.

Thurberg, BL, Rennke, H, Colvin, RB, Dikman, S, Gordon, RE, Collins, AB, Desnick, RJ & O'Callaghan, M 2002, 'Globotriaosylceramide accumulation in the fabry kidney is cleared from multiple cell types after enzyme replacement therapy', *Kidney International*, vol. 62, no. 6, pp. 1933-1946.

TKT, I 2003, 'Replgal TM (agalsidase alfa)', *Briefing Document*, <http://www.fda.gov/ohrms/dockets/ac/03/briefing/3917B2\_01\_TKT%20Replagal%20Background%20.pdf>.

Tony, M, Wagner, M, Khoury, H, Rindress, D, Papastavros, T, Oh, P & Goetghebeur, MM 2011, 'Bridging health technology assessment (HTA) with multicriteria decision analyses (MCDA): field testing of the EVIDEM framework for coverage decisions by a public payer in Canada', *BMC Health Serv Res*, vol. 11, p. 329.

Toscano, A & Schoser, B 2013, 'Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review', *Journal of Neurology*, vol. 260, no. 4, Apr, pp. 951-959.

Tsang, R, Colley, L & Lynd, LD 2009, 'Inadequate statistical power to detect clinically significant differences in adverse event rates in randomized controlled trials', *J Clin Epidemiol*, vol. 62, no. 6, Jun, pp. 609-616.

Tsuchiya, A 2012, 'Distributional judgements in the context of economic evaluation.', in J AM (ed.), *The Elgar Companion to Health Economics*, Cheltenham, UK, pp. 406-414.

Valayannopoulos, V, Nicely, H, Harmatz, P & Turbeville, S 2010, 'Mucopolysaccharidosis VI', *Orphanet Journal of Rare Diseases*, vol. 5, , pp. 5-5.

van Capelle, CI, van der Beek, NA, de Vries, JM, van Doorn, PA, Duivenvoorden, HJ, Leshner, RT, Hagemans, ML & van der Ploeg, AT 2012, 'The quick motor function test: a new tool to rate clinical severity and motor function in Pompe patients', *J Inherit Metab Dis*, vol. 35, no. 2, Mar, pp. 317-323.

van Capelle, CI, van der Beek, NA, Hagemans, ML, Arts, WF, Hop, WC, Lee, P, Jaeken, J, Frohn-Mulder, IM, Merkus, PJ, Corzo, D, Puga, AC, Reuser, AJ & van der Ploeg, AT 2010, 'Effect of enzyme therapy in juvenile patients with Pompe disease: a three-year open-label study', *Neuromuscul Disord*, vol. 20, no. 12, Dec, pp. 775-782.

van Capelle, CI, Winkel, LPF, Hagemans, MLC, Shapira, SK, Arts, WFM, van Doorn, PA, Hop, WCJ, Reuser, AJJ & van der Ploeg, AT 2008, 'Eight years experience with enzyme replacement therapy in two children and one adult with Pompe disease', *Neuromuscular Disorders*, vol. 18, no. 6, Jun, pp. 447-452.

Van Der Ploeg, AT, Clemens, PR, Corzo, D, Escolar, DM, Florence, J, Groeneveld, G, Herson, S, Kishnani, PS, Laforet, P, Lake, SL, Lange, DJ, Leshner, RT, Mayhew, JE, Morgan, C, Nozaki, K, Park, DJ, Pestronk, A, Rosenbloom, B, Skrinar, A, Van Capelle, CI, Van Der Beek, NA, Wasserstein, M & Zivkovic, SA 2010, 'A randomized study of alglucosidase alfa in late-onset Pompe's disease', *N. Engl. J. Med.*, vol. 362, no. 15, //, pp. 1396-1406.

van Dussen, L, Biegstraaten, M, Dijkgraaf, MG & Hollak, CE 2014, 'Modelling Gaucher disease progression: long-term enzyme replacement therapy reduces the incidence of splenectomy and bone complications', *Orphanet J Rare Dis*, vol. 9, no. 1, p. 112.

van Dussen, L, Biegstraaten, M, Hollak, CE & Dijkgraaf, MG 2014, 'Cost-effectiveness of enzyme replacement therapy for type 1 Gaucher disease', *Orphanet J Rare Dis*, vol. 9, p. 51.

Vedder, AC, Linthorst, GE, Houge, G, Groener, JEM, Ormel, EE, Bouma, BJ, Aerts, JMFG, Hirth, A & Hollak, CEM 2007, 'Treatment of fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg', *PLoS ONE*, vol. 2, no. 7.

Vegter, S, Rozenbaum, MH, Postema, R, Tolley, K & Postma, MJ 2010, 'Review of regulatory recommendations for orphan drug submissions in the netherlands and scotland: Focus on the underlying pharmacoeconomic evaluations', *Clinical Therapeutics*, vol. 32, no. 9, pp. 1651-1661.

Verrotti, A, Loiacono, G, Ballone, E, Mattei, PA, Chiarelli, F & Curatolo, P 2011, 'Efficacy of rufinamide in drug-resistant epilepsy: a meta-analysis', *Pediatr Neurol*, vol. 44, no. 5, May, pp. 347-349.

Visschers, RGJ, van Gemert, WG & Olde Damink, SWM 2011, 'Orphan diseases neglected: The faith of intestinal failure', *e-SPEN*, vol. 6, no. 5, pp. e232-e234.

Wagner, M 2014, 'Methodological development of a comprehensive MCDA framework based on real life issues in appraisal of treatments for rare diseases', paper presented at Health Technology Assessment International, Washington DC, USA.

Wailoo, A, Tsuchiya, A & McCabe, C 2009, 'Weighting must wait: incorporating equity concerns into cost-effectiveness analysis may take longer than expected', *PharmacoEconomics*, vol. 27, no. 12, pp. 983-989.

Waldek, S, Patel, MR, Banikazemi, M, Lemay, R & Lee, P 2009, 'Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry', *Genet Med*, vol. 11, no. 11, 11//print, pp. 790-796.

Walter, S, Weinschenk, T, Stenzl, A, Zdrojowy, R, Pluzanska, A, Szczylik, C, Staehler, M, Brugger, W, Dietrich, PY, Mendrzyk, R, Hilf, N, Schoor, O, Fritsche, J, Mahr, A, Maurer, D, Vass, V, Trautwein, C, Lewandrowski, P, Flohr, C, Pohla, H, Stanczak, JJ, Bronte, V, Mandruzzato, S, Biedermann, T, Pawelec, G, Derhovanessian, E, Yamagishi, H, Miki, T, Hongo, F, Takaha, N, Hirakawa, K, Tanaka, H, Stevanovic, S, Frisch, J, Mayer-Mokler, A, Kirner, A, Rammensee, HG, Reinhardt, C & Singh-Jasuja, H 2012, 'Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival', *Nat Med*, vol. 18, no. 8, Aug, pp. 1254-1261.

Weinreb, NJ, Deegan, P, Kacena, KA, Mistry, P, Pastores, GM, Velentgas, P & vom Dahl, S 2008, 'Life expectancy in Gaucher disease type 1', *Am J Hematol*, vol. 83, no. 12, pp. 896-900.

Welker, JA 2007, 'Implementation of electronic data capture systems: barriers and solutions', *Contemp Clin Trials*, vol. 28, no. 3, May, pp. 329-336.

Wennberg, DE, Lucas, FL, Birkmeyer, JD, Bredenberg, CE & Fisher, ES 1998, 'Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics', *JAMA*, vol. 279, no. 16, Apr 22-29, pp. 1278-1281.

White, W 2013, *The bright future of orphan drugs*, Siren Interactive, , Chicago, IL, viewed 26th November 2014, <http://www.sireninteractive.com/sirensong/the-bright-future-of-orphan-drugs/>.

Wilcken, B 2001, 'Rare diseases and the assessment of intervention: what sorts of clinical trials can we use?', *J Inherit Metab Dis*, vol. 24, no. 2, Apr, pp. 291-298.

Wilcox, WR, Banikazemi, M, Guffon, N, Waldek, S, Lee, P, Linthorst, GE, Desnick, RJ & Germain, DP 2004, 'Long-term safety and efficacy of enzyme replacement therapy for Fabry disease', *Am J Hum Genet*, vol. 75, no. 1, Jul, pp. 65-74.

Winkel, LP, Hagemans, ML, van Doorn, PA, Loonen, MC, Hop, WJ, Reuser, AJ & van der Ploeg, AT 2005, 'The natural course of non-classic Pompe's disease; a review of 225 published cases', *J Neurol*, vol. 252, no. 8, Aug, pp. 875-884.

Winkel, LPF, Van den Hout, JMP, Kamphoven, JHJ, Disseldorp, JAM, Remmerswaal, M, Arts, WFM, Loonen, MCB, Vulto, AG, Van Doorn, PA, De Jong, G, Hop, W, Smit, GPA, Shapira, SK, Boer, MA, van Diggelen, OP, Reuser, AJJ & Van der Ploeg, AT 2004, 'Enzyme replacement therapy in late-onset Pompe's disease: A three-year follow-up', *Annals of Neurology*, vol. 55, no. 4, Apr, pp. 495-502.

Wlodarczyk, J, Reid, CM & Pater, G 2011, 'Funding linked to ongoing research: impact of the bosentan patient registry on pricing in Australia', *Value Health*, vol. 14, no. 6, Sep-Oct, pp. 961-963.

Woodcock, J 2012, 'The Future of Orphan Drug Development', *Clinical Pharmacology & Therapeutics*, vol. 92, no. 2, pp. 146-148.

Wraith, JE, Clarke, LA, Beck, M, Kolodny, EH, Pastores, GM, Muenzer, J, Rapoport, DM, Berger, KI, Swiedler, SJ, Kakkis, ED, Braakman, T, Chadbourne, E, Walton-Bowen, K & Cox, GF 2004, 'Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase)', *Journal of Pediatrics*, vol. 144, no. 5, pp. 581-588, DOI 10.1016/j.jpeds.2004.01.046, <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/621/CN-00469621/frame.html>.

Wraith, JE & Jones, S 2014, 'Mucopolysaccharidosis type I', *Pediatr Endocrinol Rev*, vol. 12 Suppl 1, Sep, pp. 102-106.

Wraith, JE, Scarpa, M, Beck, M, Bodamer, OA, De Meirleir, L, Guffon, N, Meldgaard Lund, A, Malm, G, Van der Ploeg, AT & Zeman, J 2008, 'Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy', *European Journal of Pediatrics*, vol. 167, no. 3, 11/23

06/22/received

10/29/revised

10/29/accepted, pp. 267-277.

Wyatt, K, Henley, W, Anderson, L, Anderson, R, Nikolaou, V, Stein, K, Klinger, L, Hughes, D, Waldek, S, Lachmann, R, Mehta, A, Vellodi, A & Logan, S 2012a, 'The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders', *Health Technol Assess*, vol. 16, no. 39, pp. 1-543.

Wyatt, K, Henley, W, Anderson, L, Anderson, R, Nikolaou, V, Stein, K, Klinger, L, Hughes, D, Waldek, S, Lachmann, R, Mehta, A, Vellodi, A & Logan, S 2012b, 'The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders', *Health Technology Assessment*, vol. 16, no. 39, pp. 1-543.

Yang, C-C, Chien, Y-H, Lee, N-C, Chiang, S-C, Lin, S-P, Kuo, Y-T, Chen, S-S, Jong, Y-J & Hwu, W-L 2011, 'Rapid progressive course of later-onset Pompe disease in Chinese patients', *Molecular Genetics and Metabolism*, vol. 104, no. 3, Nov, pp. 284-288.

Youngkong, S, Baltussen, R, Tantivess, S, Mohara, A & Teerawattananon, Y 2012, 'Multicriteria decision analysis for including health interventions in the universal health coverage benefit package in Thailand', *Value Health*, vol. 15, no. 6, Sep-Oct, pp. 961-970.

Zimran, A, Morris, E, Mengel, E, Kaplan, P, Belmatoug, N, Hughes, DA, Malinova, V, Heitner, R, Sobreira, E, Mrsic, M, Granovsky-Grisaru, S, Amato, D & vom, D 2009, 'The female Gaucher patient: the impact of enzyme replacement therapy around key reproductive events (menstruation, pregnancy and menopause)', *Blood Cells Mol Dis*, vol. 43, pp. 264-288.

# GLOSSARY AND ABBREVIATIONS

|  |  |
| --- | --- |
| 3MSC | 3-minute stair climb |
| 6MWT | 6-minute walk test |
| 12MWT | 12-minute walk test |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AHI | Apnoea/hypopnea index |
| AMSTAR | Assessing the Methodological Quality of Systematic Reviews |
| CRIM | Cross-reactive immunologic material |
| ECG | Electrocardiogram |
| eGFR | estimated glomerular filtration rate |
| EOW | Every other week |
| ERT | Enzyme replacement therapy |
| FDA | Food and Drug Administration |
| FVC | Forced vital capacity |
| GAG | Glycosaminoglycans |
| GFR | Glomerular filtration rate |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| Hb | Haemoglobin |
| HS | Horizon Scanning |
| IAR | Infusion associated reaction |
| INAHTA | International Network of Agencies for Health Technology Assessment |
| ITI | Immune tolerance induction |
| ITT | Intention to treat |
| IV | Intravenously |
| LSDP | Life Saving Drugs Programme |
| LVMI | Left ventricular mass index |
| MD | Mean difference |
| NHMRC | National Health and Medical Research Council |
| NR | Not reported |
| NS | Not significant |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PBPA | Pharmaceutical Benefits Pricing Authority |
| PI | TGA-approved Product Information |
| PNH | Paroxysmal nocturnal haematuria |
| RCT | randomised controlled trial |
| RR | Relative risk |
| SD | Standard deviation |
| SE | Standard error |
| SR | Systematic review |
| TE | thromboembolic |
| TEAEs | treatment emergent adverse events |
| TGA | Therapeutic Goods Administration |
| ToR | Term(s) of Reference |

# APPENDIX A 2009 Outcomes of Life Saving Drugs Programme Review

## Background

The Life Saving Drugs Programme (LSDP) provides free access for eligible patients to expensive and lifesaving drugs for serious medical conditions. Drugs included on the LSDP have been shown to be effective in extending the lifespan of patients suffering from life-threatening diseases. There are no other suitable, cost-effective therapies or drugs available through the Pharmaceutical Benefits Scheme (PBS) for the conditions treated under the LSDP.

In 2009, the Australian Government completed a review of the LSDP. The purpose of the review was to examine the LSDP with a view to establishing consistent and rigorous procedures and ensuring sustainability. The terms of reference for the review specified that it was to be conducted with reference to the Government’s Expenditure Review principles of appropriateness, effectiveness, efficiency, performance assessment, integration and strategic policy alignment.

The Government has now considered the outcomes of the review and made a number of decisions on how the programme should continue. This paper summarises the outcomes of the review and the Government decisions that have been made. The status of decisions, where relevant, is also described.

Importantly, the Government has agreed to continue to supply all currently available drugs for eligible patients through the LSDP. The Government’s other decisions largely relate to enhancing performance reporting; strengthening the Government’s ability to negotiate better value for money with medicine suppliers; and improving programme governance and administration.

The Review was informed by a range of information and views, including clinical literature and research; international policies, guidelines and experiences; and through consultation with many stakeholders in the programme, such as Australian Government Departments, the Pharmaceutical Benefits Advisory Committee (PBAC), the Pharmaceutical Benefits Pricing Authority (PBPA), industry representatives, expert clinicians and consumer representatives.

Given the breadth of issues explored through the review, and raised independently by stakeholders in consultation and submissions, the Government anticipates giving further consideration to improving the programme’s operations and administration in the future. The Government has noted that stakeholders’ feedback and comments included issues that were outside of the formal terms of reference, and intends to continue to review these matters.

### The appropriateness of the LSDP

Scope

The eligibility criteria for the LSDP do not place any restrictions on the range of conditions to be treated or the types of pharmaceutical therapies. However, at the time of the review, the Programme had funded six enzyme replacement therapies (ERTs) for about 150 patients with five separate lysosomal storage disorders, which are rare inherited enzyme deficiencies.

Since then, in September 2009, the Government added Zavesca® (miglustat), an oral therapy, to the LSDP for the treatment of certain patients with Gaucher disease (in addition to the existing ERT that is available through the LSDP for eligible patients with Gaucher disease).

No decisions have been made to limit or expand the scope of the programme.

Procedures

In considering whether to fund a medicine through the LSDP, the Government requires that applications be submitted to an independent expert body - the PBAC. The PBAC must consider the evidence presented by the medicine sponsor; conclude that the medicine is not cost-effective (and therefore not suitable for listing on the PBS); and then find that the medicine meets the LSDP criteria. Positive findings are then considered by the Government for funding.

In submissions to the review, pharmaceutical companies in particular raised concerns that this process is lengthy and untargeted - due to the PBAC process and submission requirements being tailored for cost-effectiveness purposes for PBS listings.

In response to the review, the Government has reaffirmed the use of the PBAC to provide independent and expert advice on the funding of drugs through the LSDP, with regard to the programme criteria. However, the Government also acknowledged that it would be timely to review the LSDP criteria. The Government will consult with key stakeholders on any proposed changes.

The Government intends to also review the information and data that is required by the PBAC, to ensure that relevant information is being requested and considered in a targeted manner. These matters will be addressed in 2010.

### Administration of the programme funding

The LSDP differs from the PBS, as it is administered through Annual Appropriation Bills rather than a specific legislative basis. That is, the Government provides funding for the Programme each year under an annual appropriation item approved by Parliament.

The review considered the demand-driven nature of expenditure under the LSDP, and the Government’s challenge in monitoring and budgeting for such expenditure under yearly, capped appropriation (as provided by Annual Appropriation Bills).

The Government has agreed to provide the Department with greater flexibility in managing expenditure for each drug within the programme’s yearly appropriation (funding). This decision does not have any implications for stakeholders outside of the Government.

### The effectiveness of the LSDP

The approaches taken to evaluate the clinical and cost effectiveness of the medicines available through the LSDP, including data quality and availability, was a key issue considered by the review.

The review found that overall the programme has been effective in assisting patients with rare, serious medical conditions to gain access to expensive medicines which either improve the patient’s condition or in some cases simply assist in stabilisation of the condition so that further deterioration is avoided. The review concluded that the medicines were all effective as life-saving therapy.

# Appendix B PRISMA flowcharts (ToR 1)

## Gaucher disease

Figure 3 PRISMA flowchart for literature on Gaucher Type I disease (imiglucerase, velaglucerase alfa and miglustat)

Figure 3 PRISMA flowchart for literature on Gaucher Type I disease (imiglucerase, velaglucerase alfa and miglustat)

RT = enzyme replacement therapy; PICO = population, intervention, comparator, outcome criteria

## Fabry disease

Figure 4 PRISMA flowchart for literature on Fabry disease (agalsidase alfa, agalsidase beta)

Figure 4 PRISMA flowchart for literature on Fabry disease (agalsidase alfa, agalsidase beta)

HTA = health technology assessment

aReasons for exclusion of HTA and SR are described in the systematic review section of this report.

## Infantile Onset Pompe Disease

Figure 5 PRISMA flowchart for Infantile Onset Pompe Disease (alglucosidase alfa)

Figure 5 PRISMA flowchart for Infantile Onset Pompe Disease (alglucosidase alfa)

## Juvenile Onset Pompe Disease

Figure 6  PRISMA flowchart for literature on Juvenile Onset Pompe Disease (alglucosidase alfa)

Figure 6 PRISMA flowchart for literature on Juvenile Onset Pompe Disease (alglucosidase alfa)

## Mucopolysaccharidosis Types I, II and VI

Figure 7 PRISMA flowchart for literature on Mucopolysaccharidosis Types I, II and VI disease (laronidase, idursulfase, galsulfase)

Figure 7 PRISMA flowchart for literature on Mucopolysaccharidosis Types I, II and VI disease (laronidase, idursulfase, galsulfase)

HTA = health technology assessment

aExcluded studies meeting inclusion criteria are listed in Appendix C excluded studies (ToR 1) according to reason for exclusion.

## Paroxysmal Nocturnal Haematuria

Figure 7 PRISMA flowchart for literature on PNH (eculizumab)

Figure 8 PRISMA flowchart for literature on PNH (eculizumab)

# Appendix C excluded studies (ToR 1)

Studies which did not meet the PICO criteria were excluded, and have not been listed below. Some studies may have met the PICO criteria, but were excluded from the systematic review, due to duplicated data, being in a foreign language (and not appearing to be a higher level of evidence than available in English), being only a conference abstract, being a lower level of evidence (i.e. being more at risk of bias than other study designs, and hence excluded in favour of higher level evidence). These studies are listed below.

## Type I Gaucher disease (imiglucerase and velaglucerase alfa)

### Duplicated data

Ben, T, Gonzalez, DE, Zimran, A, Kabra, M, Lukina, EA, Giraldo, P, Kisinovsky, I, Bavdekar, A, Ben, D, M, F, Gupta, N, Kishnani, PS, Sureshkumar, EK, Wang, N, Crombez, E, Bhirangi, K & Mehta, A 2011, 'Achievement of therapeutic goals in patients with type 1 Gaucher disease (GD1) on velaglucerase alfa or imiglucerase: Phase III trial HGT-GCB-039 and extension', *Journal of Inherited Metabolic Disease*, vol. 34, p. S224. (same study as Ben, T. et al (2013), but with less information)

### Cohort study

Casal, JA, Lacerda, L, Perez, LF, Pinto, RA, Miranda, MCS & Tutor, JC 2002, 'Relationship between serum markers on monocyte/macrophage activation in type 1 Gaucher disease', *Clinical Chemistry and Laboratory Medicine*, vol. 40, pp. 52-55.

Doneda, D, Lopes, AL, Oliveira, AR, Netto, CB, Moulin, CC & Schwartz, IV 2011, 'Gaucher disease type I: assessment of basal metabolic rate in patients from southern Brazil', *Blood Cells Mol Dis*, vol. 46, pp. 42-46.

Erba, PA, Minichilli, F, Giona, F, Linari, S, Dambrosia, J, Pierini, A, Filocamo, M, Di, R, Buffoni, F, Brady, RO & Mariani, G 2013, 'Tc-99m-Sestamibi Scintigraphy to Monitor the Long-Term Efficacy of Enzyme Replacement Therapy on Bone Marrow Infiltration in Patients with Gaucher Disease', *Journal of Nuclear Medicine*, vol. 54, pp. 1717-1724.

Giraldo, P, Irun, P, Alfonso, P, Dalmau, J, Fernandez-Galan, MA, Figueredo, A, Hernandez-Rivas, JM, Julia, A, Luno, E, Marin-Jimenez, F, Martin-Nunez, G, Montserrat, JL, de la, S, Vidaller, A, Villalon, L & Pocovi, M 2011, 'Evaluation of Spanish Gaucher disease patients after a 6-month imiglucerase shortage', *Blood Cells Mol Dis*, vol. 46, pp. 115-118.

Grigorescu-Sido, P, Drugan, C, Alkhzouz, C, Zimmermann, A, Coldea, C, Denes, C, Grigorescu, MD, Cret, V & Bucerzan, S 2010, 'Baseline characteristics and outcome in Romanian patients with Gaucher disease type 1', *Eur J Intern Med*, vol. 21, pp. 104-113.

Grosbois, B, Rose, C, Noel, E, Serratrice, CdR, Dobbelaere, D, Gressin, V, Cherin, P, Hartmann, A, Javier, RM, Clerson, P, Hachulla, E & Jaussaud, R 2009, 'Gaucher disease and monoclonal gammopathy: A report of 17 cases and impact of therapy', *Blood Cells, Molecules, and Diseases*, vol. 43, pp. 138-139.

Hollak, C, Maas, M, Akkerman, E, den, H & Aerts, H 2001, 'Dixon quantitative chemical shift imaging is a sensitive tool for the evaluation of bone marrow responses to individualized doses of enzyme supplementation therapy in type 1 Gaucher disease', *Blood Cells Mol Dis*, vol. 27, pp. 1005-1012.

Kauli, R, Zaizov, R, Lazar, L, Pertzelan, A, Laron, Z, Galatzer, A, Phillip, M, Yaniv, Y & Cohen, IJ 2000, 'Delayed growth and puberty in patients with Gaucher disease type 1: Natural history and effect of splenectomy and/or enzyme replacement therapy', *Israel Medical Association Journal*, vol. 2, pp. 158-163.

Mistry, PK, Sirrs, S, Chan, A, Pritzker, MR, Duffy, TP, Grace, ME, Meeker, DP & Goldman, ME 2002, 'Pulmonary hypertension in type 1 Gaucher disease: genetic and epigenetic determinants of phenotype and response to therapy', *Mol Genet Metab*, vol. 77, pp. 91-98.

Oliveira, FL, Alegra, T, Dornelles, A, Krug, BC, Netto, CB, da, R, N, S, Picon, PD & Schwartz, IV 2013, 'Quality of life of brazilian patients with Gaucher disease and fabry disease', *JIMD Rep*, vol. 7, pp. 31-37.

Stirnemann, J, Boutten, A, Vincent, C, Mekinian, A, Heraoui, D, Fantin, B, Fain, O, Mentre, F & Belmatoug, N 2011, 'Impact of imiglucerase on the serum glycosylated-ferritin level in Gaucher disease', *Blood Cells Mol Dis*, vol. 46, pp. 34-38.

Stirnemann, J, Vigan, M, Hamroun, D, Heraoui, D, Rossi-Semerano, L, Berger, MG, Rose, C, Camou, F, de, R-S, Grosbois, B, Kaminsky, P, Robert, A, Caillaud, C, Froissart, R, Levade, T, Masseau, A, Mignot, C, Sedel, F, Dobbelaere, D, Vanier, MT, Valayanopoulos, V, Fain, O, Fantin, B, de, V, T, B, Mentre, F & Belmatoug, N 2012, 'The French Gaucher disease registry: clinical characteristics, complications and treatment of 562 patients', *Orphanet J Rare Dis*, vol. 7, p. 77.

Terk, MR, Dardashti, S & Liebman, HA 2000, 'Bone marrow response in treated patients with Gaucher disease: evaluation by T1-weighted magnetic resonance images and correlation with reduction in liver and spleen volume', *Skeletal Radiol*, vol. 29, pp. 563-571.

van, B, M, J, de, F, Voerman, JSA, Laman, JD, Boot, RG, Maas, M, Hollak, CEM, Aerts, JM & Rezaee, F 2007, 'Increased plasma macrophage inflammatory protein (MIP)-1(alpha) and MIP-1(beta) levels in type 1 Gaucher disease', *Biochimica et Biophysica Acta - Molecular Basis of Disease*, vol. 1772, pp. 788-796.

Vom, D, Monnighoff, I & Haussinger, D 2000, 'Decrease of plasma taurine in Gaucher disease and its sustained correction during enzyme replacement therapy', *Amino Acids*, vol. 19, pp. 585-592.

Wenstrup, RJ, Kacena, KA, Kaplan, P, Pastores, GM, Prakash-Cheng, A, Zimran, A & Hangartner, TN 2007, 'Effect of enzyme replacement therapy with imiglucerase on BMD in type 1 Gaucher disease', *J Bone Miner Res*, vol. 22, pp. 119-126.

Zimran, A, Morris, E, Mengel, E, Kaplan, P, Belmatoug, N, Hughes, DA, Malinova, V, Heitner, R, Sobreira, E, Mrsic, M, Granovsky-Grisaru, S, Amato, D & vom, D 2009, 'The female Gaucher patient: the impact of enzyme replacement therapy around key reproductive events (menstruation, pregnancy and menopause)', *Blood Cells Mol Dis*, vol. 43, pp. 264-288.

### Dose comparison (two doses of same treatment, without alternative treatment as comparator)

Altarescu, G, Schiffmann, R, Parker, CC, Moore, DF, Kreps, C, Brady, RO & Barton, NW 2000, 'Comparative efficacy of dose regimens in enzyme replacement therapy of type I Gaucher disease', Blood Cells Molecules and Diseases, vol. 26, pp. 285-290.

Chien, YH, Lee, NC, Tsai, FJ, Chao, MC & Hwu, WL 2010, 'Reduction in imiglucerase dosage causes immediate rise of chitotriosidase activity in patients with Gaucher disease', Mol Genet Metab, vol. 101, pp. 90-91.

Cole, A, Weinreb, N, Rosenbloom, B, Andersson, H, Tripuraneni, R & Belmatoug, N 2011, 'An analysis from the ICGG gaucher registry: A report of gaucher patients affected by reduced doses of imiglucerase', Pharmacoepidemiology and Drug Safety, vol. 20, p. S69.

de, F, Aerts, JM, Groener, JE, Maas, M, Akkerman, EM, Wiersma, MG & Hollak, CE 2007, 'Low frequency maintenance therapy with imiglucerase in adult type I Gaucher disease: a prospective randomized controlled trial', Haematologica, vol. 92, pp. 215-221.

Deroma, L, Sechi, A, Dardis, A, Macor, D, Liva, G, Ciana, G & Bembi, B 2013, 'Did the temporary shortage in supply of imiglucerase have clinical consequences? Retrospective observational study on 34 italian Gaucher type I patients', JIMD Rep, vol. 7, pp. 117-122.

Elstein, D, Enciu, CA, Fontaine, L & Piwko, C 2013, 'Impact of velaglucerase alfa on quality of life of adult patients with type-I gaucher disease', Value in Health, vol. 16, p. A108.

Ferreira, AC & Sequeira, S 2011, 'Effects of a shortage of imiglucerase on three patients with type I Gaucher disease', Journal of Inherited Metabolic Disease, vol. 34, p. S222.

Gonzalez, DE, Turkia, HB, Lukina, EA, Kisinovsky, I, Dridi, MF, Elstein, D, Zahrieh, D, Crombez, E, Bhirangi, K, Barton, NW & Zimran, A 2013, 'Enzyme replacement therapy with velaglucerase alfa in Gaucher disease: Results from a randomized, double-blind, multinational, Phase 3 study', Am J Hematol, vol. 88, pp. 166-171.

Grabowski, G, Kacena, K, Hollak, CEM, Zhang, L, Yee, J, Mistry, P, Zimran, A, Charrow, J & vom, D 2008, 'Dose-response relationships for enzyme replacement therapy with imiglucerase/alglucerase in patients with Gaucher disease type I', Molecular Genetics and Metabolism, vol. 93, pp. S23-S23.

Kishnani, PS 2008, 'A Multicenter, Randomized, Dose Frequency Study of the Safety and Efficacy of Cerezyme (R) Infusions Every 4 Weeks Versus Every 2 Weeks in the Maintenance Therapy of Patients with Type 1 Gaucher Disease', Blood, vol. 112, pp. 460-460.

Kishnani, PS, DiRocco, M, Kaplan, P, Mehta, A, Pastores, GM, Smith, SE, Puga, AC, Lemay, RM & Weinreb, NJ 2009, 'A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1', Mol Genet Metab, vol. 96, pp. 164-170.

Perez-Calvo, J, Giraldo, P, Pastores, GM, Fernandez-Galan, M, Martin-Nunez, G & Pocovi, M 2003, 'Extended interval between enzyme therapy infusions for adult patients with Gaucher disease type 1', J Postgrad Med, vol. 49, pp. 127-131.

Zimran, A, Elstein, D, Levy-Lahad, E, Zevin, S, Abrahamov, A & et al. 1995, 'Replacement therapy with imiglucerase for type 1 Gaucher disease', Lancet, vol. 345, pp. 1479-1480.

Zimran, A, Gonzalez, D, Crombez, E & Bhirangi, K 2010, 'Enzyme replacement therapy with velaglucerase alfa improves key clinical parameters in a pediatric subgroup with type 1 Gaucher disease', Molecular Genetics and Metabolism, vol. 99, pp. S40-S41.

Zimran, A, Lukina, A, Ben, D, M, F, Kisinovsky, I, Crombez, E, Bhirangi, K, Elstein, D & Gonzalez, E 2010, 'Enzyme replacement therapy with velaglucerase alfa significantly improves key clinical parameters in type 1 gaucher disease: Positive results from a randomized, double-blind, global, phase III study', Haematologica, vol. 95, pp. 75-76.

### Eratum

Burrow, TA & Grabowski, GA 2012, 'Erratum: Velaglucerase alfa in the treatment of Gaucher disease type 1 (Clinical Investigation (2011) 1:2 (285-293))', Clinical Investigation, vol. 2, p. 951.

### Systematic review

Cadth 2011, 'Eliglustat tartrate, miglustat, imiglucerase, velaglucerase or a combination of these for the treatment of gaucher disease: a review of clinical effectiveness and safety (Structured abstract)', *Health Technology Assessment Database*.

Connock, M, Burls, A, Frew, E, Fry-Smith, A, Juarez-Garcia, A, McCabe, C, Wailoo, A, Abrams, K, Cooper, N, Sutton, A, O'Hagan, A & Moore, D 2006, 'The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher disease: a systematic review (Structured abstract)', *Health Technology Assessment Database*, p. 1.

Hayes & Inc 2013, 'VPRIV (Velaglucerase Alfa for Injection; Shire Human Genetic Therapies Inc.) for type 1 gaucher disease (Structured abstract)', *Health Technology Assessment Database*.

Morris, JL 2012, 'Velaglucerase alfa for the management of type 1 Gaucher disease', *Clin Ther*, vol. 34, pp. 259-271.

Piran, S & Amato, D 2010, 'Gaucher disease: a systematic review and meta-analysis of bone complications and their response to treatment', *J Inherit Metab Dis*, vol. 33, pp. 271-279.

Starzyk, K, Richards, S, Yee, J, Smith, SE & Kingma, W 2007, 'The long-term international safety experience of imiglucerase therapy for Gaucher disease', *Mol Genet Metab*, vol. 90, pp. 157-163.

Vom, D, Poll, L, Di, R, Ciana, G, Denes, C, Mariani, G & Maas, M 2006, 'Evidence-based recommendations for monitoring bone disease and the response to enzyme replacement therapy in Gaucher patients', *Current Medical Research and Opinion*, vol. 22, pp. 1045-1064.

### Case series

Andersson, H 2009, 'Alglucerase (Ceredase) and imiglucerase (Cerezyme) in Gaucher disease', *P and T*, vol. 34, p. 93.

Andersson, H, Kaplan, P, Kacena, K & Yee, J 2008, 'Eight-year clinical outcomes of long-term enzyme replacement therapy for 884 children with Gaucher disease type 1', *Pediatrics*, vol. 122, pp. 1182-1190.

Arikan-Ayyildiz, Z, Yuce, A, Emre, S, Baysoy, G, Saltik-Temizel, IN & Gurakan, F 2011, 'Outcome of enzyme replacement therapy in Turkish patients with Gaucher disease: does late intervention affect the response?', *Turk J Pediatr*, vol. 53, pp. 499-507.

Arikan-Ayyildiz, Z, Yuce, A, Uslu-Kizilkan, N, Demir, H & Gurakan, F 2011, 'Immunoglobulin abnormalities and effects of enzyme replacement therapy in children with Gaucher disease', *Pediatr Blood Cancer*, vol. 56, pp. 664-666.

Balwani, M, Cox, TM, Drelichman, G, Cravo, R, Martins, AM, Lukina, E, Rosenbloom, BE, Ross, LH, Angell, J & Puga, AC 2013, 'Encore: A Randomized, Controlled, Open-Label Non-Inferiority Study Comparing Eliglustat To Imiglucerase In Gaucher Disease Type 1 Patients On Enzyme Replacement Therapy Who Have Reached Therapeutic Goals', *Blood*, vol. 122, no. 21, pp. 3468-3468.

Barton, NW, Pastores, G, Dambrosia, JM, Brady, RO & et al. 1995, 'Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources AU - Grabowski GA', *Ann. Intern. Med.*, vol. 122, pp. 33-39.

Bembi, B, Ciana, G, Mengel, E, Terk, MR, Martini, C & Wenstrup, RJ 2002, 'Bone complications in children with Gaucher disease', *British Journal of Radiology*, vol. 75, pp. A37-A43.

Benedik-Dolnicar, M & Kitanovski, L 2011, 'Individualized long-term enzyme therapy for Gaucher disease type 1 in Slovenia', *Pediatr Int*, vol. 53, pp. 1018-1022.

Brunel-Guitton, C, Rivard, GE, Galipeau, J, Alos, N, Miron, MC, Therrien, R, Mitchell, G, Lapierre, G & Lambert, M 2009, 'Enzyme replacement therapy in pediatric patients with Gaucher disease: What should we use as maintenance dosage?', *Molecular Genetics and Metabolism*, vol. 96, pp. 73-76.

Camelo, J, Cravo, R, Cabello, F, Drelichman, G, Kerstenetzky, M, Sarmiento, I & Linares, A 2013, 'Long-term imiglucerase/alglucerase treatment in Latin American children with type 1 Gaucher disease: Lessons from the International Collaborative Gaucher Group (ICGG) Gaucher Registry', *Molecular Genetics and Metabolism*, vol. 108, pp. S28-S28.

Cappellini, M, Belmatoug, N, Cole, A, vom Dahl, S, Deegan, P, Goldblatt, J, Rosenbloom, B, Tylki-Szymañska, A, Weinreb, N & Zimran, A 2010, 'Determinants of persisting thrombocytopenia in patients with type 1 Gaucher disease treated with alglucerase/imiglucerase for 4–5 years', *Blood*, vol. 116, no. 21, pp. 4719-4719.

Cappellini, M, Belmatoug, N, Cole, A, vom Dahl, S, Deegan, P, Goldblatt, J, Rosenbloom, B, van Dussen, L, Tylki-Szymańska, A & Weinreb, N 2011, 'Determinants of persisting thrombocytopenia in patients with type 1 Gaucher disease treated with imiglucerase for 4-5 years', *Haematologica*, vol. 96, no. Suppl. 2, pp. 326-326.

Charrow, J, Dulisse, B, Grabowski, GA & Weinreb, NJ 2007, 'The effect of enzyme replacement therapy on bone crisis and bone pain in patients with type 1 Gaucher disease', *Clinical Genetics*, vol. 71, pp. 205-211.

Chippington, S, McHugh, K & Vellodi, A 2008, 'Splenic nodules in paediatric Gaucher disease treated by enzyme replacement therapy', *Pediatr Radiol*, vol. 38, pp. 657-660.

Ciana, G, Deroma, L, Franzil, AM, Dardis, A & Bembi, B 2012, 'Long-term bone mineral density response to enzyme replacement therapy in a retrospective pediatric cohort of Gaucher patients', *J Inherit Metab Dis*, vol. 35, pp. 1101-1106.

Cole, A, Weinreb, N, Balwani, M, Charrow, J, Tripuraneni, R, Villalobos, J, Kerstenetzky, M & Hollak, C 2011, 'Clinical outcomes of imiglucerase after 10 years of treatment', *Pharmacoepidemiology and Drug Safety*, vol. 20, p. S69.

Deegan, PB, Pavlova, E, Tindall, J, Stein, PE, Bearcroft, P, Mehta, A, Hughes, D, Wraith, JE & Cox, TM 2011, 'Osseous manifestations of adult gaucher disease in the era of enzyme replacement therapy', *Medicine*, vol. 90, pp. 52-60.

Denes, CL, Munteanu, D, Popita, V, Drugan, C & Grigorescu-Sido, P 2009, 'Imaging findings of the outcome of enzyme replacement therapy in Romanian patients with type 1 Gaucher disease', *Clinical Therapeutics*, vol. 31, p. S201.

Dowley, M 2013, 'Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment', *Annals of Clinical Biochemistry*, vol. 50, p. 507.

El-Beshlawy, A, Ragab, L, Youssry, I, Yakout, K, El-Kiki, H, Eid, K, Mansour, IM, Abd, E-H, Yang, M & Mistry, PK 2006, 'Enzyme replacement therapy and bony changes in Egyptian pediatric Gaucher disease patients', *J. Inherited Metab. Dis.*, vol. 29, pp. 92-98.

Elstein, D, Abrahamov, A, Hadas-Halpern, I, Meyer, A & Zimran, A 1998, 'Low-dose low-frequency imiglucerase as a starting regimen of enzyme replacement therapy for patients with type I Gaucher disease', *QJM*, vol. 91, pp. 483-488.

Elstein, D, Abrahamov, A, Hadas-Halpern, I & Zimran, A 2000, 'Withdrawal of enzyme replacement therapy in Gaucher disease', *British Journal of Haematology*, vol. 110, pp. 488-492.

Elstein, D, Ben, T, Gonzalez, DE, Kabra, M, Lukina, EA & Giraldo, P 2012, 'Bone mineral density in adults with type 1 gaucher disease receiving velaglucerase alfa 60 U/KG every other week: 2-year results [abstract]', *Journal of Inherited Metabolic Disease*, vol. 35 Suppl 1, pp. S150, Abstract no: P-410.

Elstein, D, Cohn, G, Zahrieh, D, Crombez, E & Zimran, A 2013, 'A 7-year open-label study of clinical parameters and therapeutic goals in patients with type 1 Gaucher disease receiving treatment with velaglucerase alfa: Updating the long-term experience with velaglucerase alfa', *Molecular Genetics and Metabolism*, vol. 108, pp. S37-S37.

Elstein, D, Cohn, GM, Wang, N, Djordjevic, M, Brutaru, C & Zimran, A 2011, 'Early achievement and maintenance of the therapeutic goals using velaglucerase alfa in type 1 Gaucher disease', *Blood Cells Mol Dis*, vol. 46, pp. 119-123.

Elstein, D, Crombez, E, Zahrieh, D, Wang, N & Zimran, A 2014, '7-year safety and efficacy with velaglucerase alfa for treatment-naive adult patients with type 1 Gaucher disease', *Molecular Genetics and Metabolism*, vol. 111, pp. S40-S41.

Elstein, D, Haims, AH, Zahrieh, D, Cohn, GM & Zimran, A 2012, 'Impact of Velaglucerase Alfa Therapy on Bone Marrow Burden Score in Adults with Type 1 Gaucher Disease: 7-Year Experience', *European Working Group for Gaucher Disease (EWGGD)*.

Elstein, D, Haims, AH, Zahrieh, D, Cohn, GM & Zimran, A 2014, 'Impact of velaglucerase alfa on bone marrow burden score in adult patients with type 1 Gaucher disease: 7-year follow-up', *Blood Cells Mol Dis*, vol. 53, pp. 56-60.

Elstein, D, Hughes, D, Goker-Alpan, O, Stivel, M, Baris, HN, Cohen, IJ, Granovsky-Grisaru, S, Samueloff, A, Mehta, A & Zimran, A 2014, 'Outcome of pregnancies in women receiving velaglucerase alfa for Gaucher disease', *J Obstet Gynaecol Res*, vol. 40, pp. 968-975.

Elstein, D, Turkia, HB, Kabra, M, Giraldo, P, Ben, D, M, F, Gupta, N, Zahrieh, D, Crombez, E & Zimran, A 2012, 'Achievement of therapeutic goals over 2 years of velaglucerase alfa enzyme replacement therapy in patients with type 1 gaucher disease', *Molecular Genetics and Metabolism*, vol. 105, p. S28.

Elstein, D, Zimran, A, Cohn, MG & Bhirangi, K 2010, 'Five-year safety and efficacy of velaglucerase alfa in Gaucher disease type 1: Experience in clinic and home settings', *Molecular Genetics and Metabolism*, vol. 99, p. S18.

Erdemir, G, Ozkan, T, Ozgur, T, Yazici, Z & Ozdemir, O 2011, 'Pediatric Gaucher experience in South Marmara region of Turkey', *Turk J Gastroenterol*, vol. 22, pp. 500-504.

Fraticelli, P, Bonifazi, M, Lucci, M, Giori, S & Gabrielli, A 2009, 'Clinical response to low-frequency maintenance therapy with imiglucerase (Cerezyme(registered trademark)) in three adult patients with stabletype 1 Gaucher disease', *Clinical Therapeutics*, vol. 31, p. S206.

Giona, F, Palumbo, G, Amendola, A, Santoro, C & Mazzuconi, MG 2006, 'Platelet function and coagulation abnormalities in type 1 Gaucher disease patients: Effects of enzyme replacement therapy (ERT) [2]', *Journal of Thrombosis and Haemostasis*, vol. 4, pp. 1831-1833.

Giraldo, P, Solano, V, Perez-Calvo, JI, Giralt, M & Rubio-Felix, D 2005, 'Quality of life related to type 1 Gaucher disease: Spanish experience', *Quality of Life Research*, vol. 14, pp. 453-462.

Giraldo, P, Zimran, A, Mehta, A, Hughes, D, Hangartner, TN, Wang, N, Cohn, GM, Crombez, E & Elstein, D 2014, 'Safety and efficacy of long-term velaglucerase alfa therapy in treatment-naive adults with type 1 Gaucher disease: results from Phase III trials', *Molecular Genetics and Metabolism*, vol. 111, pp. S47-S47.

Goitein, O, Elstein, D, Abrahamov, A, Hadas-Halpern, I, Melzer, E, Kerem, E & Zimran, A 2001, 'Lung involvement and enzyme replacement therapy in Gaucher disease', *QJM*, vol. 94, pp. 407-415.

Goker-Alpan, O, Kasmani, S, Farwah, A & Alpan, O 2011, 'First year of clinical therapeutic experience using velaglucerase-alpha for the treatment of Gaucher disease', *Journal of Inherited Metabolic Disease*, vol. 34, p. S225.

Goldblatt, J, Fletcher, JM, McGill, J, Szer, J & Wilson, M 2011, 'Enzyme replacement therapy "drug holiday": results from an unexpected shortage of an orphan drug supply in Australia', *Blood Cells Mol Dis*, vol. 46, pp. 107-110.

Goldblatt, J, Szer, J, Fletcher, JM, McGill, J, Rowell, JA & Wilson, M 2005, 'Enzyme replacement therapy for Gaucher disease in Australia', *Intern Med J*, vol. 35, pp. 156-161.

Grabowski, GA, Barton, NW, Pastores, G, Dambrosia, JM, Banerjee, TK, McKee, MA, Parker, C, Schiffmann, R, Hill, SC & Brady, RO 1995, 'Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources', *Ann Intern Med*, vol. 122, pp. 33-39.

Grigorescu, S, Drugan, C, Cret, V, Al-Kzouz, C, Denes, C, Coldea, C & Zimmermann, A 2007, 'Outcome of enzyme replacement therapy in patients with Gaucher disease type I. The Romanian experience', *J Inherit Metab Dis*, vol. 30, pp. 783-789.

Grinzaid, KA, Geller, E, Hanna, SL, Elsas, LJ & nd 2002, 'Cessation of enzyme replacement therapy in Gaucher disease', *Genet Med*, vol. 4, pp. 427-433.

Gupta, N, Kabra, M, Shrivastava, R & Vashist, S 2009, 'Enzyme replacement therapy with imiglucerase in Indian patients with Gaucher disease', *Molecular Genetics and Metabolism*, vol. 96, p. S26.

Hangartner, T, Weinreb, N, Kaplan, P, Cole, JA, Gwosdow, A & Mistry, P 2010, 'Osteopenia in gaucher disease develops early in life: Response to imiglucerase enzyme therapy in children, adolescents and adults', *Journal of Bone and Mineral Research*, vol. 25, p. S216.

Hollak, CE, Belmatoug, N, Cole, JA, Vom, D, Deegan, PB, Goldblatt, J, Rosenbloom, B, van, D, Tylki-Szymanska, A, Weinreb, NJ, Zimran, A & Cappellini, MD 2012, 'Characteristics of type I Gaucher disease associated with persistent thrombocytopenia after treatment with imiglucerase for 4-5 years', *Br J Haematol*, vol. 158, pp. 528-538.

Hsu, CC, Chien, YH, Lai, MY & Hwu, WL 2002, 'Enzyme replacement therapy with imiglucerase in Taiwanese patients with type I Gaucher disease', *J Formos Med Assoc*, vol. 101, pp. 627-631.

Ida, H, Rennert, OM, Kobayashi, M & Eto, Y 2001, 'Effects of enzyme replacement therapy in thirteen Japanese paediatric patients with Gaucher disease', *European Journal of Pediatrics*, vol. 160, pp. 21-25.

Javier, RM, Hachulla, E, Rose, C, Gressin, V, Cherin, P, Noel, E, de, R-S, Dobbelaere, D, Hartmann, A, Jaussaud, R, Clerson, P, Grosbois, B & Roux, C 2011, 'Vertebral fractures in Gaucher disease type I: data from the French "Observatoire" on Gaucher disease (FROG)', *Osteoporosis International*, vol. 22, pp. 1255-1261.

Khalifa, AS, Tantawy, AA, Shawky, RM, Monir, E, Elsayed, SM, Fateen, E & Cooper, A 2011, 'Outcome of enzyme replacement therapy in children with Gaucher disease: The Egyptian experience', *Egyptian Journal of Medical Human Genetics*, vol. 12, pp. 9-14.

Kishnani, P, Crissman, B & Mackey, J 2008, 'Effect of dose of enzyme replacement therapy with imiglucerase on bone crises in adolescents with Gaucher disease', *Molecular Genetics and Metabolism*, vol. 93, pp. S27-S27.

Komninaka, V, Kolomodi, D, Marinakis, T, Repa, K, Christoulas, D, Voskaridou, E, Dimopoulos, MA & Terpos, E 2012, 'Replacement therapy with imiglucerase improves magnetic resonance imaging (MRI) abnormalities in almost half patients with non-neuronopathic form of gaucher disease after twelve months of therapy: Results of a semi-quantitative MRI method', *Blood*, vol. 120.

Lebel, E, Dweck, A, Foldes, AJ, Golowa, Y, Itzchaki, M, Zimran, A & Elstein, D 2004, 'Bone density changes with enzyme therapy for Gaucher disease', *J Bone Miner Metab*, vol. 22, pp. 597-601.

Mandala, E, Lafaras, C, Tsioni, K, Michelakaki, H, Koutalidou, S & Ilonidis, G 2009, 'Enzyme replacement therapy in type 1 Gaucher disease: A single center's experience', *Clinical Therapeutics*, vol. 31, pp. S209-S210.

Mehta, A, Turkia, HB, Gonzalez, DE, Kabra, M, Lukina, EA, Giraldo, P, Kisinovsky, I, Bavdekar, A, Ben, D, M, F, Gupta, N, Kishnani, PS, Sureshkumar, EK, Barton, N, Wang, N, Crombez, E, Bhirangi, K & Zimran, A 2011, 'Two-year safety and tolerability of velaglucerase alfa in patients with type 1 Gaucher disease, including patients switched from imiglucerase: Phase III trial HGT-GCB-039 and extension', *Blood*, vol. 118.

Milligan, A, Baker, R, Cooke, J, Hughes, D, Richfield, L & Mehta, A 2011, 'Clinical experience (pre and post licensing) in previously ERT-naove patients receiving velaglucerase alfa for type 1 Gaucher disease', *Journal of Inherited Metabolic Disease*, vol. 34, p. S222.

Mistry, PK, Weinreb, NJ, Kaplan, P, Cole, JA, Gwosdow, AR & Hangartner, T 2010, 'Osteopenia in Gaucher disease develops early in life: Response to imiglucerase enzyme therapy in children, adolescents and adults', *Journal of Inherited Metabolic Disease*, vol. 33, p. S127.

Mitrovic, M, Sumarac, Z, Antic, D, Bogdanovic, A, Elezovic, I, Vukosavljevic, D, Ignjatovic, S, Majkic-Singh, N & Suvajdzic, N 2012, 'Markers of coagulation activation and enhanced fibrinolysis in Gaucher type 1 patient: Effects of enzyme replacement therapy', *Blood Cells, Molecules, and Diseases*, vol. 49, pp. 58-59.

Mitrovic, M, Suvajdzic, V, Elezovic, I, Miljic, P, Sumarac, Z, Janic, D, Djordjevic, M, Petakov, M, Nikolic, T, Rodic, P & Djunic, I 2010, 'Platelet function and coagulation abnormalities in type 1 gaucher patients: Effects of enzyme replacement therapy', *Haematologica*, vol. 95, p. 70.

Mota, RM & Mankin, H 2007, 'Use of plain radiography to optimize skeletal outcomes in children with type 1 Gaucher disease in Brazil', *J Pediatr Orthop*, vol. 27, pp. 347-350.

Mrsic, M, Stavljenic-Rukavina, A, Fumic, K, Labar, B, Bogdanic, V, Potocki, K, Kardum-Skelin, I & Rovers, D 2003, 'Management of Gaucher disease in a post-communist transitional health care system: Croatian experience', *Croat Med J*, vol. 44, pp. 606-609.

Nagral, A, Mewawalla, P, Jagadeesh, S, Kabra, M, Phadke, SR, Verma, IC, Puri, RD, Gupta, N, Kishnani, PS & Mistry, PK 2011, 'Recombinant macrophage targeted enzyme replacement therapy for Gaucher disease in India', *Indian Pediatr*, vol. 48, pp. 779-784.

Parisi, MS, Mastaglia, SR, Bagur, A, Goldstein, G, Zeni, SN & Oliveri, B 2008, 'Body composition and bone metabolism in young Gaucher disease type I patients treated with imiglucerase', *Eur J Med Res*, vol. 13, pp. 31-38.

Pastores, GM, Rosenbloom, B, Weinreb, N, Goker-Alpan, O, Grabowski, G, Cohn, GM & Zahrieh, D 2014, 'A multicenter open-label treatment protocol (HGT-GCB-058) of velaglucerase alfa enzyme replacement therapy in patients with Gaucher disease type 1: safety and tolerability', *Genet Med*, vol. 16, pp. 359-366.

Pastores, GM, Rosenbloom, BE, Weinreb, NJ, Goker-Alpan, O, Mardach, R, Lipson, M, Ibrahim, J, Cohn, GM, Zahrieh, D & Mistry, PK 2011, 'Report on the safety of velaglucerase alfa enzyme replacement therapy in patients with type 1 Gaucher disease and the transition from clinic to home infusions during treatment protocol HGT-GCB-058', *Blood*, vol. 118.

Patlas, M, Hadas-Halpern, I, Abrahamov, A, Elstein, D & Zimran, A 2002, 'Spectrum of abdominal sonographic findings in 103 pediatric patients with Gaucher disease', *European Radiology*, vol. 12, pp. 397-400.

Poll, LW, Koch, JA, vom, D, Willers, R, Scherer, A, Boerner, D, Niederau, C, Haussinger, D & Modder, U 2001, 'Magnetic resonance imaging of bone marrow changes in Gaucher disease during enzyme replacement therapy: first German long-term results', *Skeletal Radiol*, vol. 30, pp. 496-503.

Poll, LW, Koch, JA, Willers, R, Aerts, H, Scherer, A, Haussinger, D, Modder, U & Vom, D 2002, 'Correlation of bone marrow response with hematological, biochemical, and visceral responses to enzyme replacement therapy of nonneuronopathic (type 1) Gaucher disease in 30 adult patients', *Blood Cells, Molecules, and Diseases*, vol. 28, pp. 209-220.

Poll, LW, Maas, M, Terk, MR, Roca-Espiau, M, Bembi, B, Ciana, G & Weinreb, NJ 2002, 'Response of Gaucher bone disease to enzyme replacement therapy', *British Journal of Radiology*, vol. 75, pp. A25-A36.

Repa, C, Marinakis, TH, Tsaftaridis, P, Karkalousos, P, Komninaka, V, Athanassaki, K, Michelakakis, H, Anagnostopoulos, NI & Symeonidis, A 2009, 'Treatment of Gaucher disease in greek adult patients: Long-term experience of a collaborative study of enzyme replacement therapy', *Clinical Therapeutics*, vol. 31, p. S210.

Robertson, PL, Maas, M & Goldblatt, J 2007, 'Semiquantitative assessment of skeletal response to enzyme replacement therapy for Gaucher disease using the bone marrow burden score', *AJR Am J Roentgenol*, vol. 188, pp. 1521-1528.

Rudzki, Z, Okon, K, Machaczka, M, Rucinska, M, Papla, B & Skotnicki, AB 2003, 'Enzyme replacement therapy reduces Gaucher cell burden but may accelerate osteopenia in patients with type I disease - a histological study', *Eur J Haematol*, vol. 70, pp. 273-281.

Serratrice, C, Bengherbia, M, Alessandrini, M, Grosbois, B, Camou, F, Pers, YM, Bismuth, M, Marie, I, Belmatoug, N & Berger, M 2014, 'Effects of switching from imiglucerase to velaglucerase alfa without dose reduction nor wash out in type 1 Gaucher disease', *Blood Cells Mol Dis*, vol. 53, pp. 94-96.

Shehi, B, Bocari, G, Vyshka, G, Xhepa, R & Alushani, D 2011, 'Gaucher disease in Albanian Children: Casuistics and Treatment', *Iran J Pediatr*, vol. 21, pp. 1-7.

Sims, KB, Pastores, GM, Weinreb, NJ, Barranger, J, Rosenbloom, BE, Packman, S, Kaplan, P, Mankin, H, Xavier, R, Angell, J, Fitzpatrick, MA & Rosenthal, D 2008, 'Improvement of bone disease by imiglucerase (Cerezyme) therapy in patients with skeletal manifestations of type 1 Gaucher disease: results of a 48-month longitudinal cohort study', *Clin Genet*, vol. 73, pp. 430-440.

Stirnemann, J, Heraoui, D, Vincent, C, Fain, O, Fantin, B, Mentre, F & Belmatoug, N 2010, 'Bone events in type 1 Gaucher disease before and during treatment', *Arthritis and Rheumatism*, vol. 62, p. 1653.

Terk, MR, Dardashti, S & Liebman, HA 2000, 'Bone marrow response in treated patients with Gaucher disease: evaluation by T1-weighted magnetic resonance images and correlation with reduction in liver and spleen volume', *Skeletal Radiol*, vol. 29, pp. 563-571.

Tukan, I, Hadas-Halpern, I, Altarescu, G, Abrahamov, A, Elstein, D & Zimran, A 2013, 'Achievement of therapeutic goals with low-dose imiglucerase in Gaucher disease: a single-center experience', *Adv Hematol*, vol. 2013, p. 151506.

Vairo, F, Alegra, T, Dornelles, A, Mittelstadt, S, Netto, CB & Schwartz, IV 2012, 'Hyperimmunoglobulinemia in pediatric Gaucher patients in Southern Brazil', *Pediatric Blood and Cancer*, vol. 59, pp. 339-339.

van, B, M, J, de, F, Voerman, JSA, Laman, JD, Boot, RG, Maas, M, Hollak, CEM, Aerts, JM & Rezaee, F 2007, 'Increased plasma macrophage inflammatory protein (MIP)-1(alpha) and MIP-1(beta) levels in type 1 Gaucher disease', *Biochimica et Biophysica Acta - Molecular Basis of Disease*, vol. 1772, pp. 788-796.

Weinreb, N, Balwanib, M, Charrowc, J, Coled, A, Tripuranenid, R, Villalobose, J, Kerstenetzkyf, M & Hollakg, C 2011, 'Continued efficacy of cerezyme after 10 years of treatment', *Molecular Genetics and Metabolism*, vol. 102, p. S45.

Weinreb, N & Invest, CZS 2008, 'Effect of enzyme replacement therapy with imiglucerase (Cerezyme.) every 4 weeks in patients with type I Gaucher disease', *Molecular Genetics and Metabolism*, vol. 93, pp. S41-S41.

Weinreb, N, Taylor, J, Cox, T, Yee, J & vom, D 2008, 'A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase', *Am J Hematol*, vol. 83, pp. 890-895.

Weinreb, NJ 2010, 'Achievement of therapeutic goals and severity scoring in Type 1 Gaucher disease', *International Journal of Clinical Pharmacology and Therapeutics*, vol. 48, pp. S20-S21.

Weinreb, NJ, Barranger, J, Packman, S, Prakash-Cheng, A, Rosenbloom, B, Sims, K, Angell, J, Skrinar, A & Pastores, GM 2007, 'Imiglucerase (Cerezyme(registered trademark)) improves quality of life in patients with skeletal manifestations of Gaucher disease', *Clinical Genetics*, vol. 71, pp. 576-588.

Weinreb, NJ, Charrow, J, Andersson, HC, Kaplan, P, Kolodny, EH, Mistry, P, Pastores, G, Rosenbloom, BE, Scott, CR, Wappner, RS & Zimran, A 2002, 'Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry', *Am J Med*, vol. 113, pp. 112-119.

Weinreb, NJ, Goldblatt, J, Villalobos, J, Charrow, J, Cole, JA, Kerstenetzky, M, vom, D & Hollak, C 2013, 'Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment', *J Inherit Metab Dis*, vol. 36, pp. 543-553.

—— 2014, 'Erratum: Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment (Journal of Inherited Metabolic Disease (2013) 36 (543-553) DOI 10.1007/s10545-012-9528-4)', *Journal of Inherited Metabolic Disease*, vol. 37, p. 147.

Weinreb, NJ, Vom, D & Cappellini, MD 2009, 'Long-term data from the ICGG gaucher registry: Clinical parameters after 10 years of treatment with imiglucerase', *Blood*, vol. 114.

Wilson, C, Spearing, R, Teague, L, Robertson, P & Blacklock, H 2007, 'The outcome of clinical parameters in adults with severe Type I Gaucher disease using very low dose enzyme replacement therapy', *Mol Genet Metab*, vol. 92, pp. 131-136.

Wine, E, Yaniv, I & Cohen, IJ 2007, 'Hyperimmunoglobulinemia in pediatric-onset type 1 Gaucher disease and effects of enzyme replacement therapy', *J Pediatr Hematol Oncol*, vol. 29, pp. 451-457.

Zaman, T & Moradian, R 2010, 'The effect of long-term imiglucerase treatment on children with Gaucher disease', *Journal of Inherited Metabolic Disease*, vol. 33, p. S146.

Zimmermann, A, Grigorescu-Sido, P, Rossmann, H, Lackner, KJ, Drugan, C, Al, K, Bucerzan, S, Nascu, I, Zimmermann, T, Leucuta, D & Weber, MM 2013, 'Dynamic changes of lipid profile in Romanian patients with Gaucher disease type 1 under enzyme replacement therapy: a prospective study', *J Inherit Metab Dis*, vol. 36, pp. 555-563.

Zimran, A, Altarescu, G, Philips, M, Attias, D, Jmoudiak, M, Deeb, M, Wang, N, Bhirangi, K, Cohn, GM & Elstein, D 2010, 'Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience', *Blood*, vol. 115, pp. 4651-4656.

Zimran, A, Giraldo, P, Zahrieh, D, Crombez, E, Cohn, G & Elstein, D 2013, 'Corrigendum to abstract "Bone mineral density change in type 1 Gaucher disease adults given velaglucerase alfa for 2years" [Molecular Genetics and Metabolism 108/2 (2013) S101]', *Molecular Genetics and Metabolism*, vol. 109, p. 119.

Zimran, A, Giraldo, P, Zahrieh, D, Crombez, E, Cohn, G, Elstein, D & Investiga Tkt Hgt Gcb, S 2013, 'Bone mineral density change in type 1 Gaucher disease adults given velaglucerase alfa for 2 years', *Molecular Genetics and Metabolism*, vol. 108, pp. S101-S101.

Zimran, A, Hughes, D, Elstein, D, Smith, L, Harmatz, P, Rhead, W, Giraldo, P, Mendelsohn, N, Park, C-H & Zahrieh, D 2013, 'Linear growth over 2 years of velaglucerase alfa therapy in children with type 1 Gaucher disease previously treated with imiglucerase', *6th International Conference on Children's Bone Health,* Rotterdam, Netherlands, vol. 2013, p. P133.

Zimran, A, Kabra, M, Giraldo, P, Dridi, MFB, Elstein, D, Gupta, N, Zahrieh, D, Crombez, E & Turkia, HB 2012, 'Safety and efficacy of velaglucerase alfa in patients with type 1 gaucher disease: 2 years of treatment in phase III trials and an extension study', *Molecular Genetics and Metabolism*, vol. 105, p. S69.

Zimran, A, Kishnani, P, Elstein, D, Gonzalez, DE, Zahrieh, D, Crombez, E & Cohn, GM 2013, 'Exploratory assessment of growth and bone marrow burden in a pooled subgroup of paediatric patients with type 1 Gaucher disease treated with long-term velaglucerase alfa', *Journal of Inherited Metabolic Disease*, vol. 36, p. S302.

Zimran, A, Kisinovsky, I, Lukina, EA, Elstein, D, Zahrieh, D, Crombez, E & Giraldo, P 2013, 'Efficacy of long-term velaglucerase alfa on haematological and visceral parameters in patients with type 1 Gaucher disease', *Journal of Inherited Metabolic Disease*, vol. 36, p. S302.

Zimran, A, Pastores, GM, Tylki-Szymanska, A, Hughes, DA, Elstein, D, Mardach, R, Eng, C, Smith, L, Heisel-Kurth, M, Charrow, J, Harmatz, P, Fernhoff, P, Rhead, W, Longo, N, Giraldo, P, Ruiz, JA, Zahrieh, D, Crombez, E & Grabowski, GA 2013, 'Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase', *Am J Hematol*, vol. 88, pp. 172-178.

### Switched case series (case series of patients switched from imiglucerase to another treatment)

Bembi, B, Sechi, A, Dardis, A, Deroma, L, Macor, D, Liva, G & Ciana, G 2013, 'Clinical follow-up in a group of Gaucher type I patients switching enzyme replacement therapy from imiglucerase to velaglucerase', *Molecular Genetics and Metabolism*, vol. 108, pp. S23-S24.

Braudeau, C, Graveleau, J, Rimbert, M, Neel, A, Hamidou, M, Grosbois, B, Besancon, A, Giraudet, S, Terrien, C, Josien, R & Masseau, A 2013, 'Altered innate function of plasmacytoid dendritic cells restored by enzyme replacement therapy in Gaucher disease', *Blood Cells, Molecules, and Diseases*, vol. 50, pp. 281-288.

Crombez, E, Kishnani, P, Ben, T, Gonzalez, D, Zimran, A, Kabra, M, Lukina, E, Giraldo, P, Kisinovsky, I, Bavdekar, A, Ben, D, M, F & Gupta, N 2012, 'Two-year efficacy and safety of velaglucerase alfa in patients with type 1 gaucher disease switching from imiglucerase: Phase III trial HGT-GCB-039 and extension', *Molecular Genetics and Metabolism*, vol. 105, pp. S25-S26.

Drelichman, G, Ponce, E, Basack, N, Freigeiro, D, Aversa, L, Graciela, E & Kohan, R 2007, 'Clinical Consequences of Interrupting Enzyme Replacement Therapy in Children with Type 1 Gaucher Disease', *Journal of Pediatrics*, vol. 151, pp. 197-201.

Elstein, D, Giraldo, P, Mehta, A, Pastores, G, Rhead, W, Smith, L, Wang, N, Crombez, E & Zimran, A 2014, 'Safety and efficacy of long-term enzyme replacement therapy with velaglucerase alfa in patients with type 1 Gaucher disease transitioned from imiglucerase', *Molecular Genetics and Metabolism*, vol. 111, pp. S41-S42.

Giraldo, P, Grabowski, G & Pastores, G 2010, 'Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase', *Eur Working Group Gaucher Dis-9th International Meeting (June 30–July 3, Cologne)*.

Grabowski, A, Pastores, G, Mardach, R, Eng, C, Smith, L, Fernhoff, P, Charrow, J, Heisel-Kurth, M, Longo, N, Rhead, W, Harmatz, P, Mehta, A, Giraldo, P, Tylki-Szymanska, A, Crombez, E & Zimran, A 2010, 'Safety and efficacy of velaglucerase alfa in patients with gaucher disease type 1 previously treated with imiglucerase: 1-year, multicenter, phase iii clinical trial', *Haematologica*, vol. 95, p. 77.

Mardach-Verdon, R, Pastores, G & Zimran, A 2010, 'Clinical and immunological response in patients with type 1 Gaucher disease transitioning from imiglucerase to velaglucerase alfa. Ongoing extension study of tkt034', *60th Annual American Society of Human Genetics Meeting*.

Mikosch, P, Reed, M, Baker, R, Holloway, B, Berger, L, Mehta, AB & Hughes, DA 2008, 'Changes of bone metabolism in seven patients with Gaucher disease treated consecutively with imiglucerase and miglustat', *Calcif Tissue Int*, vol. 83, pp. 43-54.

Pastores, GM, Rosenbloom, B, Grabowski, GA, Weinreb, N, Goker-Alpan, O, Mardach, R, Lipson, M, Ibrahim, J, Cohn, GM, Zahrieh, D & Mistry, PK 2011, 'Multicenter, open-labeltreatment protocol (HGT-GCB-058) of velaglucerase alfa enzyme replacement therapy (ERT) in type 1 Gaucher disease (GD1): 1-year analysis of safety and tolerability', *Journal of Inherited Metabolic Disease*, vol. 34, p. S223.

van, D, Cox, TM, Hendriks, EJ, Morris, E, Akkerman, EM, Maas, M, Groener, JE, Aerts, JM, Deegan, PB & Hollak, CE 2012, 'Effects of switching from a reduced dose imiglucerase to velaglucerase in type 1 Gaucher disease: clinical and biochemical outcomes', *Haematologica*, vol. 97, pp. 1850-1854.

Zimran, A, Altarescu, G & Elstein, D 2011, 'Nonprecipitous changes upon withdrawal from imiglucerase for Gaucher disease because of a shortage in supply', *Blood Cells Mol Dis*, vol. 46, pp. 111-114.

Zimran, A, Pastores, GM, Tylki-Szymanska, A, Hughes, D, Elstein, D, Mardach, R, Eng, C, Smith, L, Heisel-Kurth, M, Charrow, J, Harmatz, P, Fernhoff, P, Rhead, W, Longo, N, Giraldo, P, Zahrieh, D, Crombez, E & Grabowski, GA 2011, 'Efficacy of velaglucerase alfa in patients with type 1 Gaucher disease (GD1) transitioned from imiglucerase: Phase II/III trial TKT034 and extension 2-year results', *Journal of Inherited Metabolic Disease*, vol. 34, p. S224.

### Case study

Belmatoug, N, Launay, O & Carbon, C 1998, 'Pulmonary hypertension in type 1 Gaucher disease. Comite d'Evaluation du Traitement de la Maladie de Gaucher', *Lancet*, vol. 352, p. 240.

Benketira, A 2012, 'Clinical and therapeutic aspects of Gaucher disease in children', *Archives of Disease in Childhood*, vol. 97, p. A155.

Bozdag, SC, Topcuoglu, P, Kuzu, I & Arat, M 2013, 'Acute Lymphoblastic Leukemia During Enzyme Replacement Therapy in Type 1 Gaucher disease', *Clinical Advances in Hematology and Oncology*, vol. 11, pp. 251-252.

Burrow, TA, Cohen, MB, Bokulic, R, Deutsch, G, Choudhary, A, Falcone, Jr., R, A & Grabowski, GA 2007, 'Gaucher Disease: Progressive Mesenteric and Mediastinal Lymphadenopathy Despite Enzyme Therapy', *Journal of Pediatrics*, vol. 150, pp. 202-206.

Chen, CA, Tang, NL, Chien, YH, Zhang, WM, Wang, JK & Hwu, WL 2005, 'Type I Gaucher disease with exophthalmos and pulmonary arteriovenous malformation', *BMC Med Genet*, vol. 6, p. 25.

De, F, Van, N, C, JM, Aerts, JMFG, Maas, M, Poll, RG & Hollak, CEM 2008, 'Persistent bone disease in adult type 1 Gaucher disease despite increasing doses of enzyme replacement therapy', *Haematologica*, vol. 93, pp. 1119-1120.

Kasturi, L & Amin, A 2001, 'Enzyme replacement therapy in Gaucher disease [2]', *Indian Pediatrics*, vol. 38, pp. 686-688.

ROMANIAN, ERTI 2009, 'THE EFFECT OF IMIGLUCERASE ON BONE TISSUE AND MARROW IN THE CONTEXT OF DELAYED CONSOLIDATION OF TRAUMATIC FRACTURE IN A PATIENT WITH GAUCHER DISEASE', *Clinical Therapeutics*, vol. 31.

### Protocol only

Weinreb, N, Rosenbloom, B, Andersson, H, Cole, A, Tripuraneni, R & Belmatoug, N 2011, 'A preliminary analysis from the ICGG Gaucher registry: Short-term clinical outcomes in Gaucher patients affected by the shortage of imiglucerase', *Molecular Genetics and Metabolism*, vol. 102, p. S45.

### Abstract only

Bettman, N, Avivi, I, Katz, T & Rosenbaumab, H 2011, 'Dendritic cell dysfunction in patients with Gaucher disease', *Molecular Genetics and Metabolism*, vol. 102, p. S38.

Cenarro, A, Pocovi, M, Giraldo, P, Garcia-Otin, AL & Ordovas, JM 1999, 'Plasma lipoprotein responses to enzyme-replacement in Gaucher disease'.

Elstein, D, Benisty, J, Klutstein, M, Hadas-Halpern, I & Zimran, A 2009, 'Pulmonary arterial hypertension in Gaucher disease: Predictors of progression and effect of enzyme replacement therapy', *Molecular Genetics and Metabolism*, vol. 96, p. S23.

Khalifa, A, Tantawy, A, Sherif, E, Sadek, A & Tiseer, N 2010, 'Immune dysfunction in patients with gaucher disease: Impact of disease severity and enzyme replacement therapy', *Haematologica*, vol. 95, p. 104.

Komninaka, V, Kolomodi, D, Marinakis, T, Repa, K, Christoulas, D, Voskaridou, E, Dimopoulos, MA & Terpos, E 2012, 'Replacement therapy with imiglucerase improves magnetic resonance imaging (MRI) abnormalities in almost half patients with non-neuronopathic form of gaucher disease after twelve months of therapy: Results of a semi-quantitative MRI method', *Blood*, vol. 120.

Mehta, A, Ben Dridi, M & Gonzalez, D 2010, 'A multicenter, randomized, double-blind, head-to-head, Phase III study of velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with type 1 Gaucher disease', *60th Annual American Society of Human Genetics Meeting. Washington, DC, USA,* pp. 2-6.

Pastores, G, Zimran, A, Tylki-Szymanska, A, Mehta, A, Mardach, R, Heisel-Kurth, M, Eng, C, Smith, L, Harmatz, P, Charrow, J, Zahrieh, D & Grabowski, G 2010, 'Safety and efficacy of velaglucerase alfa in patients with type 1 Gaucher disease previously treated with imiglucerase: Ongoing extension of study TKT034', *Journal of Inherited Metabolic Disease*, vol. 33, p. S130.

Wenstrup, R, Kacena, K, Kaplan, P, Pastores, G, Prakash-Cheng, A, Zimran, A & Hangartner, T 2006, 'Bone mineral density in type 1 gaucher disease: Prevalence of fractures and effect of treatment with imiglucerase', *Journal of Inherited Metabolic Disease*, vol. 29, pp. 64-64.

Wenstrup, R, Kaplan, P, Pastores, G, Prakash-Cheng, A, Zimran, A & Hangartner, T 2007, 'The effect of enzyme replacement therapy with imiglucerase on bone mineral density in type 1 Gaucher disease', *Clinical Therapeutics*, vol. 29, pp. S117-S117.

Zimran, A, Pastores, GM, Tylki-Szymanska, A, Hughes, D, Elstein, D, Mardach, R, Eng, C, Smith, L, Heisel-Kurth, M, Charrow, J, Harmatz, P, Fernhoff, P, Rhead, W, Longo, N, Giraldo, P, Zahrieh, D, Crombez, E & Grabowski, GA 2011, '2-year safety and tolerability of velaglucerase alfa enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease (GD1) switching from imiglucerase', *Journal of Inherited Metabolic Disease*, vol. 34, p. S225.

### Foreign language (not a higher level of evidence than available in English)

'Enzymatic replacement treatment for type I Gaucher disease patients (Structured abstract)', 2011, *Health Technology Assessment Database*.

'Imiglucerase in Gaucher disease (Project record)', 2011, *Health Technology Assessment Database*.

Alfonso, P, Cenarro, A, Perez-Calvo, JI, Puzo, J, Giralt, M, Giraldo, P & Pocovi, M 2003, 'Effect of enzyme replacement therapy on lipid profile in patients with Gaucher disease', *Medicina Clinica*, vol. 120, pp. 641-646.

Cabanas, MJ, Moraga, F, Barroso, C & Castello, F 1998, 'Alglucerase and imiglucerase', *Pediatria Catalana*, vol. 58, pp. 180-181.

Drelichman, G, Linares, A, Villalobos, J, Cabello, JF, Kerstenetzky, M, Kohan, RM & Martins, AM 2012, 'Gaucher disease in Latin America: A report from the Gaucher disease international registry and the Latin Americam group for Gaucher disease', *Medicina (Argentina)*, vol. 72, pp. 273-282.

Grabowski, G, Pastores, G & Mardach, R 2010, 'Patients with Gaucher disease type 1 switching from imiglucerase to velaglucerasa alfa in clinical trial and real world settings', *Presentado en el ACMG Annual Genetics Meeting*.

Guillen-Navarro, E & Domingo-Jimenez, R 2011, 'Enzyme replacement therapy in lysosomal diseases', *Anales de Pediatria Continuada*, vol. 9, pp. 98-105.

Hellwig, B 2010, 'Gaucher disease: Velaglucerase alfa for the long-term enzyme replacement therapy', *Deutsche Apotheker Zeitung*, vol. 150, pp. 32-33.

Krug, B & Schwartz, I 'Doença de Gaucher: delineando estratégias para promoção do uso racional de imiglucerase no Brasil. 58-59. 2006', *Anais do XVIII Congresso Brasileiro de Genética Clínica*.

Krug, B, Schwartz, I & Picon, P 2006, 'Doença de Gaucher: delineando estratégias para promoção do uso racional de imiglucerase no Brasil', *Anais do XVIII Congresso Brasileiro de Genética Clínica. Ribeirão Preto: Sociedade Brasileira de Genética Clínica,* pp. 58-59.

Li, J, Zheng, JJ & Zhu, Z 2010, 'Enzyme replacement therapy with imiglucerase for gaucher disease', *Chinese Pharmaceutical Journal*, vol. 45, pp. 237-238.

Mittelstadt, SD 2012, 'Tratamento com a enzima taliglucerase alfa em pacientes com doença de Gaucher tipo I previamente tratados com imiglucerase'.

Perez, C, J, I & Castellano, PG 2002, 'Home therapy for type 1 Gaucher disease in Spain [3]', *Medicina Clinica*, vol. 119, p. 756.

Schulz, M 1998, 'Imiglucerase for the treatment of Gaucher disease', *Pharmazeutische Zeitung*, vol. 143, pp. 32-35.

Serratrice, C, Kaminsky, P, Berger, M, Grosbois, B, Pelletier, S, Leguy-Seguin, V, Bismuth, M & Belmatoug, N 2011, 'Efficacité et sécurité du relais par velaglucerase chez les patients porteurs d’une maladie de Gaucher lors de la pénurie d’imiglucerase', *La Revue de Médecine Interne*, vol. 32, pp. S273-S274.

Stirnemann, J 2006, 'Clinical study of the French cohort of Gaucher disease patients', *Revue de Medecine Interne*, vol. 27, pp. S18-S21.

Stirnemann, J 2011, 'Velaglucerase: Another enzyme therapy in Gaucher disease', *Revue du Praticien-Monographie*, vol. 61, no. 8, p. 7.

Tekin, A, TÜMER, L, GÜNDÜZ, M & HASANOĞLU, A 2005, 'Okülomotor Apraksi ile Başvuran Tip 3 Gaucher Hastasında Yüksek Doz Imiglucerase Tedavisinin Sonuçları', *Türkiye Klinikleri Pediatrik Bilimler Dergisi*, vol. 1, no. 10, pp. 12-14.

## Miglustat

### Duplicated data

Aerts, JF, van Weely, S, Zimran, A, Elstein, D, Dweck, A, Attias, D, Hadas-Halpern, I, Zevin, S & Altarescu, G 'Oral maintenance clinical trial with miglustat for type 1 Gaucher disease'. (duplicate of Elstein et al of same title)

### Lower level evidence

Agostino, A, Stefano, P, Giovanni, C, Fulvio, P & Bruno, B 2010, 'Eye Movement Impairment Recovery in a Gaucher Patient Treated with Miglustat', *Neurology Research International*, vol. 2010.

Cox, T, Lachmann, R, Hollak, C, Aerts, J, van Weely, S, Hrebicek, M, Platt, F, Butters, T, Dwek, R, Moyses, C, Gow, I, Elstein, D & Zimran, A 2000, 'Novel oral treatment of Gaucher disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis', Lancet, vol. 355, no. 9214, Apr 29, pp. 1481-1485.

Giraldo, P, Alonso, D, Acedo, M, Franco, R, Barez, A, Corrales, A, Serrano, D, Roldan, V, Latre, P, Alfonso, P & Pocovi, M 2005, 'Short-Term Effect of Oral Treatment with Miglustat in Type 1 Gaucher Disease', ASH Annual Meeting Abstracts, vol. 106, no. 11, November 16, 2005, pp. 2235-.

Giraldo, P, Andrade, MM, Medrano, B, Alfonso, P, Irun, P, Atutxa, K, Fernandez-Galan, A, Barez, A, Franco, R, Roig, I, Giner, V, Villalon, L, Martinez-Estefano, E, Luno, E, Loyola, I, Salamero, O, de la Serna, J & Pocovi, M 2013, 'Substrate Reduction Therapy With Miglustat In Type 1 Gaucher Disease In Spain. Nine Years Outcomes Update On ZAGAL Study', Blood, vol. 122, no. 21, Nov.

Giraldo, P, Irun, P, Alfonso, P, Dalmau, J, Fernandez-Galan, MA, Figueredo, A, Hernandez-Rivas, JM, Julia, A, Luno, E, Marin-Jimenez, F, Martin-Nunez, G, Montserrat, JL, de la Serna, J, Vidaller, A, Villalon, L & Pocovi, M 2011, 'Evaluation of Spanish Gaucher disease patients after a 6-month imiglucerase shortage', Blood Cells Mol Dis, vol. 46, no. 1, Jan 15, pp. 115-118.

Giraldo, P, Latre, P, Alfonso, P, Acedo, A, Alonso, D, Barez, A, Corrales, A, Franco, R, Roldan, V, Serrano, S & Pocovi, M 2006, 'Short-term effect of miglustat in every day clinical use in treatment-naive or previously treated patients with type 1 Gaucher disease', Haematologica, vol. 91, no. 5, May, pp. 703-706.

Heemstra, HE, Giezen, TJ, Mantel-Teeuwisse, AK, De Vrueh, RLA & Leufkens, HGM 2010, 'Safety-related regulatory actions for orphan drugs in the US and EU: A cohort study', Drug Safety, vol. 33, no. 2, pp. 127-137.

Heitner, R, Elstein, D, Aerts, J, Weely, S & Zimran, A 2002, 'Low-dose N-butyldeoxynojirimycin (OGT 918) for type I Gaucher disease', Blood Cells Mol Dis, vol. 28, no. 2, Mar-Apr, pp. 127-133.

Heitner, R, Elstein, D, Aerts, J & Zimran, A 2002, 'Erratum: Low-dose N-butyldeoxynojirimycin (OGT 918) for type I gaucher disease (Blood Cells, Molecules, and Diseases (2002) 28:2 (127-133))', Blood Cells, Molecules, and Diseases, vol. 28, no. 2, p. 301.

Hollak, C, Heitner, R, Hrebicek, M, Elstein, D & Zimran, A 2005, 'ADULT PATIENTS WITH TYPE I GAUCHER DISEASE (GD 1) ON LONG-TERM MIGLUSTAT TREATMENT', J Inherit Metab Dis, vol. 28, pp. 171-171.

Hollak, CEM, Kuter, D, Giraldo, P, Hughes, D, Belmatoug, N, Brand, M, Muller, A, Schaaf, B, Giorgino, R & Zimran, A 2012, 'MIGLUSTAT THERAPY IN TYPE 1 GAUCHER DISEASE: LONG-TERM TREATMENT EXPERIENCE FROM A MULTICENTER, RETROSPECTIVE COHORT STUDY', J Inherit Metab Dis, vol. 35, Sep, pp. S97-S97.

Kuter, DJ, Mehta, A, Hollak, C, Giraldo, P, Hughes, D, Belmatoug, N, Brand, M, Muller, A, Schaaf, B, Giorgino, R & Zimran, A 2011, 'Miglustat therapy in type 1 Gaucher disease: Long-term treatment experience from a multicenter, retrospective cohort study', Blood, vol. 118, no. 21.

Kuter, DJ, Mehta, A, Hollak, CE, Giraldo, P, Hughes, D, Belmatoug, N, Brand, M, Muller, A, Schaaf, B, Giorgino, R & Zimran, A 2013, 'Miglustat therapy in type 1 Gaucher disease: clinical and safety outcomes in a multicenter retrospective cohort study', Blood Cells Mol Dis, vol. 51, no. 2, Aug, pp. 116-124.

Machaczka, M, Hast, R, Dahlman, I, Lerner, R, Klimkowska, M, Engvall, M & Hagglund, H 2012, 'Substrate reduction therapy with miglustat for type 1 Gaucher disease: a retrospective analysis from a single institution', Ups J Med Sci, vol. 117, no. 1, Mar, pp. 28-34.

Puzo, J, Alfonso, P, Irun, P, Gervas, J, Pocovi, M & Giraldo, P 2010, 'Changes in the atherogenic profile of patients with type 1 Gaucher disease after miglustat therapy', Atherosclerosis, vol. 209, no. 2, Apr, pp. 515-519.

Revest, M, Perlat, A, Decaux, O, Lamy, T, Verin, M, Brissot, P & Grosbois, B 2009, '[Gaucher disease in Rennes University hospital: a 10-year retrospective study]', Rev Med Interne, vol. 30, no. 10, Oct, pp. 847-856.

Stirnemann, J, Vigan, M, Hamroun, D, Heraoui, D, Rossi-Semerano, L, Berger, MG, Rose, C, Camou, F, de Roux-Serratrice, C, Grosbois, B, Kaminsky, P, Robert, A, Caillaud, C, Froissart, R, Levade, T, Masseau, A, Mignot, C, Sedel, F, Dobbelaere, D, Vanier, MT, Valayanopoulos, V, Fain, O, Fantin, B, de Villemeur, TB, Mentre, F & Belmatoug, N 2012, 'The French Gaucher disease registry: clinical characteristics, complications and treatment of 562 patients', Orphanet J Rare Dis, vol. 7, p. 77.

Tifft, C & Yang, S 2007, 'WITHDRAWN: 105 Treat type I Gaucher disease with miglustat: Experience with two patients', *Molecular Genetics and Metabolism*.

Vicente, C, Agustin, MJ, Navarro, H, Picaza, E, Arenere, M & Idoipe, A 2009, 'Substrate reduction therapy in patients with mild-to-moderate type i gaucher disease', Pharmacy World & Science, vol. 31, no. 1, Feb, pp. 120-121.

Weinreb, NJ, Charrow, J, Andersson, HC, Kaplan, P, Kolodny, EH, Mistry, P, Pastores, G, Rosenbloom, BE, Scott, CR & Wappner, RS 2002, 'Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry', The American journal of medicine, vol. 113, no. 2, pp. 112-119.

### Switched case series (case series of patients switched from imiglucerase to another treatment)

'Miglustat: In type 1 Gaucher disease: A slight benefit after imiglucerase therapy', 2005, *Prescrire Int*, vol. 14, no. 79, pp. 168-170.

Ait-Aissa, N, Jamieson, V, Morand, O, Esparza, I & Goffin, H 2005, 'A CLINICAL STUDY TO ASSESS MIGLUSTAT AS MAINTENANCE THERAPY FOR ADULT PATIENTS WITH STABLE TYPE 1 GAUCHER DISEASE (GD 1) AFTER SWITCH FROM ENZYME REPLACEMENT THERAPY (ERT): OBJECTIVES AND STUDY DESIGN', *J Inherit Metab Dis*, vol. 28, pp. 170-170.

Cox, TM, Amato, D, Hollak, CE, Luzy, C, Silkey, M, Giorgino, R & Steiner, RD 2012, 'Evaluation of miglustat as maintenance therapy after enzyme therapy in adults with stable type 1 Gaucher disease: a prospective, open-label non-inferiority study', *Orphanet J Rare Dis*, vol. 7, p. 102.

Elstein, D, Dweck, A, Attias, D, Hadas-Halpern, I, Zevin, S, Altarescu, G & Zimran, A 2007, 'Oral maintenance with miglustat in adult patients with type 1 Gaucher disease: The patients quality-of-life perspective', *J Inherit Metab Dis*, vol. 30, Aug, pp. 120-120.

Giraldo, P, Alfonso, P, Atutxa, K, Fernandez-Galan, MA, Barez, A, Franco, R, Alonso, D, Martin, A, Latre, P & Pocovi, M 2009, 'Real-world clinical experience with long-term miglustat maintenance therapy in type 1 Gaucher disease: the ZAGAL project', *Haematologica*, vol. 94, no. 12, Dec, pp. 1771-1775.

Mehta, A 2006, 'Clinical experience with substrate reduction therapy', *Eur J Intern Med*, vol. 17 Suppl, Nov, pp. S13-15.

Mikosch, P, Reed, M, Baker, R, Holloway, B, Berger, L, Mehta, AB & Hughes, DA 2008, 'Changes of bone metabolism in seven patients with Gaucher disease treated consecutively with imiglucerase and miglustat', *Calcif Tissue Int*, vol. 83, no. 1, Jul, pp. 43-54.

Steiner, RD, Amato, D, Hollak, CEM, Luzy, C, Silkey, M, Giorgino, R & Cox, TM 2011, 'A 2-year, prospective, open-label, non-inferiority study of miglustatas maintenance therapy in adults with type 1 Gaucher disease (GD-1) stabilised on enzyme replacement therapy (ERT)', *J Inherit Metab Dis*, vol. 34, p. S200.

—— 2011, 'A 2-year, prospective, open-label, non-inferiority study of miglustatas maintenance therapy in adults with type 1 Gaucher disease (GD-1) stabilised on enzyme replacement therapy (ERT)', *J Inherit Metab Dis*, vol. 34, p. S200.

### Abstract only

Amsallem, D 2006, 'Gaucher disease linked to a deficit in saposine C with treatment by miglustat', *PRESSE MEDICALE*, vol. 35, pp. S35-S36.

Andrade, MM, Medrano, B, Alfonso, P, Irún, P, Atutxa, K, Fernandez-Galan, A, Barez, A, Franco, R, Roig, I & Giner, V 2013, 'Substrate Reduction Therapy With Miglustat In Type 1 Gaucher Disease In Spain. Nine Years Outcomes Update On ZAGAL Study', *Blood*, vol. 122, no. 21, pp. 4713-4713.

Giraldo, M, Latre, P, Acedo, A, Alonso, D, Barez, A, Martin, A, Franco, R, Fernandez-Villamor, A & Pocovi, M 2007, 'Long term efficacy and safety of miglustat therapy in type 1 Gaucher disease', *HAEMATOLOGICA-THE HEMATOLOGY JOURNAL,* vol. 92, pp. 279-279.

Giraldo, P 2005, 'Gaucher diesease: experiences with substrate reduction therapy with miglustat in Spain', *Management of Patients with Gaucher Disease: Investigating New Clinical Perspectives*, p. 12.

Zimran, A, Elstein, D, Pastores, G & Hrebícek, M 2007, 'WITHDRAWN: 95 Beneficial effects of miglustat on skeletal symptoms in type I Gaucher disease: A meta-analysis', *Molecular Genetics and Metabolism*.

### Foreign language (not a higher level of evidence than available in English)

Amsallem, D 2006, 'Maladie de Gaucher liée à un déficit en saposine C avec traitement par miglustat: D’après la communication de Daniel Amsallem', *La Presse Médicale*, vol. 35, pp. 35-36.

BERTSCHE, T & SCHULZ, M 2005, 'Miglustat bei Morbus Gaucher', *Pharmazeutische Zeitung*, vol. 150, no. 15, pp. 24-28.

Bouslimani, K, Hakem, D, Hamzaoui, N, Ouadahi, N & Berrah, A 2013, 'Diététique et prise de miglustat chez les patients souffrant de maladie de Gaucher de Type 1: expérience d’un service de médecine interne à propos de trois patients', *La Revue de médecine interne*, vol. 34, pp. A172-A173.

Cherin, P, Jaussaud, R & Pastores, G 2007, 'Traitement des complications osseuses de la maladie de Gaucher de type 1 chez l'adulte: méta-analyse des études d'enregistrement du miglustat', *La Revue de médecine interne*, vol. 28, pp. 76-77.

Dechelotte, P 2004, 'PARTENAIRES-Entretien therapeutique-Maladie de Gaucher de type 1 chez l'adulte-Prise en charge nutritionnelle lors de la mise en place d'un traitement par miglustat', *PRESSE MEDICALE*, vol. 33, no. 7, pp. 494-496.

Déchelotte, P 2004, 'Maladie de Gaucher de type 1 chez l’adulte: Prise en charge nutritionnelle lors de la mise en place d’un traitement par miglustat', *La Presse Médicale*, vol. 33, no. 7, pp. 494-496.

Giraud, E 2004, 'La maladie de Gaucher, intérêt du miglustat (zavesca)'.

Marie, I 2009, 'Combined therapy of imiglucerase and miglustat in Gaucher disease with severe bone complications', MASSON EDITEUR 21 STREET CAMILLE DESMOULINS, ISSY, 92789 MOULINEAUX CEDEX 9, FRANCE.

Niederau, C 2004, 'Kurzbewertungen-Neue Behandlungsstrategien der Gaucher-Krankheit: Substrathemmung durch Miglustat (Zavesca)', *Internistische Praxis*, vol. 44, no. 4, pp. 839-848.

—— 2004, 'Substrathemmung durch Miglustat Neue Behandlungsstrategie der Gaucher-Krankheit', *Arzneimitteltherapie*, vol. 22, no. 5, pp. 136-141.

Pastores, G, Elstein, D, Hrebicek, M & Zimran, A 2006, 'Atteintes ostéoarticulaires de la maladie de Gaucher chez l'adulte : de la physiopathologie au traitement / Effect of miglustat on skeletal symptoms in adult type 1 Gaucher disease: meta-analysis of 2-year follow-up in clinical trials', *Cambridge: European Working Group on Gaucher Disease*.

Recker, K 2003, *Morbus Gaucher-neues orales Therapiekonzept: Substratreduktion mit Miglustat*, Springer.

—— 2003, *Neues orales Therapiekonzept: Substratreduktion mit Miglustat: Morbus Gaucher;[Symposium, Paris/Frankreich, 11. Juni 2003]*, Springer.

Stirnemann, J, Heraoui, D, Fain, O, Fantin, B & Belmatoug, N 2009, 'Efficacité du miglustat dans la maladie de Gaucher: à propos de l’analyse du suivi de 8 patients suivi au Centre de Référence des Maladies Lysosomales', *La Revue de médecine interne*, vol. 30, p. S124.

Stirnemann, J 2006, '[Clinical study of the French cohort of Gaucher disease patients]', *Rev Med Interne*, vol. 27 Suppl 1, Mar, pp. S18-21.

## Enzyme Replacement Therapy

### Cohort study

Anderson, LJ, Henley, W, Wyatt, KM, Nikolaou, V, Hughes, DA, Waldek, S & Logan, S 2014, 'Long-term effectiveness of enzyme replacement therapy in adults with Gaucher disease: results from the NCS-LSD cohort study', *J Inherit Metab Dis*, vol. 37, no. 6, pp. 953-960.

Brautbar, A, Elstein, D, Pines, G, Abrahamov, A & Zimran, A 2004, 'Effect of enzyme replacement therapy on gammopathies in Gaucher disease', *Blood Cells, Molecules, and Diseases*, vol. 32, no. 1, pp. 214-217.

Clarke, JTR, Amato, D & Deber, RB 2001, 'Managing public payment for high-cost, high-benefit treatment: Enzyme replacement therapy for Gaucher disease in Ontario', *Canadian Medical Association Journal*, vol. 165, no. 5, pp. 595-596.

Donaldson, J, Khan, WS, Tailor, H, Hughes, DA, Mehta, AB & Maruthainar, N 2011, 'Gaucher disease: Outcome following total hip replacements and effect of enzyme replacement therapy in a cohort of UK Patients', *HIP International*, vol. 21, no. 6, pp. 665-671.

Elstein, Y, Eisenberg, V, Granovsky-Grisaru, S, Rabinowitz, R, Samueloff, A, Zimran, A & Elstein, D 2004, 'Pregnancies in Gaucher disease: A 5-year study', *American Journal of Obstetrics and Gynecology*, vol. 190, no. 2, Feb, pp. 435-441.

Erba, PA, Minichilli, F, Giona, F, Linari, S, Dambrosia, J, Pierini, A, Filocamo, M, Di Rocco, M, Buffoni, F, Brady, RO & Mariani, G 2013, '99mTc-sestamibi scintigraphy to monitor the long-term efficacy of enzyme replacement therapy on bone marrow infiltration in patients with gaucher disease', *Journal of Nuclear Medicine*, vol. 54, no. 10, pp. 1717-1724.

Hayes, RP, Grinzaid, KA, Duffey, EB & Elsas, ILJ 1998, 'The impact of Gaucher disease and its treatment on quality of life', *Quality of Life Research*, vol. 7, no. 6, pp. 521-534.

Lebel, E, Elstein, D, Peleg, A, Reinus, C, Zimran, A & Amir, G 2013, 'Histologic findings of femoral heads from patients with Gaucher disease treated with enzyme replacement', *American Journal of Clinical Pathology*, vol. 140, no. 1, pp. 91-96.

Lorberboym, M, Pastores, GM, Kim, CK, Hermann, G, Glajchen, N & Machac, J 1997, 'Scintigraphic monitoring of reticuloendothelial system in patients with type 1 Gaucher disease on enzyme replacement therapy', *Journal of Nuclear Medicine*, vol. 38, no. 6, pp. 890-895.

Mariani, G, Filocamo, M, Giona, F, Villa, G, Amendola, A, Erba, P, Buffoni, F, Copello, F, Pierini, A, Minichilli, F, Gatti, R & Brady, RO 2003, 'Severity of bone marrow involvement in patients with Gaucher disease evaluated by scintigraphy with 99mTc-sestamibi', *Journal of Nuclear Medicine*, vol. 44, no. 8, pp. 1253-1262.

Stirnemann, J, Belmatoug, N, Vincent, C, Fain, O, Fantin, B & Mentre, F 2010, 'Bone events and evolution of biologic markers in Gaucher disease before and during treatment', *Arthritis Research and Therapy*, vol. 12, no. 4.

van Dussen, L, Biegstraaten, M, Dijkgraaf, MG & Hollak, CE 2014, 'Modelling Gaucher disease progression: long-term enzyme replacement therapy reduces the incidence of splenectomy and bone complications', *Orphanet J Rare Dis*, vol. 9, no. 1, p. 112.

van Dussen, L, Biegstraaten, M, Hollak, CE & Dijkgraaf, MG 2014, 'Cost-effectiveness of enzyme replacement therapy for type 1 Gaucher disease', *Orphanet J Rare Dis*, vol. 9, p. 51.

Wyatt, K, Henley, W, Anderson, L, Anderson, R, Nikolaou, V, Stein, K, Klinger, L, Hughes, D, Waldek, S, Lachmann, R, Mehta, A, Vellodi, A & Logan, S 2012, 'The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders', *Health Technology Assessment*, vol. 16, no. 39, pp. 1-543.

### Case series

Abrahamov, A, Hadas-Halpern, I, Levy-Lahad, E & Zimran, A 1992, 'ENZYME REPLACEMENT THERAPY FOR CHILDREN WITH GAUCHER DISEASE LOW DOSE HIGH FREQUENCY LOWER COST HIGH EFFICACY', *Pediatric Research*, vol. 31, no. 4 PART 2, 1992, pp. 137A-137A.

Aharoni, D, Krausz, Y, Elstein, D, Hadas-Halpern, I & Zimran, A 2002, 'Tc-99m sestamibi bone marrow scintigraphy in Gaucher disease', *Clinical Nuclear Medicine*, vol. 27, no. 7, pp. 503-509.

Alentado Morell, N, Escrig Fernandez, R & Dalmau Serra, J 2005, 'Type 1 Gaucher disease: 10 Years of experience in enzyme replacement therapy', *Acta Pediatrica Espanola*, vol. 63, no. 9, pp. 373-376.

Altarescu, G, Schiffmann, R, O'Brady, R & Barton, NW 1999, 'Dose effect on enzyme replacement therapy (ERT) in type I gaucher disease', *Blood*, vol. 94, no. 10, Nov 15, pp. 209A-209A.

Anderson, LJ, Henley, W, Wyatt, KM, Nikolaou, V, Waldek, S, Hughes, DA, Pastores, GM & Logan, S 2014, 'Long-term effectiveness of enzyme replacement therapy in children with Gaucher disease: results from the NCS-LSD cohort study', *J Inherit Metab Dis*.

Andersson, H, Charrow, J, Kaplan, P, Kolodny, EH, Mistry, P, Pastores, G, Rosenbloom, BE & Wappner, RS 2000, 'The Gaucher Registry: Demographics and disease characteristics and response to enzyme replacement therapy (ERT) for 78 pediatric patients (pts)', *Blood*, vol. 96, no. 11, Nov 16, pp. 8A-8A.

Andersson, H, Kaplan, P, Kacena, K & Yee, J 2008, 'Clinical outcome following 8-year enzyme replacement therapy in 884 children with type 1 Gaucher disease (GDI)', *Mol Genet Metab*, vol. 93, no. 2, Feb, pp. S14-S14.

Andersson, H, Kaplan, P, Kacena, K & Yee, J 2008, 'CLINICAL OUTCOMES OF LONG-TERM (8 YEARS) ENZYME REPLACEMENT THERAPY IN 884 CHILDREN WITH TYPE 1 GAUCHER DISEASE', *Clin Ther*, vol. 30, 2008, pp. S101-S102.

—— 2008, 'Eight-year clinical outcomes of long-term enzyme replacement therapy in 884 children with type 1 Gaucher disease', *J Inherit Metab Dis*, vol. 31, Aug, pp. 103-103.

Andreassen, CS, Schlutter, JM, Vissing, J & Andersen, H 2014, 'Effect of enzyme replacement therapy on isokinetic strength for all major muscle groups in four patients with Pompe disease-a long-term follow-up', *Mol Genet Metab*, vol. 112, no. 1, May, pp. 40-43.

Arikan-Ayyildiz, Z, Yuce, A, Uslu-Kizilkan, N, Demir, H & Gurakan, F 2010, 'Immunoglobulin abnormalities and effects of enzyme replacement therapy in children with Gaucher disease', *Pediatr Blood Cancer*, //.

Aviezer, D, Almon-Brill, E, Shaaltiel, Y, Galili, G, Chertkoff, R, Hashmueli, S, Galun, E & Zimran, A 2008, 'Novel enzyme replacement therapy for Gaucher disease: On-going phase III clinical trial with recombinant human glucocerebrosidase expressed in plant cells', *Mol Genet Metab*, vol. 93, no. 2, Feb, pp. S15-S15.

Barton, NW, Brady, RO, Dambrosia, JM, Di Bisceglie, AM, Doppelt, SH, Hill, SC, Mankin, HJ, Murray, GJ, Parker, RI, Argoff, CE & et al. 1991, 'Replacement therapy for inherited enzyme deficiency--macrophage-targeted glucocerebrosidase for Gaucher disease', *N Engl J Med*, vol. 324, no. 21, May 23, pp. 1464-1470.

Bembi, B, Zanatta, M, Carrozzi, M, Baralle, F, Gornati, R, Berra, B & Agosti, E 1994, 'Enzyme replacement treatment in type 1 and type 3 Gaucher disease', *Lancet*, vol. 344, no. 8938, Dec 17, pp. 1679-1682.

Brady, RO & Barton, NW 1994, 'Enzyme replacement therapy for Gaucher disease: Critical investigations beyond demonstration of clinical efficacy', *Biochemical Medicine and Metabolic Biology*, vol. 52, no. 1, pp. 1-9.

Brady, RO, Dambrosia, JM & Barton, NW 1992, 'EFFECTIVENESS OF LOW-DOSE ENZYME REPLACEMENT THERAPY IN GAUCHERS-DISEASE', *Clinical Research*, vol. 40, no. 2, Apr, pp. A144-A144.

Cabrera-Salazar, MA, O'Rourke, E, Henderson, N, Wessel, H & Barranger, JA 2004, 'Correlation of surrogate markers of Gaucher disease. Implications for long-term follow up of enzyme replacement therapy', *Clinica Chimica Acta*, vol. 344, no. 1-2, pp. 101-107.

Carrozzi, M, Zanatta, M, Scabar, A & Bembi, B 1995, 'Enzyme replacement therapy for Gaucher disease types 1, 2 and 3', *Mariani Found. Paediatr. Neurol. Ser.*, vol. 4, no. Metabolic Encephalopathies, //, pp. 121-128.

Cenarro, A, Pocovi, M, Giraldo, P, Garcia-Otin, AL & Ordovas, JM 1999, 'Plasma lipoprotein responses to enzyme-replacement in Gaucher disease', *Lancet*, vol. 353, no. 9153, Feb 20, pp. 642-643.

Chan, LL & Lin, HP 2002, 'Enzyme replacement therapy for gaucher disease: The only experience in Malaysia', *Medical Journal of Malaysia*, vol. 57, no. 3, pp. 348-352.

Charrow, J, Andersson, HC, Kaplan, P, Kolodny, E, Mistry, P, Pastores, G, Rosenbloom, B, Scott, R, Wappner, R & Weinrab, N 2000, 'Response to enzyme replacement therapy in Gaucher disease patients with N370S/N370S, N370S compound heterozygotes and L444P/L444P genotypes', *American Journal of Human Genetics*, vol. 67, no. 4, Oct, pp. 427-427.

Charrow, J, Dulisse, B, Grabowski, GA & Weinreb, NJ 2007, 'The effect of enzyme replacement therapy on bone crisis and bone pain in patients with type 1 Gaucher disease - Response', *Clin Genet*, vol. 72, no. 2, Aug, pp. 161-161.

Ciana, G, Addobbati, R, Tamaro, G, Leopaldi, A, Nevyjel, M, Ronfani, L, Vidoni, L, Pittis, MG & Bembi, B 2005, 'Gaucher disease and bone: Laboratory and skeletal mineral density variations during a long period of enzyme replacement therapy', *J Inherit Metab Dis*, vol. 28, no. 5, pp. 723-732.

Ciana, G, Deroma, L, Pisa, FE, Franzil, AM, Dardis, A, Sechi, A, Malini, E & Bembi, B 2011, 'Bone mineralization in a pediatric cohort of gaucher patients under enzyme replacement therapy', *J Inherit Metab Dis*, vol. 34, p. S200.

Cohen, IJ, Katz, K, Kornreich, L, Horev, G, Frish, A & Zaizov, R 1998, 'Low-dose high-frequency enzyme replacement therapy prevents fractures without complete suppression of painful bone crises in patients with severe juvenile onset type I Gaucher disease', *Blood Cells, Molecules, and Diseases*, vol. 24, no. 3, pp. 296-302.

Damiano, AM, Pastores, GM & Ware Jr, JE 1998, 'The health-related quality of life of adults with Gaucher disease receiving enzyme replacement therapy: Results from a retrospective study', *Quality of Life Research*, vol. 7, no. 5, pp. 373-386.

De Fost, M, Hollak, CEM, Groener, JEM, Aerts, JMFG, Maas, M, Poll, LW, Wiersma, MG, Haussinger, D, Brett, S, Brill, N & Vom Dahl, S 2006, 'Superior effects of high-dose enzyme replacement therapy in type 1 Gaucher disease on bone marrow involvement and chitotriosidase levels: A 2-center retrospective analysis', *Blood*, vol. 108, no. 3, pp. 830-835.

Freedman, R, Peters, H, Curnow, L & Sahhar, M 2012, 'Receiving enzyme replacement therapy for a lysosomal storage disorder; exploring the experiences of young patients and their families', *Twin Research and Human Genetics*, vol. 15, no. 4, p. 575.

Giraldo, P, Perez-Calvo, JI, Pocovi, M, Rubio-Felix, D & Giralt, M 2002, 'Gaucher disease in Spain. Ten Years of Experience in Enzymatic Replacement Therapy', *Blood*, vol. 100, no. 11, November 16, pp. 3639-Abstract No. 3639.

Giraldo, P, Pocovi, M, Perez-Calvo, JI, Rubio-Felix, D & Giralt, M 2000, 'Report of the Spanish Gaucher disease registry: Clinical and genetic characteristics', *Haematologica*, vol. 85, no. 8, pp. 792-799.

Heitner, R, Elstein, D & Zimran, A 2001, 'A dose comparison of the efficacy and safety of oral N-butyldeoxynojirimycin (OGT 918) in clinical studies in Gaucher disease', *Blood*, vol. 98, no. 11, Nov 16, pp. 28B-28B.

Hollak, CEM, de Fost, M, van Dussen, L, vom Dahl, S & Aerts, JMFG 2009, 'Enzyme therapy for the treatment of type 1 Gaucher disease: clinical outcomes and dose - response relationships', *Expert Opin. Pharmacother.*, vol. 10, no. 16, //, pp. 2641-2652.

Hollak, CEM, Levi, M, Berends, F, Aerts, J & vanOers, MHJ 1997, 'Coagulation abnormalities in type 1 Gaucher disease are due to low-grade activation and can be partly restored by enzyme supplementation therapy', *Br J Haematol*, vol. 96, no. 3, Mar, pp. 470-476.

Ida, H, Rennert, OM, Kobayashi, M & Eto, Y 2001, 'Effects of enzyme replacement therapy in thirteen Japanese pediatric patients with Gaucher disease', *Eur. J. Pediatr.*, vol. 160, no. 1, //, pp. 21-25.

Kaplan, P, Andersson, HC, Charrow, J, Kolodny, EH, Mistry, P, Pastores, GM, Rosenbloom, BE, Scott, CR, Wappner, RS & Weinreb, NJ 2001, 'Growth improvement in response to enzyme replacement therapy (ERT) among children with Gaucher disease: The Gaucher Registry', *American Journal of Human Genetics*, vol. 69, no. 4, Oct, pp. 674-674.

Kim, HJ, Ha, MJ, Cho, JH, Kim, BS, Kim, MK, Kim, SH, Kim, HS, Kim, JS, Lim, YA, Lee, YJ, Yoo, HW & Park, CH 1999, 'Clinical accessment of therapeutic response to enzyme replacement therapy in 16 Korean Gaucher pts', *American Journal of Human Genetics*, vol. 65, no. 4, Oct, pp. A310-A310.

Kleinotiene, G & Tylki-Szymanska, A 2007, 'The analysis of the achievement of therapeutic goals in 45 polish and Lithuanian Gaucher disease patients treated with enzyme replacement therapy', *Clin Ther*, vol. 29, 2007, pp. S117-S118.

Kobayashi, M, Ida, H & Eto, Y 2000, 'Maintenance dosage efficacy of enzyme replacement therapy in 13 Japanese pediatric patients with Gaucher disease', *J Inherit Metab Dis*, vol. 23, no. Supplement 1, July, pp. 227-227.

Lerner, D, Simpson, W, Hermann, G & Balwani, M 2010, 'Bone Marrow Alteration in Patients With Type 1 Gaucher Disease on Enzyme Replacement Therapy', *American Journal of Roentgenology*, vol. 194, no. 5, May.

Lukina, E 2009, 'Latest data on Genz-112638, an investigational oral therapy for type 1 Gaucher disease: Phase II clinical trial results after 1 year of treatment', *Clin Ther*, vol. 31, no. SUPPL. 3, pp. S194-S195.

McDowell, R, Li, JS, Benjamin, DK, Jr., Morgan, C, Becker, A, Kishnani, PS & Kanter, RJ 2008, 'Arrhythmias in patients receiving enzyme replacement therapy for infantile Pompe disease', *Genet Med*, vol. 10, no. 10, Oct, pp. 758-762.

MacKenzie, JJ, Amato, D & Clarke, JTR 1998, 'Enzyme replacement therapy for Gaucher disease: The early Canadian experience', *Canadian Medical Association Journal*, vol. 159, no. 10, pp. 1273-1278.

Magnaldi, S, Longo, R, Ukmar, M, Zanatta, M, Bottega, M & Sottocasa, GL 1997, 'Bone marrow relaxation times in Gaucher disease before and after enzyme replacement therapy', *European Radiology*, vol. 7, no. 4, pp. 486-491.

Malhotra, A, Boxer, M & Mistry, PK 2004, 'Hepatic response to enzyme replacement therapy (ERT) with mannose-terminated glucocerebrosidase in type 1 Gaucher disease', *Hepatology*, vol. 40, no. 4, Oct, pp. 234A-234A.

Masek, BJ, Sims, KB, Bove, CM, Korson, MS, Short, P & Norman, DK 1999, 'Quality of life assessment in adults with type 1 Gaucher disease', *Quality of Life Research*, vol. 8, no. 3, pp. 263-268, <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/075/CN-00167075/frame.html>.

Mensah, R & Elstein, D 2005, 'Phase I/II, nine month study results of enzyme replacement therapy with gene activated human glucocerebrosidase (GA-GCB) in patients with type I Gaucher disease', *Blood*, vol. 106, no. 11, Nov 16, pp. 51B-51B.

Moennighoff, I, vom Dahl, S & Haeussinger, D 1999, 'Restoration of plasma taurine levels in patients with Gaucher disease during enzyme replacement therapy (ERT)', *Amino Acids (Vienna)*, vol. 17, no. 1, 1999, pp. 31-31.

Molzer, B, Bernheimer, H & Voigtlaender, T 2001, 'Diagnosis and follow-up of Austrian patients with Gaucher disease during enzyme replacement therapy', *J Inherit Metab Dis*, vol. 24, no. Supplement 2, 2001, pp. 162-162.

Moyses, C 2001, 'Substrate reduction therapy in type 1 Gaucher disease with OGT918', *European Journal of Human Genetics*, vol. 9, no. Supplement 1, 2001, pp. C075-C075.

Nicol, A, Mengel, E, Mani, L, Huth, M & Beck, M 2006, 'Effects of enzyme replacement therapy and age at onset of therapy on bone involvement', *Acta Paediatrica*, vol. 95, Apr, pp. 139-139.

Niederau, C, Holderer, A, Heintges, T & Strohmeyer, G 1994, 'GLUCOCEREBROSIDASE FOR TREATMENT OF GAUCHERS-DISEASE - FIRST GERMAN LONG-TERM RESULTS', *Journal of Hepatology*, vol. 21, no. 4, Oct, pp. 610-617.

Oliveri, B, Goldstein, G, Rivero, M, Parisi, MS, Aguilar, G & Mautalen, C 2003, 'Marked osteopenia and increased bone resorption in Gaucher disease patients in spite of enzyme replacement therapy', *Journal of Bone and Mineral Research*, vol. 18, Sep, pp. S388-S388.

Parco, S, Bruno, G, Durighello, M, Giorgini, R, Simeone, R & Bembi, B 1999, 'Hematologic response in type I Gaucher disease after enzyme replacement therapy', *Haematologica*, vol. 84, no. 4, Apr, pp. 376-377.

Park, JH, Moore, AF & Kuter, DJ 2006, 'Long-term follow-up of monoclonal gammopathies in Gaucher disease patients on enzyme replacement therapy', *Blood*, vol. 108, no. 11, Nov 16, pp. 952A-952A.

Pastores, GM, Sibille, AR & Grabowski, GA 1993, 'ENZYME THERAPY IN GAUCHER DISEASE TYPE-1 - DOSAGE EFFICACY AND ADVERSE-EFFECTS IN 33 PATIENTS TREATED FOR 6 TO 24 MONTHS', *Blood*, vol. 82, no. 2, Jul 15, pp. 408-416.

Patlas, M, Hadas-Halpern, I, Abrahamov, A, Zimran, A & Elstein, D 2002, 'Repeat abdominal ultrasound evaluation of 100 patients with type I Gaucher disease treated with enzyme replacement therapy for up to 7 years', *Hematology Journal*, vol. 3, no. 1, pp. 17-20.

Prater, SN, Banugaria, SG, DeArmey, SM, Botha, EG, Stege, EM, Case, LE, Jones, HN, Phornphutkul, C, Wang, RY, Young, SP & Kishnani, PS 2012, 'The emerging phenotype of long-term survivors with infantile Pompe disease', *Genet Med*, vol. 14, no. 9, Sep, pp. 800-810.

Rodrigues, F, Martins, F, Freitas, F, Diogo, L & Garcia, P 2011, 'Impact of lysosomal storage disorders on daily living of patients and their families and perceptions on enzyme replacement therapy', *J Inherit Metab Dis*, vol. 34, p. S215.

Rodrigues, F, Vaz, C, Almeida, M, Martins, F, Diogo, L & Garcia, P 2008, 'Psychological follow-up of children on enzyme replacement therapy for lisosomal storage disorders and their parents', *J Inherit Metab Dis*, vol. 31, Aug, pp. 110-110.

Rosenbaum, H, Brenner, B, Besser, M & Rowe, JM 1998, 'Type I Gaucher disease: Clinical features in 80 patients and enzyme replacement therapy results in 18 patients', *Blood*, vol. 92, no. 10, Nov 15, pp. 537A-537A.

Rosengarten, D, Abrahamov, A, Nir, A, Farber, B, Glaser, J, Zimran, A & Elstein, D 2007, 'Outcome of ten years' echocardiographic follow-up in children with Gaucher disease', *Eur J Pediatr*, vol. 166, no. 6, pp. 549-551.

Rosenthal, DI, Doppelt, SH, Mankin, HJ, Dambrosia, JM, Xavier, RJ, McKusick, KA, Rosen, BR, Baker, J, Niklason, LT, Hill, SC & et al. 1995, 'Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase', *Pediatrics*, vol. 96, no. 4 Pt 1, Oct, pp. 629-637.

Rubio-Felix, D, Giraldo, P, Perez-Calvo, JI & Giralt, M 1999, 'Type-1 Gaucher disease. Enzymatic replacement therapy and assessment of quality of life', *Blood*, vol. 94, no. 10, Nov 15, pp. 184A-185A.

Sido, PG, Drugan, C, Cret, V, Al-Kzouz, C, Denes, C, Zimmermann, A & Coldea, C 2007, 'Enzyme replacement therapy in romanian patients with type 1 Gaucher disease', *Clin Ther*, vol. 29, 2007, pp. S118-S118.

Sidransky, E, Ginns, EI, Westman, JA & Ehmann, WC 1994, 'Pathologic fractures may develop in Gaucher patients receiving enzyme replacement therapy [5]', *Am J Hematol*, vol. 47, no. 3, pp. 247-249.

Simpson Jr, WL, Hermann, G & Balwani, M 2012, 'Bone marrow alteration in patients with type 1 gaucher disease on enzyme replacement therapy', *Molecular Syndromology*, vol. 2, no. 6, p. 272.

Spada, M, Chiappa, E & Ponzone, A 1998, 'Cardiac response to enzyme-replacement therapy in Gaucher disease', *N Engl J Med*, vol. 339, no. 16, Oct 15, pp. 1165-1166.

Spada, M, Chiappa, E, Sacchetti, S, Ciriotti, G & Ponzone, A 1997, 'Reversible cardiomyopathy with enzyme replacement therapy in Gaucher disease type 1', *J Inherit Metab Dis*, vol. 20, no. SUPPL. 1, 1997, pp. 76-76.

Starzyk, KA & Kingma, W 2003, 'Long term international safety monitoring of ERT in Gaucher disease', *J Inherit Metab Dis*, vol. 26, no. Supplement 2, September, pp. 172-172.

Symeonidis, A, Richfield, L, Miligan, A, Bruce, R, Hughes, D & Mehta, A 2007, 'Achievement of the goals of therapy for patients with Gaucher disease on enzyme replacement therapy is higher among earlier-treated patients and is not influenced by disease severity at presentation', *Haematologica-the Hematology Journal*, vol. 92, Jun, pp. 277-277.

Tantawy, AA, Sherif, EM, Adly, AA, Hassanine, S & Awad, AH 2013, 'Evoked potentials and neurocognitive functions in pediatric Egyptian Gaucher patients on enzyme replacement therapy: a single center experience', *J Inherit Metab Dis*, vol. 36, no. 6, Nov, pp. 1025-1037.

Toth, J, Szucs, FZ, Benko, K & Marodi, L 2003, 'Enzyme replacement therapy in Gaucher-disease: Monitoring visceral and bone changes with MRI', (Enzimszubsztitucios terapia Gaucher-korban: Az MRI-vizsgalat szerepe a visceralis es a csontelvaltozasok monitorozasaban.), *Orv Hetil*, vol. 144, no. 16, Aprilis 20, pp. 749-755.

van Gelder, CM, van Capelle, CI, Ebbink, BJ, Moor-van Nugteren, I, van den Hout, JMP, Hakkesteegt, MM, van Doorn, PA, de Coo, IFM, Reuser, AJJ, de Gier, HHW & van der Ploeg, AT 2012, 'Facial-muscle weakness, speech disorders and dysphagia are common in patients with classic infantile Pompe disease treated with enzyme therapy', *J Inherit Metab Dis*, vol. 35, no. 3, May, pp. 505-511.

vom Dahl, S, Hollak, C, Zimran, A, Charrow, J, Kacena, K, Mistry, P & Grabowski, G 2007, 'Hepatosplenomegaly and blood parameters in Gaucher disease - Analysis of dose-response relationships in enzyme replacement therapy', *Hepatology*, vol. 46, no. 4, Oct, pp. 883A-883A.

vom Dahl, S, Niederau, C & Haussinger, D 1998, 'Loss of vision in Gaucher disease and its reversal by enzyme-replacement therapy', *N Engl J Med*, vol. 338, no. 20, May 14, pp. 1471-1472.

Weinreb, N, Andersson, H, Charrow, J, Kaplan, P, Kolodny, E, Mistry, P, Pastores, G, Rosenbloom, B, Scott, CR, Wappner, R & Zimran, A 1999, 'The gaucher registry: Clinical response after 60 mos of enzyme replacement therapy (ERT)', *Blood*, vol. 94, no. 10, Nov 15, pp. 210A-210A.

Weinreb, NJ, Andersson, H, Charrow, J, Kaplan, P & Kolodny, EH 2000, 'The Gaucher registry: Demographics and disease characteristics and response to enzyme replacement therapy (ERT) for 78 pediatric patients (PTS)', *Blood*, vol. 96, no. 11 PART I.

Weinreb, NJ, Andersson, HC, Charrow, J, Kaplan, P, Kolodny, EH, Mistry, P, Pastores, G, Rosenbloom, BE, Scott, CR & Wappner, RS 2001, 'Clinical factors influencing the achievement of a complete response (CR) after 24 months of enzyme replacement therapy (ERT) in patients with Gaucher disease (GD): The Gaucher Registry', *Blood*, vol. 98, no. 11, Nov 16, pp. 20A-20A.

Wenstrup, R, Kacena, K, Kaplan, P, Pastores, G, Prakash-Cheng, A, Zimran, A & Hangartner, T 2005, 'Effect of enzyme replacement therapy on bone mineral density in type 1 Gaucher disease', *Blood*, vol. 106, no. 11, Nov 16, pp. 54B-54B.

Zahran, AM, Elsayh, KI, El-Deek, SE & El-Baz, MA 2013, 'Oxidative Stress, Trace Elements, and Circulating Microparticles in Patients With Gaucher Disease Before and After Enzyme Replacement Therapy', *Clin Appl Thromb Hemost*, May 22.

Zaman, T & Roya, M 2006, 'Gaucher disease and enzyme replacement therapy, Iranian experience', *J Inherit Metab Dis*, vol. 29, Aug, pp. 46-46.

Zevin, S, Abrahamov, A, Hadashalpern, I, Kannai, R, Levylahad, E, Horowitz, M & Zimran, A 1993, 'ADULT-TYPE GAUCHER DISEASE IN CHILDREN - GENETICS, CLINICAL-FEATURES AND ENZYME REPLACEMENT THERAPY', *Quarterly Journal of Medicine*, vol. 86, no. 9, Sep, pp. 565-573.

Zimran, A, Elstein, D & Abrahamov, A 1995, 'Enzyme replacement therapy in type 1 and type 3 Gaucher disease', *Lancet*, vol. 345, no. 8947, Feb 18, pp. 451-452.

Zimran, A, Elstein, D, Loveday, K, Aliski, W & Fratazzi, C 2006, 'Phase I/II study of glucocerebrosidase replacement therapy in patients with type I Gaucher disease', *Acta Paediatrica*, vol. 95, Apr, pp. 143-143.

Zimran, A, Fratazzi, C, Altarescu, G, Mensah, R & Elstein, D 2007, 'Phase I/II, 9-month study results of enzyme replacement therapy with Gene-Activated (R) human glucocerebrosidase in patients with type 1 Gaucher disease', *Acta Paediatrica*, vol. 96, Apr, pp. 106-106.

Zimran, A, Loveday, K, Fratazzi, C & Elstein, D 2007, 'A pharmacokinetic analysis of a novel enzyme replacement therapy with Gene-Activated (R) human glucocerebrosidase (GA-GCB) in patients with type 1 Gaucher disease', *Blood Cells Molecules and Diseases*, vol. 39, no. 1, Jul-Aug, pp. 115-118.

### Abstract only

Aerts, JM 2008, 'Enzyme replacement therapy versus substrate deprivation in the treatment of lysosomal disorders', *Chemistry and Physics of Lipids*, vol. 154, Aug, pp. S19-S19.

De Vries, JM, Van Der Beek, NAME, Hagemans, MLC, Hop, WCJ, Reuser, AJJ, Van Doorn, PA & Van Der Ploeg, AT 2011, 'Enzyme Replacement Therapy and prognostic factors for response an ongoing open-label cohort study in adults with Pompe disease', *J Inherit Metab Dis*, vol. 34, p. S221.

Garcia, CS, Santin, J, Mello, AS, Pires, GD, Peres, A & Coelho, JC 2014, 'Gaucher disease: Levels of inflammatory factors in patients with and without enzyme replacement therapy', *J Inherit Metab Dis*, vol. 37, no. 1, p. S144.

Hilz, M, Hoppe, U & Koehn, J 2013, 'Stapedius Reflex Testing Demonstrates Impaired Small Muscle Function in Untreated Pompe Patients and Improvement after Enzyme Replacement Therapy', *Neurology*, vol. 80, Feb 12.

Hilz, MJ, Hoppe, U & Koehn, J 2013, 'Stapedius reflex testing demonstrates improvement of small muscle function with enzyme replacement therapy', *J Neurol Sci*, vol. 333, p. e454.

Hwu, WL, Byrne, B, Wraith, E, Leslie, N, Mandel, H, Nicolino, M & Kishnani, PS 2008, 'Alglucosidase ALEA in infants and children with Pompe disease', *J Inherit Metab Dis*, vol. 31, Aug, pp. 130-130.

Laforet, P, Clemens, PR, Corzo, D, Escolar, D, Florence, J, van der Ploeg, A, Lake, S, Mayhew, J, Pestronk, A, Rosenbloom, B, Skrinar, A & Wasserstein, M 2008, 'Safety and efficacy results from a randomized, double-blind, placebo-controlled study of alglucosidase alfa for the treatment of Pompe disease in juveniles and adults', *Neuromuscular Disorders*, vol. 18, no. 9-10, Oct, pp. 832-833.

Nicolino, M, Byrne, B, Hwu, WL, Leslie, N, Mandel, H, Wraith, E & Kishnani, PS 2008, 'Alglucosidase alpha in infants and children with Pompe's disease', *European Journal of Neurology*, vol. 15, Aug, pp. 176-176.

Petakov, M, Suvajdzic, N, Petakov, M, Macut, D, Ognjanovic, S, Elezovic, V, Djurovic, M & Damjanovic, S 2010, 'Serum IGF1 levels in adult patients with type 1 Gaucher disease', *Endocrine Abstracts*, vol. 22, p. P505.

Piran, S & Amato, D 2008, 'Gaucher Disease: A Systematic Review and Meta-Analysis of Bone Complications and Their Response to Treatment', *Blood*, vol. 112, no. 11, Nov 16, pp. 458-458.

Weinreb, N, Andersson, H, Charrow, J, Kaplan, P, Kolodny, E, Mistry, P, Pastores, G, Rosenbloom, B, Scott, CR, Wappner, R & Zimran, A 1999, 'The Gaucher Registry: Demographics and disease characteristics of 996 patients (PTS) on enzyme replacement therapy (ERT) compared to 438 untreated PTS', *Blood*, vol. 94, no. 10, Nov 15, pp. 211A-211A.

Weinreb, NJ & Lee, RE 2004, 'Changing patterns of mortality in Gaucher disease prior to and following the advent of enzyme replacement therapy', *Blood*, vol. 104, no. 11, Nov 16, pp. 36B-36B.

### Foreign language (not a higher level of evidence than available in English)

Roca, M, Mota, J, Giraldo, P, Perez Calvo, J, Gomez Pereda, R & Giralt, M 1997, 'Magnetic resonance in the diagnosis of extent and osseous complications of Gaucher disease type 1', *Rev Clin Esp*, vol. 197, no. 8, pp. 550-554.

### Non-systematic review

Roca, M, Mota, J, Giraldo, P, Perez Calvo, J, Gomez Pereda, R & Giralt, M 1997, 'Magnetic resonance in the diagnosis of extent and osseous complications of Gaucher disease type 1', *Rev Clin Esp*, vol. 197, no. 8, pp. 550-554.

## 

## Fabry disease

### Agalsidase alfa or beta versus placebo

### Systematic Review/Health Technology Assessment[[41]](#footnote-41)

Alegra, T, Vairo, F, de, SMV, Krug, BC & Schwartz, IVD 2012, 'Enzyme replacement therapy for Fabry disease: A systematic review and meta-analysis', *Genet Mol Biol*, vol. 35, no. 4 (suppl), pp. 947-954.

Connock, M, Juarez-Garcia, A, Frew, E, Mans, A, Dretzke, J, Fry-Smith, A & Moore, D 2006, 'A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1', *Health Technol Assess*, vol. 10, no. 20, Jun, pp. iii-iv, ix-113.

Lidove, O, Joly, D, Barbey, F, Bekri, S, Alexandra, JF, Peigne, V, Jaussaud, R & Papo, T 2007, 'Clinical results of enzyme replacement therapy in Fabry disease: a comprehensive review of literature', *International Journal of Clinical Practice*, vol. 61, no. 2, pp. 293-302.

Lidove, O, West, ML, Pintos-Morell, G, Reisin, R, Nicholls, K, Figuera, LE, Parini, R, Carvalho, LR, Kampmann, C, Pastores, GM & Mehta, A 2010, 'Effects of enzyme replacement therapy in Fabry disease - A comprehensive review of the medical literature', *Genetics in Medicine*, vol. 12, no. 11, pp. 668-679.

Rombach, SM, Smid, BE, Linthorst, GE, Dijkgraaf, MGW & Hollak, CEM 2014, 'Natural course of Fabry disease and the effectiveness of enzyme replacement therapy: a systematic review and meta-analysis - Effectiveness of ERT in different disease stages', *J. Inherited Metab. Dis.*, vol. 37, no. 3, //, pp. 341-352.

### Cohort study

Rombach, SM, Smid, BE, Bouwman, MG, Linthorst, GE, Dijkgraaf, MGW & Hollak, CEM 2013, 'Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain', *Orphanet Journal of Rare Diseases*, vol. 8, Mar.

Sirrs, SM, Bichet, DG, Casey, R, Clarke, JT, Lemoine, K, Doucette, S & West, ML 2014, 'Outcomes of patients treated through the Canadian Fabry disease initiative', *Mol Genet Metab*, vol. 111, no. 4, Apr, pp. 499-506.

Uceyler, N, He, L, Schonfeld, D, Kahn, AK, Reiners, K, Hilz, MJ, Breunig, F & Sommer, C 2011, 'Small fibers in Fabry disease: Baseline and follow-up data under enzyme replacement therapy', *Journal of the Peripheral Nervous System*, vol. 16, no. 4, pp. 304-314.

van Breemen, MJ, Rombach, SM, Dekker, N, Poorthuis, BJ, Linthorst, GE, Zwinderman, AH, Breunig, F, Wanner, C, Aerts, JM & Hollak, CE 2011, 'Reduction of elevated plasma globotriaosylsphingosine in patients with classic Fabry disease following enzyme replacement therapy', *Biochim Biophys Acta*, vol. 1812, no. 1, Jan, pp. 70-76.

Weidemann, F, Niemann, M, Stoerk, S, Breunig, F, Beer, M, Sommer, C, Herrmann, S, Ertl, G & Wanner, C 2013, 'Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications', *J. Intern. Med.*, vol. 274, no. 4, //, pp. 331-341.

### Case series

Andrikos, E, Iatrou, C, Boletis, JN, Diamandopoulos, A, Katsinas, C, Kalaitzidis, K, Galinas, A, Xaidara, A, Pappas, M & Siamopoulos, KC 2010, 'Evolution of Fabry disease in male patients: The Greek experience', *Clinical Nephrology*, vol. 73, no. 1, pp. 58-63.

Biancini, GB, Vanzin, CS, Rodrigues, DB, Deon, M, Ribas, GS, Barschak, AG, Manfredini, V, Netto, CBO, Jardim, LB, Giugliani, R & Vargas, CR 2012, 'Globotriaosylceramide is correlated with oxidative stress and inflammation in Fabry patients treated with enzyme replacement therapy', *Biochim. Biophys. Acta, Mol. Basis Dis.*, vol. 1822, no. 2, pp. 226-232.

Campbell, RC, Jackson, L, Thomas, CP, Birrer, E, Guasch, T, Laney, DA, Charrow, J, Widera, S, Warnock, DG & Investigators, F 2010, 'FABRY NEPHROPATHY AND THE FABRAZYME AND ARBS AND ACE INHIBITOR TREATMENT (FAACET) STUDY: DETERMINANTS OF PROTEINURIA DURING THE TITRATION PHASE', *Clinical Therapeutics*, vol. 32, pp. S115-S115.

Cartwright, DJ, Cole, AL, Cousins, AJ & Lee, PJ 2004, 'Raised HDL cholesterol in Fabry disease: Response to enzyme replacement therapy', *Journal of Inherited Metabolic Disease*, vol. 27, no. 6, pp. 791-793.

Fujii, H, Kono, K, Yamamoto, T, Onishi, T, Goto, S, Nakai, K, Kawai, H, Hirata, KI, Fukagawa, M & Nishi, S 2012, 'Effect of enzyme replacement therapy on serum asymmetric dimethylarginine levels, coronary flow reserve and left ventricular hypertrophy in patients with Fabry disease', *Clinical Kidney Journal*, vol. 5, no. 6, pp. 512-518.

Goker-Alpan, O, Nedd, K, Shankar, S, Lien, YH, Weinreb, N, Wijatyk, A, Chang, P & Martin, R 2014, 'HGT-REP-059 treatment protocol: effect and tolerability of open-label agalsidase alfa in patients with Fabry disease', *Molecular Genetics and Metabolism*, vol. 111, no. 2, pp. S48-S48.

Kovacevic-Preradovic, T, Zuber, M, Attenhofer, JCH, Widmer, U, Seifert, B, Schulthess, G, Fischer, A & Jenni, R 2008, 'Anderson-Fabry disease: long-term echocardiographic follow-up under enzyme replacement therapy', *Eur J Echocardiogr*, vol. 9, no. 6, //, pp. 729-735.

Lin, HY, Liu, HC, Huang, YH, Liao, HC, Hsu, TR, Shen, CI, Li, ST, Li, CF, Lee, LH, Lee, PC, Huang, CK, Chiang, CC, Lin, CY, Lin, SP & Niu, DM 2013, 'Effects of enzyme replacement therapy i for cardiac-type Fabry patients with a Chinese hotspot late-onset Fabry mutation (IVS4+919G>A)', *BMJ Open*, vol. 3, no. 7.

Lin, H-Y, Huang, Y-H, Liao, H-C, Liu, H-C, Hsu, T-R, Shen, C-I, Li, S-T, Li, C-F, Lee, L-H, Lee, P-C, Huang, C-K, Chiang, C-C, Lin, S-P & Niu, D-M 2014, 'Clinical observations on enzyme replacement therapy in patients with Fabry disease and the switch from agalsidase beta to agalsidase alfa', *J. Chin. Med. Assoc.*, vol. 77, no. 4, pp. 190-197.

Linthorst, GE, Hollak, CE, Donker-Koopman, WE, Strijland, A & Aerts, JM 2004, 'Enzyme therapy for Fabry disease: neutralizing antibodies toward agalsidase alpha and beta', *Kidney International*, vol. 66, no. 4, pp. 1589-1595.

Linthorst, GE, Van Breemen, MJ, Rombach, SM, Dekker, N, Zwinderman, AH, Breunig, F, Wanner, C, Aerts, JMFG & Hollak, CEM 2010, 'Reduction of elevated plasma globotriaosylsphingosine following enzyme replacement therapy in patients with classic fabry disease', *Journal of Inherited Metabolic Disease*, vol. 33, p. S133.

Lobo, T, Morgan, J, Bjorksten, A, Nicholls, K, Grigg, L, Centra, E & Becker, G 2008, 'Cardiovascular testing in Fabry disease: Exercise capacity reduction, chronotropic incompetence and improved anaerobic threshold after enzyme replacement', *Internal Medicine Journal*, vol. 38, no. 6 A, pp. 407-414.

Mehta, A, Beck, M, Elliott, P, Giugliani, R, Linhart, A, Sunder-Plassmann, G, Schiffmann, R, Barbey, F, Ries, M & Clarke, JT 2009, 'Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data', *Lancet*, vol. 374, no. 9706, Dec 12, pp. 1986-1996.

Mignani, R, Feriozzi, S, Pisani, A, Cioni, A, Comotti, C, Cossu, M, Foschi, A, Giudicissi, A, Gotti, E, Lozupone, VA, Marchini, F, Martinelli, F, Bianco, F, Panichi, V, Procaccini, DA, Ragazzoni, E, Serra, A, Soliani, F, Spinelli, L, Torti, G, Veroux, M, Cianciaruso, B & Cagnoli, L 2008, 'Agalsidase therapy in patients with Fabry disease on renal replacement therapy: a nationwide study in Italy', *Nephrol Dial Transplant*, vol. 23, no. 5, May, pp. 1628-1635.

Pisani, A, Spinelli, L, Sabbatini, M, Andreucci, MV, Procaccini, D, Abbaterusso, C, Pasquali, S, Savoldi, S, Comotti, C & Cianciaruso, B 2005, 'Enzyme replacement therapy in Fabry disease patients undergoing dialysis: Effects on quality of life and organ involvement', *American Journal of Kidney Diseases*, vol. 46, no. 1, pp. 120-127.

Pisani, A, Spinelli, L, Visciano, B, Capuano, I, Sabbatini, M, Riccio, E, Messalli, G & Imbriaco, M 2013, 'Effects of switching from agalsidase Beta to agalsidase alfa in 10 patients with anderson-fabry disease', *JIMD Rep*, vol. 9, pp. 41-48.

Rombach, SM, Aerts, J, Poorthuis, B, Groener, JEM, Donker-Koopman, W, Hendriks, E, Mirzaian, M, Kuiper, S, Wijburg, FA, Hollak, CEM & Linthorst, GE 2012, 'Long-Term Effect of Antibodies against Infused Alpha-Galactosidase A in Fabry Disease on Plasma and Urinary (lyso)Gb3 Reduction and Treatment Outcome', *Plos One*, vol. 7, no. 10, Oct.

Smid, BE, Hoogendijk, SL, Wijburg, FA, Hollak, CE & Linthorst, GE 2013, 'A revised home treatment algorithm for Fabry disease: influence of antibody formation', *Mol Genet Metab.*, vol. 108, no. 2, Feb, pp. 132-137. [Molecular genetics and metabolism].

Thompson, L, Bleakley, C & Hallows, L 2010, 'Experience of switching enzyme replacement therapy (ERT) products in patients with Anderson fabry disease: A specialist nurse perspective', *Journal of Inherited Metabolic Disease*, vol. 33, p. S153.

Tondel, C, Bostad, L, Larsen, KK, Hirth, A, Vikse, BE, Houge, G & Svarstad, E 2013, 'Agalsidase benefits renal histology in young patients with Fabry disease', *Journal of the American Society of Nephrology*, vol. 24, no. 1, pp. 137-148.

Tondel, C, Bostad, L & Svarstad, E 2010, 'Renal follow-up biopsies in young male fabry patients on enzyme replacement therapy', *Clinical Therapeutics*, vol. 32, pp. S105-S107.

Tsuboi, K 2007, 'Enzyme replacement therapy in patients with Fabry's disease', *Journal of International Medical Research*, vol. 35, no. 4, pp. 574-581.

Tsuboi, K & Yamamoto, H 2012, 'Clinical observation of patients with Fabry disease after switching from agalsidase beta (Fabrazyme) to agalsidase alfa (Replagal)', *Genetics in Medicine*, vol. 14, no. 9, pp. 779-786.

—— 2014, 'Clinical course of patients with Fabry disease who were switched from agalsidase-beta to agalsidase-alpha', *Genet Med*, Mar 20.

Wakabayashi, T, Sakuma, M, Morita, A, Ohashi, T, Eto, Y & Ida, H 2013, 'The effect of switching treatment from agalsidase-(beta) to agalsidase-(alpha) on renal function in 18 adults with Fabry disease', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, p. S282.

Warnock, GD, Jackson, L, Thomas, C, Phillips, E, Guasch, T, Laney, AD, Charrow, J & Widera, S 2010, 'Fabry nephropathy (FN) and the agalsidase beta and ARBs and ACE inhibitor treatment (FAACET) study: Determinants of proteinuria during the titration phase', *Molecular Genetics and Metabolism*, vol. 99, no. 2, p. S38.

Weidemann, F, Kramer, J, Duning, T, Lenders, M, Canaan-Kuhl, S, Krebs, A, Gonzalez, HG, Sommer, C, Uceyler, N, Niemann, M, Stork, S, Schelleckes, M, Reiermann, S, Stypmann, J, Brand, SM, Wanner, C & Brand, E 2014, 'Patients with Fabry Disease after Enzyme Replacement Therapy Dose Reduction Versus Treatment Switch', *Journal of the American Society of Nephrology*, vol. 25, no. 4, pp. 837-849.

West, M & Lemoine, K 2006, 'Effect of changing therapy from agalsidase beta to agalsidase alfa in patients with Fabry disease', *Acta Paediatrica*, vol. 95, Apr, pp. 136-136.

Wuest, W, Machann, W, Breunig, F, Weidemann, F, Koestler, H, Hahn, D, Wanner, C & Beer, M 2011, 'Right ventricular involvement in patients with Fabry's disease and the effect of enzyme replacement therapy', *RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin*, vol. 183, no. 11, pp. 1037-1042.

### Erratum

Tsuboi, K & Yamamoto, H 2012, 'Erratum: Clinical observation of patients with Fabry disease after switching from agalsidase beta (Fabrazyme) to agalsidase alfa (Replagal) (Genetics in Medicine (2012) DOI:10.1038/gim.2012.39)', *Genetics in Medicine*, vol. 14, no. 8, p. 762.

WCB WR, MM, R Finkel, S Packman 2009, 'Erratum', *American Journal of Nephrology*, vol. 29, no. 5, pp. 361-361.

### Agalsidase alfa versus placebo

### Dose comparison (two doses of same treatment, without alternative treatment as comparator)

Hughes, DA, Deegan, PB, Milligan, A, Wright, N, Butler, LH, Jacobs, A & Mehta, AB 2013, 'A randomised, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of three dosing schedules of agalsidase alfa enzyme replacement therapy for Fabry disease', Mol Genet Metab, vol. 109, no. 3, Jul, pp. 269-275.

### Wrong outcomes

Hajioff, D, Enever, Y, Quiney, R, Zuckerman, J, Macdermot, K & Mehta, A 2003, 'Hearing loss in Fabry disease: The effect of agalsidase alfa replacement therapy', Journal of Inherited Metabolic Disease, vol. 26, no. 8, pp. 787-794.

Hajioff, D, Goodwin, S, Quiney, R, Zuckerman, J, MacDermot, KD & Mehta, A 2003, 'Hearing improvement in patients with Fabry disease treated with agalsidase alfa', Acta paediatrica (Oslo, Norway : 1992). Supplement, vol. 92, no. 443, pp. 28-30; discussion 27.

### Duplicated data

Moore, DF, Scott, LT, Gladwin, MT, Altarescu, G, Kaneski, C, Suzuki, K, Pease-Fye, M, Ferri, R, Brady, RO, Herscovitch, P & Schiffmann, R 2001, 'Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy', Circulation, vol. 104, no. 13, Sep 25, pp. 1506-1512.

Schiffmann, R, Hauer, P, Freeman, B, Ries, M, Scott, LJC, Polydefkis, M, Brady, RO, McArthur, JC & Wagner, K 2006, 'Enzyme replacement therapy and intraepidermal innervation density in fabry disease', Muscle Nerve, vol. 34, no. 1, pp. 53-56.

Schiffmann, R, Martin, RA, Reimschisel, T, Johnson, K, Castaneda, V, Lien, YH, Pastores, GM, Kampmann, C, Ries, M & Clarke, JTR 2010, 'Four-Year Prospective Clinical Trial of Agalsidase Alfa in Children with Fabry Disease', J. Pediatr. (N. Y., NY, U. S.), vol. 156, no. 5, pp. 832-837, e832/831.

Schiffmann, R, Ries, M, Blankenship, D, Nicholls, K, Mehta, A, Clarke, JT, Steiner, RD, Beck, M, Barshop, BA, Rhead, W, West, M, Martin, R, Amato, D, Nair, N & Huertas, P 2013, 'Changes in plasma and urine globotriaosylceramide levels do not predict Fabry disease progression over 1 year of agalsidase alfa', Genet Med, vol. 15, no. 12, Dec, pp. 983-989.

Thurberg, BL, Rennke, H, Colvin, RB, Dikman, S, Gordon, RE, Collins, AB, Desnick, RJ & O'Callaghan, M 2002, 'Globotriaosylceramide accumulation in the fabry kidney is cleared from multiple cell types after enzyme replacement therapy', Kidney International, vol. 62, no. 6, pp. 1933-1946.

West, M, Nicholls, K, Mehta, A, Clarke, JTR, Steiner, R, Beck, M, Barshop, BA, Rhead, W, Mensah, R, Ries, M & Schiffmann, R 2009, 'Agalsidase alfa and kidney dysfunction in Fabry disease', Journal of the American Society of Nephrology, vol. 20, no. 5, pp. 1132-1139.

### Cohort study

Germain, DP, Weidemann, F, Abiose, A, Patel, MR, Cizmarik, M, Cole, JA, Beitner-Johnson, D, Benistan, K, Cabrera, G, Charrow, J, Kantola, I, Linhart, A, Nicholls, K, Niemann, M, Scott, CR, Sims, K, Waldek, S, Warnock, DG, Strotmann, J & Fabry, R 2013, 'Analysis of left ventricular mass in untreated men and in men treated with agalsidase-beta: data from the Fabry Registry', *Genetics in Medicine*, vol. 15, no. 12, pp. 958-965.

Hoffmann, B, Beck, M, Sunder-Plassmann, G, Borsini, W, Ricci, R, Mehta, A & Invest, FOSE 2007, 'Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy - A retrospective analysis from the Fabry outcome survey', *Clinical Journal of Pain*, vol. 23, no. 6, pp. 535-542.

Hoffmann, B, Garcia de Lorenzo, A, Mehta, A, Beck, M, Widmer, U & Ricci, R 2005, 'Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey)', *J Med Genet*, vol. 42, no. 3, Mar, pp. 247-252.

Hoffmann, B, Schwarz, M, Mehta, A, Keshav, S & Fabry Outcome Survey European, I 2007, 'Gastrointestinal symptoms in 342 patients with Fabry disease: Prevalence and response to enzyme replacement therapy', *Clinical Gastroenterology and Hepatology*, vol. 5, no. 12, pp. 1447-1453.

### Case series

Baehner, F, Kampmann, C, Whybra, C, Miebach, E, Wiethoff, CM & Beck, M 2003, 'Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study', *Journal of Inherited Metabolic Disease*, vol. 26, no. 7, pp. 617-627.

Barbey, F & Livio, F 2006, 'Safety of enzyme replacement therapy', *Fabry Disease: Perspectives from 5 Years of FOS*.

Beck, M, Ricci, R, Widmer, U, Dehout, F, García De Lorenzo, A, Kampmann, C, Linhart, A, Sunder-Plassmann, G, Houge, G, Ramaswami, U, Gal, A & Mehta, A 2004, 'Fabry disease: Overall effects of agalsidase alfa treatment', *European Journal of Clinical Investigation*, vol. 34, no. 12, pp. 838-844.

Bongiorno, MR, Pistone, G & Arico, M 2003, 'Fabry disease: Enzyme replacement therapy', *Journal of the European Academy of Dermatology and Venereology*, vol. 17, no. 6, pp. 676-679.

Breunig, F, Weidemann, F, Strotmann, J, Knoll, A & Wanner, C 2006, 'Clinical benefit of enzyme replacement therapy in Fabry disease', *Kidney International*, vol. 69, no. 7, pp. 1216-1221.

Cybulla, M, Walter, KN, Schwarting, A, Divito, R, Feriozzi, S & Sunder-Plassmann, G 2009, 'Kidney transplantation in patients with Fabry disease', *Transpl Int*, vol. 22, no. 4, Apr, pp. 475-481.

Cybulla, M, West, M, Nicholls, K, Torras, J, Neumann, P, Sunder-Plassmann, G & Feriozzi, S 2014, 'Efficacy and safety of enzyme replacement therapy (ERT) in acohort of kidney transplant recipients with Fabry disease', *Nephrology Dialysis Transplantation*, vol. 29, p. iii349.

Dehout, F, Roland, D, Treille de Granseigne, S, Guillaume, B & Van Maldergem, L 2004, 'Relief of gastrointestinal symptoms under enzyme replacement therapy [corrected] in patients with Fabry disease', *J Inherit Metab Dis*, vol. 27, no. 4, pp. 499-505.

Dehout, F, Schwarting, A, Beck, M, Mehta, A, Ricci, R & Widmer, U 2003, 'Effects of enzyme replacement therapy with agalsidase alfa on glomerular filtration rate in patients with Fabry disease: preliminary data', *Acta Paediatr Suppl*, vol. 92, no. 443, Dec, pp. 14-15; discussion 15.

Feriozzi, S 2009, 'Agalsidase alfa slows the decline in renal function in patients with Fabry disease (vol 29, pg 353, 2009)', *American Journal of Nephrology*, vol. 29, no. 5.

Feriozzi, S, Schwarting, A, Sunder-Plassmann, G, West, M & Cybulla, M 2009, 'Agalsidase Alfa Slows the Decline in Renal Function in Patients with Fabry Disease', *Am. J. Nephrol.*, vol. 29, no. 5, pp. 353-361.

Feriozzi, S, Torras, J, Cybulla, M, Nicholls, K, Sunder-Plassmann, G & West, M 2012, 'The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy', *Clin J Am Soc Nephrol*, vol. 7, no. 1, Jan, pp. 60-69.

Hajioff, D, Hegemannn, S, Conti, G, Beck, M, Sunder-Plassmann, G, Widmer, U, Mehta, A & Keilmann, A 2006, 'Agalsidase alpha and hearing in Fabry disease: Data from the Fabry Outcome Survey', *European Journal of Clinical Investigation*, vol. 36, no. 9, pp. 663-667.

Hartung, R, Schaefer, E, Mengel, E & Beck, M 2006, 'Infusion reactions to agalsidase alfa in relation to Fabry genotype', *Acta Paediatrica*, vol. 95, Apr, pp. 137-137.

Hilz, MJ, Brys, M, Marthol, H, Stemper, B & Duetsch, M 2004, 'Enzyme replacement therapy improves function of C-, Aδ-, and Aβ-nerve fibers in Fabry neuropathy', *Neurology*, vol. 62, no. 7, pp. 1066-1072.

Hoffmann, B, Schwarz, M, Mehta, A & Keshav, S 2007, 'Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy', *Clin Gastroenterol Hepatol*, vol. 5, no. 12, pp. 1447-1453.

Hughes, DA, Barba Romero, MA, Hollak, CE, Giugliani, R & Deegan, PB 2011, 'Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS--the Fabry Outcome Survey', *Mol Genet Metab*, vol. 103, no. 3, Jul, pp. 207-214.

Imbriaco, M, Pisani, A, Spinelli, L, Cuocolo, A, Messalli, G, Capuano, E, Marmo, M, Liuzzi, R, Visciano, B, Cianciaruso, B & Salvatore, M 2009, 'Effects of enzyme-replacement therapy in patients with Anderson-Fabry disease: A prospective longterm cardiac magnetic resonance imaging study', *Heart*, vol. 95, no. 13, pp. 1103-1107.

Jardim, L, Vedolin, L, Schwartz, IV, Burin, MG, Cecchin, C, Kalakun, L, Matte, U, Aesse, F, Pitta-Pinheiro, C, Marconato, J & Giugliani, R 2004, 'CNS involvement in Fabry disease: clinical and imaging studies before and after 12 months of enzyme replacement therapy', *Journal of Inherited Metabolic Disease*, vol. 27, no. 2, pp. 229-240.

Jardim, LB, Gomes, I, Netto, CB, Nora, DB, Matte, US, Pereira, F, Burin, MG, Kalakun, L, Giugliani, R & Becker, J 2006, 'Improvement of sympathetic skin responses under enzyme replacement therapy in Fabry disease', *Journal of Inherited Metabolic Disease*, vol. 29, no. 5, pp. 653-659.

Kampmann, C, Linhart, A, Devereux, RB & Schiffmann, R 2009, 'Effect of agalsidase alfa replacement therapy on Fabry disease-related hypertrophic cardiomyopathy: a 12- to 36-month, retrospective, blinded echocardiographic pooled analysis', *Clin Ther*, vol. 31, no. 9, Sep, pp. 1966-1976.

Kisinovsky, I, Caceres, G, Coronel, C & Reisin, R 2013, 'Home infusion program for Fabry disease: experience with agalsidase alfa in Argentina', *Medicina (B Aires)*, vol. 73, no. 1, //, pp. 31-34.

Kleinert, J, Dehout, F, Schwarting, A, de Lorenzo, AG, Ricci, R, Kampmann, C, Beck, M, Ramaswami, U, Linhart, A, Gal, A, Houge, G, Widmer, U, Mehta, A & Sunder-Plassmann, G 2005, 'Anemia is a new complication in Fabry disease: data from the Fabry Outcome Survey', *Kidney International*, vol. 67, no. 5, pp. 1955-1960.

Mehta, A, Beck, M, Elliott, P, Giugliani, R, Linhart, A, Sunder-Plassmann, G, Schiffmann, R, Barbey, F, Ries, M & Clarke, JT 2009, 'Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data', *Lancet*, vol. 374, no. 9706, Dec 12, pp. 1986-1996.

Palla, A, Hegemann, S, Widmer, U & Straumann, D 2007, 'Vestibular and auditory deficits in Fabry disease and their response to enzyme replacement therapy', *Journal of neurology*, vol. 254, no. 10, pp. 1433-1442.

Palla, A, Widmer, U & Straumann, D 2003, 'Head-impulse testing in Fabry disease - Vestibular function in male and female patients', *Acta Paediatrica, International Journal of Paediatrics, Supplement*, vol. 92, no. 443, pp. 38-42.

Pano, A, Goker-Alpan, O, Longo, N, McDonald, M, Shankar, S, Shen, YH, Chang, P & Schiffmann, R 2014, 'Safety and effect of open-label agalsidase alfa in treatment-naive children with Fabry disease', *Molecular Genetics and Metabolism*, vol. 111, no. 2, Feb, pp. S84-S84.

Parini, R, Santus, F, Pintos-Morell, G, Ramaswami, U, Beck, M & Kalkum, G 2009, 'Prevalence of gastrointestinal symptoms and effectiveness of enzyme replacement therapy with agalsidase alfa in children - Data from FOS - Fabry outcome survey', *Molecular Genetics and Metabolism*, vol. 98, no. 1-2, p. 82.

Ramaswami, U, Parini, R, Kampmann, C & Beck, M 2011, 'Safety of agalsidase alfa in patients with Fabry disease under 7 years', *Acta Paediatr*, vol. 100, no. 4, Apr, pp. 605-611.

Ramaswami, U, Wendt, S, Pintos-Morell, G, Parini, R, Whybra, C, Leal, JAL, Santus, F & Beck, M 2007, 'Enzyme replacement therapy with agalsidase alfa in children with Fabry disease', *Acta Paediatrica*, vol. 96, no. 1, Jan, pp. 122-127.

Ries, M, Clarke, JTR, Whybra, C, Timmons, M, Robinson, C, Schlaggar, BL, Pastores, G, Lien, YH, Kampmann, C, Brady, RO, Beck, M & Schiffmann, R 2006, 'Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease', *Pediatrics*, vol. 118, no. 3, pp. 924-932.

Rivera Gallego, A, Lopez Rodriguez, M, Barbado Hernandez, FJ, Barba Romero, MA, Garcia De Lorenzo, YMA, Pintos Morell, G, Barba, MA, Gomez Huertas, E, Herrera, J, Bonal, AJ, Pintos, GJ, Ballarin, J, Torra, J, Torras, J, Torregrosa, V, Gonzalez, J, Martin, I, Hernandez, S, Barbado, FJ, Garcia-Consuegra, J, Lopez, M, Garcia De Lorenzo, A, Paniaga, J, Fernandez, V, Andreu, J, Febrer, I, Perez Garcia, A & Rivera, A 2006, 'Fabry disease in Spain: First analysis of the response to enzyme replacement therapy', *Medicina Clinica*, vol. 127, no. 13, pp. 481-484.

Russo, R, Pisani, A, Messalli, G & Imbriaco, M 2012, 'Effects of switch therapy with agalsidase-alfa in patients with anderson-fabry disease (AFD) previously treated with agalsidase-beta: A prospective cardiac magnetic resonance imaging study', *Nephrology Dialysis Transplantation*, vol. 27, pp. ii323-ii324.

Schiffmann, R, Askari, H, Timmons, M, Robinson, C, Benko, W, Brady, RO & Ries, M 2007, 'Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing', *J. Am. Soc. Nephrol.*, vol. 18, no. 5, pp. 1576-1583.

Schiffmann, R, Castaneda, V, Lien, YH, Chang, P, Martin, R, Pastores, G & Wijatyk, A 2013, 'Agalsidase alfa in paediatric patients with Fabry disease: A 7-year open-label study', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, pp. S300-S301.

Schiffmann, R, Martin, RA, Reimschisel, T, Johnson, K, Castaneda, V, Lien, YH, Pastores, GM, Kampmann, C, Ries, M & Clarke, JTR 2010, 'Four-Year Prospective Clinical Trial of Agalsidase Alfa in Children with Fabry Disease', *Journal of Pediatrics*, vol. 156, no. 5, pp. 832-837.e831.

Schiffmann, R, Ries, M, Timmons, M, Flaherty, JT & Brady, RO 2006, 'Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting', *Nephrol Dial Transplant*, vol. 21, no. 2, Feb, pp. 345-354.

Schwarting, A, Dehout, F, Feriozzi, S, Beck, M, Mehta, A & Sunder-Plassman, G 2006, 'Enzyme replacement therapy and renal function in 201 patients with fabry disease', *Clin. Nephrol.*, vol. 66, no. 2, pp. 77-84.

Schwarting, A, Sunder-Plassmann, G, Mehta, A & Beck, M 2006, 'Effect of enzyme replacement therapy with agalsidase alfa on renal function in patients with Fabry disease: data from FOS - the Fabry Outcome Survey', *Fabry Disease: Perspectives from 5 Years of FOS*.

Thofehrn, S, Netto, C, Cecchin, C, Burin, M, Matte, U, Brustolin, S, Nunes, ACF, Coelho, J, Tsao, M, Jardim, L, Giugliani, R & Barros, EJG 2009, 'Kidney Function and 24-Hour Proteinuria in Patients with Fabry Disease during 36 Months of Agalsidase Alfa Enzyme Replacement Therapy: A Brazilian Experience', *Renal Failure*, vol. 31, no. 9, pp. 773-778.

Undas, A, Rys, D, Brzezinska-Kolarz, B, Padjas, A & Musial, J 2004, 'The first Polish experience with enzyme replacement therapy in patients with Fabry disease', *Polskie Archiwum Medycyny Wewnetrznej*, vol. 112, no. 6, pp. 1479-1486.

Weidemann, F, Breunig, F, Beer, M, Sandstede, J, Turschner, O, Voelker, W, Ertl, G, Knoll, A, Wanner, C & Strotmann, JM 2003, 'Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study', *Circulation*, vol. 108, no. 11, pp. 1299-1301, DOI 10.1161/01.CIR.0000091253.71282.04,

Weidemann, F, Niemann, M, Breunig, F, Herrmann, S, Beer, M, Stork, S, Voelker, W, Ertl, G, Wanner, C & Strotmann, J 2009, 'Long-Term Effects of Enzyme Replacement Therapy on Fabry Cardiomyopathy Evidence for a Better Outcome With Early Treatment', *Circulation*, vol. 119, no. 4, Feb, pp. 524-529.

Whybra, C, Kampmann, C, Krummenauer, F, Ries, M, Mengel, E, Miebach, E, Baehner, F, Kim, K, Bajbouj, M, Schwarting, A, Gal, A & Beck, M 2004, 'The Mainz Severity Score Index: a new instrument for quantifying the Anderson-Fabry disease phenotype, and the response of patients to enzyme replacement therapy', *Clin Genet*, vol. 65, no. 4, Apr, pp. 299-307.

Whybra, C, Kampmann, C, Miebach, E, Gal, A, Baron, K & Beck, M 2008, 'Long-term efficacy and safety of agalsidase alfa in women with Fabry disease', *Journal of Inherited Metabolic Disease*, vol. 31, Aug, pp. 107-107.

Whybra, C, Miebach, E, Mengel, E, Gal, A, Baron, K, Beck, M & Kampmann, C 2009, 'A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease', *Genet Med*, vol. 11, no. 6, Jun, pp. 441-449.

Zamorano, J, Serra, V, De Isla, LP, Feltes, G, Calli, A, Barbado, FJ, Torras, J, Hernandez, S, Herrera, J, Herrero, JA & Pintos, G 2011, 'Usefulness of tissue Doppler on early detection of cardiac disease in Fabry patients and potential role of enzyme replacement therapy (ERT) for avoiding progression of disease', *European Journal of Echocardiography*, vol. 12, no. 9, pp. 671-677.

### Erratum

'Erratum: Agalsidase alfa slows the decline in renal function in patients with Fabry disease (American Journal of Nephrology (2009) 29 (353-361))', 2009, *American Journal of Nephrology*, vol. 29, no. 5, pp. 353-361.

Hajioff, D, Hegemann, S, Conti, G, Beck, M, Sunder-Plassmann, G, Widmer, U, Mehta, A & Keilmann, A 2007, 'Erratum: Agalsidase alpha and hearing in Fabry disease: Data from the Fabry outcome survey (European Journal of Clinical Investigation (2006) 36, (663-667))', *European Journal of Clinical Investigation*, vol. 37, no. 10, p. 828.

### Agalsidase beta versus placebo

### Duplicated data

Germain, DP, Waldek, S, Banikazemi, M, Bushinsky, DA, Charrow, J, Desnick, RJ, Lee, P, Loew, T, Vedder, AC, Abichandani, R, Wilcox, WR & Guffon, N 2007, 'Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease', *J Am Soc Nephrol*, vol. 18, no. 5, May, pp. 1547-1557.

Wijburg, F, Benichou, B, Bichet, DG, Dostalova, G, Clarke, L, Fainboim, A, Fellgiebel, A, Forcelini, C, Haack, KA, Hopkin, R, Scott, CR, Shankar, S, Tylki-Szymanska, A, Tondel, C & Ramaswami, U 2013, 'A randomized, multicenter, multinational, phase 3B, open-label, parallel-group study of agalsidase beta in treatment-naive male pediatric patients with Fabry disease without severe symptoms: Baseline demographics and clinical data', *Molecular Genetics and Metabolism*, vol. 108, no. 2, Feb, pp. S99-S99.

Wilcox, WR, Banikazemi, M, Guffon, N, Waldek, S, Lee, P, Linthorst, GE, Desnick, RJ & Germain, DP 2004, 'Long-term safety and efficacy of enzyme replacement therapy for Fabry disease', *Am J Hum Genet*, vol. 75, no. 1, Jul, pp. 65-74.

### Cohort study

Collin, C, Briet, M, Tran, TC, Beaussier, H, Benistan, K, Bensalah, M, Mousseaux, E, Froissart, M, Bozec, E, Laurent, S, Boutouyrie, P & Germain, DP 2012, 'Long-term changes in arterial structure and function and left ventricular geometry after enzyme replacement therapy in patients affected with Fabry disease', *Eur J Prev Cardiol*, vol. 19, no. 1, Feb, pp. 43-54.

Germain, DP, Weidemann, F, Abiose, A, Patel, MR, Cizmarik, M, Cole, JA, Beitner-Johnson, D, Benistan, K, Cabrera, G, Charrow, J, Kantola, I, Linhart, A, Nicholls, K, Niemann, M, Scott, CR, Sims, K, Waldek, S, Warnock, DG & Strotmann, J 2013, 'Analysis of left ventricular mass in untreated men and in men treated with agalsidase-(beta): Data from the Fabry Registry', *Genetics in Medicine*, vol. 15, no. 12, pp. 958-965.

Hilz, MJ, Koehn, J, Kolodny, EH, Brys, M, Moeller, S & Stemper, B 2011, 'Metronomic breathing shows altered parasympathetic baroreflex function in untreated Fabry patients and baroreflex improvement after enzyme replacement therapy', *J Hypertens*, vol. 29, no. 12, Dec, pp. 2387-2394.

Hilz, MJ, Marthol, H, Schwab, S, Kolodny, EH, Brys, M & Stemper, B 2010, 'Enzyme replacement therapy improves cardiovascular responses to orthostatic challenge in Fabry patients', *J Hypertens*, vol. 28, no. 7, Jul, pp. 1438-1448.

Motwani, M, Banypersad, S, Woolfson, P & Waldek, S 2012, 'Enzyme replacement therapy improves cardiac features and severity of Fabry disease', *Molecular Genetics and Metabolism*, vol. 107, no. 1-2, pp. 197-202.

### Case series

Alamartine, E 2005, 'Enzyme replacement therapy in nine patients with Fabry disease', *Medecine/Sciences*, vol. 21, no. SPEC. ISS. NOV., pp. 62-65.

Banikazemi, M, Ullman, T & Desnick, RJ 2005, 'Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy', *Mol Genet Metab*, vol. 85, no. 4, Aug, pp. 255-259.

Beer, M, Weidemann, F, Breunig, F, Knoll, A, Koeppe, S, Machann, W, Hahn, D, Wanner, C, Strotmann, J & Sandstede, J 2006, 'Impact of Enzyme Replacement Therapy on Cardiac Morphology and Function and Late Enhancement in Fabry's Cardiomyopathy', *American Journal of Cardiology*, vol. 97, no. 10, pp. 1515-1518.

Bodensteiner, D, Scott, CR, Sims, KB, Shepherd, GM, Cintron, RD & Germain, DP 2008, 'Successful reinstitution of agalsidase beta therapy in Fabry disease patients with previous IgE-antibody or skin-test reactivity to the recombinant enzyme', *Genet. Med.*, vol. 10, no. 5, pp. 353-358.

Borgwardt, L, Feldt-Rasmussen, U, Rasmussen, AK, Ballegaard, M & Meldgaard Lund, A 2013, 'Fabry disease in children: agalsidase-beta enzyme replacement therapy', *Clin Genet*, vol. 83, no. 5, May, pp. 432-438.

Choi, JH, Cho, YM, Suh, KS, Yoon, HR, Kim, GH, Kim, SS, Ko, JM, Lee, JH, Park, YS & Yoo, HW 2008, 'Short-term efficacy of enzyme replacement therapy in Korean patients with Fabry disease', *J Korean Med Sci*, vol. 23, no. 2, Apr, pp. 243-250.

Cianciaruso, B, Pisani, A, Andreucci, MV, Parente, N, Andria, G, Federico, S, Sabbatini, M & Sessa, A 2003, 'Anderson-Fabry's disease: diagnostic problems, therapeutic relevance, and clinical experience in the treatment of the disease with enzyme replacement therapy in nephropathic patients', *Giornale italiano di nefrologia : organo ufficiale della Società italiana di nefrologia*, vol. 20, no. 2, pp. 113-119.

Cousins, A, Fondo, A, Murphy, E & Lachmann, R 2010, 'Patient experience of dose reductions of fabrazyme(R)', *Journal of Inherited Metabolic Disease*, vol. 33, p. S157.

Dominguez, RO, Amartino, H, Chamoles, NA, Amores, M, Larralde, M, Tanus, E, Michref, A, Gullone, N, Badia, J, Schenone, A, Blanco, M & Marschoff, E 2006, 'Neuropathic pain in Fabry's disease: Heterogeneous remission in three years of enzyme replacement therapy', *Revista de Neurologia*, vol. 43, no. 4, pp. 201-206.

Elliott, PM, Kindler, H, Shah, JS, Sachdev, B, Rimoldi, OE, Thaman, R, Tome, MT, McKenna, WJ, Lee, P & Camici, PG 2006, 'Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with α galactosidase A', *Heart (London, U. K.)*, vol. 92, no. 3, //, pp. 357-360.

Engelen, MA, Brand, E, Baumeister, TB, Marquardt, T, Duning, T, Osada, N, Schaefer, RM & Stypmann, J 2012, 'Effects of enzyme replacement therapy in adult patients with Fabry disease on cardiac structure and function: A retrospective cohort study of the Fabry Münster Study (FaMüS) data', *BMJ Open*, vol. 2, no. 6.

Eto, Y, Ohashi, T, Utsunomiya, Y, Fujiwara, M, Mizuno, A, Inui, K, Sakai, N, Kitagawa, T, Suzuki, Y, Mochizuki, S, Kawakami, M, Hosoya, T, Owada, M, Sakuraba, H & Saito, H 2005, 'Enzyme replacement therapy in Japanese Fabry disease patients: the results of a phase 2 bridging study', *J Inherit Metab Dis*, vol. 28, no. 4, pp. 575-583.

Feldt-Rasmussen, U, Watt, T, Burlina, AP, Cazzorla, C, Schonfeld, D, Banikazemi, M, Hopkin, RJ, Martins, AM, Sims, K, Beitner-Johnson, D & O'Brien, F 2012, 'Agalsidase beta treatment is associated with improvement in quality of life in patients with fabry disease: Findings from the fabry registry', *Clinical Therapeutics*, vol. 34, no. 4, p. e26.

Frustaci, A, Morgante, E, Antuzzi, D, Verardo, R, Russo, MA & Chimenti, C 2009, 'Low accessibility of human cardiomyocytes with advanced Fabry disease to enzyme replacement therapy', *European Heart Journal*, vol. 30, p. 548.

Fujiwara, M, Ohashi, T, Kobayashi, M, Hiroyuki, I & Yoshikatsu, E 2007, 'The cardiac effects of enzyme replacement therapy for fabry disease: Comparison of clinical course between female and male patients', *Tokyo Jikeikai Medical Journal*, vol. 122, no. 6, pp. 295-304.

Germain, D, Abiose, A, Patel, M, Cizmarik, M & Strotmann, J 2012, 'Agalsidase beta treatment improves left ventricular hypertrophy when treatment is initiated early: Data from the fabry registry', *Molecular Genetics and Metabolism*, vol. 105, no. 2, p. S30.

Germain, DP, Abiose, A, Patel, MR, Weidemann, F, Benistan, K, Waldek, S & Strotmann, J 2012, 'CARDIAC OUTCOMES OF AGALSIDASE BETA TREATMENT FOR FABRY DISEASE: ANALYSIS OF CARDIOVASCULAR DISEASE PROGRESSION IN MEN ENROLLED IN THE FABRY REGISTRY', *Journal of Inherited Metabolic Disease*, vol. 35, pp. S92-S92.

Ghali, J, Nicholls, K, Denaro, C, Sillence, D, Chapman, I, Goldblatt, J, Thomas, M & Fletcher, J 2012, 'Effect of reduced agalsidase Beta dosage in fabry patients: the Australian experience', *JIMD reports*, vol. 3, pp. 33-43.

Guffon, N & Fouilhoux, A 2004, 'Clinical benefit in Fabry patients given enzyme replacement therapy--a case series', *J Inherit Metab Dis*, vol. 27, no. 2, pp. 221-227.

Juan, P, Hernan, A, Beatriz, SA, Gustavo, C, Antonio, M, Eduardo, T, Raul, D, Margarita, L, Mariana, B, Daniela, G & Marina, S 2014, 'Fabry Disease: Multidisciplinary Evaluation After 10 Years of Treatment with Agalsidase Beta', *JIMD Rep*, May 22.

Kakosova, V, Hlavata, A, Bzduch, V & Foltanova, T 2013, 'Experiences with enzyme replacement therapy of Fabry disease in Slovakia', *International Journal of Clinical Pharmacy*, vol. 35, no. 5, pp. 988-989.

Kalliokoski, RJ, Kantola, I, Kalliokoski, KK, Engblom, E, Sundell, J, Hannukainen, JC, Janatuinen, T, Raitakari, OT, Knuuti, J, Penttinen, M, Viikari, J & Nuutila, P 2006, 'The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease', *J Inherit Metab Dis*, vol. 29, no. 1, Feb, pp. 112-118.

Koskenvuo, JW, Hartiala, JJ, Nuutila, P, Kalliokoski, R, Viikari, JS, Engblom, E, Penttinen, M, Knuuti, J, Mononen, I & Kantola, IM 2008, 'Twenty-four-month alpha-galactosidase A replacement therapy in Fabry disease has only minimal effects on symptoms and cardiovascular parameters', *Journal of Inherited Metabolic Disease*, vol. 31, no. 3, Jun, pp. 432-441.

Linthorst, GE, Hollak, CEM, Donker-Koopman, WE, Strijland, A & Aerts, JMFG 2004, 'Enzyme therapy for fabry disease: neutralizing antibodies toward agalsidase alpha and beta', *Kidney Int.*, vol. 66, no. 4, pp. 1589-1595.

Lorenzen, JM, Dietrich, B, Fiedler, J, Jazbutyte, V, Fleissner, F, Karpinski, N, Weidemann, F, Wanner, C, Asan, E, Caprio, M, Ertl, G, Bauersachs, J & Thum, T 2013, 'Pathologic endothelial response and impaired function of circulating angiogenic cells in patients with Fabry disease', *Basic Research in Cardiology*, vol. 108, no. 1.

MacHann, W, Breunig, F, Weidemann, F, Sandstede, J, Hahn, D, Kostler, H, Neubauer, S, Wanner, C & Beer, M 2011, 'Cardiac energy metabolism is disturbed in Fabry disease and improves with enzyme replacement therapy using recombinant human galactosidase A', *European Journal of Heart Failure*, vol. 13, no. 3, pp. 278-283.

Mendes, CSC, Rand, MH, Kyosen, SO & Martins, AM 2010, 'Neurologic assessment in patients with fabry disease before and after enzyme replacement therapy (ERT) with agalsidase beta', *Journal of Inherited Metabolic Disease*, vol. 33, p. S157.

Messalli, G, Imbriaco, M, Avitabile, G, Russo, R, Iodice, D, Spinelli, L, Dellegrottaglie, S, Cademartiri, F, Salvatore, M & Pisani, A 2012, 'Role of cardiac MRI in evaluating patients with Anderson-Fabry disease: assessing cardiac effects of long-term enzyme replacement therapy', *Radiol Med*, vol. 117, no. 1, Feb, pp. 19-28.

Ohashi, T, Sakuma, M, Kitagawa, T, Suzuki, K, Ishige, N & Eto, Y 2007, 'Influence of antibody formation on reduction of globotriaosylceramide (GL-3) in urine from Fabry patients during agalsidase beta therapy', *Mol Genet Metab*, vol. 92, no. 3, Nov, pp. 271-273.

Prabakaran, T, Birn, H, Bibby, BM, Regeniter, A, Sorensen So, S, Feldt-Rasmussen, U, Nielsen, R & Christensen, EI 2014, 'Long-term enzyme replacement therapy is associated with reduced proteinuria and preserved proximal tubular function in women with Fabry disease', *Nephrology Dialysis Transplantation*, vol. 29, no. 3, pp. 619-625.

Sestito, S, Di Vito, R, Maccarone, M, Parini, R, Dizione, L & Concolino, D 2010, 'Home treatment using agalsidase alfa among patients with Fabry disease in Italy', *Minerva Pediatrica*, vol. 62, no. 5.

Smid, BE, Rombach, SM, Aerts, J, Kuiper, S, Mirzaian, M, Overkleeft, HS, Poorthuis, B, Hollak, CEM, Groener, JEM & Linthorst, GE 2011, 'Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients', *Orphanet Journal of Rare Diseases*, vol. 6, Oct.

Spinelli, L, Pisani, A, Sabbatini, M, Petretta, M, Andreucci, MV, Procaccini, D, Lo Surdo, N, Federico, S & Cianciaruso, B 2004, 'Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease', *Clin Genet*, vol. 66, no. 2, Aug, pp. 158-165.

Tahir, H, Jackson, LL & Warnock, DG 2007, 'Antiproteinuric therapy and fabry nephropathy: Sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-β', *Journal of the American Society of Nephrology*, vol. 18, no. 9, pp. 2609-2617.

Tran, TC, Benistan, K, Froissart, M & Germain, DP 2009, 'LONG-TERM OUTCOME OF AGALSIDASE BETA THERAPY IN 10 ADULT MALE PATIENTS WITH FABRY DISEASE AND RENAL ALLOGRAFT', *Clinical Therapeutics*, vol. 31, pp. S39-S40.

Warnock, D, Guasch, A, Thomas, C, Wanner, C, Campbell, R & Vujkovac, B 2013, 'The fabrazyme(registered trademark), angiotensin receptor blocker and ACE inhibitor treatment study for fabry nephropathy (For the faacet investigators)', *Nephrology Dialysis Transplantation*, vol. 28, p. i321.

Warnock, DG, Germain, DP, Beitner-Johnson, D, Lemay, R & Wanner, C 2011, 'Progression of chronic kidney disease (CKD) in adult male Fabry patients treated with enzyme replacement therapy (ERT)', *American Journal of Kidney Diseases*, vol. 57, no. 4, p. A103.

Warnock, DG, Ortiz, A, Mauer, M, Linthorst, GE, Oliveira, JP, Serra, AL, Marodi, L, Mignani, R, Vujkovac, B, Beitner-Johnson, D, Lemay, R, Cole, JA, Svarstad, E, Waldek, S, Germain, DP & Wanner, C 2012, 'Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation', *Nephrol Dial Transplant*, vol. 27, no. 3, Mar, pp. 1042-1049.

Watt, T, Burlina, AP, Cazzorla, C, Schonfeld, D, Banikazemi, M, Hopkin, RJ, Martins, AM, Sims, K, Beitner-Johnson, D, O'Brien, F & Feldt-Rasmussen, U 2010, 'Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry', *Genet Med*, vol. 12, no. 11, Nov, pp. 703-712.

Wilcox, WR, Linthorst, GE, Germain, DP, Feldt-Rasmussen, U, Waldek, S, Richards, SM, Beitner-Johnson, D, Cizmarik, M, Cole, JA, Kingma, W & Warnock, DG 2012, 'Anti-(alpha)-galactosidase A antibody response to agalsidase beta treatment: Data from the Fabry Registry', *Molecular Genetics and Metabolism*, vol. 105, no. 3, pp. 443-449.

Wraith, JE & Investigators, A-S 2006, 'Agalsidase beta (recombinant human alpha-galactosidase A) therapy in paediatric patients with Fabry disease', *Journal of Inherited Metabolic Disease*, vol. 29, Aug, pp. 28-28.

Wraith, JE, Tylki-Szymanska, A, Guffon, N, Lien, YH, Tsimaratos, M, Vellodi, A & Germain, DP 2008, 'Safety and Efficacy of Enzyme Replacement Therapy with Agalsidase Beta: An International, Open-label Study in Pediatric Patients with Fabry Disease', *Journal of Pediatrics*, vol. 152, no. 4, pp. 563-570.e561.

### Agalsidase alfa versus agalsidase beta

### Duplicated data

Vedder, AC, Breunig, F, Donker-Koopman, WE, Mills, K, Young, E, Winchester, B, Ten Berge, IJ, Groener, JE, Aerts, JM, Wanner, C & Hollak, CE 2008, 'Treatment of Fabry disease with different dosing regimens of agalsidase: effects on antibody formation and GL-3', *Mol Genet Metab*, vol. 94, no. 3, Jul, pp. 319-325.

Vedder, AC, Linthorst, GE, Houge, G, Groener, JEM, Ormel, EE, Bouma, BJ, Aerts, JMFG, Hirth, A & Hollak, CEM 2007, 'Treatment of fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg', *Plos One*, vol. 2, no. 7.

## Infantile Onset Pompe Disease

### Duplicated data

Prater, SN, Banugaria, SG, Case, LE, MacKey, JF, Canfield, MM, DeArmey, SL & Kishnani, PS 2011, 'The emerging phenotype of long-term infantile Pompe survivors on enzyme replacement therapy', *Mol Genet Metab*, vol. 102, no. 3, p. 250.

### Foreign language (not a higher level than available in English)

'Pompe's disease: 5 years of successful treatment with alglucosidase alfa', 2012, *Neurologie und Rehabilitation*, vol. 18, no. 1, p. 81.

### Cost-effectiveness

Kanters, TA, Hoogenboom-Plug, I, Rutten-Van, MMP, Redekop, WK, van, dPAT & Hakkaart, L 2014, 'Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease', *Orphanet J Rare Dis*, vol. 9, //, p. 75.

### Case series

Amalfitano, A, Bengur, AR, Morse, RP, Majure, JM, Case, LE, Veerling, DL, Mackey, J, Kishnani, P, Smith, W, McVie-Wylie, A, Sullivan, JA, Hoganson, GE, Phillips, JA, 3rd, Schaefer, GB, Charrow, J, Ware, RE, Bossen, EH & Chen, YT 2001, 'Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial', *Genet Med*, vol. 3, no. 2, Mar-Apr, pp. 132-138.

Angelini, C, Semplicini, C, Tonin, P, Filosto, M, Pegoraro, E, Soraru, G & Fanin, M 2009, 'Progress in enzyme replacement therapy in glycogen storage disease type II', *Therapeutic Advances in Neurological Disorders*, vol. 2, no. 3, pp. 143-153.

Ansong, AK, Li, JS, Nozik-Grayck, E, Ing, R, Kravitz, RM, Idriss, SF, Kanter, RJ, Rice, H, Chen, YT & Kishnani, PS 2006, 'Electrocardiographic response to enzyme replacement therapy for Pompe disease', *Genet Med*, vol. 8, no. 5, May, pp. 297-301.

Barker, PC, Pasquali, SK, Darty, S, Ing, RJ, Li, JS, Kim, RJ, DeArmey, S, Kishnani, PS & Campbell, MJ 2010, 'Use of cardiac magnetic resonance imaging to evaluate cardiac structure, function and fibrosis in children with infantile Pompe disease on enzyme replacement therapy', *Mol Genet Metab*, vol. 101, no. 4, Dec, pp. 332-337.

Byrne, BJ, Kishnani, PS, Case, LE, Merlini, L, Mueller-Felber, W, Prasad, S & van der Ploeg, A 2011, 'Pompe disease: Design, methodology, and early findings from the Pompe Registry', *Mol Genet Metab*, vol. 103, no. 1, May, pp. 1-11.

Case, LE, Hanna, R, Frush, DP, Krishnamurthy, V, DeArmey, S, Mackey, J, Boney, A, Morgan, C, Corzo, D, Bouchard, S, Weber, TJ, Chen, Y-T & Kishnani, PS 2007, 'Fractures in children with Pompe disease: a potentiallong-term complication', *Pediatr Radiol*, vol. 37, no. 5, May, pp. 437-445.

Chakrapani, A, Vellodi, A, Robinson, P, Jones, S & Wraith, JE 2010, 'Treatment of infantile Pompe disease with alglucosidase alpha: The UK experience', *J Inherit Metab Dis*, vol. 33, no. 6, pp. 747-750.

Chen, CA, Chien, YH, Hwu, WL, Lee, NC, Wang, JK, Chen, LR, Lu, CW, Lin, MT, Chiu, SN, Chiu, HH & Wu, MH 2011, 'Left ventricular geometry, global function, and dyssynchrony in infants and children with pompe cardiomyopathy undergoing enzyme replacement therapy', *Journal of Cardiac Failure*, vol. 17, no. 11, pp. 930-936.

Chien, YH, Lee, NC, Peng, SF & Hwu, WL 2006, 'Brain development in infantile-onset pompe disease treated by enzyme replacement therapy', *Pediatr Res*, vol. 60, no. 3, pp. 349-352.

Cho, A, Kim, SJ, Lim, BC, Hwang, H, Park, JD, Kim, GB, Jin, DK, Lee, J, Ki, CS, Kim, KJ, Hwang, YS & Chae, JH 2012, 'Infantile Pompe disease: Clinical and genetic characteristics with an experience of enzyme replacement therapy', *J Child Neurol*, vol. 27, no. 3, pp. 319-324.

Cook, AL, Kishnani, PS, Carboni, MP, Kanter, RJ, Chen, YT, Ansong, AK, Kravitz, RM, Rice, H & Li, JS 2006, 'Ambulatory electrocardiogram analysis in infants treated with recombinant human acid alpha-glucosidase enzyme replacement therapy for Pompe disease', *Genet Med*, vol. 8, no. 5, May, pp. 313-317.

D'Angona, AL, Finn, P, Murray, J, McVie-Wylie, A & Andrews, L 2013, 'Safety evaluation of a second generation enzyme replacement therapy', *FASEB Journal*, vol. 27, Apr.

Jones, HN, Muller, CW, Lin, M, Banugaria, SG, Case, LE, Li, JS, O'Grady, G, Heller, JH & Kishnani, PS 2010, 'Oropharyngeal dysphagia in infants and children with infantile Pompe disease', *Dysphagia*, vol. 25, no. 4, Dec, pp. 277-283.

Kishnani, PS, Nicolino, M, Voit, T, Rogers, RC, Tsai, AC, Waterson, J, Herman, GE, Amalfitano, A, Thurberg, BL, Richards, S, Davison, M, Corzo, D & Chen, YT 2006, 'Chinese hamster ovary cell-derived recombinant human acid alpha-glucosidase in infantile-onset Pompe disease', *J Pediatr*, vol. 149, no. 1, Jul, pp. 89-97.

Kishnani, PS, Goldenberg, PC, DeArmey, SL, Heller, J, Benjamin, D, Young, S, Bali, D, Smith, SA, Li, JS, Mandel, H, Koeberl, D, Rosenberg, A & Chen, YT 2010, 'Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants', *Molecular Genetics and Metabolism*, vol. 99, no. 1, pp. 26-33.

Klinge, L, Straub, V, Neudorf, U, Schaper, J, Bosbach, T, Gorlinger, K, Wallot, M, Richards, S & Voit, T 2005, 'Safety and efficacy of recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease: Results of a phase II clinical trial', *Neuromuscular Disorders*, vol. 15, no. 1, pp. 24-31.

Klinge, L, Straub, V, Neudorf, U & Voit, T 2005, 'Enzyme replacement therapy in classical infantile pompe disease: Results of a ten-month follow-up study', *Neuropediatrics (Stuttgart, Ger.)*, vol. 36, no. 1, //, pp. 6-11.

Levine, JC, Kishnani, PS, Chen, YT, Herlong, JR & Li, JS 2008, 'Cardiac remodeling after enzyme replacement therapy with acid (alpha)-glucosidase for infants with Pompe disease', *Pediatric Cardiology*, vol. 29, no. 6, pp. 1033-1042.

Muller, CW, Jones, HN, O'Grady, G, Suarez, HA, Heller, JH & Kishnani, PS 2009, 'Language and speech function in children with infantile Pompe disease', *Journal of Pediatric Neurology*, vol. 7, no. 2, pp. 147-156.

Prater, SN, Patel, TT, Buckley, AF, Mandel, H, Vlodavski, E, Banugaria, SG, Feeney, EJ, Raben, N & Kishnani, PS 2013, 'Skeletal muscle pathology of infantile Pompe disease during long-term enzyme replacement therapy', *Orphanet J Rare Dis*, vol. 8, no. 1.

Rossi, M, Parenti, G, Della Casa, R, Romano, A, Mansi, G, Agovino, T, Rosapepe, F, Vosa, C, Del Giudice, E & Andria, G 2007, 'Long-term enzyme replacement therapy for pompe disease with recombinant human alpha-glucosidase derived from Chinese hamster ovary cells', *J Child Neurol*, vol. 22, no. 5, pp. 565-573.

Spiridigliozzi, GA, Heller, JH, Case, LE, Jones, HN & Kishnani, PS 2012, 'Early cognitive development in children with infantile Pompe disease', *Mol Genet Metab*, vol. 105, no. 3, Mar, pp. 428-432.

Spiridigliozzi, GA, Heller, JH & Kishnani, PS 2012, 'Cognitive and adaptive functioning of children with infantile Pompe disease treated with enzyme replacement therapy: long-term follow-up', *Am J Med Genet C Semin Med Genet*, vol. 160C, no. 1, Feb 15, pp. 22-29.

Thurberg, BL, Lynch Maloney, C, Vaccaro, C, Afonso, K, Tsai, AC, Bossen, E, Kishnani, PS & O'Callaghan, M 2006, 'Characterization of pre- and post-treatment pathology after enzyme replacement therapy for Pompe disease', *Lab Invest*, vol. 86, no. 12, Dec, pp. 1208-1220.

van Capelle, CI, Goedegebure, A, Homans, NC, Hoeve, HL, Reuser, AJ & van der Ploeg, AT 2010, 'Hearing loss in Pompe disease revisited: results from a study of 24 children', *J Inherit Metab Dis*, vol. 33, no. 5, Oct, pp. 597-602.

Van Gelder, C, Kroos, M, Ozkan, L, Plug, I, Reuser, A & Van Der Ploeg, A 2013, 'Antibody formation to enzyme therapy in classic infantile Pompe disease: Implications of patient age', *BMC Musculoskeletal Disorders*, vol. 14, no. 1.

Wasant, P, Vatanavicharn, N, Liammongkolkul, S & Hwu, WL 2008, 'Pompe disease in Thai infants - Report of 4 cases', *J Inherit Metab Dis*, vol. 31, Aug, pp. 117-117.

Yang, CF, Liu, HC, Hsu, TR, Tsai, FC, Chiang, SF, Chiang, CC, Ho, HC, Lai, CJ, Yang, TF, Chuang, SY, Lin, CY & Niu, DM 2014, 'A large-scale nationwide newborn screening program for pompe disease in Taiwan: Towards effective diagnosis and treatment', *American Journal of Medical Genetics, Part A*, vol. 164, no. 1, pp. 54-61.

Young, SP, Zhang, H, Corzo, D, Thurberg, BL, Bali, D, Kishnani, PS & Millington, DS 2009, 'Long-term monitoring of patients with infantile-onset Pompe disease on enzyme replacement therapy using a urinary glucose tetrasaccharide biomarker', *Genetics in Medicine*, vol. 11, no. 7, pp. 536-541.

### Case series focusing on CRIM status or antibodies

Banugaria, SG, Patel, TT & Kishnani, PS 2012, 'Immune modulation in Pompe disease treated with enzyme replacement therapy', *Expert Review of Clinical Immunology*, vol. 8, no. 6, Aug, pp. 497-499.

Banugaria, SG, Prater, SN, Ng, YK, Kobori, JA, Finkel, RS, Ladda, RL, Chen, YT, Rosenberg, AS & Kishnani, PS 2011, 'The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease', *Genet Med*, vol. 13, no. 8, Aug, pp. 729-736.

Banugaria, SG, Prater, SN, Ng, YK, Kobori, JA, Finkel, RS, Ladda, RL & Kishnani, PS 2010, 'The role of anti-rhGAA antibody titers and clinical outcomes in infantile pompe disease patients', *Mol Genet Metab*, vol. 99, no. 3, p. 199.

Banugaria, SG, Prater, SN, Patel, TT, DeArmey, SM, Milleson, C, Sheets, KB, Bali, DS, Rehder, CW, Raiman, JAJ, Wang, RA, Labarthe, F, Charrow, J, Harmatz, P, Chakraborty, P, Rosenberg, AS & Kishnani, PS 2013, 'Algorithm for the Early Diagnosis and Treatment of Patients with Cross Reactive Immunologic Material-Negative Classic Infantile Pompe Disease: A Step towards Improving the Efficacy of ERT', *PLoS One*, vol. 8, no. 6.

Elder, ME, Nayak, S, Collins, SW, Lawson, LA, Kelley, JS, Herzog, RW, Modica, RF, Lew, J, Lawrence, RM & Byrne, BJ 2013, 'B-Cell depletion and immunomodulation before initiation of enzyme replacement therapy blocks the immune response to acid alpha-glucosidase in infantile-onset Pompe disease', *J Pediatr*, vol. 163, no. 3, Sep, pp. 847-854 e841.

Kishnani, PS, Goldenberg, PC, DeArmey, SL, Heller, J, Benjamin, D, Young, S, Bali, D, Smith, SA, Li, JS, Mandel, H, Koeberl, D, Rosenberg, A & Chen, YT 2010, 'Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants', *Molecular Genetics and Metabolism*, vol. 99, no. 1, pp. 26-33.

Messinger, YH, Mendelsohn, NJ, Rhead, W, Dimmock, D, Hershkovitz, E, Champion, M, Jones, SA, Olson, R, White, A, Wells, C, Bali, D, Case, LE, Young, SP, Rosenberg, AS & Kishnani, PS 2012, 'Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease', *Genetics in Medicine*, vol. 14, no. 1, pp. 135-142.

### Abstract only

'Use of alglucosidase alfa (Myozyme?) within NHS Wales (Structured abstract)', 2007, *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000466/frame.html>.

Austin, S & Kishnani, P 2013, 'Long term outcome and clinical experience on immune tolerance induction therapies in infantile Pompe disease', *BMC Musculoskeletal Disorders*, vol. 14, no. 1.

Banugaria, S, Prater, S, Bali, D, Rehder, C, Rosenberg, A & Kishnani, P 2012, 'Long term outcome and clinical experience on immune tolerance induction therapies in infantile pompe disease', *Mol Genet Metab*, vol. 105, no. 2, p. S20.

Banugaria, S, Prater, S, Patel, T, DeArmey, S, Milleson, C, Raiman, J, Wang, R, Labarthe, F, Joel, C, Harmatz, P, Charkraborty, P & Priya, K 2013, 'Approach to management of cross-reactive immunologic material (CRIM)-negative infantile pompe patients treated with ERT: Role of immune modulation in changing the natural history', *Mol Genet Metab*, vol. 108, no. 2, Feb, pp. S23-S23.

Broomfield, AA, Crook, V, Finnegan, N, Fletcher, J, Stewart, C, Cleary, M, Chakrapani, A, Malaiya, N, Jones, S, Chikermane, A, Vellodi, A & Fenton, M 2012, 'LEFT VENTRICULAR FUNCTION IN INFANTILE POMPE PATIENTS ON ENZYME REPLACEMENT THERAPY (ERT)', *J Inherit Metab Dis*, vol. 35, Sep, pp. S12-S12.

Capelle, Cv 2008, 'Pompe Disease in Children-Early to Mid-stage', *Clinical Therapeutics*, vol. 30, no. SUPPL. 1, pp. S11-S12.

Chien, Y-H, Hwu, W-L, Lee, N-C, Chen, C-A, Tsai, F-J, Tsai, W-H, Huang, H-J, Hsu, W-C, Tsai, T-H & Shieh, J-Y 2013, 'Long-term follow-up results in patients with classic infantile Pompe disease receiving enzyme therapy since newborn', *Mol Genet Metab*, vol. 108, no. 2, Feb, pp. S29-S30.

Corzo, D, Byrne, B, Hwu, WL, Leslie, N, Mandel, H & Nicolino, M 2008, 'Alglucosidase Alfa (Myozyme(registered trademark)) in Infants and Children with Rapidly Progressive Pompe Disease', *Clinical Therapeutics*, vol. 30, no. SUPPL. 1, pp. S9-S10.

Fenton, M, Burch, M, Andrews, R & Broomfield, A 2013, 'Cardiac Hypertrophy in Pompe disease is Significantly Reduced During Enzyme Replacement Therapy. A United Kingdom Cohort', *Circulation*, vol. 128, no. 22.

Guo, J, Kelton, CM & Guo, JJ 2012, 'Recent developments in pompe disease therapy', *Value in Health*, vol. 15, no. 4, p. A14.

Hilz, M, Hoppe, U, Moeller, S & Kohn, J 2013, 'Stapedius reflex testing shows altered small muscle function in untreated Pompe patients and improvement after enzyme replacement therapy', *BMC Musculoskeletal Disorders*, vol. 14, no. 1.

Kishnani, P, Byrne, B, Hwu, WL, Leslie, N, Mandel, H, Wraith, J & Nicolino, M 2008, 'Alglucosidase alfa in infants and children with advanced pompe disease', *Mol Genet Metab*, vol. 93, no. 3, Mar, pp. 254-254.

Kishnani, P, Hwu, WL, Leslie, N, Wraith, J & Nicolino, M 2008, 'ALGLUCOSIDASE ALFA IN INFANTS AND CHILDREN WITH POMPE DISEASE', *Clinical Therapeutics*, vol. 30, pp. S114-S114.

Koeberl, D, Kishnani, P, Goldenberg, P, Dearmey, S, Heller, J, Benjamin, D, Young, S, Bali, D, Smith, SA, Li, J, Mandel, H, Rosenburg, A & Chen, YT 2009, 'Cross-reacting immunologic material status affects outcomes in infants with Pompe disease treated with alglucosidase alfa', *Mol Genet Metab*, vol. 96, no. 2, pp. S28-S29.

Lianou, D, Syrengelas, D, Andreou, N, Chantzopoulos, I, Mavridou, I & Michelakakis, H 2013, 'Pompe disease (PD): Clinical outcome in infants and children treated with recombinant human acid alpha-glucosidase (rhGAA)', *European Journal of Paediatric Neurology*, vol. 17, p. S132.

Mandel, H, Bar-Joseph, G, Lorber, A, Khoury, A, Natan, D, Eldad, DJ, Zeigler, M & Bercovich, M 2009, 'Enzyme replacement therapy in Pompe disease in Northern Israel - A six year follow-up', *Mol Genet Metab*, vol. 98, no. 1-2, p. 81.

Mandel, H, Gruber, M, Goldsher, D, Chistyakov, A, Kaplan, B, Zaaroor, M & Hafner, H 2007, 'Longer Survival by Enzyme Replacement Therapy Unmasks the Underrecognition of Otoneurologic Involvement in Infantile-Onset Pompe Disease', *Clinical Therapeutics*, vol. 29, no. SUPPL. C, pp. S109-S110.

Nicolino, M, Byrne, B, Spencer, C, Levine, J, Leslie, N, Wraith, E & Kishnani, P 2008, 'Clinical benefit of treatment with alglucosidase alfa in infants and children with advanced Pompe disease', *Clinical Therapeutics*, vol. 30, pp. S33-S33.

Spencer, CT, Levine, J, Corzo, D, Colan, SD, Graham, D, Kishnani, PS, Nicolino, M, Li, J, Leslie, N, Wraith, E, Mandel, H, Hwu, W-L & Byrne, BJ 2008, 'Clinical Response to Recombinant Acid alpha-Glucosidase is Predicted by Cardiac Outcome Measures in Children with Pompe Disease', *Circulation*, vol. 118, no. 18, Oct 28, pp. S881-S881.

Tolun, AA, Hwu, PWL, Chien, YH, Vaisnins-Carroll, A, Bali, D, Millington, D, Kishnani, PS & Young, SP 2011, 'Monitoring urinary glucose tetrasaccharide biomarker in patients with infantile and late-onset Pompe disease identified through newborn screening', *Mol Genet Metab*, vol. 102, no. 3, pp. 316-317.

Van Gelder, C, Plug, I, Kroos, M, Reuser, A & Van Der Ploeg, A 2013, 'A higher dose of enzyme therapy in patients with classic infantile Pompe disease seems to improve ventilator-free survival and motor function', *BMC Musculoskeletal Disorders*, vol. 14, no. 1.

van Gelder, CM, Kroos, MA, Ozkan, L, Plug, I, Reuser, AJJ & van der Ploeg, AT 2012, 'ANTIBODY FORMATION TO ENZYME THERAPY IN CLASSIC INFANTILE POMPE DISEASE: IMPLICATIONS OF PATIENT AGE', *J Inherit Metab Dis*, vol. 35, Sep, pp. S12-S12.

Van Gelder, CM, Kroos, MA, Ozkan, L, Van Der Ploeg, AT & Reuser, AJJ 2011, 'Crim status, antibody formation and neutralizing antibodies in patients with classic infantile Pompe disease treated with enzyme-replacement therapy', *J Inherit Metab Dis*, vol. 34, p. S226.

Wraith, E, Byrne, B, Hwu, WL, Leslie, N, Mandel, H, Nicolino, M & Kishnani, PS 2008, 'Alglucosidase alfa in infants and children with Pompe disease', *Neuromuscular Disorders*, vol. 18, no. 9-10, Oct, pp. 800-800.

Yanovitch, TL, Casey, R, Banugaria, SG & Kishnani, PS 2010, 'Improvement of bilateral ptosis on higher dose enzyme replacement therapy in Pompe disease', *J Neuroophthalmol*, vol. 30, no. 2, Jun, pp. 165-166.

### Review

Alfadhel, M, Al-Thihli, K, Moubayed, H, Eyaid, W & Al-Jeraisy, M 2013, 'Drug treatment of inborn errors of metabolism: A systematic review', *Archives of Disease in Childhood*, vol. 98, no. 6, pp. 454-461.

Dupont, AG & Van Wilder, PB 2011, 'Access to orphan drugs despite poor quality of clinical evidence', *British Journal of Clinical Pharmacology*, vol. 71, no. 4, pp. 488-496.

Kanters, TA, De Sonneville-Koedoot, C, Redekop, WK & Hakkaart, L 2013, 'Systematic review of available evidence on 11 high-priced inpatient orphan drugs', *Orphanet J Rare Dis*, vol. 8, no. 1.

Mitsumoto, J, Dorsey, ER, Beck, CA, Kieburtz, K & Griggs, RC 2009, 'Pivotal studies of orphan drugs approved for neurological diseases', *Ann Neurol*, vol. 66, no. 2, pp. 184-190.

Wang, RY, Bodamer, OA, Watson, MS & Wilcox, WR 2011, 'Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals', *Genetics in Medicine*, vol. 13, no. 5, pp. 457-484.

## Juvenile Onset Pompe Disease

### Guidelines

'Use of alglucosidase alfa (Myozyme?) within NHS Wales (Structured abstract)', 2007, *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000466/frame.html>.

### Juvenile-late onset not separated

Anderson, L, Henley, W, Wyatt, K, Nikolaou, V, Waldek, S, Hughes, D, Lachmann, R & Logan, S 2014, 'Effectiveness of enzyme replacement therapy in adults with late-onset Pompe disease: results from the NCS-LSD cohort study', *Journal of Inherited Metabolic Disease*, vol. 37, no. 6, pp. 945-952.

Angelini, C, Semplicini, C, Ravaglia, S, Bembi, B, Servidei, S, Pegoraro, E, Moggio, M, Filosto, M, Sette, E, Crescimanno, G, Tonin, P, Parini, R, Morandi, L, Marrosu, G, Greco, G, Musumeci, O, Iorio, G, Siciliano, G, Donati, MA, Carubbi, F, Ermani, M, Mongini, T & Toscano, A 2012, 'Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years', *Journal of Neurology*, vol. 259, no. 5, pp. 952-958, DOI 10.1007/s00415-011-6293-5, <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/454/CN-00900454/frame.html

http://download.springer.com/static/pdf/762/art%253A10.1007%252Fs00415-011-6293-5.pdf?auth66=1422315887\_49f4be2f11d872527d0e0b5e6a46399f&ext=.pdf>.

Angelini, C, Semplicini, C, Ravaglia, S, Moggio, M, Comi, GP, Musumeci, O, Pegoraro, E, Tonin, P, Filosto, M, Servidei, S, Morandi, L, Crescimanno, G, Marrosu, G, Siciliano, G, Mongini, T, Toscano, A & Italian Grp, G 2012, 'New motor outcome function measures in evaluation of Late-Onset Pompe disease before and after enzyme replacement therapy', *Muscle & Nerve*, vol. 45, no. 6, Jun, pp. 831-834.

Angelini, C, Semplicini, C, Tonin, P, Filosto, M, Pegoraro, E, Soraru, G & Fanin, M 2009, 'Progress in Enzyme Replacement Therapy in Glycogen Storage Disease Type II', *Ther Adv Neurol Disord*, vol. 2, no. 3, May, pp. 143-153.

de Vries, JM, van der Beek, NAME, Hop, WCJ, Karstens, FPJ, Wokke, JH, de, VM, van, EBGM, Kuks, JBM, van, dKAJ, Notermans, NC, Faber, CG, Verschuuren, JJGM, Kruijshaar, ME, Reuser, AJJ, van, DPA & van, dPAT 2012, 'Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study', *Orphanet J Rare Dis*, vol. 7, //, p. 73.

Gungor, D, de Vries, JM, Brusse, E, Kruijshaar, ME, Hop, WCJ, Murawska, M, van den Berg, LEM, Reuser, AJJ, van Doorn, PA, Hagemans, MLC, Plug, I & van der Ploeg, AT 2013, 'Enzyme replacement therapy and fatigue in adults with Pompe disease', *Mol. Genet. Metab.*, vol. 109, no. 2, //, pp. 174-178.

Gungor, D, Kruijshaar, ME, Plug, I, D'Agostino, RB, Hagemans, MLC, Doorn, PA, Reuser, AJJ & Ploeg, AT 2013, 'Impact of enzyme replacement therapy on survival in adults with Pompe disease: Results from a prospective international observational study', *Orphanet Journal of Rare Diseases*, vol. 8, no. 1, DOI 10.1186/1750-1172-8-49, <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/995/CN-00916995/frame.html

http://www.ojrd.com/content/pdf/1750-1172-8-49.pdf>.

Güngör, D, Schober, AK, Kruijshaar, ME, Plug, I, Karabul, N, Deschauer, M, van Doorn, PA, van der Ploeg, AT, Schoser, B & Hanisch, F 2013, 'Pain in adult patients with Pompe disease: A cross-sectional survey', *Molecular Genetics and Metabolism*, vol. 109, no. 4, pp. 371-376.

Forsha, D, Li, JS, Smith, PB, van der Ploeg, AT, Kishnani, P, Pasquali, SK & Late-Onset Treatment Study, I 2011, 'Cardiovascular abnormalities in late-onset Pompe disease and response to enzyme replacement therapy', *Genetics in Medicine*, vol. 13, no. 7, Jul, pp. 625-631.

Pichiecchio, A, Poloni, GU, Ravaglia, S, Ponzio, M, Germani, G, Maranzana, D, Costa, A, Repetto, A, Tavazzi, E, Danesino, C, Moglia, A & Bastianello, S 2009, 'Enzyme replacement therapy in adult-onset glycogenosis II: Is quantitative muscle MRI helpful?', *Muscle and Nerve*, vol. 40, no. 1, pp. 122-125.

Ravaglia, S, Pichiecchio, A, Ponzio, M, Danesino, C, Saeidi Garaghani, K, Poloni, GU, Toscano, A, Moglia, A, Carlucci, A, Bini, P, Ceroni, M & Bastianello, S 2010, 'Changes in skeletal muscle qualities during enzyme replacement therapy in late-onset type II glycogenosis: temporal and spatial pattern of mass vs. strength response', *J Inherit Metab Dis*, vol. 33, no. 6, Dec, pp. 737-745.

Regnery, C, Kornblum, C, Hanisch, F, Vielhaber, S, Strigl-Pill, N, Grunert, B, Mller-Felber, W, Glocker, FX, Spranger, M, Deschauer, M, Mengel, E & Schoser, B 2012, '36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy', *J Inherit Metab Dis.*, vol. 35, no. 5, Sep, pp. 837-845. [Journal of inherited metabolic disease].

Strothotte, S, Strigl-Pill, N, Grunert, B, Kornblum, C, Eger, K, Wessig, C, Deschauer, M, Breunig, F, Glocker, FX, Vielhaber, S, Brejova, A, Hilz, M, Reiners, K, Müller-Felber, W, Mengel, E, Spranger, M & Schoser, B 2010, 'Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial', *Journal of Neurology*, vol. 257, no. 1, pp. 91-97.

Toscano, A & Schoser, B 2013, 'Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review', *Journal of Neurology*, vol. 260, no. 4, Apr, pp. 951-959.

van der Meijden, JC, Gungor, D, Kruijshaar, ME, Muir, ADJ, Broekgaarden, HA & van der Ploeg, AT 2014, 'Ten years of the international Pompe survey: patient reported outcomes as a reliable tool for studying treated and untreated children and adults with non-classic Pompe disease', *Journal of Inherited Metabolic Disease*.

Van der Ploeg, AT, Barohn, R, Carlson, L, Charrow, J, Clemens, PR, Hopkin, RJ, Kishnani, PS, Laforêt, P, Morgan, C, Nations, S, Pestronk, A, Plotkin, H, Rosenbloom, BE, Sims, KB & Tsao, E 2012, 'Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa', *Molecular Genetics and Metabolism*, vol. 107, no. 3, pp. 456-461.

Van Der Ploeg, AT, Clemens, PR, Corzo, D, Escolar, DM, Florence, J, Groeneveld, G, Herson, S, Kishnani, PS, Laforet, P, Lake, SL, Lange, DJ, Leshner, RT, Mayhew, JE, Morgan, C, Nozaki, K, Park, DJ, Pestronk, A, Rosenbloom, B, Skrinar, A, Van Capelle, CI, Van Der Beek, NA, Wasserstein, M & Zivkovic, SA 2010, 'A randomized study of alglucosidase alfa in late-onset Pompe's disease', *N. Engl. J. Med.*, vol. 362, no. 15, //, pp. 1396-1406.

Vianello, A, Semplicini, C, Paladini, L, Concas, A, Ravaglia, S, Servidei, S, Toscano, A, Mongini, T, Angelini, C & Pegoraro, E 2013, 'Enzyme Replacement Therapy Improves Respiratory Outcomes in Patients with Late-Onset Type II Glycogenosis and High Ventilator Dependency', *Lung*, vol. 191, no. 5, Oct, pp. 537-544.

### Not a higher level than available in English (foreign language)

'Alglucosidase alpha (Myozyme) for treatment of patients with late-onset Pompe disease (Structured abstract)', 2011, *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32011000221/frame.html>.

'Pompe's disease: 5 years of successful treatment with alglucosidase alfa', 2012, *Neurologie und Rehabilitation*, vol. 18, no. 1, p. 81.

'Alglucosidase alfa (Myozyme ®) in late-onset Pompe disease (Structured abstract)', 2014, *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32014001015/frame.html>.

Baños Álvarez, I & Miranda Machado, PA 2014, 'Enfermedad de Pompe de inicio tardío con compromiso respiratorio severo, influencia de la terapia de reemplazo enzimático', *Revista de Patologia Respiratoria*, vol. 17, no. 1, pp. 23-26.

Bereznai, B, Trauninger, A, Gyoergy, I, Szakszon, K, Almassy, Z, Pal, E, Herczegfalvi, A, Vardi Visy, K, Illes, Z & Molnar Maria, J 2011, 'Clinical manifestation, disease course and response to enzyme replacement therapy in Hungarian patients with Pompe's disease', (Pompe-kor fenotipusvariacioi, korlefolyasa es az enzimpotlo kezeles eredmenyei: hazai tapasztalatok), *Orvosi Hetilap*, vol. 152, no. 39, Sep, pp. 1569-1575.

Fath, R 2006, 'Enzyme replacement therapy in Pompe's disease is now approved: Markedly prolonged survival for patients', *Nervenheilkunde*, vol. 25, no. 6, pp. 490-491.

Merk, T, Wibmer, T, Schumann, C & Krüger, S 2007, 'Enzyme replacement therapy in Pompe's disease', *Medizinische Klinik*, vol. 102, no. 7, pp. 570-573.

Regnery, C 2012, 'Clinical process study into the enzyme-replacement therapy with alglucosidase-α over 36 months in Pompe disease in the adult age', Copyright (C) 2015 American Chemical Society (ACS). All Rights Reserved. thesis, <http://d-nb.info/102522406X/34>.

Ressiot, E, Leblanc, A, Tirel-Badets, A, Viakhireva, I, Blanchard, C & Zagnoll, F 2011, 'Q16 Bénéfices du traitement par l'alphaglucosidase acide recombinante humaine (MYOZYME®) dans la forme tardive de la maladie de pompe: à propos de cinq cas', *Revue Neurologique*, vol. 167, no. 2, p. A31.

Strothotte, S 2011, 'Clinical progress documentation of the enzyme replacement therapy with alglucosidase alfa over one year in 44 adult patients with glycogenose type II', Copyright (C) 2015 American Chemical Society (ACS). All Rights Reserved. thesis, <http://d-nb.info/1018163549/34>.

Zagnoli, F 2013, 'Late-onset Pompe disease: Modest effect for the replacement for ERT, but a first treatment in myology', *Revue du Praticien*, vol. 63, no. 9 SUPPL., p. S5.

李燕燕 2003, 'Genzyme 公司的 Myozyme 开始 pompe 病研究', *国外药讯*, no. 9, pp. 31-31.

### Could not extract outcomes

Haaker, G, Forst, J, Forst, R & Fujak, A 2014, 'Orthopedic management of patients with Pompe disease: a retrospective case series of 8 patients', *TheScientificWorldJournal*, vol. 2014, 2014, pp. 963861-963861.

Ishigaki, K, Yoshikawa, Y, Kuwatsuru, R, Oda, E, Murakami, T, Sato, T, Saito, T, Umezu, R & Osawa, M 2012, 'High-density CT of muscle and liver may allow early diagnosis of childhood-onset Pompe disease', *Brain & Development*, vol. 34, no. 2, Feb, pp. 103-106.

Papadimas, GK, Terzis, G, Methenitis, S, Spengos, K, Papadopoulos, C, Vassilopoulou, S, Kavouras, S, Michelakakis, H & Manta, P 2011, 'Body composition analysis in late-onset Pompe disease', *Molecular Genetics and Metabolism*, vol. 102, no. 1, Jan, pp. 41-43.

Park, JS, Kim, HG, Shin, JH, Choi, YC & Kim, DS 2014, 'Effect of enzyme replacement therapy in late onset Pompe disease: open pilot study of 48 weeks follow-up', *Neurological Sciences*.

Rossi, M, Parenti, G, Della Casa, R, Romano, A, Mansi, G, Agovino, T, Rosapepe, F, Vosa, C, Del Giudice, E & Andria, G 2007, 'Long-term enzyme replacement therapy for pompe disease with recombinant human alpha-glucosidase derived from chinese hamster ovary cells', *J Child Neurol*, vol. 22, no. 5, May, pp. 565-573.

Yang, C-C, Chien, Y-H, Lee, N-C, Chiang, S-C, Lin, S-P, Kuo, Y-T, Chen, S-S, Jong, Y-J & Hwu, W-L 2011, 'Rapid progressive course of later-onset Pompe disease in Chinese patients', *Molecular Genetics and Metabolism*, vol. 104, no. 3, Nov, pp. 284-288.

Yanovitch, TL, Casey, R, Banugaria, SG & Kishnani, PS 2010, 'Improvement of Bilateral Ptosis on Higher Dose Enzyme Replacement Therapy in Pompe Disease', *Journal of Neuro-Ophthalmology*, vol. 30, no. 2, Jun, pp. 165-166.

### Wrong population

Anonymous 2007, 'Alglucosidase alfa: new drug. Pompe disease: a short-term benefit', *Prescrire Int*, vol. 16, no. 92, //, pp. 240-241.

Ansong, AK, Li, JS, Nozik-Grayck, E, Ing, R, Kravitz, RM, Idriss, SF, Kanter, RJ, Rice, H, Chen, YT & Kishnani, PS 2006, 'Electrocardiographic response to enzyme replacement therapy for Pompe disease', *Genetics in Medicine*, vol. 8, no. 5, May, pp. 297-301.

Chen, CA, Chien, YH, Hwu, WL, Lee, NC, Wang, JK, Chen, LR, Lu, CW, Lin, MT, Chiu, SN, Chiu, HH & Wu, MH 2011, 'Left ventricular geometry, global function, and dyssynchrony in infants and children with pompe cardiomyopathy undergoing enzyme replacement therapy', *Journal of Cardiac Failure*, vol. 17, no. 11, pp. 930-936.

Corzo, D, Byrne, B, Hwu, WL, Leslie, N, Mandel, H & Nicolino, M 2008, 'Alglucosidase Alfa (Myozyme(registered trademark)) in Infants and Children with Rapidly Progressive Pompe Disease', *Clinical Therapeutics*, vol. 30, no. SUPPL. 1, pp. S9-S10.

Hundsberger, T, Roesler, KM & Findling, O 2014, 'Cessation and resuming of alglucosidase alfa in Pompe disease: a retrospective analysis', *Journal of Neurology*, vol. 261, no. 9, Sep, pp. 1684-1690.

Hunley, TE, Corzo, D, Dudek, M, Kishnani, P, Amalfitano, A, Chen, YT, Richards, SM, Phillips, JA, Fogo, AB & Tiller, GE 2004, 'Nephrotic syndrome complicating alpha-glucosidase replacement therapy for Pompe disease', *Pediatrics*, vol. 114, no. 4, Oct, pp. E532-E535.

Illes, Z, Mike, A, Trauninger, A, Várdi, K & Váczi, M 2014, 'Motor function and respiratory capacity in patients with late-onset pompe disease', *Muscle and Nerve*, vol. 49, no. 4, pp. 603-606.

Lianou, D, Syrengelas, D, Andreou, N, Chantzopoulos, I, Mavridou, I & Michelakakis, H 2013, 'Pompe disease (PD): Clinical outcome in infants and children treated with recombinant human acid alpha-glucosidase (rhGAA)', *European Journal of Paediatric Neurology*, vol. 17, p. S132.

Lin, DS, Chiang, MF, Ho, CS, Hsiao, CD, Lin, CY, Wang, NL, Chuang, CK, Huang, YW, Chang, PC & Liu, HL 2013, 'Low-frequency enzyme replacement therapy in late-onset pompe disease', *Muscle and Nerve*, vol. 47, no. 4, pp. 612-613.

Marzorati, M, Porcelli, S, Bellistri, G, Morandi, L & Grassi, B 2012, 'Exercise testing in late-onset glycogen storage disease type II patients undergoing enzyme replacement therapy', *Neuromuscular Disorders*, vol. 22, Dec 1, pp. S230-S234.

Marzorati, M, Porcelli, S, Reggiori, B, Morandi, L & Grassi, B 2012, 'Improved Exercise Tolerance after Enzyme Replacement Therapy in Pompe Disease', *Medicine and Science in Sports and Exercise*, vol. 44, no. 5, May, pp. 771-775.

Nicolino, M, Byrne, B, Wraith, JE, Leslie, N, Mandel, H, Freyer, DR, Arnold, GL, Pivnick, EK, Ottinger, CJ, Robinson, PH, Loo, JC, Smitka, M, Jardine, P, Tat•, L, Chabrol, B, McCandless, S, Kimura, S, Mehta, L, Bali, D, Skrinar, A, Morgan, C, Rangachari, L, Corzo, D & Kishnani, PS 2009, 'Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease', *Genet Med.*, vol. 11, no. 3, Mar, pp. 210-219. [Genetics in medicine : official journal of the American College of Medical Genetics].

Papadimas, G, Terzis, G, Papadopoulos, C, Areovimata, A, Spengos, K, Kavouras, S & Manta, P 2012, 'Bone density in patients with late onset Pompe disease', *International Journal of Endocrinology and Metabolism*, vol. 10, no. 4, 2012, pp. 599-603.

Phillips, D 2012, 'Concurrent validity and responsiveness of the Peabody Developmental Motor Scales-2 in infants and children with Pompe disease undergoing enzyme replacement therapy', Ph.D. thesis, University of North Carolina at Chapel Hill, c8h, <http://proxy.library.adelaide.edu.au/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2012250378&site=ehost-live&scope=site>.

Ravaglia, S, Danesino, C, Moglia, A, Costa, A, Cena, H, Maccarini, L, Carlucci, A, Pichiecchio, A, Bini, P, De Filippi, P & Rossi, M 2010, 'Changes in nutritional status and body composition during enzyme replacement therapy in adult-onset type II glycogenosis', *European Journal of Neurology*, vol. 17, no. 7, Jul, pp. 957-962.

Ravaglia, S, Danesino, C, Pichiecchio, A, Repetto, A, Poloni, GU, Rossi, M, Fratino, P, Moglia, A & Costa, A 2008, 'Enzyme replacement therapy in severe adult-onset glycogen storage disease type II', *Advances in Therapy*, vol. 25, no. 8, Aug, pp. 820-829.

Sacconi, S, Bocquet, JD, Chanalet, S, Tanant, V, Salviati, L & Desnuelle, C 2010, 'Abnormalities of cerebral arteries are frequent in patients with late-onset Pompe disease', *Journal of Neurology*, vol. 257, no. 10, Oct, pp. 1730-1733.

Sacconi, S, Wahbi, K, Theodore, G, Garcia, J, Salviati, L, Bouhour, F, Vial, C, Duboc, D, Laforet, P & Desnuelle, C 2014, 'Atrio-ventricular block requiring pacemaker in patients with late onset Pompe disease', *Neuromuscular Disorders*, vol. 24, no. 7, Jul, pp. 648-650.

Saux, A, Laforet, P, Pages, AM, Figarella-Branger, D, Pellissier, JF, Pages, M & Labauge, P 2008, 'A retrospective study of six patients with late-onset Pompe disease', *Revue Neurologique*, vol. 164, no. 4, pp. 336-342.

Schneider, I, Hanisch, F, Muller, T, Schmidt, B & Zierz, S 2013, 'Respiratory function in late-onset Pompe disease patients receiving long-term enzyme replacement therapy for more than 48 months', *Wiener medizinische Wochenschrift (1946)*, vol. 163, no. 1-2, 2013-Jan, pp. 40-44.

Schneider, I, Hanisch, F, Muller, T & Zierz, S 2012, 'Respiratory function in late onset Pompe disease patients upon long-term enzyme replacement therapy', *Klinische Neurophysiologie*, vol. 43, no. 1.

Terzis, G, Dimopoulos, F, Papadimas, GK, Papadopoulos, C, Spengos, K, Fatouros, I, Kavouras, SA & Manta, P 2011, 'Effect of aerobic and resistance exercise training on late-onset Pompe disease patients receiving enzyme replacement therapy', *Molecular Genetics and Metabolism*, vol. 104, no. 3, Nov, pp. 279-283.

Terzis, G, Krase, A, Papadimas, G, Papadopoulos, C, Kavouras, SA & Manta, P 2012, 'Effects of exercise training during infusion on late-onset Pompe disease patients receiving enzyme replacement therapy', *Molecular Genetics and Metabolism*, vol. 107, no. 4, Dec, pp. 669-673.

Thurberg, BL, Lynch Maloney, C, Vaccaro, C, Afonso, K, Tsai, AC, Bossen, E, Kishnani, PS & O'Callaghan, M 2006, 'Characterization of pre- and post-treatment pathology after enzyme replacement therapy for Pompe disease', *Lab Invest*, vol. 86, no. 12, Dec, pp. 1208-1220.

Vielhaber, S, Brejova, A, Debska-Vielhaber, G, Kaufmann, J, Feistner, H, Schoenfeld, MA & Awiszus, F 2011, '24-Months results in two adults with Pompe disease on enzyme replacement therapy', *Clinical Neurology and Neurosurgery*, vol. 113, no. 5, Jun, pp. 350-357.

Wu, KHC, Devine, KT, Tchan, M & Sillence, DO 2012, 'An observational study of nine adult late-onset pompe disease patients treated or untreated with acid alpha-glucosidase enzyme replacement therapy', *Twin Research and Human Genetics*, vol. 15, no. 4, p. 565.

### Protocol only

*Observational Study About the Evolution of Severe Late Onset Pompe Disease Patient With Pulmonary Dysfunction and Receiving Myozyme - terminated trial*, ORPHA172900, Genzyme europe, France.

*A Prospective, Open-Label Study of the Effect and Safety of rhGAA in Patients With Advanced Late-Onset Pompe Disease Receiving Respiratory Support (Phase III) -Terminated* ORPHA77215, Genzyme europe, France.

*Single-Center, Open-Label Study of Safety, Pharmacokinetics and Efficacy of rhGAA in Patients With Late-Onset Pompe Disease*, ORPHA80891, Genzyme europe, Netherlands.

'ISRCTN72578000: Protocolised follow-up of Pompe patients recieving enzyme replacement therapy ona compasionate use basis' 2007, Recruitment in progress, ISRCTN Registry, Netherlands, <http://www.isrctn.com/ISRCTN72578000?q=Pompe&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=advanced-search>.

### Non-systematic review

Angelini, C & Semplicini, C 2012, 'Enzyme Replacement Therapy for Pompe Disease', Current Neurology and Neuroscience Reports, vol. 12, no. 1, Feb, pp. 70-75.

Beck, M 2009, 'Alglucosidase alfa: Long term use in the treatment of patients with Pompe disease', Therapeutics and clinical risk management, vol. 5, 2009, pp. 767-772.

Chien, YH, Lee, NC, Huang, PH, Lee, WT, Thurberg, BL & Hwu, WL 2012, 'Early pathologic changes and responses to treatment in patients with later-onset Pompe disease', Pediatric Neurology, vol. 46, no. 3, pp. 168-171.

Fiumara, A 2014, 'Enzyme replacement therapy (ERT) in pompe disease', Italian Journal of Pediatrics, vol. 40.

Hobson-Webb, LD, Proia, AD, Thurberg, BL, Banugaria, S, Prater, SN & Kishnani, PS 2012, 'Autopsy findings in late-onset Pompe disease: A case report and systematic review of the literature', Molecular Genetics and Metabolism, vol. 106, no. 4, Aug, pp. 462-469.

Khallaf, HHA, Propst, J, Geffrard, S, Botha, E & Pervaiz, MA 2013, 'CRIM-Negative Pompe Disease Patients with Satisfactory Clinical Outcomes on Enzyme Replacement Therapy', JIMD reports, vol. 9, 2013, pp. 133-137.

Miura, A 2008, 'Myozyme: clinical benefits in Pompe disease', Saibo, vol. 40, no. 5, //, pp. 214-217.

Parenti, G & Andria, G 2011, 'Pompe Disease: From New Views on Pathophysiology to Innovative Therapeutic Strategies', Current Pharmaceutical Biotechnology, vol. 12, no. 6, Jun, pp. 902-915.

Pascual Pascual, SI 2009, 'Phenotype variations in early onset pompe disease: Diagnosis and treatment results with myozyme®', Advances in Experimental Medicine and Biology, vol. 652, pp. 39-46<http://www.scopus.com/inward/record.url?eid=2-s2.0-77950361615&partnerID=40&md5=b5389f4dbfb1896614ab37386755fea4>.

Patel, TT, Banugaria, SG, Case, LE, Wenninger, S, Schoser, B & Kishnani, PS 2012, 'The impact of antibodies in late-onset Pompe disease: A case series and literature review', Molecular Genetics and Metabolism, vol. 106, no. 3, Jul, pp. 301-309.

Ploeg, Avd, Hagemans, M, Beek, Nvd, Capelle, Cv, Doorn, PAv, Laforêt, P & Reuser, AJ 2008, 'Natural Course and Effects of Enzyme Therapy in Adults with Pompe Disease', Clinical Therapeutics, vol. 30, no. SUPPL. 1, pp. S15-S16.

Vitacca, M & Filosto, M 2010, 'Multidisciplinary neurological and pneumological management of patients with glycogenosis type II', Rassegna di Patologia dell'Apparato Respiratorio, vol. 25, no. 5, pp. 263-271.

## Mucopolysaccharidosis Types I, II & VI

### MPS I: Laronidase versus placebo

### Systematic Review / Health Technology Assessment[[42]](#footnote-42)

Connock, M, Juarez-Garcia, A, Frew, E, Mans, A, Dretzke, J, Fry-Smith, A & Moore, D 2006, 'A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type I', *Health Technology Assessment*, vol. 10, no. 20, pp. iii-87.

El Dib, RP & Pastores, GM 2007, 'Laronidase for treating mucopolysaccharidosis type I', *Genetics and Molecular Research*, vol. 6, no. 3, pp. 667-674.

Jameson, E, Jones, S & Wraith James, E 2013, 'Enzyme replacement therapy with laronidase (Aldurazyme®) for treating mucopolysaccharidosis type I', *Cochrane Database of Systematic Reviews*, no. 11, DOI 10.1002/14651858.CD009354.pub3

### Cohort study

Clarke, LA, Wraith, JE, Beck, M, Kolodny, EH, Pastores, GM, Muenzer, J, Rapoport, DM, Berger, KI, Sidman, M, Kakkis, ED & Cox, GF 2009, 'Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I', *Pediatrics*, vol. 123, no. 1, pp. 229-240, DOI 10.1542/peds.2007-3847

Clarke, LA, Wraith, JE, Beck, M, Kolodny, EH, Pastores, GM & Muenzers, J 2007, 'A phase III extension study of Aldurazyme (R) (Laronidase) in mucopolysaccharidosis I', *Clinical Therapeutics*, vol. 29, pp. S111-S111.

Dornelles, AD, De Camargo Pinto, LL, De Paula, AC, Steiner, CE, Lourenco, CM, Ae Kim, C, Horovitz, DDG, Ribeiro, EM, Valadares, ER, Goulart, I, De Souza, ICN, Da Costa Neri, JI, Santana-da-Silva, LC, Silva, LR, Ribeiro, M, De Oliveira Sobrinho, RP, Giugliani, R & Schwartz, IVD 2014, 'Enzyme replacement therapy for mucopolysaccharidosis type I among patients followed within the MPS Brazil network', *Genetics and Molecular Biology*, vol. 37, no. 1, pp. 23-29.

Giugliani, R, Rojas, VM, Martins, AM, Valadares, ER, Clarke, JTR, Goes, JEC, Kakkis, ED, Worden, MA, Sidman, M & Cox, GF 2009, 'A dose-optimization trial of laronidase (Aldurazyme (R)) in patients with mucopolysaccharidosis I', *Molecular Genetics and Metabolism*, vol. 96, no. 1, Jan, pp. 13-19.

### Case series

Arora, RS, Mercer, J, Thornley, M, Tylee, K & Wraith, JE 2007, 'Enzyme replacement therapy in 12 patients with MPS I-H/S with homozygous p.Leu490Pro mutation', *J Inherit Metab Dis*, vol. 30, no. 5, Oct, p. 821.

Braunlin, EA, Berry, JM & Whitley, CB 2006, 'Cardiac Findings After Enzyme Replacement Therapy for Mucopolysaccharidosis Type I', *American Journal of Cardiology*, vol. 98, no. 3, pp. 416-418.

Cox-Brinkman, J, Smeulders, MJC, Hollak, CEM & Wijburg, FA 2007, 'Restricted upper extremity range of motion in mucopolysaccharidosis type I: No response to one year of enzyme replacement therapy', *Journal of Inherited Metabolic Disease*, vol. 30, no. 1, pp. 47-50.

Kakavanos, R, Turner, CT, Hopwood, JJ, Kakkis, ED & Brooks, DA 2003, 'Immune tolerance after long-term enzyme-replacement therapy among patients who have mucopolysaccharidosis I', *Lancet*, vol. 361, no. 9369, //, pp. 1608-1613.

Kakkis, ED, Muenzer, J, Tiller, GE, Waber, L, Belmont, J, Passage, M, Izykowski, B, Phillips, J, Doroshow, R, Walot, I, Hoft, R & Neufeld, EF 2001, 'Enzyme-replacement therapy in mucopolysaccharidosis I', *N. Engl. J. Med.*, vol. 344, no. 3, //, pp. 182-188.

Martins, AM, Micheletti, C, Tavares Silva, C, Meloni Vicente, C, Santos Braghiroli, P, Canossa, S, Aquino, R, Silva, D, Culson-Thomas, V & Toma, L 2009, 'MPS I patients in enzyme replacement therapy with laronidase in doble dose every two weeks and glycosaminoglycans measurements', *Molecular Genetics and Metabolism*, vol. 98, no. 1-2, pp. 87-88.

Pereira, VG, Martins, AM, Micheletti, C & D'Almeida, V 2008, 'Mutational and oxidative stress analysis in patients with mucopolysaccharidosis type I undergoing enzyme replacement therapy', *Clinica Chimica Acta*, vol. 387, no. 1-2, pp. 75-79.

Ruiz-Cruz, ED, Campos-Garcia, FJ, Carpio-Hernandez, JC, Vega- Ramirez, ME, Marquez-Gutierrez, MA, Ricardez-Marcial, EF, Franco-Ornelas, SJ & Gonzalez-Vite, M 2013, 'Clinical outcome of 5 Mexican patients with Mucopolysaccharidosis type I in enzyme replacement therapy', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, pp. S302-S303.

Valayannopoulos, V, Chabli, A, Romano, S, Mahlaoui, N, Caillaud, C, Le Merrer, M & de Lonlay, P 2006, 'Experience with laronidase treatment in 5 MPS I patients with various phenotypes and indications', *Journal of Inherited Metabolic Disease*, vol. 29, Aug, pp. 65-65.

Vera, M, Le, S, Kan, SH, Garban, H, Naylor, D, Mlikotic, A, Kaitila, I, Harmatz, P, Chen, A & Dickson, P 2013, 'Immune response to intrathecal enzyme replacement therapy in mucopolysaccharidosis I patients', *Pediatric Research*, vol. 74, no. 6, pp. 712-720.

Wraith, JE, Beck, M, Lane, R, van der Ploeg, A, Shapiro, E, Xue, Y, Kakkis, ED & Guffon, N 2007, 'Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human alpha-L-iduronidase (laronidase)', *Pediatrics*, vol. 120, no. 1, Jul, pp. e37-46.

Wynn, RF, Mercer, J, Page, J, Carr, TF, Jones, S & Wraith, JE 2009, 'Use of enzyme replacement therapy (Laronidase) before hematopoietic stem cell transplantation for mucopolysaccharidosis I: experience in 18 patients', *J Pediatr*, vol. 154, no. 1, Jan, pp. 135-139.

### MPS II: Idursulfase versus placebo

### Systematic Review42

da Silva, EMK, Strufaldi, MWL, Andriolo, RB & Silva, LA 2011, 'Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome)', *Cochrane Database Syst Rev*, no. 11, //, p. CD008185.

### Dose comparison (two doses of same treatment, without alternative treatment as comparator)

Muenzer, J, Gucsavas-Calikoglu, M, McCandless, SE, Schuetz, TJ & Kimura, A 2007, 'A phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome)', *Molecular genetics and metabolism*, vol. 90, no. 3, pp. 329-337, DOI 10.1016/j.ymgme.2006.09.001

### Cohort Study

Barbier, AJ, Bielefeld, B, Whiteman, DA, Natarajan, M, Pano, A & Amato, DA 2013, 'The relationship between anti-idursulfase antibody status and safety and efficacy outcomes in attenuated mucopolysaccharidosis II patients aged 5 years and older treated with intravenous idursulfase', *Mol Genet Metab*, vol. 110, no. 3, Nov, pp. 303-310.

Brown, IFR, Hall, CW & Neufeld, EF 1982, 'Administration of iduronate sulfatase by plasma exchange to patients with the Hunter syndrome: A clinical study', *American Journal of Medical Genetics*, vol. 13, no. 3, pp. 309-318.

Burton, BK, Guffon, N, Roberts, J, van der Ploeg, AT & Jones, SA 2010, 'Home treatment with intravenous enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II - data from the Hunter Outcome Survey', *Mol Genet Metab*, vol. 101, no. 2-3, Oct-Nov, pp. 123-129.

Burton, BK & Whiteman, DA 2011, 'Incidence and timing of infusion-related reactions in patients with mucopolysaccharidosis type II (Hunter syndrome) on idursulfase therapy in the real-world setting: a perspective from the Hunter Outcome Survey (HOS)', *Mol Genet Metab*, vol. 103, no. 2, Jun, pp. 113-120.

Giugliani, R, Hwu, WL, Tylki-Szymanska, A, Whiteman, DA & Pano, A 2014, 'A multicenter, open-label study evaluating safety and clinical outcomes in children (1.4-7.5 years) with Hunter syndrome receiving idursulfase enzyme replacement therapy', *Genet Med*, vol. 16, no. 6, Jun, pp. 435-441.

Jones, SA, Parini, R, Harmatz, P, Giugliani, R, Fang, J & Mendelsohn, NJ 2013, 'The effect of idursulfase on growth in patients with Hunter syndrome: data from the Hunter Outcome Survey (HOS)', *Mol Genet Metab*, vol. 109, no. 1, May, pp. 41-48.

Muenzer, J, Beck, M, Eng, CM, Giugliani, R, Harmatz, P, Martin, R, Ramaswami, U, Vellodi, A, Wraith, JE, Cleary, M, Gucsavas-Calikoglu, M, Puga, AC, Shinawi, M, Ulbrich, B, Vijayaraghavan, S, Wendt, S, Conway, AM, Rossi, A, Whiteman, DA & Kimura, A 2011, 'Long-term, open-labeled extension study of idursulfase in the treatment of Hunter syndrome', *Genet Med*, vol. 13, no. 2, Feb, pp. 95-101.

Muenzer, J, Beck, M, Giugliani, R, Suzuki, Y, Tylki-Szymanska, A, Valayannopoulos, V, Vellodi, A & Wraith, JE 2011, 'Idursulfase treatment of Hunter syndrome in children younger than 6 years: results from the Hunter Outcome Survey', *Genet Med*, vol. 13, no. 2, Feb, pp. 102-109.

Tylki-Szymanska A 2011 trial completed, 'Safety and Clinical Outcomes in Hunter Syndrome Patients 5 Years of Age and Younger Receiving Idursulfase Therapy'.

White, KK, Hale, S & Goldberg, MJ 2010, 'Musculoskeletal health in Hunter disease (MPS II): ERT improves functional outcomes', *Journal of Pediatric Rehabilitation Medicine*, vol. 3, no. 2, pp. 101-107.

Zuber, Z, Rozdzynska-Swiatkowska, A, Jurecka, A & Tylki-Szymanska, A 2014, 'The effect of recombinant human iduronate-2-sulfatase (Idursulfase) on growth in young patients with mucopolysaccharidosis type II', *PLoS One*, vol. 9, no. 1, p. e85074.

### Case series

Alcalde-Martín, C, Muro-Tudelilla, JM, Cancho-Candela, R, Gutiérrez-Solana, LG, Pintos-Morell, G, Martí-Herrero, M, Munguira-Aguado, P & Galán-Gómez, E 2010, 'First experience of enzyme replacement therapy with idursulfase in Spanish patients with Hunter syndrome under 5 years of age: Case observations from the Hunter Outcome Survey (HOS)', *European Journal of Medical Genetics*, vol. 53, no. 6, pp. 371-377.

Buraczewska, M, O'Leary, D, Walsh, O, Monavari, A & Crushell, E 2013, 'Parental experience of enzyme replacement therapy for hunter syndrome', *Irish Medical Journal*, vol. 106, no. 4.

Cho, SY, Huh, R, Chang, MS, Lee, J, Kwun, Y, Maeng, SH, Kim, SJ, Sohn, YB, Park, SW, Kwon, EK, Han, SJ, Jung, J & Jin, DK 2014, 'Impact of enzyme replacement therapy on linear growth in Korean patients with mucopolysaccharidosis type II (Hunter syndrome)', *J Korean Med Sci*, vol. 29, no. 2, Feb, pp. 254-260.

Jurecka, A, Zuber, Z, Opoka-Winiarska, V, Wegrzyn, G & Tylki-Szymańska, A 2012, 'Effect of rapid cessation of enzyme replacement therapy: A report of 5 cases and a review of the literature', *Molecular Genetics and Metabolism*, vol. 107, no. 3, pp. 508-512.

Kim, J, Park, MR, Kim, DS, Lee, JO, Maeng, SH, Cho, SY, Han, Y, Ahn, K & Jin, DK 2013, 'IgE-mediated anaphylaxis and allergic reactions to idursulfase in patients with Hunter syndrome', *Allergy*, vol. 68, no. 6, Jun, pp. 796-802.

Ko, K, Yi, SH, Jin, DK & Kwon, JY 2011, 'The effect of enzyme replacement therapy on carpal tunnel syndrome in patients with mucopolysaccharidosis type II (Hunter syndrome): Electrophysiological findings', *Developmental Medicine and Child Neurology*, vol. 53, p. 62.

Lampe, C, Atherton, A, Burton, BK, Descartes, M, Giugliani, R, Horovitz, DD, Kyosen, SO, Magalhaes, TS, Martins, AM, Mendelsohn, NJ, Muenzer, J & Smith, LD 2014, 'Enzyme Replacement Therapy in Mucopolysaccharidosis II Patients Under 1 Year of Age', *JIMD Rep*, Feb 11.

Lampe, C, Bosserhoff, A-K, Burton, BK, Giugliani, R, de, SCF, Bittar, C, Muschol, N, Olson, R & Mendelsohn, NJ 2014, 'Long-term experience with enzyme replacement therapy (ERT) in MPS II patients with a severe phenotype: an international case series', *J Inherit Metab Dis*, //.

Malik, V, Nichani, J, Rothera, MP, Wraith, JE, Jones, SA, Walker, R & Bruce, IA 2013, 'Tracheostomy in mucopolysaccharidosis type II (Hunter's Syndrome)', *International Journal of Pediatric Otorhinolaryngology*, vol. 77, no. 7, pp. 1204-1208.

Manara, R, Priante, E, Grimaldi, M, Santoro, L, Astarita, L, Barone, R, Concolino, D, Di Rocco, M, Donati, MA, Fecarotta, S, Ficcadenti, A, Fiumara, A, Furlan, F, Giovannini, I, Lilliu, F, Mardari, R, Polonara, G, Procopio, E, Rampazzo, A, Rossi, A, Sanna, G, Parini, R & Scarpa, M 2011, 'Brain and spine MRI features of Hunter disease: Frequency, natural evolution and response to therapy', *Journal of Inherited Metabolic Disease*, vol. 34, no. 3, pp. 763-780.

Marucha, J, Jurecka, A, Syczewska, M, Rozdzynska-Swiatkowska, A & Tylki-Szymanska, A 2012, 'Restricted joint range of motion in patients with MPS II: correlation with height, age and functional status', *Acta Paediatrica*, vol. 101, no. 4, Apr, pp. E183-E188.

Okuyama, T, Tanaka, A, Suzuki, Y, Ida, H, Tanaka, T, Cox, GF, Eto, Y & Orii, T 2010, 'Japan Elaprase® Treatment (JET) study: Idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (Mucopolysaccharidosis II, MPS II)', *Molecular Genetics and Metabolism*, vol. 99, no. 1, pp. 18-25.

Okuyama, T, Tanaka, A, Tanaka, T, Ida, H, Suzuki, Y, Cox, GF, Eto, Y & Orii, T 2009, 'Idursulfase enzyme replacement therapy in seriously ill, Japanese men with Hunter syndrome', *Molecular Genetics and Metabolism*, vol. 98, no. 1-2, p. 65.

Pano, A, Barbier, AJ, Bielefeld, B, Whiteman, DAH & Amato, DA 2013, 'Immunogenicity of idursulfase and clinical outcomes in very young Mucopolysaccharidosis II (MPS II) patients (16months to 7.5 years old)', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, p. S278.

Scarpa, M, Morin, I, Giugliani, R & Tylki-Szymanska, A 2013, 'Idursulfase treatment in six female patients with Hunter syndrome: Data from the Hunter Outcome Survey (HOS)', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, p. S290.

Schulze-Frenking, G, Jones, SA, Roberts, J, Beck, M & Wraith, JE 2011, 'Effects of enzyme replacement therapy on growth in patients with mucopolysaccharidosis type II', *J Inherit Metab Dis*, vol. 34, no. 1, Feb, pp. 203-208.

Valayannopoulos, V, Arnoux, JB, Kossorotoff, M, Chabli, A, Caillaud, C, Lemoine, M, Lyonnet, S, Lemerrer, M, Cormier-Daire, V & De Lonlay, P 2010, 'Cognitive outcome in 14 MPS II patients treated with idursulfase', *Journal of Inherited Metabolic Disease*, vol. 33, p. S149.

### Erratum

Muenzer, J, Beck, M, Eng, CM, Giugliani, R, Harmatz, P, Martin, R, Ramaswami, U, Vellodi, A, Wraith, JE, Cleary, M, Gucsavas-Calikoglu, M, Puga, AC, Shinawi, M, Ulbrich, B, Vijayaraghavan, S, Wendt, S, Conway, AM, Rossi, A, Whiteman, DAH & Kimura, A 2013, 'Erratum: Long-term, open-labeled extension study of idursulfase in the treatment of Hunter syndrome (Genetics in Medicine (2013) 13:2 (95-101) DOI: 10.1097/GIM.0b013e3181fea459)', *Genetics in Medicine*, vol. 15, no. 10, p. 849.

Muenzer, J, Wraith, JE, Beck, M, Giugliani, R, Harmatz, P, Eng, CM, Vellodi, A, Martin, R, Ramaswami, U, Gucsavas-Calikoglu, M, Vijayaraghavan, S, Wendt, S, Puga, AC, Ulbrich, B, Shinawi, M, Cleary, M, Piper, D, Conway, AM & Kimura, A 2006, 'Erratum: A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome) (Genetics in Medicine (August 2006) 8, 8, (465-473))', *Genetics in Medicine*, vol. 8, no. 9, p. 599.

### MPS VI: Galsulfase versus placebo

### Systematic Review42

El, DRP & Pastores, GM 2009, 'A systematic review of new advances in the management of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): focus on galsulfase', *Biologics*, vol. 3, //, pp. 459-468.

### Cohort study

Harmatz, P, Yu, ZF, Giugliani, R, Schwartz, IVD, Guffon, N, Teles, EL, Miranda, MCS, Wraith, JE, Beck, M, Arash, L, Scarpa, M, Ketteridge, D, Hopwood, JJ, Plecko, B, Steiner, R, Whitley, CB, Kaplan, P, Swiedler, SJ, Hardy, K, Berger, KI & Decker, C 2010, 'Enzyme replacement therapy for mucopolysaccharidosis VI: Evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase', *Journal of Inherited Metabolic Disease*, vol. 33, no. 1, pp. 51-60.

Hendriksz, CJ, Giugliani, R, Harmatz, P, Lampe, C, Martins, AM, Pastores, GM, Steiner, RD, Leao, TE & Valayannopoulos, V 2013, 'Design, baseline characteristics, and early findings of the MPS VI (mucopolysaccharidosis VI) Clinical Surveillance Program (CSP)', *J Inherit Metab Dis*, vol. 36, no. 2, //, pp. 373-384.

Kampmann, C, Lampe, C, Whybra-Truempler, C, Wiethoff, CM, Mengel, E, Arash, L, Beck, M & Miebach, E 2014, 'Mucopolysaccharidosis VI: cardiac involvement and the impact of enzyme replacement therapy', *J. Inherited Metab. Dis.*, vol. 37, no. 2, //, pp. 269-276.

### Case series

Bagewadi, S, Roberts, J, Mercer, J, Jones, S, Stephenson, J & Wraith, J 2008, 'Home treatment with Elaprase (R) and Naglazyme (R) is safe in patients with mucopolysaccharidoses types II and VI, respectively', *Journal of Inherited Metabolic Disease*, vol. 31, no. 6, Dec, pp. 733-737.

Brands, MMMG, Oussoren, E, Hagemans, MLC & Van Der Ploeg, AT 2011, 'Enzyme replacement therapy in 10 Dutch mucopolysaccharidosis type VI patients', *Journal of Inherited Metabolic Disease*, vol. 34, p. S214.

Brands, MMMG, Oussoren, E, Ruijter, GJG, Vollebregt, AAM, van den Hout, HMP, Joosten, KFM, Hop, WCJ, Plug, I & Van der Ploeg, AT 2013, 'Up to five years experience with 11 mucopolysaccharidosis type VI patients', *Molecular Genetics and Metabolism*, vol. 109, no. 1, pp. 70-76.

Giugliani, R, Lampe, C, Guffon, N, Ketteridge, D, Leão-Teles, E, Wraith, JE, Jones, SA, Piscia-Nichols, C, Lin, P, Quartel, A & Harmatz, P 2014, 'Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)-10-year follow-up of patients who previously participated in an MPS VI survey study', *American Journal of Medical Genetics, Part A*.

Giugliani, R, Lampe, C, Guffon, N, Ketteridge, D, Leao-Teles, E, Wraith, JE, Jones, SA, Piscia-Nichols, C, Quartel, A & Harmatz, P 2013, 'Longitudinal natural history and galsulfase treatment in Mucopolysaccharidosis VI (MPSVI, Maroteaux-Lamy syndrome): 10 year follow-up of patients who previously participated in a MPSVI survey study', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, p. S273.

Harmatz, P, Guffon, N, Garcia, P, Cheng, S, Lagan, K & Decker, C 2010, 'A phase 4 two dose level study of galsulfase in mucopolysaccharidosis VI infants', *Journal of Inherited Metabolic Disease*, vol. 33, p. S144.

Horovitz, DD, Magalhaes, TS, Acosta, A, Ribeiro, EM, Giuliani, LR, Palhares, DB, Kim, CA, de Paula, AC, Kerstenestzy, M, Pianovski, MA, Costa, MI, Santos, FC, Martins, AM, Aranda, CS, Correa Neto, J, Holanda, GB, Cardoso, L, Jr., da Silva, CA, Bonatti, RC, Ribeiro, BF, Rodrigues Mdo, C & Llerena, JC, Jr. 2013, 'Enzyme replacement therapy with galsulfase in 34 children younger than five years of age with MPS VI', *Mol Genet Metab*, vol. 109, no. 1, May, pp. 62-69.

Horovitz, DDG, Magalhaes, T, Costa, APE, Carelli, LE, Silva, DSE, Riello, A & Llerena, JC 2011, 'Spinal cord compression in young children with type VI mucopolysaccharidosis', *Molecular Genetics and Metabolism*, vol. 104, no. 3, Nov, pp. 295-300.

Horovitz, DDG, Ribeiro, EM, Acosta, A, Giuliani, L, Kerstenestzy, M, Kim, CA, Magalhaes, TSPC, Palhares, D & Llerena, JC 2009, 'Enzyme replacement therapy in eight mucopolysaccharidosis type VI Brazilian children under age three: Preliminary data', *Molecular Genetics and Metabolism*, vol. 98, no. 1-2, p. 67.

Jurecka, A, Rozdzynska, A, Marucha, J, Czartoryska, B & Tylki-Szymanska, A 2010, 'Polish patients with Maroteaux-Lamy syndrome (mucopolisaccharidosis type VI)', *Pediatria Polska*, vol. 85, no. 4, pp. 311-319.

Kantaputra, PN, Kayserili, H, Güven, Y, Kantaputra, W, Balci, MC, Tanpaiboon, P, Uttarilli, A & Dalal, A 2014, 'Oral manifestations of 17 patients affected with mucopolysaccharidosis type VI', *Journal of Inherited Metabolic Disease*, vol. 37, no. 2, pp. 263-268.

Micheletti, C, Mendes, CC, Silva, LF, Silveira, MT, Pedroso, A & Martins, AM 2009, 'Experience of enzyme replacement therapy in patients with mucopolysaccharidoses type VI', *Molecular Genetics and Metabolism*, vol. 98, no. 1-2, p. 73.

Pitz, S, Ogun, O, Arash, L, Miebach, E & Beck, M 2009, 'Does enzyme replacement therapy influence the ocular changes in type VI mucopolysaccharidosis?', *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie*, vol. 247, no. 7, pp. 975-980, DOI 10.1007/s00417-008-1030-1

Pitz, S, Ogun, O, Bajbouj, M, Arash, L, Schulze-Frenking, G & Beck, M 2007, 'Ocular changes in patients with mucopolysaccharidosis I receiving enzyme replacement therapy: a 4-year experience', *Archives of ophthalmology*, vol. 125, no. 10, pp. 1353-1356, DOI 10.1001/archopht.125.10.1353

Ribeiro, EM, Ribeiro, EM, Magalhaes, TSPC, Horovitz, D, Acosta, A, Giuliani, L, Palhares, D, Kim, CA, Paula, AC, Kerstenestzy, M, Pianovski, MAD, Costa, MIF, Santos, FC, Martins, AM, Aranda, CS, Soares, N, Cardoso Jr, L, Llerena Jr, JC & Bruno, CA 2010, 'Enzyme replacement therapy in 25 mucopolysaccharidosis type VI Brazilian children under age five years', *Journal of Inherited Metabolic Disease*, vol. 33, p. S155.

Valayannopoulos, V, Barbier, V, Boddaert, N, Arnoux, JB, Lemerrer, M & De Lonlay, P 2009, 'High prevalence of mental impairment in a series of 6 patients with mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome', *Molecular Genetics and Metabolism*, vol. 98, no. 1-2, p. 80.

### ERT for MPS I, MPS II and/or MPS VI

### Case series

Brands, MMMG, Frohn-Mulder, IM, Hagemans, MLC, Hop, WCJ, Oussoren, E, Helbing, WA & Van Der Ploeg, AT 2013, 'Mucopolysaccharidosis: Cardiologic features and effects of enzyme-replacement therapy in 24 children with MPS I, II and VI', *Journal of Inherited Metabolic Disease*, vol. 36, no. 2, pp. 227-234.

Burton, BK, Wiesman, C, Paras, A, Kim, K & Katz, R 2009, 'Home infusion therapy is safe and enhances compliance in patients with mucopolysaccharidoses', *Molecular Genetics and Metabolism*, vol. 97, no. 3, pp. 234-236.

Coman, DJ, Hayes, IM, Collins, V, Sahhar, M, Wraith, JE & Delatycki, MB 2008, 'Enzyme Replacement Therapy for Mucopolysaccharidoses: Opinions of Patients and Families', *Journal of Pediatrics*, vol. 152, no. 5, pp. 723-727.

Jurecka, A, Malinova, V & Tylki-Szymanska, A 2014, 'Effect of rapid cessation of enzyme replacement therapy: A report of 5 more cases', Molecular Genetics and Metabolism, vol. 111, no. 2, pp. 212-213.

Lin, S-P, Shih, S-C, Chuang, C-K, Lee, K-S, Chen, M-R, Niu, D-M, Chiu, PC, Lin, SJ & Lin, H-Y 2014, 'Characterization of Pulmonary Function Impairments in Patients With Mucopolysaccharidoses-Changes With Age and Treatment', Pediatric Pulmonology, vol. 49, no. 3, Mar, pp. 277-284.

Miebach, E 2009, 'Management of infusion-related reactions to enzyme replacement therapy in a cohort of patients with mucopolysaccharidosis disorders', Int J Clin Pharmacol Ther, vol. 47 Suppl 1, pp. S100-106.

## Paroxysmal Nocturnal Haematuria

### Duplicated data

Connock, M, Wang, D, Fry-Smith, A & Moore, D 2008, 'Prevalence and prognosis of paroxysmal nocturnal haemoglobinuria and the clinical and cost-effectiveness of eculizumab (Provisional abstract)', *NHS Economic Evaluation Database (NHSEED)*, no. 4, p. 1, <http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22009101584/frame.html>.

Hill, A, Rother, RP, Risitano, AM, Cole, DS, Cullen, MJ, Richards, SJ, Selleri, C, Ricci, P, Rotoh, B, Luzzatto, L & Hillmen, P 2007, 'Blockade of intravascular hemolysis in PNH with the terminal complement inhibitor eculizumab unmasks low-level hemolysis potentially occurring through C3 opsonization', *Haematologica-the Hematology Journal*, vol. 92, Jun, pp. 24-24.

Hill, A, Rother, RP, Wang, X, Sapsford, RJ, Collinson, PO, Gaze, DC, Morris, SM, Scally, A, Quinn-Senger, K, Richards, SJ, Bessel, M, Kelly, R, Hillmen, P & Gladwin, M 2009, 'Eculizumab Reduces Pulmonary Hypertension through Inhibition of Hemolysis-Associated Nitric Oxide Consumption in Patients with Paroxysmal Nocturnal Hemoglobinuria [Abstract No. 486]', *Blood*, vol. 112, no. 11, p. 185, <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/913/CN-00782913/frame.html>.

Kelly, RJ, Hill, A, Arnold, LM, Brooksbank, GL, Richards, SJ, Cullen, M, Mitchell, LD, Cohen, DR, Gregory, WM & Hillmen, P 2011, 'Long term treatment with eculizumab in paroxysmal nocturnal haemoglobinuria (PNH): sustained efficacy and improved survival', *British Journal of Haematology*, vol. 153, Apr, pp. 26-26.

Roeth, A, Hock, C, Tokareva, O, Konik, A & Duehrsen, U 2011, 'Role of bone marrow failure in paroxysmal nocturnal hemoglobinuria (PNH) patients chronically treated with Eculizumab', *Onkologie*, vol. 34, Sep, pp. 115-115.

### Abstract only

Alexander, W, Bessler, M & Parker, CJ 2008, 'American Society of Hematology 49th Annual Meeting: Eculizumab (Soliris) for paroxysmal nocturnal hemolysis', *P and T*, vol. 33, no. 2, pp. 111-112.

Alexander, W & Kelly, RJ 2011, 'http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3086088/', *P and T*, vol. 36, no. 2, p. 103.

Arnold, LM, Brooksbank, GL, Kelly, RJ, Hill, A, Richards, SJ, Senior, R, Downing, T, McKinley, C, Brown, J, Momoh, I, Elebute, M & Hillmen, P 2011, 'Continued benefit from prolonged treatment with eculizumab in 130 patients with PNH in the UK: Home delivery of eculizumab is safe, convenient and associated with very high levels of patient satisfaction', *Blood*, vol. 118, no. 21.

Bessler, M, Schrezenmeier, H, Maciejewski, JP, Hill, A, Rollins, SA, Young, NS & Luzzatto, L 2007, 'Significant Disease Burden in Paroxysmal Nocturnal Hemoglobinuria Patients with Lower Levels of Hemolysis, Mild Anemia and Minimal Transfusion: Clinical Improvement with Eculizumab Therapy', *ASH Annual Meeting Abstracts*, vol. 110, no. 11, November 16, 2007, pp. 840-.

Brodsky, RA, De Castro, C, Schrezenmeier, H, Risitano, AM, Schubert, J, Maciejewski, JP, Duehrsen, U, Luzzatto, L, Muus, P, Szer, J, Socie, G & Hillmen, P 2010, 'Long term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal hemoglobinuria (PNH)', *Blood*, vol. 116, no. 21.

Brodsky RA, HP, Schubert J, Luzzatto L, Socie G, Mojcik CF, Rother RP, Young NS 2007, 'Safety and efficacy of eculizumab in paroxysmal nocturnal hemoglobinuria evolving from patients with myelodysplastic syndrome and aplastic anemia', *Journal of Clinical Oncology*, vol. 25, No 18S ASCO Annual Meeting Proceedings, no. 7033.

de Andres, AM, Sola, N, Creus, N, Codina, C & Ribas, J 2010, 'Evaluation of the use of eculizumab for treatment of paroxysmal nocturnal hemoglobinuria', *Pharmacy World & Science*, vol. 32, no. 2, Apr, pp. 299-300.

de Latour, RP, Fremeaux-Bacchi, V, Porcher, R, Rodriguez-Otero, P, Abbes, S, Roncelin, S & Socie, G 2013, 'Complement assessment in patients with paroxysmal nocturnal haemoglobinuria treated by eculizumab', *Bone Marrow Transplantation*, vol. 48, Apr, pp. S414-S415.

De Latour, RP, Fremeaux-Bacchi, V, Porcher, R, Rodriguez-Otero, P, Roncellin, S, Abbes, S & Socie, G 2012, 'CH50 activity correlates with residual intravascular hemolysis in PTS with paroxysmal nocturnal hemoglobinuria treated by eculizumab

', *Blood*, vol. 120, no. 21.

DeZern, AE, Dorr, D & Brodsky, RA 2012, 'Predictors of response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria', *Blood*, vol. 120, no. 21.

Fernandez-Jurado, A 2013, 'ORPHAN DRUGS: ECULIZUMAB IN THE TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA', *Basic & Clinical Pharmacology & Toxicology*, vol. 113, Oct, pp. 4-4.

Haughton, J, Kelly, RJ, Richards, SJ, Arnold, LM, Wood, A, Downing, T, McKinley, C, Davies, M, Hillmen, P & Hill, A 2012, 'Improved outcomes of budd-chiari syndrome in paroxysmal nocturnal hemoglobinuria with eculizumab therapy', *Blood*, vol. 120, no. 21.

—— 2013, 'Early diagnosis and immediate treatment with eculizumab improves the outcome of Budd-Chiari syndrome (BCS) in paroxysmal nocturnal haemoglobinuria (PNH)', *British Journal of Haematology*, vol. 161, Apr, pp. 71-72.

Helley, D, Darnige, L, De Latour, RP, Zemori, L, Socie, G & Fischer, AM 2011, 'Antiphospholipid antibodies in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab', *Journal of Thrombosis and Haemostasis*, vol. 9, p. 624.

Hill, A 2009, 'Eculizumab (Soliris) reduces pulmonary hypertension in paroxysmal nocturnal hemoglobinuria', *P and T*, vol. 34, no. 2, p. 98.

—— 2009, 'PNH: New options', *Leukemia Research*, vol. 33, pp. S20-S21.

Hill, A, Bessler, M, Schrezenmeier, H, Maciejewski, JP, Rollins, SA, Young, NS & Luzzatto, L 2008, 'Significant disease burden in paroxysmal nocturnal haemoglobinuria (PNH) patients with lower levels of haemolysis, mild anaemia and minimal transfusion: clinical improvement with eculizumab therapy', *British Journal of Haematology*, vol. 141, Apr, pp. 66-67.

Hill, A, Kelly, R, Kulasekararaj, A, Gandhi, S, Mitchell, L, Elebute, M, Richards, S, Cullen, M, Arnold, L, Large, J, Wood, A, Downing, T, McKinley, C, Brooksbank, G, Cohen, D, Gregory, W, Marsh, J, Mufti, G & Hillmen, P 2013, 'Eculizumab in paroxysmal nocturnal haemoglobinuria (PNH): a report of all 153 patients treated in the UK', *British Journal of Haematology*, vol. 161, Apr, pp. 3-4.

Hill, A, Kelly, RJ, Kulasekararaj, AG, Gandhi, SA, Mitchell, LD, Elebute, M, Richards, SJ, Cullen, M, Arnold, LM, Large, J, Wood, A, Brooksbank, GL, Downing, T, McKinley, C, Cohen, D, Gregory, WM, Marsh, JCW, Mufti, GJ & Hillmen, P 2012, 'Eculizumab in paroxysmal nocturnal hemoglobinuria (PNH): A report of all 153 patients treated in the UK', *Blood*, vol. 120, no. 21.

Hill, A, Muus, P, Duhrsen, U, Socie, G, Risitano, A, De Paz, R, Van den Neste, E, Zanella, A, Lai, JS, Hillmen, P, Rother, R & Cella, D 2008, 'IMPROVEMENT IN FATIGUE WITH ECULIZUMAB TREATMENT OF PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) OCCURS INDEPENDENT OF CHANGES IN ANEMIA', *Haematologica-the Hematology Journal*, vol. 93, Jun, pp. 359-359.

Hill, A, Rother, R, Wang, X, Sapsford, R, Collinson, P, Gaze, D, Morris, S, Scally, A, Quinn-Senger, K, Richards, S, Bessler, M, Kelly, R, Hillmen, P & Galdwin, M 2009, 'Eculizumab reduces pulmonary hypertension through inhibition of haemolysis-associated nitric oxide consumption in patients with Paroxysmal nocturnal haemoglobinuria', *Haematologica*, vol. 94, p. 450.

Hill, A, Rother, RP, Risitano, AM, Cole, DS, Cullen, MJ, Richards, SJ, Selleri, C, Ricci, P, Rotoli, B, Luzzatto, L & Hillmen, P 2006, 'Blockade of Intravascular Hemolysis in PNH with the Terminal Complement Inhibitor Eculizumab Unmasks Low-Level Hemolysis Potentially Occurring through C3 Opsonization', *ASH Annual Meeting Abstracts*, vol. 108, no. 11, November 16, 2006, pp. 972-.

Hill, A, Socie, G, Muus, P, Schrezenmeier, H, Hochsmann, B, Maciejewski, J, Weitz, IC, Bessler, M & Risitano, AM 2010, 'Terminal complement inhibitor eculizumab improves complement-mediated platelet consumption and thrombocytopenia in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)', *British Journal of Haematology*, vol. 149, p. 10.

Hochsmann, B, Von Zabern, I, Leichtle, R, Kaiser, S, Flegel, WA & Schrezenmeier, H 2010, 'Paroxysmal Nocturnal Hemoglobinuria (PNH) and targeted therapy with C5 antibody eculizumab-consequences for transfusion medicine', *Vox Sanguinis*, vol. 99, no. supp 1, pp. 373-374.

Hochsmann, B, Von Zabern, I, Leichtle, R & Schrezenmeier, H 2010, 'Development of Ferritin levels during therapy with C5 antibody eculicumab in paroxysmal nocturnal hemoglobinuria (PNH)', *Onkologie*, vol. 33, no. 6, pp. 113-114.

Kulasekararaj, AG, Odunsi, D, Krishnamurthy, P, Janet, H, Momoh, I, Mufti, GJ, Marsh, JCW & Elebute, M 2010, 'Low level residual extravascular haemolysis is commom following eculizumab treatment in paroxysmal nocturnal haemoglobinuria(PNH), but does not affect transfusion requirement', *Blood*, vol. 116, no. 21.

Lisukov, I, Kulagin, A, Maschan, A, Shilova, E, Abdulkadyrov, K, Zaritskiy, A, Ivanova, V, Bogdanova, Y, Volkova, S, Gavrilenko, A, Kaporskaya, TS, Meresiy, S, Schneider, T, Yakupova, S, Anchukova, L, Bakirov, B, Kosacheva, N, Krinitsina, T, Ustyantseva, V, Shatokhin, Y, Rumyantsev, A & Afanasyev, B 2013, 'Data from the Russian cohort of the international disease registry for paroxysmal nocturnal hemoglobinuria (PNH)', *Blood*, vol. 122, no. 21.

Marando, L, Seneca, E, Ranaldi, D, Alfinito, F, Lucia Ferrara, IL, Pulini, S, La Barba, G, Fabbiano, F, Marino, A, Capalbo, S, Fenu, S, Carella, AM, Iori, AP, Notaro, R, Risitano, AM & Rotoli, B 2009, 'Beyond eculizumab (EC): Can we improve the hematological response in paroxysmal nocturnal hemoglobinuria (PNH) patients? What, to whom and why', *Haematologica*, vol. 94, p. 134.

Mojik CF, YN, Luzzatto L, Socie G, Hillmen P, Brodsky RA 2007, 'Safety and efficacy of eculizumab with conomitant erythropoietin therapy in patients with paroxysmal nocturnal hemoglobinuria (PNH)', *Am Soc Clin Onc*, vol. 25, no. 18.

Munoz-Linares, C, Pastrana, M, Ojeda, E, Fores, R, Cabero, M, Morillo, D, Bautista, G, Navarro, B, Krsnik, I, Gil, S, Regidor, C, De LaIglesia, A, Bueno, JL, Garcia-Marco, JA & Cabrera, JR 2013, 'Paroxysmal nocturnal hemoglobinuria and thrombosis before and after eculizumab', *Blood*, vol. 122, no. 21.

Muus, P, Duhrsen, U, Elebute, M, Browne, P, Urbano-Ispizua, A, Coutre, S, Van Den Neste, E, De Paz, R, Konkle, B, Moskovits, T, Nakamura, R, Zanella, A, Hillmen, P, Rother, RP & Soci, G 2007, 'The clinical benefit of eculizumab is demonstrable in all subpopulations of patients with paroxysmal nocturnal hemoglobinuria (PNH) with hemolysis', *Haematologica-the Hematology Journal*, vol. 92, Jun, pp. 137-138.

Muus, P, Luzzatto, L, Rotoli, B, Young, NS, Schubert, J, Urbano-Ispizua, A, Coyle, L, DeCastro, C, Fu, CL, Maciejewski, JP, Kroon, HA, Rother, RP, Hillmen, P & Schrezenmeier, H 2007, 'OP04 Safety and efficacy of the terminal complement inhibitor eculizumab in patients with paroxysmal nocturnal hemoglobinuria: Shepherd Phase III clinical study results', *Leukemia Research*, vol. 31, Supplement 2, no. 0, 9//, pp. S32-S33.

Reiss, UM, Schwartz, J, Sakamoto, KM, Puthenveetil, G, Ogawa, M & Ware, RE 2011, 'Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria', *Blood*, vol. 118, no. 21.

Risitano, A, Alfinito, F, Seneca, E, Marando, L, Boschetti, C, Bonfigli, S, Fenu, S, Re, F, Gosetti, G, Khursigara, G, Rother, R, Zanella, A & Rotoli, B 2009, 'Efficacy of the complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria patients never transfused', *Haematologica*, vol. 94, p. 237.

Risitano, AM, Seneca, E, Marando, L, Imbriaco, M, Soscia, E, Soscia, F, Micol Pizzuti, L, Malcovati, L, Fenu, S, Paola Iori, A, Notaro, R, Matarazzo, M & Rotoli, B 2009, 'From renal siderosis due to perpetual hemosiderinuria to possible liver overload due to extravascular hemolysis: Changes in iron metabolism in paroxysmal nocturnal hemoglobinuria (PNH) patients on eculizumab', *Blood*, vol. 114, no. 22.

Risitano, AM, Seneca, E, Marando, L, Imbriaco, M, Soscia, E, Soscia, F, Pizzuti, LM, Malcovati, L, Iori, AP, Notaro, R, Matarazzo, M & Rotoli, B 2009, 'Iron metabolism in paroxysmal nocturnal hemoglobinuria (PNH) patients on eculizumab: From perpetual hemosiderinuria and renal siderosis to possible liver overload due to extravascular hemolysis', *Haematologica*, vol. 94, pp. 35-36.

Roeth, A, Schubert, J, Hock, C, Christoph, S & Duehrsen, U 2008, 'Effect of Reducing Intravascular Hemolysis on Ferritin Homeostasis in Eculizumab Treated Paroxysmal Nocturnal Hemoglobinuria (PNH) Patients', *ASH Annual Meeting Abstracts*, vol. 112, no. 11, November 16, 2008, pp. 3437-.

Rondelli, T, Risitano, AM, De Latour, RP, Peruzzi, B, Patrizia, R, Barcellini, W, Iori, AP, Boschetti, C, Valle, V, Fremeaux-Bacchi, V, De Angioletti, M, Socie, G, Luzzatto, L & Notaro, R 2012, 'Genetic polymorphism of the complement receptor-1 (CR1) gene correlates with the clinical response to eculizumab of patients with paroxysmal nocturnal hemoglobinuria (PNH)', *Blood*, vol. 120, no. 21.

Roth, A, Hock, C, Tokareva, O, Konik, A & Duhrsen, U 2011, 'Role of bone marrow failure in paroxysmal nocturnalhemoglobinuria (PNH) patients chronically treated withEculizumab', *Onkologie*, vol. 34, p. 115.

Rother, RP, Hall, C, Marsh, J, Elebute, D, Mojcik, CF, Rollins, SA, Richards, S, Cullen, M & Hillmen, P 2003, 'Eculizumab, a C5 complement-blocking antibody, abolishes hemolysis and reduces transfusion dependency in patients with paroxysmal nocturnal hemoglobinuria (PNH)', *Molecular Immunology*, vol. 40, no. 2-4, Sep, pp. 197-197.

Schrezenmeier, H, Schubert, J, Luzzatto, L, Muus, P, Socie, G, Risitano, AM, Hill, A & Hillmen, P 2009, 'Effects of eculizumab therapy in patients with paroxysmal nocturnal hemoglobinuria (PNH) receiving concurrent immunosuppressive therapy for bone marrow insufficiency', *Blood*, vol. 114, no. 22.

Schubert, J 2009, 'Blockade of terminal complement cascade. Clinical effects of eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PNH)', *European Journal of Immunology*, vol. 39, p. S293.

Seneca, E, Marando, L, Alfinito, F, Cerciello, G, Boschetti, C, Bonfigli, S, Fenu, S, Re, F, Gosetti, G, Khursigara, G, Rother, R, Zanella, A, Risitano, AM & Rotoli, B 2009, 'Clinical benefit from eculizumab in paroxysmal nocturnal hemoglobinuria patients (PNH) who have not received previous transfusions', *Haematologica*, vol. 94, p. 134.

Socie, G, Muus, P, Schrezenmeier, H, Hochsmann, B, Maciejewski, JP, Weitz, IC, Hill, A, Bessler, M & Risitano, AM 2009, 'Terminal complement inhibitor eculizumab improves complement-mediated platelet consumption and thrombocytopenia in patients with paroxysmal nocturnal hemoglobinuria (PNH)', *Blood*, vol. 114, no. 22.

Socie, G, Schrezenmeier, H, Muus, P, Szer, J, Urbano-Ispizua, A, Maciejewski, JP, Brodsky, RA, Bessler, M, Kanakura, Y, Rosse, WF, Khursigara, G, Bedrosian, CL & Hillmen, P 2012, 'Eculizumab protects against te and prolongs survival in patients with paroxysmal nocturnal hemoglobinuria: An international PNH registry study', *Blood*, vol. 120, no. 21.

Usuki, K, Urabe, A, Kawaguchi, T, Miyasaka, N, Miura, O, Morishita, E, Arima, N, Morita, Y, Nishiwaki, K, Ninomiya, H, Gotoh, A, Imashuku, S, Shichishima, T, Nishimura, JI & Kanakura, Y 2013, 'Management of pregnancy in Paroxysmal Nocturnal Hemoglobinuria (PNH): A report of 10 cases from the working group on pregnancy of the Japan PNH study group', *Blood*, vol. 122, no. 21.

Waldner, B 2009, 'Eculizumab (Soliris (R)): a promising treatment of haemolytic anaemia in paroxysmal nocturnal haemoglobinuria', *Bone Marrow Transplantation*, vol. 43, Mar, pp. S362-S362.

Weitz, I, Rochanda, L & Liebman, H 2009, 'Effect of eculizimab therapy on thrombocytopenia in patients with Paroxysmal nocturnal hemoglobinuria', *Haematologica*, vol. 94, p. 238.

Weitz, IC, Ghods, M, Rochanda, L, Prazavi, P, Zwicker, J, Furie, B & Liebman, H 2008, 'Eculizumab Therapy Results in Rapid and Sustained Decreases in Markers of Thrombin Generation and Inflammation in Patients with PNH', *ASH Annual Meeting Abstracts*, vol. 112, no. 11, November 16, 2008, pp. 407-.

### Case series

DeZern, AE, Dorr, D & Brodsky, RA 2013, 'Predictors of hemoglobin response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria', *Eur J Haematol*, vol. 90, no. 1, Jan, pp. 16-24.

Hill, A, Hillmen, P, Richards, SJ, Elebute, D, Marsh, JC, Chan, J, Mojcik, CF & Rother, RP 2005, 'Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria', *Blood*, vol. 106, no. 7, Oct 1, pp. 2559-2565.

Hillmen, P, Hall, C, Marsh, JC, Elebute, M, Bombara, MP, Petro, BE, Cullen, MJ, Richards, SJ, Rollins, SA, Mojcik, CF & Rother, RP 2004, 'Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria', *N Engl J Med*, vol. 350, no. 6, Feb 5, pp. 552-559.

Hochsmann, B, Leichtle, R, von Zabern, I, Kaiser, S, Flegel, WA & Schrezenmeier, H 2012, 'Paroxysmal nocturnal haemoglobinuria treatment with eculizumab is associated with a positive direct antiglobulin test', *Vox Sang*, vol. 102, no. 2, Feb, pp. 159-166.

Kanakura, Y, Ohyashiki, K, Shichishima, T, Okamoto, S, Ando, K, Ninomiya, H, Kawaguchi, T, Nakao, S, Nakakuma, H, Nishimura, J, Kinoshita, T, Bedrosian, CL, Ozawa, K & Omine, M 2013, 'Long-term efficacy and safety of eculizumab in Japanese patients with PNH: AEGIS trial', *Int J Hematol*, vol. 98, no. 4, Oct, pp. 406-416.

Kanakura, Y, Ohyashiki, K, Shichishima, T, Okamoto, S, Ando, K, Ninomiya, H, Kawaguchi, T, Nakao, S, Nakakuma, H, Nishimura, J, Kinoshita, T, Bedrosian, CL, Valentine, ME, Khursigara, G, Ozawa, K & Omine, M 2011, 'Safety and efficacy of the terminal complement inhibitor eculizumab in Japanese patients with paroxysmal nocturnal hemoglobinuria: the AEGIS clinical trial', *Int J Hematol*, vol. 93, no. 1, Jan, pp. 36-46.

Kim, JS, Lee, JW, Kim, BK, Lee, JH & Chung, J 2010, 'The use of the complement inhibitor eculizumab (Soliris(R)) for treating Korean patients with paroxysmal nocturnal hemoglobinuria', *Korean J Hematol*, vol. 45, no. 4, Dec, pp. 269-274.

Reiss, UM, Schwartz, J, Sakamoto, KM, Puthenveetil, G, Ogawa, M, Bedrosian, CL & Ware, RE 2014, 'Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria', *Pediatr Blood Cancer*, vol. 61, Apr 29, pp. 1544-1550.

Roth, A, Hock, C, Konik, A, Christoph, S & Duhrsen, U 2011, 'Chronic treatment of paroxysmal nocturnal hemoglobinuria patients with eculizumab: safety, efficacy, and unexpected laboratory phenomena', *Int J Hematol*, vol. 93, no. 6, Jun, pp. 704-714.

### Foreign language (not a higher level of evidence than available in English)

Abdel-Kader Martín, L, Castillo Muñoz, MA, Alegre del Rey, EJ, Muñoz Muñoz, N & Muñoz Muñoz, JA 2011, 'Eculizumab (Soliris®) Assessment of effectivity and safety of the drug and economic analysis of use in Paroxysmal Nocturnal Haemoglobinuria therapy (Structured abstract)', *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000771/frame.html>.

López Rubio, M, Morado, M, Gaya, A, Alonso Rosa, D, Ojeda, E, Muñoz, JA, Pérez De Mendiguren, B, Monteagudo, MD, Durán, JM, Fisac, RM, Moreno, D & Villegas, AM 2011, 'Paroxysmal nocturnal hemoglobinuria therapy with eculizumab: Spanish experience', *Medicina Clinica*, vol. 137, no. 1, pp. 8-13.

Moncharmont, P, Barraco, F, Bernaud, J, Raffin, A, Michallet, M & Rigal, D 2009, 'Follow-up of patients with paroxystic nocturnal haemoglobinuria treated by eculizumab', *Immuno-Analyse et Biologie Specialisee*, vol. 24, no. 2, pp. 86-91.

Paladio, N 2009, 'Eculizumab for the treatment of paroxysmal nocturnal haemoglobinuria (Structured abstract)', *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32010000742/frame.html>.

Pichon Riviere, A, Augustovski, F, Garcia Marti, S, Alcaraz, A, Glujovsky, D, Lopez, A, Rey-Ares, L, Bardach, A & Regueiro, A 2011, 'Effectiveness of eculizumab in the treatment of paroxysmal nocturnal hemoglobinuria (Structured abstract)', *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32011000968/frame.html>.

### Wrong comparator

Canalejo, K, Cervantes, NR, Felippo, M, Sarandria, C & Aixala, M 2014, 'Paroxysmal nocturnal haemoglobinuria. Experience over a 10years period', *International Journal of Laboratory Hematology*, vol. 36, no. 2, Apr, pp. 213-221.

### Wrong outcome

Alfinito, F, Ruggiero, G, Sica, M, Udhayachandran, A, Rubino, V, Pepa, RD, Palatucci, AT, Annunziatella, M, Notaro, R, Risitano, AM & Terrazzano, G 2012, 'Eculizumab treatment modifies the immune profile of PNH patients', *Immunobiology*, vol. 217, no. 7, Jul, pp. 698-703.

Arcavi, M, Ceballo, F, Brodsky, AL, Halperin, NS, Cantenys, N, Colin, LB, Malusardi, C & Lazarowski, A 2013, 'Ham test for therapeutic monitoring of eculizumab in paroxysmal nocturnal hemoglobinuria', *Blood*, vol. 122, no. 21.

Arnold, LM, Stephenson, J, Kelly, RJ, Buchanan, D, Hill, A, Stichler, A, Bagabag, J, Jones, G, Bilbrough, C & Hillmen, P 2009, 'Home infusion of eculizumab: A survey of a unique model of drug delivery for patients in the NCG PNH service', *British Journal of Haematology*, vol. 145, p. 43.

Ceballo, F, Brodsky, AL, Halperin, NS, Cantenys, N, Colin, LB, Malusardi, C & Lazarowski, A 2013, *Ham Test For Therapeutic Monitoring Of Eculizumab In Paroxysmal Nocturnal Hemoglobinuria*, vol. 122.

Darnige, L, Peffault de Latour, R, Zemori, L, Socie, G, Fischer, A-M & Helley, D 2011, 'Antiphospholipid antibodies in patients with paroxysmal nocturnal haemoglobinuria receiving eculizumab', *Br. J. Haematol.*, vol. 153, no. 6, //, pp. 789-791.

Helley, D, de Latour, RP, Porcher, R, Rodrigues, CA, Galy-Fauroux, I, Matheron, J, Duval, A, Schved, JF, Fischer, AM & Socie, G 2010, 'Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab', *Haematologica*, vol. 95, no. 4, Apr, pp. 574-581.

Helley, D, Peffault De Latour, R, Porcher, R, Rodrigues, CA, Matheron, J, Galy-Fauroux, I, Duval, A, Socie, G & Fischer, AM 2009, 'Coagulation activation and endothelial dysfunction in patients with paroxysmal nocturnal hemoglobinuria. Beneficial effect of eculizumab treatment', *Journal of Thrombosis and Haemostasis*, vol. 7, no. S2, p. 616.

Hill, A, Rother, RP, Arnold, L, Kelly, R, Cullen, MJ, Richards, SJ & Hillmen, P 2010, 'Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization', *Haematologica*, vol. 95, no. 4, Apr, pp. 567-573.

Hill, A, Sapsford, RJ, Scally, A, Kelly, R, Richards, SJ, Khurisgara, G, Sivananthan, MU & Hillmen, P 2012, 'Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function', *British Journal of Haematology*, vol. 158, no. 3, Aug, pp. 409-414.

Hochsmann, Bt, Rojewski, M, Flegel, WA & Schrezenmeier, H 2008, 'Direct Antiglobulin Test, Ferritin and GPI-Negative Cell Populations in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) during Eculizumab Therapy: Extravascular Hemolysis Unmasked by Efficient Eculizumab-Mediated Inhibition of Intravascular Hemolysis', *ASH Annual Meeting Abstracts*, vol. 112, no. 11, November 16, 2008, pp. 3440-.

Kelly, R, Richards, S, Arnold, L, Valters, G, Cullen, M, Hill, A & Hillmen, P 2009, 'A spontaneous reduction of clone size in paroxysmal nocturnal hemoglobinuria patients treated with eculizumab for greater than 12 months', *Blood*, vol. 114, no. 22.

Konik, A, Duhrsen, U & Roth, A 2010, 'Longitudinal analysis of the monospecific coombs test in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) chronically treated with Eculizumab', *Onkologie*, vol. 33, Oct, pp. 50-50.

Kulasekararaj, AG, Potter, VT, Gandhi, SA, Benson-Quarm, N, Large, J, Pagliuca, A, Mufti, GJ & Marsh, J 2013, 'Feasibility and optimal schedule of using eculizumab in patients with Hemolytic Paroxysmal Nocturnal Hemoglobinuria (hPNH) with Severe Aplastic Anemia (SAA) prior to Haemopoietic Stem Cell Transplant (HSCT)', *Blood*, vol. 122, no. 21.

Munoz, C, Garcia-Marco, JA, Gil, S, Ojeda, E, Fores, R, Bautista, G, Krsnik, I, Navarro, B, De La Iglesia, A, Juan, IS, Regidor, C, Millan, I, Cabrera, JR, Piris, M, Santero, M, Claros, N, Beltran, P, Cabero, M, Morillo, D, Martin, T, Gonzalo, R & Azcoitia, B 2011, 'Analysis of procoagulants phospholipids in plasma of paroxysmal nocturnal hemoglobinuria patients,processed in differents preanalytic conditions', *Blood*, vol. 118, no. 21.

Nishimura, J, Yamamoto, M, Hayashi, S, Ohyashiki, K, Ando, K, Brodsky, AL, Noji, H, Kitamura, K, Eto, T, Takahashi, T, Masuko, M, Matsumoto, T, Wano, Y, Shichishima, T, Shibayama, H, Hase, M, Li, L, Johnson, K, Lazarowski, A, Tamburini, P, Inazawa, J, Kinoshita, T & Kanakura, Y 2014, 'Genetic variants in C5 and poor response to eculizumab', *N Engl J Med*, vol. 370, no. 7, Feb 13, pp. 632-639.

Nishimura, JI, Yamamoto, M, Hayashi, S, Ohyashiki, K, Ando, K, Noji, H, Kitamura, K, Eto, T, Takahashi, T, Masuko, M, Matsumoto, T, Wano, Y, Shichishima, T, Shibayama, H, Hase, M, Lan, L, Johnson, K, Tamburini, P, Inazawa, J, Kinoshita, T & Kanakura, Y 2013, 'A rare genetic polymorphism in C5 confers poor response to the anti-C5 monoclonal antibody eculizumab in 11 japanese patients with PNH', *Blood*, vol. 122, no. 21.

Richards, SJ, Cullen, MJ, Dickinson, AJ, Hill, A, Buchanon, D, Arnold, L, Elebute, M, Rother, RP & Hillmen, P 2006, 'Long term stability of red cell responses in patients with paroxysmal nocturnal haemoglobinuria (PNH) on eculizumab therapy: implications for the future treatment and management of PNH', *British Journal of Haematology*, vol. 133, Apr, pp. 16-16.

Risitano, AM, Imbriaco, M, Marando, L, Seneca, E, Soscia, E, Malcovati, L, Iori, AP, Pane, F, Notaro, R & Matarazzo, M 2012, 'From perpetual haemosiderinuria to possible iron overload: iron redistribution in paroxysmal nocturnal haemoglobinuria patients on eculizumab by magnetic resonance imaging', *Br J Haematol*, vol. 158, no. 3, Aug, pp. 415-418.

Risitano, AM, Marando, L, Ranaldi, D, Seneca, E, Serio, B, Gianfaldoni, G, Antonioli, E, Milano, F, Amendola, A, Boschetti, C, Barcellini, W, Di Bona, E, Carella, AM, Barbano, F, Bonfigli, S, Capalbo, S, Fabbiano, F, Pulini, S, Marino, A, Pietrogrande, F, Iuliano, F, Rodeghiero, F, Zanella, A, Iori, A, Notaro, R, Luzzatto, L & Rotoli, B 2008, 'C3-Mediated Extravascular Hemolysis as Additional Mechanism of Disease in Paroxysmal Nocturnal Hemoglobinuria (PNH) Patients Treated by the Complent Inhibitor Eculizumab', *ASH Annual Meeting Abstracts*, vol. 112, no. 11, November 16, 2008, pp. 485-.

Risitano, AM, Notaro, R, Marando, L, Serio, B, Ranaldi, D, Seneca, E, Ricci, P, Alfinito, F, Camera, A, Gianfaldoni, G, Amendola, A, Boschetti, C, Di Bona, E, Fratellanza, G, Barbano, F, Rodeghiero, F, Zanella, A, Iori, AP, Selleri, C, Luzzatto, L & Rotoli, B 2009, 'Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab', *Blood*, vol. 113, no. 17, Apr 23, pp. 4094-4100.

Rondelli, T, Risitano, AM, Peffault de Latour, R, Sica, M, Peruzzi, B, Ricci, P, Barcellini, W, Iori, AP, Boschetti, C, Valle, V, Fremeaux-Bacchi, V, De Angioletti, M, Socie, G, Luzzatto, L & Notaro, R 2014, 'Polymorphism of the complement receptor 1 gene correlates with the hematologic response to eculizumab in patients with paroxysmal nocturnal hemoglobinuria', *Haematologica*, vol. 99, no. 2, Feb, pp. 262-266.

Seregina, E, Nikulina, O, Tsvetaeva, N, Balandina, A & Ataullakhanov, F 2013, 'Effect of eculizumab administrations on the haemostatic changes in patients with paroxysmal nocturnal hemoglobinuria', *Journal of Thrombosis and Haemostasis*, vol. 11, p. 836.

Tabacco, P, Risitano, AM, Seneca, E, Marando, L, Barbano, F, Valle, G, Ritrovato, G, Carella, AM & Rotoli, B 2009, '51-Cr labelled red blood cells (RBC) kinetics in paroxysmal nocturnal hemoglobinuria (PNH) patients with suboptimal response to the complement inhibitor eculizumab: physiopathologic insights and therapeutic suggestions', *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 36, Sep, pp. S459-S459.

Villegas, A, Gonzalez, A, Matute, F, Nieto, JM & de la Fuente, F 2013, 'Value Of Magnetic Resonance Imaging In The Study and Follow-Up Of Paroxysmal Nocturnal Hemoglobinuria', *Blood*, vol. 122, no. 21, Nov 15.

Weitz, IC, Razavi, P, Rochanda, L, Zwicker, J, Furie, B, Manly, D, Mackman, N, Green, R & Liebman, HA 2012, 'Eculizumab therapy results in rapid and sustained decreases in markers of thrombin generation and inflammation in patients with PNH independent of its effects on hemolysis and microparticle formation', *Thromb Res*, vol. 130, no. 3, Sep, pp. 361-368.

Zeerleder, S, Van Bijnen, S, Wouters, D, Van Mierlo, GJ & Muus, P 2013, 'Neutrophil extracellular trap formation in PNH patients with and without a history of thrombosis-effects of eculizumab', *Blood*, vol. 122, no. 21.

### Wrong study type

All Wales Medicines Strategy Group 2009, 'Eculizumab (Soliris®) for the treatment of paroxysmal nocturnal haemoglobinuria (Structured abstract)', *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000414/frame.html>.

Connock, M, Wang, D, Fry-Smith, A & Moore, D 2008, 'Prevalence and prognosis of paroxysmal nocturnal haemoglobinurea and the clinical and cost-effectiveness of eculizumab (Structured abstract)', *Health Technology Assessment Database*, no. 4, p. 1, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32008100046/frame.html>.

Curran, KJ, Kernan, NA, Prockop, SE, Scaradavou, A, Small, TN, Castro-Malaspina, H, Araten, D, DiMichele, D, O'Reilly, RJ & Boulad, F 2010, 'Paroxysmal Nocturnal Hemoglobinuria (PNH) In Pediatric Patients: Review of a Single Center Series', *ASH Annual Meeting Abstracts*, vol. 116, no. 21, November 19, 2010, pp. 2231-.

Curran, KJ, Kernan, NA, Prockop, SE, Scaradavou, A, Small, TN, Kobos, R, Castro-Malaspina, H, Araten, D, DiMichele, D, O'Reilly, RJ & Boulad, F 2012, 'Paroxysmal nocturnal hemoglobinuria in pediatric patients', *Pediatr Blood Cancer*, vol. 59, no. 3, Sep, pp. 525-529.

Dmytrijuk, A, Robie-Suh, K, Cohen, MH, Rieves, D, Weiss, K & Pazdur, R 2008, 'FDA report: eculizumab (Soliris) for the treatment of patients with paroxysmal nocturnal hemoglobinuria', *Oncologist*, vol. 13, no. 9, Sep, pp. 993-1000.

Gribkova, I, Tsvetaeva, N, Seregina, E, Nikulina, O, Balandina, A, Gorbatenko, A & Sinauridze, E 2014, 'Effect of eculizumab therapy on the coagulation status of patients with paroxysmal nocturnal hemoglobinuria', *Journal of Thrombosis and Haemostasis*, vol. 12, Jun, pp. 13-13.

Hill, A, Rother, RP & Hillmen, P 2005, 'Improvement in the symptoms of smooth muscle dystonia during eculizumab therapy in paroxysmal nocturnal hemoglobinuria', *Haematologica*, vol. 90, no. 12 Suppl, 2005-Dec, pp. ECR40-ECR40.

Joppi, R, Bertele, V & Garattini, S 2013, 'Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU', *European Journal of Clinical Pharmacology*, vol. 69, no. 4, pp. 1009-1024.

Kanters, TA, De Sonneville-Koedoot, C, Redekop, WK & Hakkaart, L 2013, 'Systematic review of available evidence on 11 high-priced inpatient orphan drugs', *Orphanet Journal of Rare Diseases*, vol. 8, no. 1.

Kelly, R, Arnold, L, Richards, S, Hill, A, Bomken, C, Hanley, J, Loughney, A, Beauchamp, J, Khursigara, G, Rother, RP, Chalmers, E, Fyfe, A, Fitzsimons, E, Nakamura, R, Gaya, A, Risitano, AM, Schubert, J, Norfolk, D, Simpson, N & Hillmen, P 2010, 'The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab', *Br J Haematol*, vol. 149, no. 3, May, pp. 446-450.

Kelly, R, Arnold, L, Richards, S, Hill, A, vanBijnen, S, Muus, P, Dorr, D, Brodsky, R, Khursigara, G, Rother, RP & Hillmen, P 2008, 'Modification of the Eculizumab Dose to Successfully Manage Intravascular Breakthrough Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria', *ASH Annual Meeting Abstracts*, vol. 112, no. 11, November 16, 2008, pp. 3441-.

Kelly, R, Arnold, LM, Richards, SJ, Hill, A, Bomken, C, Hanley, J, Loughney, A, Beauchamp, J, Khursigara, G, Rother, RP, Chalmers, E, Gartnavel, AF, Fitzsimons, E, Nakamura, R, Gaya, A, Rotoli, B, Risitano, A, Schubert, J & Hillmen, P 2009, 'SUCCESSFUL PREGNANCY OUTCOME IN PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA ON LONG TERM ECULIZUMAB', *Haematologica-the Hematology Journal*, vol. 94, Jun, pp. 452-452.

Kelly, RJ, Arnold, LM, Richards, SJ, Hill, A, Van Bijnen, S, Muus, P, Dorr, D, Brodsky, R, Beauchamp, J, Khursigara, G, Rother, RP & Hillmen, P 2009, 'Modification of the standard Eculizumab dose to successfully manage intravascular haemolysis breakthrough in patients with Paroxysmal nocturnal haemoglobinuria', *Haematologica*, vol. 94, pp. 239-240.

Munoz-Linares, C, Ojeda, E, Fores, R, Pastrana, M, Cabero, M, Morillo, D, Bautista, G, Banos, I, Monteserin, C, Bravo, P, Jaro, E, Cedena, T, Steegmann, JL, Villegas, A & Cabrera, JR 2014, 'Paroxysmal nocturnal hemoglobinuria: a single Spanish center's experience over the last 40 yr', *Eur J Haematol*, Apr 23.

Sallerfors, B, Franzén, T, Jansson, L, Kuric, N, Olsson, P, Sjögren, P, Svanberg, T, Widgren, B & Sjövall, H 2012, 'Eculizumab treatment in paroxysmal nocturnal hemoglobinuria (Structured abstract)', *Health Technology Assessment Database*, no. 4, <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000132/frame.html>.

Schubert, J, Hillmen, P, Roth, A, Young, NS, Elebute, MO, Szer, J, Gianfaldoni, G, Socie, G, Browne, P, Geller, R, Rother, RP & Muus, P 2008, 'Eculizumab, a terminal complement inhibitor, improves anaemia in patients with paroxysmal nocturnal haemoglobinuria', *Br J Haematol*, vol. 142, no. 2, Jun, pp. 263-272.

# APPENDIX D critical appraisal checklists to determine risk of bias (ToR 1)

Table 151 Methodological checklist: systematic reviews (AMSTAR; Shea et al 2009)

| **Methodology question** | **Answer** |
| --- | --- |
| 1. **Was an ‘a priori’ design provided?**   The research question and inclusion criteria should be established before the conduct of the review.  *Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objective to score a “yes”* | Yes  No  Can’t answer  Not applicable |
| 1. **Was there duplicate study selection and data extraction?**   There should be at least two independent data extractors and a consensus process for disagreements should in place.  *Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other’s work.* | Yes  No  Can’t answer  Not applicable |
| 1. **Was a comprehensive literature search performed?**   At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and Medline). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialised registers, or experts in the particular field of study, and by reviewing the references of the studies found.  *Note: If at least 2 sources + one supplementary strategy used, select “Yes” (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary)* | Yes  No  Can’t answer  Not applicable |
| 1. **Was the status of publication (i.e. grey literature) used as an inclusion criterion?**   The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.  *Note: If review indicates that there was a search for “grey literature” or “unpublished literature”, indicate “yes”. SIGLE database, dissertations, conference proceedings, and trial registers are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.* | Yes  No  Can’t answer  Not applicable |
| 1. **Was a list of studies (included and excluded) provided?**   A list of included and excluded studies should be provided.  *Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select “no”.* | Yes  No  Can’t answer  Not applicable |
| 1. **Where the characteristics of the included studies provided?**   In an aggregated form such as a table, data from original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.  *Note: Acceptable if not in table format as long as they are described as above.* | Yes  No  Can’t answer  Not applicable |
| 1. **Was the scientific quality of the included studies assessed and documented?**   ‘A priori’ methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.  *Note: Can include use of a quality scoring tool or checklist, e.g. Jadad scale, risk of bias, sensitivity analysis, etc. or description of quality items, with some kind of result for EACH study (“low”, or “high” is fine, as long as it is clear which studies scored “low” and which scored ”high”; a summary score/range for all studies is not acceptable).* | Yes  No  Can’t answer  Not applicable |
| 1. **Was the scientific quality of the included studies used appropriately in formulating conclusions?**   The results of the methodological rigour and scientific quality should be considered in the analysis and the conclusions of the review, and explicity stated in formulating recommendations.  *Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies”. Cannot score “yes” for this question if scored “no” for question 7.* | Yes  No  Can’t answer  Not applicable |
| 1. **Were the methods used to combine the findings of the studies appropriate?**   For the pooled results, a test should be done to ensure the studies were combinable, to assess their heterogeneity (i.e. Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).  *Note: Indicate “yes” if they mention or describe heterogeneity, i.e. if they explain that they cannot pool because of heterogeneity/ variability between interventions.* | Yes  No  Can’t answer  Not applicable |
| 1. **Was the likelihood of publication bias assessed?**   An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available test (e.g. Egger regression test, Hedges-Olken).  *Note: If no test values or funnel plot indicated, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.* | Yes  No  Can’t answer  Not applicable |
| 1. **Was the conflict of interest included?**   Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.  *Note: To get a “yes”, must indicate source of funding or support for the systematic review AND for each of the included studies.* | Yes  No  Can’t answer  Not applicable |

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010. Available from http://amstar.ca/docs/AMSTARguideline.pdf

Table 152 Methodology checklist: randomised controlled trials (SIGN 50)

| **Reference**: | In this study this criterion is: |
| --- | --- |
| ***Internal validity*** |
| The study addresses an appropriate and clearly focused question | ++, +, -, U |
| The assignment of subjects to treatment groups is randomized | ++, +, -, U |
| An adequate concealment method is used | ++, +, -, U |
| Subjects and investigators are kept ‘blind’ about treatment allocation | ++, +, -, U |
| The treatment and control groups are similar at the start of the trial | ++, +, -, U |
| The only difference between groups is the treatment under investigation | ++, +, -, U |
| All relevant outcomes are measured in a standard, valid and reliable way | ++, +, -, U |
| What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? |  |
| All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat) | ++, +, -, U |
| Where the study is carried out at more than one site, results are comparable for all sites | ++, +, -, U, N/A |
| ***Overall assessment of the study*** |  |
| How well was the study done to minimise bias? | ++, +, - |
| If coded as +, or – what is the likely direction in which bias might affect the study results? |  |
| Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention? |  |
| Are the results of this study directly applicable to the patient group targeted by this guideline? |  |
| The study addresses an appropriate and clearly focused question | ++, +, -, U |
| The assignment of subjects to treatment groups is randomised | ++, +, -, U |
| An adequate concealment method is used | ++, +, -, U |
| Subjects and investigators are kept ‘blind’ about treatment allocation | ++, +, -, U |

++: well covered; +: adequately addressed; -: poorly addressed; U: unclear; N/A: not applicable

Table 153 Methodology checklist: cohort studies (SIGN 50)

| **Reference**: | In this study this criterion is: |
| --- | --- |
| ***Internal validity*** |
| The study addresses an appropriate and clearly focused question | ++, +, -, U |
| The two groups being studied are selected from the source populations that are comparable in respects other than the factor under investigation | ++, +, -, U |
| The study indicates how many of the people asked to take part did so, in each of the groups being studied | ++, +, -, U |
| The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis | ++, +, -, U |
| What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? |  |
| Comparison is made between full participants and those lost to follow up, by exposure status | ++, +, -, U |
| The outcomes are clearly defined | ++, +, -, U |
| The assessment of outcome is made blind to exposure status | ++, +, -, U |
| Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome | ++, +, -, U, N/A |
| The measure of assessment of exposure is reliable | ++, +, -, U |
| Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable | ++, +, -, U |
| Exposure level or prognostic factor is assessed more than once | ++, +, -, U |
| The main potential confounders are identified and taken into account in the design and analysis | ++, +, -, U |
| Confidence intervals are provided | ++, +, -, U |
| ***Overall assessment of the study*** |  |
| How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? | ++, +, - |
| If coded as +, or – what is the likely direction in which bias might affect the study results? |  |
| Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention? |  |
| Are the results of this study directly applicable to the patient group targeted by this guideline? |  |

++: well covered; +: adequately addressed; -: poorly addressed; U: unclear; N/A: not applicable

Overall assessment of the study: ++ All or most of the criteria have been fulfilled. When they have not been fulfilled the conclusions of the review are thought very unlikely to alter; + Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions; - Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

Table 154 Methodology checklist: case series (NHS CRD; Khan 2001)

| **Methodology question** | **Answer** |
| --- | --- |
| Is the study based on a representative sample selected from a relevant population? |  |
| Are the criteria for inclusion explicit? |  |
| Did all individuals enter the survey at a similar point in their disease progression? |  |
| Was follow-up long enough for important events to occur? |  |
| What percentage of the series was followed up? |  |
| Were outcomes assessed using objective criteria or was blinding used? |  |
| If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors? |  |
| Overall |  |

Note: amended to include the follow-up rate

# Appendix E study profiles (ToR 1)

## Medicines to treat Gaucher disease

### Imiglucerase

Table 155 Study profiles for studies on alglucerase/imiglucerase vs standard therapy

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| (Schiffmann et al. 2002)  United States | RCT  Level II evidence  Superiority analysis  Low risk of bias  (amended from moderate risk of bias, after additional information provided by author) | N = 29 adults with Type 1 Gaucher, who had had a splenectomy, and were naïve to ERT  Vitamin D  Mean age 38.3±10.2 years  Mean liver volume 3446±505 ml  Mean bone density 151.1±23.4 SEQCT, mg/cm3  Vitamin D +ERT  Mean age 36.2±8.5 years  Mean liver volume 3716±1969 ml  Mean bone density 151.8±18.4 SEQCT, mg/cm3  ERT alone  Mean age 34.8±6.3 years  Mean liver volume 3412±1016 ml  Mean bone density 150.1±19 SEQCT, mg/cm3 | Inclusion  Patients aged 18 to 60, who underwent complete splenectomy prior to 1993 (a year before initiation of study), naïve to ERT.  Exclusion  Patients who were bedridden or wheelchair-bound for ≥2 consecutive months. Patients who were oestrogen or testosterone deficient. Patients who took medications that modified calcium and bone metabolism. | Intervention 1 (Group 2) (ERT + vitamin D)  ITT n = 10  LTF = 1/10  Alglucerase/imiglucerase at 60 IU/kg every 2 weeks for 6 months  Calcitriol (0.25 – 3.0 µg/day and dietary calcium content adjusted to 600 mg/day)  Intervention 2 (Group 3) (ERT alone)  ITT n = 10  LTF = 1/10  Alglucerase/imiglucerase at 60 IU/kg every 2 weeks for 6 months  Diet of 1000 mg calcium/day.  Comparator (Group 1) (Vitamin D alone)  ITT n = 9  LTF = 2/9  Calcitriol (0.25 – 3.0 µg/day and dietary calcium content adjusted to 600 mg/day) | Bone marrow fat fraction (surrogate for bone disease)  Haemoglobin  Platelets  Liver volume | 6 months (until no ERT group started receiving ERT) | Author was contacted for additional data. |

ERT = enzyme replacement therapy; ITT = intention to treat; LTF = lost to follow-up; RCT = randomised controlled trial; SEQCT = single energy quantitative computed tomography

### Velaglucerase

Table 156 Study profiles for studies on velaglucerase alfa (compared to imiglucerase or extension studies subsequent to trial)

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| (Ben Turkia et al. 2013)  Tunisia, Paraguay, USA, Israel, Spain, India, Argentina, UK, Russia | RCT  Level II evidence  Non-inferiority  Low risk of bias | N = 34  Intervention  N = 17  Median age (range) = 36 (7-60) years  8 (47%) male  59% previous splenectomy  Comparator  N = 17  Median age (range) = 27 (3 – 71) years  8 (47%) male  59% previous splenectomy | Inclusion  Treatment naïve Type 1 Gaucher patients, ≥2 years old (all required to have anaemia), females of child-bearing age on contraception, judged sufficiently cooperative by investigator  Exclusion  Received treatment for Gaucher disease within 12 months, were antibody positive, had experienced an anaphylactic reaction, had been exposed to investigational drugs or devices within 30 days, had red blood cell growth factor or chronic systematic corticosteroids within 6 months, a positive test for HIV, or hepatitis B or C, or anaemia at screening due to folic acid, vitamin B12, or iron deficiency, or unable to comply with protocol. | Intervention  Velaglucerase alfa  60-min intravenous infusion at dose 60 U/kg (based on baseline weight) every other week for 39 weeks  Comparator  Imiglucerase  Dosing as above | Haemoglobin  Platelet counts  Spleen volume  Safety | 9 months |  |

### Miglustat

Table 157 Study profiles for studies on miglustat (compared to imiglucerase or extension study)

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| (Elstein, D et al. 2007)  Israel | RCT  Level II evidence  Non-inferiority  Moderate risk of bias (no blinding due to infusion and no infusion conditions, very small samples) | N = 24  Intervention  5 (42%) male  11 (92%) Ashkenazi Jew  Mean age = 34.6±11.1 years  Mean severity scoring index = 9.17±4.78  Comparator  6 (50%) male  12 (100%) Ashkenazi Jew  Mean age = 40.4±15.7 years  Mean severity scoring index = 10.42±4.01 | Inclusion  Adults patients with Type 1 Gaucher disease receiving ERT with imiglucerase for >2years. Constant dose >6 months before enrolment.  Exclusion  Inability to use adequate contraception, clinically significant diarrhoea over previous 6 months, positive HIV or hepatitis B surface antigen test; and/or a history of, or predisposition to cataracts. | Intervention  PP, n = 10 (ITT = 12)  LTF = 2  Miglustat, 100-mg x 3 daily (adjusted in cases of adverse events)  Comparator  ITT, n = 12  LTF = 1  Imiglucerase  30 units/kg body weight/ month in majority, 60 units/kg/month in 3 | Safety  Effectiveness:  Quality of life: SF-36, a modified Medical Outcomes Study Health Distress and 2 surveys assessing symptoms and treatment-related issues  Liver and spleen volumes were measured by computerised tomography (CT) scanning at baseline and after six months | 6 months | 12 additional patients randomised to miglustat + imiglucerase, not included here  Outcome reporting bias – did not report items which were not significantly different between groups.  2 patients discontinued miglustat due to AEs. |
| (Elstein, D et al. 2007)  Israel | Extension study (case series)  Level IV evidence  High risk of bias |  |  |  | Quality of life: SF-36, (as above)  Organ volumes  Chitotriosidase level | additional 18 months (24 months from baseline) |  |

AEs = adverse events; CI = 95% confidence interval; HR = hazard ratio; IQR = inter-quartile range; ITT = intention to treat; LTF = loss to follow-up; OR = odds ratio; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation

## Medicines to treat Fabry disease

### Agalsidase alfa and agalsidase beta

Table 158 Study Profiles for systematic reviews assessing agalsidase alfa and agalsidase beta

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| (El Dib, R P, Nascimento & Pastores 2013)  USA | Level I:  Systematic review of randomised placebo controlled trials  Low risk of bias | Fabry disease (Anderson-Fabry disease) - diagnosis by accepted criteria based on concentration of enzyme or by mutation analysis | Randomised or quasi-randomised controlled trials comparing ERT (agalsidase alfa or beta) in any amount given for a period of at least one month with another ERT or to standard therapy | Agalsidase alfa (0.2 mg/kg or unspecified dose every 2 weeks ) versus placebo (delivered as per treatment group)  Agalsidase beta (1 mg/kg every 2 weeks) versus placebo (delivered as per treatment group)  Agalsidase alfa versus agalsidase beta (both at 0.2 mg/kg every 2 weeks) | Primary  Death (n)  Changes in Gb3 levels (% change in concentration from baseline, histological score)  Pain (McGill Pain Questionnaire, The Brief Pain Inventory)  Secondary  Renal function (serum creatinine, creatinine and inulin clearance, proteinuria, glomeruli changes)  Cardiac function (echocardiograph, exercise tolerance)  Histologic analysis of endothelial Gb3 deposits (histological score)  GFR (ml/min, mg/24 hours)  Adverse events (n)  Quality of life (Short Form 36) | Up to 36 months |  |
| (Schaefer, Tylki-Szymanska & Hilz 2009)  Germany | Level I:  Systematic review of randomised placebo controlled trials  Low risk of bias | Fabry disease | Inclusion  Prospectively designed clinical studies evaluating ERT with quantifiable endpoints – double blind or open-label  Exclusion  Review articles, case reports, case studies, letters to the editor, articles based on registry data, retrospective studies, *post hoc* analysis | Double blind RCTs only:  Agalsidase alfa (0.2 mg/kg or unspecified dose every 2 weeks ) versus placebo (delivery as per treatment group)  Agalsidase beta (1 mg/kg every 2 weeks) versus placebo (delivery as per treatment)  Agalsidase alfa versus agalsidase beta (both at 0.2 mg/kg every 2 weeks) | Gb3 accumulation (plasma, kidney, urine, cardiac, skin Gb3 concentrations or histological scores)  Neuropathy and pain assessment (McGill Pain Questionnaire, The Brief Pain Inventory, number of pain medications required)  Kidney function (GFR, proteinuria)  Cardiac function (echocardiograph, exercise tolerance) | Up to 36 months |  |

ERT = enzyme replacement therapy; Gb3 = globotriaosylceramide; GFR = glomerular filtration rate

### Alglucosidase alfa to treat Infantile Onset Pompe Disease

Table 159 Study profiles for studies on alglucosidase alfa

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| (Kishnani, PS et al. 2007)  US, Europe, Taiwan, Israel | Historical control study  Open-label  Level: III-3  Quality: + (SIGN) | Study population  N = 18  Male 61.1%  Race White 38.9%  Black 22.2%  Hispanic 11.1%  Asian 16.7%  Ageat first symptoms, months, mean (SD):1.6 (1.78); range: 0.0-5.5 months  Age at diagnosis, months, Mean (SD) 3.7 (2.17); range 0.2-6.8 months  Age at first infusiona, months, mean (SD): 4.6 (1.67); range 1.2-6.1 months  CRIM negative 3/18 (17%)  The proportion of patients receiving immunosuppressives was not reported  Historical control groupb  N = 62  Male 45.2%  Race White 50.0%  Black 6.5%  Hispanic 1.6%  Asian 29.0%  Age at first symptoms, mean ± SD: 1.9 ± 1.79; range 0.0 to 5.9 months  Age at diagnosisc, mean ± SD: 3.6 ± 1.94; range -4.4 to 6.6 months  Age at death, median (95% CI): 7.5 (6.7-8.6); range 0.3 to 43.9 months  CRIM status not reported | Inclusion  *Intervention group*  Skin fibroblast GAA activity <1% of normal mean  Hypertrophic cardiomyopathy (LVMI ≥65g/m2)  ≤ 26 weeks of age  *Historical control group*  Untreated patients identified from retrospective chart review (Kishnani, PS, Hwu, et al. 2006)  Documented cardiomyopathy first identified ≤26 weeks of age  Confirmed diagnosis ≤26 weeks of age  First symptoms by ≤26 weeks of age  Exclusion  *Intervention group*  Respiratory insufficiency: O2 saturation <90% or CO2 partial pressure >55mmHg (venous) or >40mmHg (arterial) in room air, or any ventilator use.  Major congenital abnormality  Clinically significant intercurrent illness unrelated to Pompe disease  Any prior GAA treatment  *Historical control group*  GAA activity level >1% of the mean of the normal range  LVMI<65g/m2 at the last visit prior to 26 weeks of age  Documented major congenital abnormality or clinically significant diseases  Any known ventilator use between 0 and 6 months of age, due to reasons other than procedure-related use | Intervention  ITT n = 18  LTF = 0  Alglucosidase alfa (rhGAA)  Randomly assigned to either 20mg/kg (n = 9) or 40mg/kg (n = 9) every other week.  Comparator  ITT n = 62  LTF = 1 (date of death not recorded)  Analysis set = 61  Standard care | Comparison with historical cohort  Survival at 18 months of age  Invasive ventilator-free survival at 18 months of age  Ventilator-free survival at 18 months of age  Analyses: Kaplan-Meier proportion and Cox proportional hazards analysisd  Change from baseline  Cardiac response: left ventricular mass index, ejection fraction  Physical growth  Motor development: AIMS, Pompe PEDI  Cognitive function (modified Bayly Scales of Infant Development, second edition (BSID-II)  Muscle GAA activity and glycogen content  Safety  AEs  Infusion-associated reactions  Vital signs  Development of anti-rhGAA IgG antibodies | Intervention group  Efficacy outcomes: up to 18 months of age (3 patients did not reach were only aged 14.4, 15.9 and 17.9 at the end of the study)  Safety data were analysed for the duration of treatment (range 52-106 weeks)  Control group  Median age at death: 7.5 months, range 0.3 to 43.9 months | Patients diagnosed at 6 months of age and younger, with severe GAA deficiency and rapidly progressing infantile-onset Pompe disease  No ventilator use at initiation of treatment |
| (Kishnani, P S et al. 2009)  Extension study of Kishnani 2007 | Historical control  Level III-3  Quality: + (SIGN) | As for Kishnani et al (2007) | As for Kishnani et al (2007) | Intervention  ITT n = 18  LTF = 0  Alglucosidase alpha at dose to which they were initially assigned.  Comparator  ITT n = 62  LTF = 1(date of death not recorded)  Analysis set = 61  Standard care | Comparison with historical cohort  Survival at 24 and 36 months of age  Invasive ventilator-free survival at 24 and 36 months of age  Ventilator-free survival at 24 and 36 months of age  Analyses: Kaplan-Meier proportion and Cox proportional hazards analysisd | Intervention group  Median duration of treatment: 121 weekse  Range: 60-150 weeks  Control group  Median age at death: 7.5 months, range 0.3 to 43.9 months | Extension study of Kishnani et al (2007) |
| (Nicolino, M et al. 2009)  US, Europe, Israel | Historical control  Level III-3  Quality: + (SIGN) | Study population  N = 21  Male 48%  Race White 71%  Black 10%  Asian 14%  Age at first symptomsb, mean ± SD: 3.9 ±2.8 months; range 0.0 to 12.6 months  Age at diagnosisb, mean ± SD: 8.8 ±5.4 months; range 1.5 to 22.6 months  Age at first infusionb, mean ± SD: 15.7±11.0 months; range 3.7 to 43.1 months  Ventilator support at baseline:  Invasive 24%  Noninvasive 10%  No ventilator support 67%  CRIM negative 2/21 (9.5%)  The proportion of patients receiving immunosuppressives was not reported  Historical controlb  Male 42%  Race White 47%  Black 14%  Asian 33%  Age at first symptomsb, mean ± SD: 3.1±2.75 months; range 0.0 to 12 months  Age at diagnosisb, mean ± SD: 5.8±3.81 months; range -5.1 to 22.7 months  Age at deathb, median : 9.8 months; range 5.9 to 47.9 months  CRIM status not reported | Inclusion  *Intervention group*  Documented onset of symptoms by 12 months of age  Skin fibroblast GAA activity ≤2% of the normal mean  Age 6-36 months at enrolment  Abnormal left ventricular mass indices (LVMI ≥65g/m2 for patients aged ≤12, or >79g/m2 for patients aged >12 months)  *Historical control group*  Untreated patients identified from retrospective chart review (Kishnani, PS, Hwu, et al. 2006)  Documented GAA enzyme deficiency or GAA mutation  Onset of signs or symptoms by 12 months of age  Screened with additional criteria to resemble the clinical characteristics of the treated population  Exclusion  *Intervention group*  Clinical signs or symptoms of cardiac failure with ejection fraction <40%  Major congenital anomaly  Intercurrent organic disease  Prior treatment with ERT  *Historical Control group*  As above | Intervention  ITT n = 22  LTF = 1 (died before beginning treatment)  Alglucosidase alfa biweekly  Initial dose: 20mg/kg every 2 weeks  After at least 26 weeks of treatment, dose augmentation to 40mg/kg every 2 weeks was allowed if the patient’s clinical condition had significantly deteriorated relative to baseline  Comparator  ITT n = 84  LTF = 0  Standard care | Comparison with historical cohort  Survival over the course of treatment  Invasive ventilator-free survival  Ventilator-free survival  Analyses: Kaplan-Meier time-to-event and Cox proportional hazards analysisd  Change from baselineU  LVMI  Cardiac shortening fraction  Growth  Motor development and functional independence (AIMS, PDMS-2, Pompe PEDI)  GAA activity  Glycogen content in quadriceps muscle tissue  Safety  AEs, including infusion-associated reactions  Vital signs  Anti-rhGAA IgG antibody formation | Intervention group  Median duration of treatment: 120 weeks Range: 0.6-168 weeks  Control group  Median age at death 9.8 months, range 8.6 to 10.8 months | Heterogeneous population of Pompe patients with onset of symptoms in infancy and evidence of cardiomyopathy who were at variable stages of disease progression when treatment initiated  Some patients were receiving ventilator support at baseline |
| (Chen et al. 2009)  Taiwan | Historic control study  Level: III-3  Quality: - (SIGN) | Study population  N = 14  3 groups in treated patients: newborn screening (N = 5), Clin-E:started ERT <5months age (N = 4); Clin-L: ≥5 months (N = 5)  Age at diagnosis, mean ± SD: 2.6 ± 1.9 months; range 9 days to 6.2 months  NBS 18.0 ± 8.7 days  Clin-E 2.9 ± 1.0 months  Clin L 4.2 ± 1.4 months  Age at first ERT, mean ± SD: 3.3 ± 2.3 months  NBS 23.6 ±9.0 days  Clin-E 3.1 ± 1.1 months  Clin L 5.9 ± 0.4 months  Cardiomegaly 100%  Hepatomegaly 36%  Historical control groupU  N = 26  No details provided | Inclusion  *Intervention group*  GAA activity <5% normal mean in mononuclear blood cells  Born after or survived to December 2002 (when ERT available)  *Historical control group*  GAA activity <5% normal mean in mononuclear blood cells  Born before June 2002 and died before ERT available  Exclusion  None | Intervention  ITT n = 14  LTF = 0  Alglucosidase alfa 20mg/kg every other week  Comparator  ITT n = 26  LTF = 0  Standard care | Comparison with historical cohort  Survival  Survival free of long-term ventilator dependence  Kaplan-Meier time to event analysis  Log-rank test for differences in survival distributions  Change from baseline  Left ventricular ejection fraction  LVMI  Arrhythmias | Intervention group  Duration of treatment, mean ±SD: 2.0 ±1.7 years  Median 1.6 years, range 0.26 to 5.2 years  Control group  Not reported | Historical controls born before June 2002  Treated patients born after or survived to December 2002  Very poorly reported |
| (Chien et al. 2009)  Taiwan | Historical control  Level: III-3  Quality: - (SIGN) | Study population  N = 6  Age at diagnosis: median 20.5 days, range 7 to 40  Age at first infusion: median 27.5 days, range 12 days to 14 months  GAA activity in fibroblasts, mean ± SD: 0.20 ±0.25 nmol/mg/hr (normal >60nmol/mg/hr)  CRIM positive 100%  Historical control group  N = 11  No details provided | Inclusion  *Intervention group*  Provisional diagnosis from newborn screening dried blood spot specimen  Confirmed diagnosis by GAA activity in whole blood.  *Historical control group*  Patients who were treated at the same centre who died before the availability of ERT (these patients were included in the retrospective chart review conducted by Kishnani et al (2006))  Documented GAA enzyme deficiency or GAA mutation  Onset of signs or symptoms by 12 months of age | Intervention  ITT n = 6  LTF = 0  Alglucosidase alfa 20mg/kg every other week  Patients with cardiomyopathy at diagnosis commenced treatment within 7 days of diagnosis (N = 5); asymptomatic patients commenced when Pompe-associated symptoms appeared (N = 1)  Historical comparator  ITT, n = 11  Standard care | Comparison with historical cohort  Survival  Survival free of ventilation  Independent walking  Time to walking  Analysis: Kaplan-Meier analysis  Change from baseline  Cardiac parameters  Motor and cognitive development  Muscle histology | To 15-40 months of age  Duration of treatment 14 to 33 months |  |
| Long-term outcomes |  |  |  |  |  |  |  |
| (Prater et al. 2012)  US, Europe, Taiwan, Israel | Case series  Level: IV  Quality: Moderate (NHS CRD) | N = 11  CRIM positive 100%  Age at diagnosisb, median (range): 3.2 months (-0.5 to 5.5 months)  Age at treatment initiation, median (range): 4.9 months (0.2 to 6.0 months)  Age at study database lock, median (range): 8.0 years (5.4-12.0 years) | Inclusion  Onset of symptoms≤6 months of corrected gestational age  GAA activity in skin fibroblast or muscle biopsy <1% of the control mean value  Presence of cardiomyopathy (LVMI >64g/m2  Absence of ventilator support before the start of ERT  Age at ERT initiation ≤6months by corrected gestational age  Survival to age ≥5 years at the most recent assessment | Intervention  Alglucosidase alfa by infusion at cumulative doses of 20-40mg/kg | Invasive ventilator-free survival  Cardiac status  Musculoskeletal, gross motor, ambulation and bone density assessments  Physical growth  Speech and hearing  Swallowing, gastrointestinal and nutrition outcomes | NA | Non-comparative |

AE = adverse event; AIMS = Alberta Infant Motor Scale; anti-rhGAA = anti-recombinant human acid alfa-glucosidase; BSID-II = Bayley Scales of Infant Development, second edition; CI = 95% confidence interval; CRIM = cross-reactive immunological material; ERT = enzyme replacement therapy; GAA = acid alfa-glucosidase; HR = hazard ratio; IgG = immunoglobulin G; IQR = inter-quartile range; ITT = intention to treat; LTF = loss to follow-up; LVMI = left ventricular mass index; MDI = Mental Development Index; S CRD = National Health Centre for Reviews and Dissemination checklist; OR = odds ratio; PDMS-2 = Peabody Development Motor Scale, version 2; PEDI = Paediatric Evaluation of Disability Inventory; RR = relative risk; SD = standard deviation; SIGN = Scottish Intercollegiate Guidelines Network

a Untreated historical control group identified by applying the study inclusion and exclusion criteria to a group of 168 patients with infantile-onset Pompe disease identified through a retrospective chart review(Kishnani, PS, Hwu, et al. 2006). The historical cohort of 168 patients came from nine countries, with birth dates ranging from before 1985 to 2002.

b Ages were corrected for gestational age at birth

c Negative values are indicative of prenatal diagnosis

d Cox proportional hazards analysis with model terms of age at diagnosis, age at symptom onset, and treatment as a time-varying covariate.

e Source: (Kishnani, PS, Hwu, et al. 2006)

## Alglucosidase alfa to treat Juvenile Onset Pompe disease

Table 160 Study profiles alglucosidase alfa to treat juvenile onset Pompe disease

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| (Bembi et al. 2010)  Italy | Multicentre observational case series  Level: IV  Quality: high (NHS CRD; KHAN 2001) | Study population  Juvenile  N = 7  Male 71.4%  Ageat first symptoms, years, mean (SD):2.5 (1.3)  Age at diagnosis, years, mean (SD): 2.8 (1.4)  Age at starting ERT, years, mean (SD): 12.0 (3.3)  Adult  N = 17  Male 52.9%  Ageat first symptoms, years, mean (SD):26.6 (12.8)  Age at diagnosis, years, mean (SD): 34.5 (14.9)  Age at starting ERT, years, mean (SD): 47.6 (10.7) | Inclusion  Age: 7 – 65 years  Muscle weakness or respiratory functional impairment:  Walton scalea ≥ 1  Decreased vital capacity ≤ 80%  GAA deficiency: blood lymphocytes, fibroblasts, muscle biopsy  Juvenile onset defined as onset of first symptoms at ≤ 16 years  Adult onset defined as onset of first symptoms at > 16 years  Exclusion  Age ≥ 65 years  Co-morbidities that may influence the outcome measures  Conditions that could determine adverse immunological reactions | Intervention  Alglucosidase alfa (rhGAA) biweekly infusion (20 mg/kg) for at least 36 months | Change from baseline  6MWT (Walton scorea)  Respiratory parameters:  Daily ventilator support  pCO2 (mmHg)b  VC (%)  FEVI (%) | Data was collected at time-points:  Baseline (T0)  12 months  24 months  36 months | Data was synthesised separately for juvenile and adult patients |
| (van Capelle et al. 2010)  Netherlands | Case reports  Quality: NA | Study population  N = 3 JOPD (2 additional patients had infantile onset Pompe disease)  Patient 1:  Age at diagnosis (y) 3.5  Age at first symptoms (y) 2.7  Age at start therapy (y) 5.9  Patient 2:  Age at diagnosis (y) 11.6  Age at first symptoms (y) 6.5  Age at start therapy (y) 12.7  Patient 4:  Age at diagnosis (y) 3  Age at first symptoms (y) 2.5  Age at start therapy (y) 12.9 | Inclusion  Confirmed diagnosis of Pompe disease documented by deficient alfa-glucosidase activity in fibroblasts and/or DNA analysis  Aged between 5 and 18 years  Demonstrable muscle weakness by manual muscle testing  Able to provide 3 reproducible FVC measurements in sitting position (within 5% of one another)  Able to walk 10 m  Exclusion  Patients requiring invasive ventilation or non-invasive ventilation whilst awake or in an upright position. Patients had not previously received ERT. | Intervention  Alglucosidase alfa biweekly  20mg/kg | For individual patients:  Hand-held dynamometry  (HHD)  Manual muscle testing (MMT)  6MWT  Quick motor function test (QMFT) | 3 years | 2 out of the 5 included patients had symptom onset before 2 years of age and therefore were not classified as juvenile onset patients for this review. |
| (Winkel, LPF et al. 2004)  Netherlands | Case reports  Quality:NA | Study population  N = 2 JOPD (1 additional patient had infantile onset Pompe disease)  Patient 1:  Age at diagnosis (y) 11  Age at first symptoms (y) 10  Age at start therapy (y) 16  Patient 2:  Age at diagnosis (y) 10  Age at first symptoms (y) 7  Age at start therapy (y) 32 | Inclusion  Clinical and laboratory findings consistent with late-onset Pompe disease  Diagnosis before the age of 15 and confirmed by acid gAA deficiency and lysosomal glycogen storage in open muscle tissue  Age > 4 years, < 35 years at inclusion  Exclusion  Developmental delays not explained by Pompe disease, allergies and other conditions that potentially could interfere with outcome evaluation | Alglucosidase alfa Initially rabbit milk source 20 mg/kg/week | Pulmonary function (EVC/FEV1)  Muscle strength (HHD)  Muscle Function (GMFM)  Disability (PEDI) | 3 years | 1 out of the 3 included patients was an infantile onset patient (patient 3) |
| (van Capelle et al. 2008)  Netherlands  Extension of Winkel et al 2004 | Case reports  Quality: NA | Study population  N = 2 JOPD  As above | Inclusion  As above  Exclusion  As above | Intervention  Alglucosidase alfa Initially rabbit milk source 20mg/kg/week, then transitioning to hamster ovary source at 10mg/kg/week (weeks 1-12), then  20mg/kg biweekly (weeks 13-26), then 30-40 mg/kg biweekly thereafter. | Ventilation hours  HHD  GMFM  FSS | 8 years | Extension to van Capelle 2004  1 out of the 3 included patients was an infantile onset patient (patient 3) |
| (Bernstein et al. 2010)  United States | Case reports  Quality: NA | Study population  N = 3 JOPD  Patient 1:  Age at diagnosis (y) 23  Age at first symptoms (y) 9  Age at start therapy (y) 52  Patient 2:  Age at diagnosis (y) 13  Age at first symptoms (y) 10  Age at start therapy (y) 34  Patient 3:  Age at diagnosis (y) 16  Age at first symptoms (y) < 3  Age at start therapy (y) 16 | NR | Alglucosidase alfa infusions at 20 mg/kg bi weekly | Time to resolution of gastrointestinal symptoms after start of ERT | 6 months to 2 years |  |
| (Kobayashi et al. 2010)  Japan | Case reports | N = 4 JOPD  Patient 1:  Age at onset (y) 4  Age at start therapy (y) 28  Patient 2:  Age at onset (y) 4  Age at start therapy (y) 17  Patient 3:  Age at onset (y) 13  Age at start therapy (y) 23  Patient 4:  Age at onset (y) 13  Age at start therapy (y) 44 | NR | Chinese hamster Recombinant gAA at 20 mg/kg biweekly | Pulmonary function at baseline and 12 months  Survival | 12 months |  |
| (Sugai et al. 2010)  Japan | Case report | N=1  Single female patient aged 26 years, onset of disease at 15 years  Patient on invasive ventilation |  | Myozyme administered intravenously at 20mg/kg of body weight every other week | Muscle weight measured by muscle volume analyser in kg  Muscle strength measured by conventional handheld dynamometer in Newtons | 13 months |  |
| (Deroma et al. 2014)  Italy | Case series | N=5  Five children, three males, four asymptomatic and disease discovered incidentally  Study also included three with infantile onset  Patient 3:  Age at onset (y): 2  Age at start therapy (y): 12.3  Patient 4:  Age at onset (y): 4.5  Age at start therapy (y): 11.9  Patient 5:  Age at onset (y): 2.6  Age at start therapy (y): 10.3  Patient 6:  Age at onset (y): 9  Age at start therapy (y): 11.6  Patient 7:  Age at onset (y): 8  Age at start therapy (y): 9.6 |  | Started therapy between 1 year and 7 months and 10 years and 4 months after onset; biweekly infusions of 20mg/kg recombinant alpha-glucosidase | FVC (% of predicted)  6MWT (metres walked)  Global motor disability (modified Walton Scale) | Four to five years |  |
| (Orlikowski et al. 2011)  France | Case reports | N=2  Two juvenile onset patients included in case series of five patients; aged 14 (patient 5) and 16 years (patient 1) at onset; very severe disease | Pompe disease defined by documented deficit in endogenous acid alpha-glucosidase, symptomatic diaphragmatic dysfunction and inability to walk unassisted. | Intravenous infusions of alglucosidase alfa at dose of 20mg/kg given every other week for 52 weeks | Respiratory function measured by slow vital capacity, maximal inspiratory pressure and maximal expiratory pressure, time to hypercapnia.  Muscle function by motor function measure scale.  Quality of life measured by SF-36.  Fatigue by fatigue severity scale. | 52 weeks |  |
| (Korpela et al. 2009)  Finland | Case report  Quality: NA | N=1  A juvenile onset Pompe patient diagnosed by genetic analysis  Age of symptom onset: 15 years  Age at treatment onset: 20 years | NA | Alglucosidase-alfa at 20 mg/kg biweekly | Pulmonary function  FVC (%), FEV1, VC, MEF, PEF  Muscle strength  Grip test  Muscle function  6MWT | 12 months |  |
| (Merk et al. 2009)  Germany | Case report  Quality: NA | N=1  Case study included 4 late-onset Pompe patients (one of whom was a juvenile onset patient) who received ERT for a minimum of 6 months  Age of symptom onset (y): 15  Age at diagnosis (y): 29  Age at treatment onset (y): 41 | NA | Myozyme at 20 mg/kg biweekly | FEV1 (ml)  Pimax (%)  6MWT | 6 months |  |
| (Ishigaki et al. 2012)  Japan | Case report  Quality; NA | N=1  A boy who underwent diagnosis and treatment for JOPD  Age of symptom onset (y): 2  Age at diagnosis (y): 5  Start of treatment (y): 10 | NA | Alglucosidase alfa at 20 mg/lg biweekly | Respiratory function  SpO2  VC (%)  Motor function  Grip power  MMT  Time required to change position (rolling sitting, modified Gower’s manoeuvre, climbing stairs)  6MWT  Cardiac function  Echography | 24 months |  |
| (Furusawa et al. 2014)  Japan | Case report  Quality; NA | N=1  A female patient with JOPD  Age of symptom onset (y): 15  Age at diagnosis (y): 21  Start of treatment (y): 37 | NA | ERT (not described) | Respiratory function  %VC  Muscle strength  Pinch power (N) | 4 years |  |
| (Fecarotta et al. 2013)  Italy | Case report  Quality; NA | N=1  A boy who underwent diagnosis and treatment for JOPD  Age at symptom onset (y): 2  Age at diagnosis (y): 2.3  Start of treatment (y): 2.3 | NA | Alglucosidase alfa at 20 mg/kg biweekly | Swallowing function (DSS, adapted by Gates et al, 2006) | 36 months |  |
| (Papadimas et al. 2011)  Greece | Case reports | N=2  Greek patients with late-onset Pompe disease  Patient 1  Age at symptom onset (y): 17  Age at diagnosis (y): 19  Start of treatment (y): 40  Patient 2  Age at symptom onset (y): 11  Age at diagnosis (y): 16  Start of treatment (y): 37 | NA | Alglucosidase alfa at 20 mg/kg biweekly | Respiratory function  VC (%)  FEV1 (%)  Fatigue (FSS) | 3 years | Respiratory function and Fatigue not measured in patient 1 due to patient’s disabilities. |

## Medicines to treat MPS I, II, VI

### Laronidase

Table 161 Study profiles for studies on laronidase for MPS I

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| (Wraith, J. E. et al. 2004)  UK, Canada, US | RCT  Level II evidence  Superiority analysis  Low risk of bias | N = 45 patients with MPS I  Intervention  Male:female, n = 11:11  Mean age = 15.6 years (range 7 – 43)  Mean weight = 35.3 kg  16 White (73%)  0/22 Hurler  18/22 Hurler-Scheie (82%)  4/22 Scheie (18%)  Comparator  Male:female, n = 11:12  Mean age = 15.4 years (range 6 – 39)  Mean weight = 40.3 kg  21 white (91%)  1/23 Hurler (4%)  19/23 Hurler-Scheie (83%)  3/23 Scheie (13%) | Inclusion  At least 5 years old, have MPS I, confirmed by clinical disease and fibroblast or leukocyte activity. Able to perform a forced vital capacity manoeuvre ≤80% of normal. Able to stand independently and walk a minimum of 5 metres in 6 minutes.  Exclusion  Prior tracheostomy or bone marrow transplant, pregnancy or lactation, administration of any investigational drug in previous 30 days, medical condition or other that would influence compliance, or known hypersensitivity to laronidase or components of laronidase or placebo. | Intervention  ITT n = 22  LTF = 0/22  Laronidase 100 U/kg (0.58 mg/kg) intravenously weekly for 26 weeks  Comparator  ITT n = 23  LTF = 0/23  Placebo intravenously weekly for 26 weeks  Drug, dosage, duration | Forced vital capacity (FVC)  6-minute walk test | 26 weeks |  |

FVC = forced vital capacity; ITT = intention to treat; LTF = ; RCT = randomised controlled trial; MPS I = mucopolysaccharidosis I

### Idursulfase

Table 162 Study profiles for studies on idursulfase for MPS II

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Meunzer  2006  USA, UK, Germany, Brazil | RCT  Level II evidence  Double-blind study followed by open-label extension trial  Moderate risk of bias | N = 96 patients with MPS II  Intervention – weekly (n = 32)  Mean age = 15.1 years (range 6.3 – 26.0)  Mean height = 128.5 ± 2.6 cm  Mean weight = 37.8 ± 2.3 kg  28 White (87.5%)  Age at diagnosis = 62.1 ± 9 mo  Intervention – EOW (n = 32)  Mean age = 14.4 years (range 5.4 – 30.9)  Mean height = 128.0 ± 2.6 cm  Mean weight = 36.7 ± 2.3 kg  27 White (84%)  Age at diagnosis = 52.3 ± 6.9 mo  Comparator – placebo (n = 32)  Mean age = 13.1 years (range 5.0 – 29.0)  Mean height = 124.2 ± 2.3 cm  Mean weight = 33.6 ± 2.3 kg  24 White (75%)  Age at diagnosis = 57.1 ± 9.4 mo | Inclusion  MPS II diagnosis based on both clinical criteria (hepatosplenomegaly, radiographic evidence of dysostosis multiplex, valvular heart disease or obstructive airway disease) and biochemical criteria (deficiency of I2S enzyme activity of ≤10% of lower limit of normal range in plasma, fibroblasts or leukocytes and normal enzyme activity of another sulfatase)  Able to reproducibly perform pulmonary function testing  Abnormal FVC of < 80% of predicted  Exclusion  Previous tracheostomy  Previous bone marrow or cord blood transplant | Intervention  Idursulfase 0.5 mg/kg weekly or  Idursulfase 0.5 mg/kg EOW and placebo on alternate weeks  Comparator  Placebo weekly | Primary  Two-component composite scorea (ITT analysis)  6MWT (m)  FVC (L, % predicted)  Liver and spleen volumes (ml)  Urine GAG level (µg/mg creatinine)  Joint mobility (goniometry)  Safety  Adverse events (n)  Antibodies (% patients) | Double-blind phase: 18 weeks  Open-label phase: 53 weeks |  |

6MWT = 6 minute walk test; EOW – every other week; FVC = forced vital capacity; ITT = intention to treat; L = litres; m = metres; ml = millilitres; mo = months; RCT = randomised controlled trial; MPS VI = mucopolysaccharidosis VI

aThe two-component composite score for each patient was calculated by summing the ranks of the two individual components according to the procedure described by O’Brien, 1984.

### Galsulfase

Table 163 Study profiles for studies on galsulfase for MPS VI

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Harmatz  2006  USA, Brazil, France, Portugal, UK, Germany | RCT  Level II evidence  Double-blind, multi-centre trial, followed by an open-label extension trial  High risk of bias | N = 29 patients with MPS VI  Intervention (n = 19)  Female n = 12 (63%)  Mean age (SD) = 13.7 (6.47) years  White n = 16 (84%)  Mean height (SD) = 104.4 (12.87) cm  Mean weight (SD) = 24.6 (9.14) kg  Comparator (n = 19)  Female n = 14 (70%)  Mean age (SD) = 10.7 (4.35) years  White n = 15 (75%)  Mean height (SD) = 100.3 (13.54) cm  Mean weight (SD) = 20.8 (7.85) kg | Inclusion  At least 7 years of age  Biochemical or genetic proof supporting MPS VI diagnosis  Able to walk unaided for ≥ 5 m and ≤ 270 m in the first 6 minutes, or ≤ 400 m total in 12 minutes, in a 12MWT  Exclusion  Significant spinal cord compression  Medical condition or other extenuating circumstance that could interfere with study compliance | Intervention  Galsulfase at 1mg/kg  Delivered diluted in 250 ml sterile 9% saline over 4 hours, weekly  Comparator  Placebo solution  Delivered as for intervention | Primary  Endurance (12MWT)  Secondary  3MSC (n)  Urine GAG level (µg/mg)  Safety  Adverse events (n) | Double-blind phase - 24 weeks  Open-label phase -48 weeks |  |

3MSC = 3 minutes stair climb; 12MWT = 12 minute walk test; GAG = glycosaminoglycan; RCT = randomised controlled trial; MPS VI = mucopolysaccharidosis VI; SD = standard deviation

## Eculizumab to treat Paroxysmal Nocturnal Haematuria

Table 164 Study profiles for included studies on eculizumab

| Author (Year) / Country | Study Design/ Level of Evidence/ Type of analysis/  Risk of bias | Study sample characteristics | Eligibility criteria | Intervention drug treatment details  Comparator drugs treatment details | Outcomes reported (relevant to the review) / measurement tools and scale | Duration of follow-up | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Main studies |  |  |  |  |  |  |  |
| (Hillmen et al. 2006)  US, Canada, Europe and Australia  TRIUMPH | Randomised, double-blind, placebo-controlled trial  Type of analysis: superiority  Level: II  Quality: ++ (SIGN) | N = 87 (34 sites)  Randomisation ratio 1:1  Eculizumab N = 43  Male: 20 (47%)  Age, median (range):41 (20-85) yrs  Caucasian: 37 (86.0%)a  Disease duration, median (range): 4.3 (0.9-29.8) yrs  Median GPI-deficient granulocyte clone: 81.0%b  History of AA: 6 (14%)  History of MDS: 2 (5%)  History of thrombosis: 9 (21%)  Use of anticoagulants: 21 (49%)  Placebo N = 44  Male:15 (34%)  Age, median (range):35 (18-78) yrs  Caucasian: 41 (93.2%)a  Disease duration, median (range): 9.2 (0.5-38.5) yrs  Median GPI-deficient granulocyte clone: 82.7%b  History of AA: 12 (27%)  History of MDS: 0 (0%)  History of thrombosis: 8 (18%)  Use of anticoagulants: 11 (25%) | Inclusion  ≥18 years  ≥4 transfusions during previous 12 months  ≤1 transfusion in 13 weeks pre-randomisation  PNH type III RBC proportion of ≥10%  LDH ≥1.5 x ULN  Platelet count ≥100,000/mm3  Vaccinated against *N. meningitides.*  Exclusion  Mean haemoglobin level >10.5g/dL before transfusion during the previous 12 months  Complement deficiency  Active bacterial infection  History of meningococcal disease  Undergone bone marrow transplantation  No transfusion during 13 week pre-randomisation period | Eculizumab:  ITT n = 43  LTF = 2 (4.7%)  1 pregnancy, 1 unwilling to travel  Both included in analysis (not stated how missing data handled)  600mg per week (±2 days) for 4 weeks,  900mg at week 5,  then 900mg every 2 weeks (±2 days) through week 26  Placebo:  ITT n = 44  LTF = 0  10 patients discontinued due to perceived lack of efficacy  Placebo infusion  600mg per week for 4 weeks,  900mg at week 5,  Then 900mg every 2 weeks through week 26 | Primary  ITT analysis  Number of packed red cells transfused during the 26-week treatment period  Secondary  Transfusion independence  Change in level of fatigue (FACIT-Fatigue instrument)c  Exploratory  Quality of life (EORTC QLQ-C30, scale 0-100)  Safety  Adverse events | 26 weeks | Randomisation stratified according to number of packed RBSs transfused during the past year.  Disease duration, history of AA and use of anticoagulants appear to differ between randomised groups. |
| (Brodsky et al. 2008)  US, Europe, Australia, Canada  SHEPHERD | Open-label case series: before-and-after treatment  Level: IV  Quality: Moderate (NHS CRD) | N = 97  Male 49.5%  Age, median 41 years (range 18-78)  Race, 90.7% Caucasian  Duration of PNH, median 4.9 years (range 0.1-31.4)  Platelet count, median (range): 136 (23-355) x 109/L  PNH type III RBC clone, median 33.5% (range 7.7-98.8)  Pre-study transfusion requirements, median 8.0 (range 0-66) units in 12 months before study  LDH levels, median 2051 (range 537-5245) U/L  History of thrombosis: 42 (43%) | Inclusion  ≥18 years  ≥1 transfusion in the past 2 years  Diagnosis of PNH made more than 6 months prior  PNH type III RBC proportion of ≥10%  LDH at least 1.5 x ULN  Platelet count ≥30x109/L  Vaccinated against *N. meningitides*.  Exclusion  Absolute neutrophil count <0.5x109/L  Complement deficiency  Active bacterial  Prior meningococcal disease  Prior bone marrow transplantation | ITT n = 97  LTF = 1 (AE unrelated to study drug)  Eculizumab infusion  600mg every 7 (±2) days for 4 weeks,  900mg 7 (±2) days later,  then 900mg every 14 (±2) days for a total of 52 weeks | Secondary  Change in level of fatigue (FACIT-Fatigue instrument)c  Additional  Quality of life (EORTC QLQ-C30)  Thrombosis  Transfusion requirements (ITT analysis)  Safety: AEs, clinical laboratory results, ECG data, and vital signs | 52 weeks | Generally broader inclusion criteria compared to TRIUMPH, especially in regard to baseline platelet counts and transfusion requirements |
| (Hillmen et al. 2004)  UK | Open-label case series: before-and-after treatment  Level: IV  Quality: mod-high (NHS CRD) | N = 11  Male 55%  Age, median (range): 48 (21-67) yrs  Duration PNH, median (range): 8.6 (1.7-37.4) years  Baseline platelet count <150,000/m3: 45%  History of AA: 73%  Receiving cyclosporine: 18%  Receiving warfarin: 55%  History of thrombosis prior to treatment: 18%  PNH granulocyte clone size, median (range): 97.0% ( 47.8-99.8)d | Inclusion  ≥18 years of age  Diagnosis of PNH at least 6 months earlier  Detectable GPI-deficient haemopoietic clone  At least 4 red-cell transfusion in preceding 12 months  Negative throat culture for *Neisseria meningitides and N. gonorrhoeae*  Vaccinated against *N. meningitides* | ITT n = 11  LTF = 0  Eculizumab infusion  600mg per week for 4 weeks,  900mg at week 5,  Then 900mg every 2 weeks through week 12 | Rate of transfusion with packed red cells  QoL EORTC QLQ-C30  Safety: deaths, AEs | 12 weeks | Phase 2 pilot study |
| (Hill et al. 2005)  UK  Extension study of Hillmen 2004 | Open-label case series: before-and-after treatment  Level: IV  Quality: mod-high (NHS CRD) | N = 11  As for Hillmen et al (2004) | As for Hillmen et al (2004) | ITT n = 11  LTF = 0  Eculizumab infusion  900mg IV every 14 days  2 patients had interval reduced to 12 days to maintain eculizumab serum levels ≥ 35ug/mL | Rate of transfusion with packed red cells  QoL EORTC QLQ-C30  Safety: deaths, AEs | 52-week extension study |  |
| Combined extension study |  |  |  |  |  |  |  |
| (Hillmen et al. 2007)  US, Europe, Australia, Canada | Open-label case series  Common 104-week extension study of Hillmen 2004, TRIUMPH and SHEPHERD  Level: IV  Quality: moderate (NHS CRD) | N = 195e  187 in extension study  Base Gender: male 89 (45.6%)  History of AA or MDS 59 (30.3%)  History of previous thrombosis 62 (31.8%)  Use of antithrombotic agents: 109 (56%)  Use of cyclosporine 13 (6.7%)  Use of NSAID 17 (8.7%)  Age, median (range): 39 (18-85) years  Disease duration, median (range): 5.5 (0.12-38.5) years  PNH type III RBC proportions, median (range): 32.3% (2.4-98.8)  Reticulocyte count (x 1012/L), median (range): 0.164 (0.036-0.757)  LDH (U/L), median (range): 2139 (499-10,300)  Platelet count, median (range): 149 (23-547) | Participation in one of three parent studies: Hill et al (2004), Hillmen et al (2006), or Brodsky et al (2008) | ITT = 195  LTF = 8 (4.1%)  (195 enrolled in parent studies)  Eculizumab infusion  Ongoing treatment: 900mg every 14 (±2) days, up to week 102.  Patients previously in placebo arm: 600mg per week for 4 weeks,  900mg at week 5, then 900mg every 2 weeks. | Number of thromboembolic events  Incidence of TE events  TE was defined by the same major adverse vascular event (MAVE) criteria in all parent studies | Total patient years on eculizumab treatment = 281.0 years (195 patients). | Does not provide details of type and severity of TE events during treatment. |
| (Hillmen et al. 2010)  US, Europe, Australia, Canada | Open-label case series  Common 104-week extension study of Hillmen 2004, TRIUMPH and SHEPHERD  Level: IV  Quality: Moderate (NHS CRD) | N = 195  187 (96%) in extension study  As for Hillmen et al (2007) | Participation in one of three parent studies: Hill et al (2004), Hillmen et al (2006), or Brodsky et al (2008) | ITT n = 195  LTF = 8  Only 189 included in results  Eculizumab infusion as in Hillmen et al 2007 | Renal function:  Serum creatinine  Urinary protein  GFR  GFR estimated using the modification of diet in renal disease study formula equation.  Efficacy  Change in renal function defined as a categorical documented change in chronic kidney disease (CKD) stage level or fulfilling the criteria of no CKD  CKD stages were defined using the Kidney Disease Outcomes Quality Initiativef | 18 months |  |
| (Hillmen et al. 2013)  US, Europe, Australia, Canada | Open-label case series  Common 104-week extension study of Hillmen 2004, TRIUMPH and SHEPHERD  Level: IV  Quality: Moderate (NHS CRD) | N = 195  187 (96%) in extension study  As for Hillmen et al (2007) | Participation in one of three parent studies: Hill et al (2004), Hillmen et al (2006), or Brodsky et al (2008) | ITT = 195  LTF = 19  19 (9.7%) patients discontinued treatment:  9 due to AE  7 withdrew consent  2 on decision of the investigator  1 noncompliant with protocol.  8 occurred during a parent study  11 extension study  Eculizumab  600mg infusion per week for 4 weeks, followed 1 week later by a single 900mg dose, and then a maintenance dose of 900mg every 14 (±2) days. | Rate of TEs  Transfusion requirements (number of units of transfused packed RBC administered  Transfusion independence (not requiring a transfusion during the previous 6 months)  Renal function (CKD stage)  Safety  AEs (coded using MEDRA version 6.1)  Clinical laboratory tests  Vital signs | 36 months cut-off for safety and efficacy assessment  Overall median treatment duration 30.3 months Range: 10.0-66.1 months  Interquartile range: 26.2-33.1 months |  |
| Other studies |  |  |  |  |  |  |  |
| (Kelly, RJ et al. 2011)  UK | Historic control study  Level: III-3  Quality: - (SIGN) | Eculizumab N = 79c  Recruited 2002-2010  “Historic controls” N = 30 (cared for in the 7 years prior to the availability of eculizumab)  Eculizumab treated patients:  At diagnosis:  Male 40 (51%)  Age at diagnosis, median (range): 37 (12-79) years  History of AA/MDS: 24 (30%)  History of thrombosis: 4 (5%)  Haemoglobinuria: 50 (63%)  Anaemia: 69/73 (95%)  LDH, IU/L, median (range): 2872 (587-10,300) (normal value 430IU/L)  At start of eculizumab:  Age, years, median (range): 46 (14-84)  LDH, IU/L, median (range):2872 (587-10,300)  PNH clone size, %, median (range):  Type III RBC: 25.0 (2.4-79.6)  Granulocyte: 96.4 (41.8-100)  Receiving anticoagulation: 46 (58%)  No transfusion supportg: 4 (5%)  **No information on controls** | Inclusion  Either:  Transfusion dependent haemolysis (≥4 transfusions in 12 months), or  A significant PNH-related complication regardless of transfusion history, or  Profound symptoms  Vaccinated with tetravalent meningococcal vaccine | N = 79  Eculizumab  600mg IV infusion each week for 4 doses, followed by a 900mg infusion after a further week. Then 900mg dose every 14 (±2) days  After the initial 2-5 doses, therapy was administered at the patient’s home  Control  N = 30 patients who were under care prior to eculizumab availability  **No information on controls.**  (N = 79 age- and sex-matched normal controls) | Survival  Thrombotic events  Transfusion independence  Transfusion requirements | Mean duration of eculizumab treatment 39 months, range 1-98 months |  |
| (Socie et al. 2012)  Data from international PNH registry | Abstract only | N = 1047  Mean age 45 years  Female 51.3%  Caucasian 82.9%  Receiving anti-coagulants 28%  Eculizumab 51% | Exclusion  Missing key demographic data or dates of eculizumab use  No follow-up information | Intervention  Eculizumab  Control  No eculizumab | Cumulative incidence of mortality at 1 and 2 years | Mean ± SD follow-up 22.5 ± 18.4 months |  |

AA = aplastic anaemia; AE = adverse event; CKD = chronic kidney disease; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Treatment and Research of Cancer Quality of Life Questionnaire instrument; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; GFR = glomerular filtration rate; GPI = glycosylphosphatidylinositol; IU/L = international units per litre; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; MDS = myelodysplasia; N SAID = non-steroidal anti-inflammatory drug; PNH = paroxysmal nocturnal haemoglobinuria; QoL = quality of life; RBC = red blood cell; SD = standard deviation; SHEPHERD = Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Haemoglobinuria; TE = thrombotic event; TRIUMPH = Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomised, Multicentre, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Haemoglobinuria; U/L = units per litre

Table 165 Demographic and baseline characteristics for patients in the TRIUMPH trial

|  | Eculizumab (n = 43) | Placebo (n = 44) |
| --- | --- | --- |
| Gender, n (%)  Male  Female | 20 (46.5)  23 (53.5) | 15 (34.1)  29 (65.9) |
| Age (years), median (range) | 41 (20-85) | 35 (18-78) |
| Race, n (%)  White  Other  Not reported | 37 (86.0)  5 (11.6)  1 (2.3) | 41 (93.2)  2 (4.6)  1 (2.3) |
| Disease duration (years), median (range) | 4.3 (0.9-29.8) | 9.2 (0.5-38.5) |
| Transfusion history, units of PRBCs transfused in prior 12 months |  |  |
| Mean (g/dL) (SD)  Median (range) | 19.2 (8.41)  18 (7-36) | 19.9 (9.28)  17 (7-44) |
| Categorised, n (%)b  4-14 units  15-25 units  >25 units | 15 (25)  17 (40)  11 (26) | 15 (34)  18 (41)  11 (25) |
| Thrombosis history, n (%)  Any thrombosis event  Cerebrovascular accident  Mesenteric vein thrombosis  Thrombophlebitis/deep vein thrombosis | 9(20.9)  1 (2.3)  0 (0.0)  4 (9.3) | 8 (18.2)  0 (0.0)  2 (4.5)  6 (13.6) |
| Concomitant antithrombotic agents, n (%) | 24 (56) | 20 (45) |
| Use of anticoagulant agents (coumarins or heparins), n (%) | 21 (49) | 11 (25) |
| Use of corticosteroids or androgenic steroids, n (%) | 12 (28) | 12 (27) |
| Haemoglobin set value (g/dL), mean (SD) | 7.8 (0.79) | 7.7 (0.75) |
| Aplastic anaemia, n (%)  Yes  No | 6 (14.0)  37 (86.0) | 12 (27.3)  32 (72.7) |
| Myelodysplastic syndrome, n (%)  Yes  No | 2 (4.7)  41 (95.3) | 0 (0.0)  44 (1000 |
| Baseline PNH type III RBCs (%)  Mean (SD)  Median (range) | 28.0 (133)  25.6 92.4-54.0) | 35.1 (18.2)  34.4 (6.6-88.0) |
| Baseline GPI-deficient granulocytes, median (%) | 81.0% | 82.7% |
| Baseline free haemoglobin (mg/dL), median (range) | 40.5 (7.5-764.0) | 46.2 (11.2-502.0) |
| Baseline LDH (U/L), mean (SD) | 2,200 (1,034) | 2,258 (1,027) |
| FACIT-F scorea, mean (SD) | 36.7 (10.5) | 34.3 (12.0) |
| Platelet count (x109/L), mean (SD) | 188.8 (83.3) | 166.0 (94.2) |
| Haemoglobin (g/dL), mean (SD) | 10.0 (1.2) | 9.7 (1.2) |

Source: Hillmen et al (2006) and Dmytrijuk et al (2008)

FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; LDH = lactate dehydrogenase; SD = standard deviation; TRIUMPH = Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomised, Multicentre, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Haemoglobinuria; MI U/L = units per litre

a The FACIT-Fatigue tool was administered prior to transfusion

b Source: (Schubert et al. 2008)

Table 166 Kidney disease outcomes quality initiative (CKD stages)

| Stage | Criteria |
| --- | --- |
| Stage 1 | GFR >90 mL/min/1.73m2  And evidence of kidney damage, which may include spot urinalysis with proteinuria or by abnormal imaging findings |
| Stage 2 | GFR 60-90 mL/min/1.73m2  And evidence of kidney damage, which may include spot urinalysis with proteinuria or by abnormal imaging findings |
| Stage 3 | GFR 30-60 mL/min/1.73m2 |
| Stage 4 | GFR 15-30 mL/min/1.73m2 |
| Stage 5 | GFR <15 mL/min/1.73m2 |

Source: Extracted from (Hillmen et al. 2010)

CKD = chronic kidney disease; GFR = glomerular filtration rate

Table 167 Body of evidence profiles (modified GRADE output)

**Author(s):**   
**Date:**   
**Question:**   
**Countries/Settings:**   
**Bibliography:**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **No of patients** | | **Effect** | | **Quality** | **Importance** |
|
| **No of studies** | **Design/ Level of evidence** | **Risk of bias** | **Inconsistency** | **Indirect-ness** | **Imprecision** | **Other consider-ations** | **Intervention** | **Comparator** | **Relative (95% CI)** | **Absolute** |
| **Health outcome (follow-up mean XX; assessed with: XX tool)** | | | | | | | | | | | | |
|  |  |  |  |  |  |  | x/X (X%) | x/X  (X%) | RR X  (X to X) | X | ⊕⊕⊕⊝ LOW/ MODERATE /HIGH |  |
|  | X%  (range reported if unable to meta-analyse) | X  (range reported if unable to meta-analyse) |
|  | X% | X |

CI = confidence interval; RR = relative risk

|  |
| --- |
| GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate. |

Table 168 Summary of findings table (modified GRADE output)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient or population:**  **Settings:**  **Intervention:**  **Comparison:** | | | | | | |
| **Outcomes** | **Illustrative comparative risks\* (95% CI)** | | **Relative effect (95% CI)** | **No of Participants (studies)** | **Quality of the evidence (GRADE)** | **Comments** |
| Assumed risk | Corresponding risk |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; | | | | | | |
| GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate. | | | | | | |
| **Evidence Statement** | | | | | | |

Table 169 Overview of systematic reviews (modified GRADE output)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Interventions for [Condition] in [Population]** | | | | | | | |
| **Outcomes** | **Intervention and Comparison intervention** | **Illustrative comparative risks\* (95% CI)** | | **Relative effect (95% CI)** | **No of Participants (studies)** | **Quality of the evidence (GRADE)** | **Comments**  **(e.g. quality of SR)** |
| Assumed risk | Corresponding risk |
|  |  | **With comparator** | **With intervention** |  |  |  |  |
| **Health Outcome** | | | | | | | |
|  |  | **Study population** | | **RR X**  (X to X) | XX (X studies) | ⊕⊕⊕⊝ **low/moderate/high** |  |
| **X per 100** | **X per 100** (X to X) |
| **Moderate** | |
| **X per 100** | **X per 100** (X to X) |
| **High** | |
| **X per 100** | **X per 100** (X to X) |

CI = confidence interval; RR = relative risk; SR = systematic review

|  |
| --- |
| GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate. |
| **Evidence Statement** |

# APPENDIX F Horizon scanning sources (ToR 2)

Table 170 Horizon scanning sources used to address ToR 2

| Early assessment & alert systems | - |
| --- | --- |
| National Horizon Scanning Centre | http://www.birmingham.ac.uk/research/activity/mds/domains/health-pop/healthcare-evaluation-and-methodology/nihr-horizon-scanning-centre/index.aspx |
| EuroScan | http://euroscan.org.uk/ |
| Health organisations | - |
| National Health Service | http://www.nhs.uk/news/pages/newsarticles.aspx?TopicId = Medication |
| HTA / independent research organisations | - |
| Canadian Agency for Drugs and Technologies in Health (CADTH)  CADTH Health Technology Update & CADTH Issues in Emerging Technology | http://www.cadth.ca/en/products/health-technology-assessment?&type = 22  http://www.cadth.ca/en/products/environmental-scanning  http://www.cadth.ca/en/products/environmental-scanning/health-technology-update  http://www.cadth.ca/en/products/environmental-scanning/issues-in-emerging-health-technologies |
| National Institutes for Health (Product Development Pipeline) | http://www.ott.nih.gov/service/product-development-pipeline |
| National Institute for Health & Clinical Excellence (NICE) | http://www.evidence.nhs.uk/about-evidence-services/content-and-sources/medicines-information |
| INAHTA database – new additions | http://www.inahta.org/hta-tools-resources/database/ |
| National Coordinating Centre for Health Technology Assessment | http://www.ncchta.org |
| Blue Cross and Blue Shield Associations Technology Evaluation Center - TEC assessments (and In press) | http://www.bcbs.com/blueresources/tec/  http://www.ahrq.gov/research/findings/evidence-based-reports/index.html |
| ECRI Institute Health Technology Trends  ECRI Institute Health Technology Forecast database  ECRI Institute Hotline Responses | https://www.ecri.org/Products/Pages/Health\_Technology\_Forecast.aspx  https://www.ecri.org/Products/Pages/Health\_Technology\_Forecast.aspx  https://www.ecri.org/Products/Pages/Health\_Technology\_Hotline\_Responses.aspx |

ECRI = Emergency Care research Institute

| Marketing authorisation agencies | - |
| --- | --- |
| Australian Therapeutic Goods Administration | http://www.tga.gov.au/ |
| US Food and Drug Administration (FDA)  FDA Office of Orphan Drugs Development | http://www.fda.gov/default.htm  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm |
| European Medicines Agency (EMA) | http://www.ema.europa.eu/ema/  http://www.ema.europa.eu/ema/index.jsp?curl = pages/medicines/landing/epar\_search.jsp&mid = WC0b01ac058001d124 |
| News | - |
| PharmaTimes | http://www.pharmatimes.com/ |
| Pharmalive | https://www.outcomes-marketing.com/ (Outcomes Marketing website has a link to Pharmalive)  http://www.pmlive.com/, the online branch of “PMGroup Worldwide Limited”, a multi-channel media group in the pharmaceutical industry |
| News Medical | http://www.news-medical.net/ |
| AlphaGalileo | http://www.alphagalileo.org/ |
| ASHP Pharmacists Advancing Healthcare News | http://www.ashp.org/menu/News |
| AHA Emerging Science Series | http://my.americanheart.org/professional/Sessions/AdditionalMeetings/EmergingScienceSeries/New-Emerging-Science-Series\_UCM\_424613\_Article.jsp |
| Healio | http://www.healio.com/ |
| EurekAlert! | http://www.eurekalert.org/ |
| Fierce Markets Network | http://www.fiercehealthcare.com/ |
| MDLinx | http://www.mdlinx.com/ |
| Medpage Today | http://www.medpagetoday.com/ |
| Search engines | - |
| Google  Advanced search – first 50 results | http://www.google.com/advanced\_search |
| Google Scholar – first 50 results | http://scholar.google.com.au/ |
| Other |  |
| Current Controlled Trials metaRegister (US and UK clinical trial registers) | http://controlled-trials.com/ |
| Australian Clinical Trials Register | http://www.australianclinicaltrials.gov.au/trials |
| Orphanet | http://www.orphanet.org |
| Eurordis | www.eurordis.org |
| Innovative Health Technologies | http://www.york.ac.uk/res/iht/introduction.htm |
| F1000Poster | http://f1000.com/posters |

AHA = American Heart Association; ASHP = American Society of Health-System Pharmacists

Impact summaries

| Proprietary product name: Inovelon |
| --- |
| Active / functional agent: rufinamide |
| Purpose and target group: patients with Lennox-Gestaut (LG) epilepsy |
| Stage of development  🞎 Yet to emergea  🞎 Phase I trialsb  🞎 Phase 2 trialsc  🞎 Phase 3 trialsd  🞎 Phase 4 trialse  🞎 Establishedf  🞎 Established but changed indicationg |
| *Australian utilisation* |
| ARTG approval |
| ⮽ No  🞎 Yes  ARTG number |
| Trials underway or completed ⮽  Limited use 🞎  Widely diffused but different indication 🞎 |

| **Country / jurisdiction** | Trials underway or completed? | Regulatory approval (date)? | Reimbursement approval? |
| --- | --- | --- | --- |
| USA |  | Yes: 2008 | Orphan |
| Europe | yes | Yes: 2007 | Orphan |

ARTG = Australian Register of Therapeutic Goods

Notes

a Technology is yet to emerge in Australia.

b Only used in scientific studies with small numbers of patients (usually n<100). Studies of pharmacodynamics/pharmacokinetics or safety trials. Note that it has been specified that drugs at Phase 0 will be excluded, but if at a later stage of development overseas, these drugs will be eligible for inclusion.

c Drugs in efficacy trials, usually against a placebo. Usually studies of several hundred patients.

d Confirmation of safety and efficacy in larger studies, at least 1000 patients.

e Postmarketing studies to optimise use of the drug and further investigate factors such as medium to long term adverse events, and risks vs benefits.

f Licensed or available for marketing and in general use outside clinical trials.

g A drug widely used for one or more clinical indications, but now being used for a new clinical indication.

Précis

Easai Inc provides rufinamide with the aim of reducing seizures in patients with LG epilepsy. The technology is available through medical practitioners. Rufinamide has orphan designation for this indication in the US and Europe, however is not listed on the ARTG.

Background

Rufinamide is an anti-epileptic drug used to prevent seizures in LG epilepsy. It is used as an adjunctive treatment because this type of severe epilepsy requires multiple medications to control.

LG epilepsy begins in young children under four years of age and is characterised by multiple seizure types including tonic, atonic, myoclonic and atypical absence seizures. The condition is associated with some degree of impaired intellectual functioning or information processing, and also developmental delays and behavioural disturbances (National Institute of Neurological Disorders and Stroke 2014). There is no cure for the disease, and controlling seizures is the primary aim of treatment. Tolerance to treatment changes over time such that new medication regimes may be required as the child matures.

Clinical need and burden of disease

Approximately 1-2% of the population have epilepsy, primarily diagnosed in childhood and older age, and LG epilepsy comprises between three and 11 per cent of these cases (Epilepsy Action Australia 2014). It is a severe form of epilepsy where seizures can be difficult to control, thus multiple medications are required. There is significant impact on families coping with a child with LG epilepsy, in terms of managing seizures and the day-to-day challenges of living with a child with developmental delay or behavioural issues.

Diffusion

This treatment is discussed as a treatment for LG epilepsy in several narrative and systematic review articles from the US and Europe, and review compares the primary clinical trial and its extension with studies of clinical practice from the US and Europe (Resnick et al. 2011). Its use as an anti-epileptic was mentioned in the literature as early as 2006 (Cheng-Hakimian, Anderson & Miller 2006).

Comparators

This is an adjunct treatment and would always be used in conjunction with other anti-epileptic treatments.

Safety and effectiveness issues

One double-blind, randomised controlled trial of patients with LG epilepsy compared rufinamide as an adjunctive treatment (n = 74) to placebo as an adjunctive treatment (n = 64) in patients with a median age of 12 years (Glauser et al. 2008). There was a 32.7% decrease in the number of seizures in the rufinamide group compared to a 11.7% reduction in the placebo group (p≤0.01) in the first 28 days, and .the percentage of rufinamide-treated patients who experienced at least a 50% reduction in tonic–atonic seizure frequency per 28 days, relative to baseline, was greater in the rufinamide group than in the placebo group (42.5% vs 16.7%; OR, 3.81; p = 0.002). Six patients, all in the rufinamide group, withdrew from the study because of adverse events; somnolence and vomiting were significantly more common in the rufinamide group. Adverse events considered serious (diarrhoea, upper respiratory infection, rash) were experienced by two patients in each group (Glauser et al. 2008).

A trial conducted more recently in Japan randomised n = 59 patients (n = 29 to adjunctive rufinamide and n = 30 to adjunctive placebo) (Ohtsuka et al. 2014). Patients in the rufinamide arm had a median age of 16.0 years and in the placebo arm the median age was 13.9 years. This study found a reduction in total seizures of 32.9% in the rufinamide group and 3.1% in the placebo group (p<0.001). Treatment-related adverse events occurred in 62.1% of patients in the rufinamide group and 16.7% in the placebo group, and five patients discontinued the study due to adverse events, four in the rufinamide group and one in the placebo group.(Ohtsuka et al. 2014)

Cost impact

No pricing information is available at the present time.

Ethical, cultural or religious considerations

None apparent.

Sources of further information

List of studies included

Total number of studies 2

Level II evidence 2

| Proprietary product name: MABTHERA, Rituximab |
| --- |
| Active / functional agent: rituximab |
| Purpose and target group: patients with myasthenia gravis refractory to existing treatments |
| Stage of development  🞎 Yet to emergea  ⮽ Phase I trialsb for this indication  🞎 Phase 2 trialsc  🞎 Phase 3 trialsd  🞎 Phase 4 trialse  🞎 Establishedf established for other conditions  ⮽ Established but changed indicationg |
| *Australian utilisation* |
| ARTG approval |
| ⮽ No  🞎 Yes  ARTG number |
| Trials underway or completed 🞎  Limited use 🞎  Widely diffused but different indication ⮽ |

| **Country / jurisdiction** | Trials underway or completed? | Regulatory approval (date)? | Reimbursement approval? |
| --- | --- | --- | --- |
| USA, UK, France, Spain, Sweden, Austria, China | Observational studies only |  |  |

ARTG = Australian Register of Therapeutic Goods

Notes

a Technology is yet to emerge in Australia.

b Only used in scientific studies with small numbers of patients (usually n<100). Studies of pharmacodynamics/pharmacokinetics or safety trials. Note that it has been specified that drugs at Phase 0 will be excluded, but if at a later stage of development overseas, these drugs will be eligible for inclusion.

c Drugs in efficacy trials, usually against a placebo. Usually studies of several hundred patients.

d Confirmation of safety and efficacy in larger studies, at least 1000 patients.

e Postmarketing studies to optimise use of the drug and further investigate factors such as medium to long term adverse events, and risks vs benefits.

f Licensed or available for marketing and in general use outside clinical trials.

g A drug widely used for one or more clinical indications, but now being used for a new clinical indication.

Précis

Roche provides MABTHERA (rituximab) with the aim of treating non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis and granulomatosis with polyangiitis (Wegener’s) (GPA) and Microscopic polyangiitis (MPA); however the drug is currently not listed for myasthenia gravis.

Background

Myasthenia gravis is an autoimmune disorder that leads to muscle weakness. Antibodies attack the neuromuscular juncture, interfering with the transmission of messages from the nerves to the muscles (Better Health Channel 2014). This results in weak and tired muscles, vision problems, swallowing and breathing difficulties and shortness of breath. The condition is treatable, however for some people their condition is refractory to treatment and this group is the group of interest for this drug.

Rituximab is a monoclonal antibody that binds to CD20 B lymphocytes surface antigen and was originally developed for the treatment of B-cell lymphomas. It is listed on the Australian Therapeutic Goods Register (ATGR) for use in patients with non-Hodgkins lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis and granulomatosis with polyangiitis (Wegener’s) (GPA) and Microscopic polyangiitis (MPA) however it is not currently listed for myasthenia gravis. It is registered with the same indications on the FDA and EMA.

Clinical need and burden of disease

According to Orphanet, myasthenia gravis has a prevalence of 20 per 100 000 population. In Australia, the prevalence in was estimated at 1.2 per 10 000 in 2009 (Better Health Channel 2014). Whilst the disease is treatable with a range of options including anti- acetylcholinesterase agents,corticosteroids, other immunosuppressive drugs and plasmapheresis, in some patients the disease does not respond to treatment. In these people, the condition can be life threatening as there is a risk of muscle weakness impacting on their ability to breathe.

Diffusion

Rituximab has been widely used for myasthenia gravis in research settings, however not in controlled trials. A recent systematic review identified no randomised controlled studies but examined 15 small, uncontrolled observational studies (Iorio et al. 2014). Studies included in the review were conducted in Australia, France, Spain, Sweden, UK, USA, Austria, and China. Three phase II trials are listed on clinicaltrials.gov, two are complete (one in France in one in the USA) and one is recruiting (in the USA). All three use a single group assignment without any controls. No trials were identified on the European trials register.

Comparators

There are efficacious treatments available for myasthenia gravis however a proportion of people remain refractory to any of these treatments.

Safety and effectiveness issues

Despite no clinical trials, small observational studies have identified improvements in patients otherwise refractory to treatment. In the previously mentioned systematic review, adverse effects were reported in about four per cent of patients. These included infections, prolonged B-cell depletion and heart failure after infusion of rituximab.

Cost impact

Rituximab is listed on the PBS as a chemotherapy item (in the highly specialised drugs program) and the cost is between $3723.85 and $5172.02 depending on the dose and setting.

Ethical, cultural or religious considerations

None apparent.

Sources of further information

List of studies included

Total number of studies 1

Level IV evidence 1 (systematic review of small observational studies)

# Appendix G Summary table of drugs which may be relevant to the LSDP (ToR 2)

Table 171 Summary table of selected new and emerging drugs that target diseases/conditions of potential relevance to the Life Saving Drugs Program in the future (ToR 2)

| Condition, by organ, body system or primary site |  | Estimated prevalence# |  | Drug / drug class (brand name) |
| --- | --- | --- | --- | --- |
|  | ≤1 per 100,000 | <1 per 10,000 | <1 per 2,000 |  |
| Distinct diseases / conditions |  |  |  |  |
| *Autoimmune disorders* |  |  |  |  |
| Behcet’s disease | - | 0.4 per 10,000 | - | apremilast  gevokizumab |
| Chronic inflammatory demyelinating polyneuropathy | - | 0.4 per 10,000 | - | fingolomod (Gilenya) |
| Lambert-Eaton myasthenic syndrome | 1 per 100,000 | - | - | amifampridine (Firdapse) |
| Sarcoidosis | - | - | 0.3 per 2,000 | golimumab (Simponi)  ustekinumab (Stelara) |
| Systemic sclerosis | - | - | 0.5 per 2,000 | tocilizumab (Actemra)  pomalidomide (Pomalyst)  LPA-1/LPA-3 antagonist |
| Thrombotic thrombocytopenic purpura | - | - | 0.5 per 2,000 | caplacizumab  human coagulation active plasma, solvent/detergent treated (Octaplas LG) |
| *Diseases of the brain and nervous system, including neurodegenerative disorders* |  |  |  |  |
| Amyotrophic lateral sclerosis | - | 0.5 per 10,000 | - | arimoclomol  autologous bone-marrow-derived mesenchymal stem cells  repository corticotropin injection, subcutaneous (HP Acthar Gel)  human spinal cord-derived neural stem cells  GDNF-producing stem cell therapy  ozanezumab  tirasemtiv |
| Huntington’s disease | - | 0.7 per 10,000 | - | pridopidine  cysteamine  SIRT-1 inhibitor |
| Lennox-Gestaut epilepsy, second-line treatment | - | - | 1.5 per 10,000 | rufinamide (Inovelon) |
| *Blood / bone marrow / immune system* |  |  |  |  |
| Beta-thalassemia | 0.5 per 100,000 | - | - | ACE-536 recombinant fusion protein  HQK-1001  LentiGlobin gene therapy |
| Congenital factor X deficiency | 0.2 per 100,000 | - | - | Human coagulation factor X |
| Congenital factor XIII deficiency | 0.05 per 100,000 | - | - | catridecacog (NovoThirteen) |
| Congenital erythropoietic porphyria | 0.3 per 1,000,000 (worldwide) | - | - | afamelanotide |
| Essential thrombocythemia | - | - | 0.5 per 2,000 | anagrelide hydrochloride  gandotinib |
| Haemophilia A | - | 0.7 per 10,000 | - | recombinant human factor VIII-FC (Eloctate) |
| Haemophilia B | - | 0.2 per 10,000 | - | recombinant factor IX fusion protein (Alprolix)  AMT060, factor IX gene therapy  rIX-FP  N9-GP |
| Hereditary angioedema | 1 per 100,000 | - | - | human C1 esterase inhibitors (Berinert, Cinryze)  icatibant (Firazyr)  conestat alfa (Ruconest) |
| Malaria | - | 0.3 per 10,000 | - | artesunate injection (Nuartez)  tafenoquine |
| Myelofibrosis | 1 per 100,000 | - | - | fedratinib  gandotinib  simtuzumab |
| Polycythemia vera | - | - | 0.6 per 2,000 | gandotinib  ruxolitinib |
| Sickle cell anaemia | - | - | 0.3 per 2,000 | hydroxycarbamide  Aes-103  HQK-1001  L-glutamine  purified poloxamer 188  rivipansel |
| von Willebrand disease | - | - | 0.3 per 2,000 | BAX111 / rhVWF |
| *Cardiovascular diseases* |  |  |  |  |
| Familial isolated dilated cardiomyopathy | - | - | 0.4 per 2,000 | Ixmyelocel-T |
| *Cancer, blood / bone marrow / immune system* |  |  |  |  |
| Acute lymphoblastic leukaemia | - | 0.4 per 10,000 | - | clofarabine (Evoltra)  nelarabine (Atriance)  inotuzumab ozogamicin / CD22-targeted cytotoxic agent |
| Acute lymphocytic leukaemia |  | unknown |  | Inotuzumab ozogamicin |
| Acute myeloid leukaemia | - | - | 0.2 per 2,000 | AT91813  activated allogeneic natural killer cells, CND0-109  cytarabine + daunorubicin liposome injection, CPX-351  decitabine (Dacogen)  lestaurtinib  midostaurin  quizartinib  tosedostat  vosaroxin  daunorubicin  gemtuzumab ozagamicin |
| Anaplastic large cell lymphoma | - | 0.2 per 10,000 | - | Crizotinib (Xalkori) |
| Chronic lymphocytic leukaemia / small lymphocytic lymphoma | - | - | 0.5 per 2,000 | KPT-330 / selective inhibitor of nuclear export (Selinexor)  dinaciclib  ibrutinib  idelalisib (P13K delta inhibitor)  ISF35 / gene encoding chimeric CD40 ligand  milatuzumab  obtinutuzumab  olertuzumab  ublituxumab  veltuzumab  idelasib  rituximab |
| Chronic lymphocytic leukaemia, refractory | - | - | 0.5 per 2,000 (all chronic lymphocytic leukaemia) | ofatumumab |
| Chronic myeloid leukaemia | - | 0.9 per 10,000 | - | imatinib (Glivec)  dasatinib (Sprycel)  nilotinib (Tasigna) |
| Diffuse large B cell lymphoma | - | - | 0.4 per 2,000 | SNS01-T / DNA plasmid vector |
| Follicular lymphoma | - | - | 0.7 per 2,000 | dasiprotimut-T (BiovaxID)  IPI-145 (p13K delta/gamma inhibitor)  Ocaratuzumab  rituximab |
| Hairy cell leukaemia | - | - | 0.7 per 2,000 | cladribine (Litak, Leustatin)  moxetumumab pasudotox |
| Hodgkin’s lymphoma | - | - | 0.2 per 2,000 | lucatumumab |
| MALT lymphoma | - | 0.4 per 10,000 | - | antibiotic therapy |
| Mantle cell lymphoma | - | 0.4 per 10,000 | - | dasiprotimut-T (BiovaxID)  ibrutinib  SNS01-T / DNA plasmid vector |
| Multiple myeloma, including relapsed /refractory / progressive | - | - | 0.2 per 2,000 | bendamustine-bortezomib-dexamethasone  pomalidomide ± dexamethasone  carfilzomib  KPT-330 / selective inhibitor of nuclear export (Selinexor)  Lenalidomide (Revlimid)#  BI-505 / anti-cellular adhesion molecule  BT-062 (indatuximab ravtansine)  daratumumab  elotuzumab  ibrutinib  ixazomib  panobinostat  plitidepsin  tabalumab  SNS01-T / DNA plasmid vector |
| Myeloid dysplastic syndromes | - | 0.5 per 10,000 | - | azacitidine  rigosertib (Estybon)  sapacitabine  omacetaine mepesuccinate (Synribo)  ezatiostat (Telintra) |
| T cell lymphoma | - | - | 0.5 per 2,000 (10–15% of non-Hodgkin’s lymphoma) | pralatrexate (Folotyn)  romidepsin (Istodax)  brentuximab vedotin (Adcetris) |
| T cell lymphoma, cutaneous | - | 0.2 per 10,000 | - | mogamulizumab |
| Thymic epithelial tumours | - | 0.1 per 10,000 | - | milciclib |
| *Cancer, brain / nervous system* |  |  |  |  |
| Brain stem tumour (glioma) | - | 0.4 per 10,000 | - | ICT-107 / dendritic cancer vaccine |
| Glioma, high grade (i.e. glioblastoma multiforme, which is frequently refractory to standard treatment including surgery, radiotherapy and temozolomide) | 1 per 100,000 | - | - | bevacizumab  chloroquine  TNT-1B mAB (Cotara)  paclitaxel poliglumex (Opaxio)  olaptesed pegol (pre-clinical studies only for this indication)  trabedersen |
| Neuroblastoma | - | - | 0.2 per 2,000 | eflornithine |
| *Cancer, connective tissues / bone* |  |  |  |  |
| Osteosarcoma | - | 0.5 per 10,000 | - | mifamurtide |
| *Cancer, endocrine system* |  |  |  |  |
| Adrenal cortical carcinoma | - | 0.1 per 10,000 | - | mitotane (Lysodren) |
| Medullary thyroid carcinoma, unresectable, locally advanced or metastatic | - | 0.7 per 10,000 | - | vandetanib (Caprelsa) |
| Follicular, medullary, anaplastic cancer and metastatic or locally advanced papillary thyroid | 0.1 per 100,000 (anaplastic thyroid carcinoma) | - | - | lenvatinib |
| Pancreatic neuroendocrine tumours, unresectable and well-differentiated | 1 per 100,000 | - | - | sunitinib (Sutent) |
| *Cancer, gastrointestinal tract* |  |  |  |  |
| Gastrointestinal stromal tumours | - | - | 0.3 per 2,000 | masitinib |
| *Cancer, head and neck* |  |  |  |  |
| Squamous cell carcinoma, Ep-CAM-positive | - | - | 0.8 per 2,000 (~80% of all squamous cell carcinomas of head and neck) | VB4-845 |
| Squamous cell carcinoma, HPV-16 expressing | - | - | 0.8 per 2,000 | GL-0810 / HPV-16 cancer vaccine |
| *Cancer, liver* |  |  |  |  |
| Hepatocellular carcinoma, second-line treatment for metastatic disease | 1 per 100,000 | - | - | G-202, “prodrug” for administration following therapy with sorafenib  pexastimogene devacirepvec (Pexa-Vac; JX-594)  lyso-thermosensitive liposomal doxorubicin (ThermoDox)  YQ23 / stabilized non-polymeric diaspirin cross-linked xtetrameric haemoglobin(animal studies only) |
| *Cancer, lung* |  |  |  |  |
| Mesothelioma | - | 0.3 per 10,000 | - | amatuximab  BAY 94-9343 / antimesothelin-ADC |
| *Cancer, skin* |  |  |  |  |
| Melanoma, invasive | - | - | 1‑2 per 2,000 (all melanoma) | pegylated arginine deiminase |
| Melanoma, stage IIB to IV | - | - | As above | Paclitaxel protein-bound particles for injection suspension (Abraxane)  autologous tumour cell vaccine (FANG Vaccine)  lambrolizumab  nivolumab / anti-PD-1 mAb  POL-103A / polyvalent melanoma vaccine  rose bengal disodium  talimogene laherparepvec  trametinib + dabrafenib  veliparib |
| Melanoma, stage II, stage III, stage IV | - | - | As above | coxsackievirus A21 (Cavatak) |
| Melanoma, stage IIB to IV | - | - | As above | melapuldencel-T / autologous dendritic cell vaccine |
| Uveal melanoma, metastatic | <1 per 100,000 | - | - | vincristine liposomal (Marqibo) |
| *Cancer, urinary system* |  |  |  |  |
| Renal cell carcinoma | - | 0.4 per 10,000 | - | prophage cancer vaccine (Oncophage) |
| *Cancer, various sites / non-specific to site* |  |  |  |  |
| Soft tissue sarcoma | - | - | 0.5 per 2,000 | MORAb-004  TH-302 / hypoxia-activated prodrug  aldoxorubicin |
| *Digestive / gastrointestinal system and liver diseases* |  |  |  |  |
| Familial adenomatous polyposis | - | - | 0.2 per 2,000 | RNA interference with CEQ508  eflornithine + sulindac |
| Primary biliary cirrhosis | - | - | 0.3 per 2,000 | sodium bile acid cotransporter inhibitor  obeticholic acid |
| Primary sclerosing cholangitis | - | - | 0.2 per 2,000 | sodium bile acid cotransporter inhibitor |
| *Hepatic circulation* |  |  |  |  |
| Hepatic veno-occlusive disease |  |  |  | defibrotide (Defitelo) |
| *Lysosomal storage diseases* |  |  |  |  |
| Alpha-mannosidosis | 0.2 per 100,000 | - | - | recombinant human alpha-mannosidase (Lamazym) |
| Cholesteryl ester storage disease | - | unknown | - | SBC-102 / recombinant human lysosomal acid lipase (Sebelipase) |
| Krabbe disease | 1 per 100,000 | - | - | Proposed chaperone therapies:  α-lobeline  3′,4′,7-trihydroxyisoflavone |
| Lysosomal acid lipase deficiency disorders | - | 0.2 per 10,000 | - | SBC-102 / recombinant human lysosomal acid lipase (Sebelipase) |
| Metachromatic leukodystrophy | 0.1 per 100,000 | - | - | cerebroside sulfatase  lentiviral haemopoietic stem cell gene therapy |
| Morquio A syndrome | 0.6 per 100,000 | - | - | elsosulfase alfa (Vimizim) |
| Niemann-Pick disease | - | 0.2 per 10,000 | - | miglustat (Zavesca)  rhASM |
| Sanfilippo syndrome (Mucopolysaccharidosis type IIIA) | 0.3 per 100,000 | - | - | sulfamidase enzyme replacement therapy |
| *Metabolic and enzyme deficiency disorders, not including lysosomal storage diseases* |  |  |  |  |
| Adrenoleukodystrophy | - | 0.4 per 10,000 | - | LentiD gene therapy |
| Adenosine monophosphate deaminase deficiency | <0.2 per 1,000,000 | - | - | Ex-vivo stem cell gene therapy |
| Familial chylomicronaemia syndrome (homozygous lipoprotein lipase deficiency) | 1 per 1,000,000 | - | - | alipogene tiparvovec gene therapy (Glybera); LCQ908 / diacylglycerol acyltransferase-1 inhibitor (Pradigastat) |
| Hereditary tyrosinaemia type I | 0.04–0.05 per 100,000 | - | - | nitisinone (Orfadin) |
| Homocystinuria | - | 0.2 per 10,000 | - | betaine anhydrous (Cystadane) |
| Hypophosphatasia | 0.33 per 100,000\*\* | - | - | ENB-0040 / recombinant fusion protein (asfotase alfa) |
| Lipodystrophy disorders | 0.1‑0.2 per 100,000 | - | - | human recombinant methionyl leptin (metreleptin) |
| Wilson’s disease | - | 0.6 per 10,000 | - | zinc acetate dihydrate |
| *Mitochondrial diseasesa* |  |  |  |  |
| Mitochondrial myopathy | <1 per 1,000,000 | - | - | idebenone |
| Respiratory-chain diseasesb | - | - | 0.2‑0.3 per 2,000 (~1 per 8,500) | vatiquinone, cofactor EPI-743 |
| *Musculoskeletal system* |  |  |  |  |
| Duchenne muscular dystrophy | - | 0.5 per 10,000 | - | GSK-2402968 (Drisapersen)  AAV1-FS344 / gene therapy-delivered myostatin inhibitor  eteplirsen, antisense oligonucleotide  halofuginone hydrobromide  idebenone |
| *Respiratory system and pulmonary circulation* |  |  |  |  |
| Cystic fibrosis, *Pseudomonas aeruginosa* infectionc | - | - | 0.3 per 2,000 | aztreonam (Cayston)  levofloxacin (Aeroquin)  liposomal amikacin for inhalation (Arikace) |
| Chronic thromboembolic pulmonary hypertension | - | 0.3 per 10,000 | - | riociguat (Adempas)  sodium nitrite  beraprost 314dlung |
| Idiopathic pulmonary fibrosis | - |  | 0.2 per 2,000 | LPA1 receptor antagonist  pirfenidone (Esbriet)  purified bovine type V collagen  nintedanib / triple kinase inhibitor  recombinant human pentraxin-2 protein  IL4/IL13 bi-specific antibody  simtuzumab  STX-100 anti-integrin alphaVbeta6 mAb  tralokinumab |
| Pulmonary arterial hypertension | - | 0.2 per 10,000 | - | macitentan (Opsumit)  selexipag |
| Pulmonary tuberculosis | - | - | 0.4 per 2,000 (all tuberculosis) | delamanid |
| Tuberculosis | - | - | 0.4 per 2,000 | ethylenediamine |
| *Skin* |  |  |  |  |
| Epidermolysis bullosa | - | 1 per 42,000 | - | ABH001, human fibroblast derived dermal substitute  thymosin beta-4 peptide |
| Netherton syndrome | 0.5–1.35 per 100,000 | - | - | *ex vivo SPINK5* gene-corrected keratinocytes |
| *Urinary system / kidney* |  |  |  |  |
| Autosomal dominant polycystic kidney disease | <1 per 100,000 | - | - | tolvaptan (Samsca) |
| Nephrogenic diabetes insipidus | 0.15 per 100,000 | - | - | various chaperone therapies are proposed |
| Primary hyperoxaluria | 0.2 per 100,000 | - | - | oxalobacter formigenes (Oxabact) |
| *Various sites / systemic diseases* |  |  |  |  |
| Alagille syndrome | 0.4 per 100,000 | - | - | sodium bile acid contransporter inhibitor |
| Alpha-1-antitrypsin deficiency | - | 0.5 per 10,000 | - | adeno-associated virus vector-mediated gene therapy, rAAV1-CB-hAATsic |
| Secondary systemic amyloidosis | - | - | 0.3 per 2,000 | eprodisate (Kiacta) |
| Rare phenotypes / genotypes of common diseases |  |  |  |  |
| *Cancer, breast* |  |  |  |  |
| *HER2*-positive metastatic breast cancer, no prior anti-*HER2* therapy or chemotherapy for metastatic disease | - | - | 0.22 per 2,000 | pertuzumab, recombinant humanised (Perjeta) |
| *Cancer, gastrointestinal tract* |  |  |  |  |
| *ErbB2*-positive oesophageal cancer | - | 0.7 per 10,000 | - | lapatinib (Tykerb) |
| *HER2-*postive advanced adenocarcinoma of the stomach and gastroesophageal junction | - | Up to 1 per 10,000 | - | MM-111 / bispecific antibody mAb |
| *Cancer, skin* |  |  |  |  |
| Melanoma, MAGE-A3-positive (stage IIB to IV) | - | - | 1‑2 per 2,000 | astuprotimut-R |
| Melanoma, *V600* mutation in *BRAF* gene | - | - | 1‑2 per 2,000d | vemurafenib (Zelboraf) |
| *Cancer, urinary system* |  |  |  |  |
| Renal cell carcinoma, HLA-A2-positive | - | 0.4 per 10,000 (renal cell carcinoma overall) | - | IMA901 / peptide vaccine |
| Renal cell cancer, metastatic | - | 0.4 per 10,000 | - | MVA-5T4 |
| Renal cell carcinoma (advanced), after failure of one prior systemic therapy | - | 0.4 per 10,000 | - | axitinib (Inlyta) |

CF = cystic fibrosis; *CFTR* =cystic fibrosis transmembrane conductance regulator

aMitochondrial diseases are a group of rare diseases with caused by a range of mutations in mitochondrial or nuclear DNA. Different mitochondrial diseases affect different body systems and display a diverse range of phenotypes. The nervous system is commonly affected, as are other organ systems with high energy demands.

bThe respiratory-chain is a series of metabolic reactions involved in cellular respiration, a process by which cells derive energy from breaking down large molecules (nutrients) into smaller molecules (waste products).

c*Pseudomonas aeruginosa* is a common infection among people with cystic fibrosis; prevalence cited is for cystic fibrosis overall

dNote, the estimated prevalence is above the threshold of <1 in 2,000, but this represents prevalence for melanoma overall. The mutation specific indication shown here would presumably bring the prevalence within the <1 per 2,000 threshold as *BRAF V600*-positive melanoma accounts for about 50 per cent of all melanoma. Note also that the estimated prevalence is dependent on the time period used in the calculation; the figure here is based on five-year prevalence.

#Estimated prevalences from Orphanet prevalence of rare diseases: Bibliographic data 2014

\*Lifetime prevalence

\*\*Prevalence at birth

# Appendix H International systems comparison data template (ToR 3)

Table 172 Example of evidence table (ToR 3)

| References: |
| --- |
| Name of the funding body: |
| Country: |
| Programme inception |
| Type (national health service, social insurance etc.): |
| Membership (universal, membership to fund etc.): |
| Reimbursement level (full drug price, full treatment price, patient contribution etc.): |
| **Decision-making process** |
| Definition of rare disease: |
| Definition of ultra-rare disease: |
| Driver of the consideration for reimbursement (egg government body, drug company): |
| Decision-maker: |
| Others involved in the decision-making process (egg Advisory committee): |
| A separate review process (yes/no):  If yes, what’s the difference? |
| Brief description of the process: |
| Eligibility criteria: |
| Basis of positive or negative recommendation (meeting eligibility criteria, cost-effectiveness, budget impact or other) |
| Differences in the decision-making process between a normal drug and a drug for treatment of rare diseases (egg lower level of clinical evidence and high cost-effectiveness ratio)? |
| Drugs reimbursed currently and their indications: |
| Further comments: |

# Appendix I Summary tables for international comparison

Table 173 Funding bodies and coverage

| Country | Brief description |
| --- | --- |
| Australia | Medicare is the publicly funded universal health system in Australia. It coexists with a private health system. |
| Canada (ISPOR 2011) | The publicly-funded healthcare system does not prescription medications, except for drugs administered in hospitals and for certain special populations in some provinces. Private insurers reimburse drug costs for the majority of the population (66%). |
| The United Kingdom | The health care system is primarily public, with 80% of the funding comes from taxation, 12% from national insurance, and the remaining 8% from charges and miscellaneous, trust interest receipts and capital receipts. The UK also has private healthcare sectors which are considerably smaller than its public equivalents. |
| Belgium (Denis et al. 2011) | The Belgian health care system is characterised by a compulsory health insurance system. It covers 99.9% of the population and is funded primarily from health insurance contributions and general taxation |
| Austria (ISPOR 2009a) | In the Austria health care system, virtually all individuals receive publicly funded care. Private health insurance in Austria is generally used to complement the public health services supplied by the state. |
| The Netherlands (Schafer et al. 2010) | Healthcare in the Netherlands is financed by a dual system: i) all regular (short-term) medical treatment reimbursed via obligatory health insurance with private health insurance companies; and ii) long-term treatments are covered by a state-controlled mandatory insurance. |
| Sweden (ISPOR 2009e) | The Swedish health care system is a government-funded national health service, with its funding mainly from proportional taxes levied by county councils and municipalities. |
| Spain (ISPOR 2009d) | In Spain, public health care insurance coverage is provided for >99.5% of the population |
| Italy (Garau & Mestre-Ferrandiz 2009; ISPOR 2008) | The Italian National Health Service provides universal coverage and free healthcare to all Italian, which is financed by general taxation. |
| Germany (ISPOR 2009c) | In Germany, about 85%-90% of the population is covered by statutory health funds via a basic health insurance plan, formally insured under the legislation set with the Sozialgesetzbuch V (SGB V), which provides a standard level of coverage. The other 10%-15% opt for private health insurance, which frequently offers additional benefits. |
| France (Garau & Mestre-Ferrandiz 2009; ISPOR 2009b) | The French health care system is a universal health care, largely financed by obligatory national health insurance |
| Japan (Gao, Song & Tang 2013; Song et al. 2012) | In Japan, medical services are covered through a universal health care insurance system. The Employees’ Health Insurance is a community-based system. Anyone who is staying in Japan for more than a year and is not covered by Employees’ Health Insurance is obliged to apply for national health insurance |
| South Korea (Gao, Song & Tang 2013; Soo 2014) | South Korea has a national health insurance system, which covers over 97.5% of citizens. The remaining 2.5% of the population are covered by a Medical Aid Program for the poor (Gao, Song & Tang 2013; Soo 2014). |
| China (Gong & Jin 2012) | China has multi-layered medical insurance system. The basic social insurance covers urban employees, urban non-employees and rural population under various medical insurance schemes. The public medical insurance program is provided by the government to employees working in state agencies, such as civil services. Commercial health insurance in China serves as a supplement to social medical insurance, targeting mainly the upper class. |

ISPOR = International Society for Pharmacoeconomics and Outcomes Research

Table 174 Mechanisms for the evaluation of drugs for rare diseases, summary by country

| Country / funding body (references) | Separate review process? | Program details / eligibility criteria |
| --- | --- | --- |
| Australia | No. | Not applicable. |
| **Europe** |  |  |
| Belgium | No publicly available information. | Not applicable. |
| Austria | No publicly available information. | Not applicable. |
| Dutch Duel insurance system (Garau & Mestre-Ferrandiz 2009) | Non-hospital treatments: No. However, some “modifiers” are acceptable for orphan drugs (see Table 175).  Hospital-based treatments: Yes | Hospital-based treatments: For hospital (intramural) treatments, a new instrument (the diagnosis/treatment combinations (DBCs)) for the performance-based costing system for hospital care and for mental health care was introduced in 2005. For rare diseases, if there is no DBC, OMPs that are used in hospitals may be provisionally listed via a policy rule with the condition of collecting further evidence and having a re-appraisal in no more than 3 years’ time. |
| Swedish National Health Service (Garau & Mestre-Ferrandiz 2009; ISPOR 2009e) | No | Not applicable. |
| Spanish national Health Service (Garau & Mestre-Ferrandiz 2009; ISPOR 2009d) | No | Not applicable. |
| Italian National Health Service (Garau & Mestre-Ferrandiz 2009) | Yes and No  Three mechanisms for public funding of pharmaceuticals:  1) Standard process  2) Under the Law 648/96  3) Orphan drug specific process (funding for access to drugs for rare diseases before marketing authorisation) | 1. Standard process: medicines authorised either by the EMEA centralised procedure or the national procedure have to go through the standard assessment of clinical value performed by the Italian Pharmaceutical Agency (Agenzia Italiana del Farmaco - AIFA). There are two committees work together within the AIFA, the Technical Scientific Committee (CTS) and the Pricing and Reimbursement Committee (CPR). The remit of the CTS is to examine the dossiers submitted by manufacturers and to provide the CPR with an assessment of the efficacy of the new drug. The CPR, in turn, sets the price of new medicines and chooses their reimbursement class. 2. Law 648/96: relates to a national law supporting the provision of treatments for conditions that have no valid alternative therapy available. The law allows the Italian National Health Service to reimburse medicines for which results of Phase II trials are available and which meet one of the following characteristics: i ) they are authorised in other countries; ii) they are being tested in a Phase III clinical trial; and iii) they are marketed for another therapeutic indication. 3. Orphan drug specific process: 5% AIFA special fund, a contribution paid by pharmaceutical companies to AIFA to be reinvested for the promotion of independent research and access to treatments for rare diseases. According to the regulation, half of the fund should be devoted to providing access to medicines for rare diseases before marketing authorisation. The other half of the fund should be devoted to promoting independent research and other correlated activities (for example, pharmacovigilance programmes, communication and promotion of appropriate use of available medicines). |
| German Statutory Health Insurance (Garau & Mestre-Ferrandiz 2009) | No. However, as the there is no alternative therapeutic option (comparator) existing for a majority of orphan drugs, they will not be assessed by IQWiG and will generally be granted reimbursement status with no price limit. | Not applicable. |
| French National Health Insurance (Garau & Mestre-Ferrandiz 2009) | No. However, clinical evidence used for the assessment of the medical value (Service Médical rendu (SMR) of orphan drugs reflects the limitations associated with rare conditions. See Table 175. | Not applicable. |
| National Health Service (NHS), England and Wales (Canadian Agency for Drugs and Technologies in Health 2013; Department of Health & The Rt Hon Earl Howe 2012; National Institute for Health and Care Excellence 2013) | Yes, but only for ultra-orphan drugs: Highly specialised technologies programme (interim process) | Since April 2013, the National Institute for Health and Care Excellence (NICE) has been responsible for evaluating highly specialised health technologies for people in England with very rare (ultra-orphan) diseases. NICE has developed interim processes and methods built on the decision-making framework developed by the Advisory Group for National Specialised Services (AGNSS), which previously evaluated these technologies.  The evaluation of technologies by the “highly specialised technologies programme” engages a specific evaluation committee that is an independent advisory body. The committee, comprising individuals who work in the National Health Service, pharmaceutical and medical devices industries, patient and caregiver organisations, and relevant academic disciplines, makes recommendations to NICE for or against the use of a technology based on its costs and benefits.  AGNSS followed a multi-criteria decision analysis framework that used a broad range of criteria beyond cost-effectiveness and holistic view across all of the criteria. The two-step procedure involved an initial assessment of nine entry criteria relating to the rarity of the condition and complexity of its care. Once accepted, the application was assessed based on 12 core criteria organised into the following 4 subgroups: i) health gain; ii) societal value; iii) reasonable cost; and iv) best practice. |
| NHS Scotland (Canadian Agency for Drugs and Technologies in Health 2013) | No. However, some “modifiers” are acceptable for orphan drugs. See Table 175. | Not Applicable. |
| **Canada** |  |  |
| Ontario health authority (Canadian Agency for Drugs and Technologies in Health 2013) | Yes, Ontario’s DRD Evaluation Framework | Eligibility criteria:  a) disease incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year;  b) lack of availability or feasibility of adequately powered randomised controlled trials detecting clinically relevant outcomes, given the rarity of the disease.  No restriction on the types of rare diseases considered for evaluation.  The evaluation is conducted by a separate 5-member DRD Working Group and reports directly to the Executive Officer of the Ontario Public Drug Programs. The evaluation framework uses an evidence-based process. The framework consists of five steps:   * Assesses whether a submitted disease meets the framework’s criteria of “rare” * Gains an understanding of the natural history of the disease * Assesses the potential effectiveness of the drug, based on the best available evidence * Evaluates budget and cost impact * Identifies whether any additional follow-up data is needed. |
| Alberta health authority (Rare Disease Drug Program) (Alberta Health and Wellness 2008; Canadian Agency for Drugs and Technologies in Health 2013) | Yes, Rare Disease Drug Program | Eligibility criteria:   1. A genetic lysosomal storage disorder occurring in < 1 in 50,000 Canadians, as determined by Alberta Health, egg Fabry disease, Pompe disease, and Gaucher disease. 2. Albertans with rare diseases, who have government sponsored drug coverage and whose physician has applied for coverage 3. An individual or family must reside in Alberta for 5 years to be eligible for the program. The residency requirement will be waived for individuals moving to Alberta from another province in Canada if they were covered by that province’s program for these drugs.   In addition, applicants must consent to the following conditions:   * Conditional initial and continued coverage are dependent upon clinical outcomes. * Ongoing clinical outcome monitoring is mandatory. * Inadequate patient response or deterioration, as defined by pre-established withdrawal criteria for a specific drug and/or as assessed by the program’s clinical review panel, will dictate coverage discontinuation.   Note that the presence of a significant illness likely to affect life expectancy, outside of the rare disease itself, is considered a contraindication to the rare disease funding.  Submitted applications are reviewed by Alberta’s Rare Disease Clinical Review Panel, which is a Ministry-appointed panel consisting of rare-disease-treating specialists and other health care professionals with related clinical expertise. Final coverage decisions for rare disease drug funding are made by Alberta’s Minister of Health |
| Alberta health authority (Short Term Exceptional Drug Therapy) (Canadian Agency for Drugs and Technologies in Health 2013) | Yes, Alberta’s Short Term Exceptional Drug Therapy | Eligibility criteria:  Diseases currently eligible for coverage consideration include: Gaucher disease, Fabry Disease, MPS-I (Hurler/Hurler Scheie), Hunter disease and Pompe disease;  Therapies without current public or private funding options; and  For in-patients whose drug therapy (oncology drugs included) costs are expected to be between $1,500 and $50,000; or  For Outpatients with rare clinical conditions (excluding oncology indications) if the total drug cost is expected to be < $100,000 per year.  Specialist physician working at an Alberta Health Services facility and actively treating a patient for a rare clinical condition can submit requests to fund high-cost non-formulary drugs for rare conditions. Specific funding criteria are used to objectively review requests on a case-by-case basis. If approved, funding is provided for an agreed upon duration beyond which resubmission would be required. |
| **Asia** |  |  |
| Japanese statutory health insurance  (Japan Intractable Diseases Information Center 2014) | Yes. The Specified Diseases Treatment Research Program. | Eligibility criteria: patients that have any of the 56 diseases covered by the Specified Disease Treatment Research Program and be beneficiaries of public health insurance.  Each one of the 56 diseases has a criterion for designation. Based on a doctor’s diagnosis, a patient must file an application to the government of the prefecture he or she lives in. If the application is accepted, a Certificate of a Recipient of Designated Disease Treatment is issued. |
| South Korea national health insurance service (Soo 2014) | No. | Not applicable. |
| Chinese medical insurance system  (Ngorsuraches et al. 2012) | No | Not applicable. |

AGNSS = Advisory Group for National Specialised Services; AIFA = Italian Pharmaceutical Agency (Agenzia Italiana del Farmaco); CPR = Pricing and Reimbursement Committee; CTS = Technical Scientific Committee; DBC = Drug-based combination ; DRD = drugs for rare diseases; EMA = European Medicines Agency; IQWiG = Insititute for Quality and Efficiency in Healthcare Germany; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MPS = mucopolysaccharidosis; NICE = National Institute of Health and Clinical Excellence; NHS = National Health Service; OMP = Orphan medical product; SMR = Service Médical rendu

Table 175 Basis of the decision to reimburse drugs for orphan diseases, summary by country

| Country / Funding body (references) | Decision maker and others involved in the process? | What is the basis for a positive or negative recommendation (e.g. cost effectiveness / budget impact) | What aspects are different in the consideration of the reimbursement of a drug for a rare disease (e.g. lower level of clinical evidence and high cost-effectiveness ratio)? |
| --- | --- | --- | --- |
| Australia (The Department of Health 2015) | Applicant: Drug company  Decision maker: Minister for Health | The drug must meet each of the following criteria:  1. There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration (TGA).  2. The disease is identifiable with reasonable diagnostic precision.  3. Epidemiological and other studies provide evidence acceptable to the PBAC that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease.  4. There is evidence acceptable to the PBAC to predict that a patient’s lifespan will be substantially extended as a direct consequence of the use of the drug.  5. The drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme (PBS) listing because it fails to meet the required cost effectiveness criteria.  6. There is no alternative drug listed on the PBS or available for public hospital in-patients, which can be used as lifesaving treatment for the disease.  7. There is no alternative non-drug therapeutic modality which is recognised by medical authorities as a suitable and cost effective treatment for this condition.  8. The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian. | A medicine can only be considered for inclusion through the Life Saving Drugs Program (LSDP) if it does not meet the cost-effectiveness criteria for PBS listing. |
| **Europe** |  |  |  |
| Belgium (Denis et al. 2011) | Applicant: Drug company  Evaluator / Recommendation: Drug Reimbursement Committee. The DRC consists of representatives of universities  (seven individuals); health insurance funds (eight);  physicians (four); pharmacists (three); pharmaceutical  companies (two); Ministries of Social  Affairs, Health and Economic Affairs (three);  and the National Institute for Health and Disability  Insurance (one).  Decision maker: Minister of Social Affairs | The basis for a positive recommendation is based on multiple criteria:   * Therapeutic value, * Price and proposed reimbursement tariff; * The importance of the drug in clinical practice; and * The budget impact of the drug.   Denis *et al* identified additional factors that may play role in the decision making process:   * Price adjustments; and * Employment incentives. | Economic evaluations of orphan drugs are not required for reimbursement purposes. |
| Austria (ISPOR 2009a) | Applicant: Drug company  Evaluator: Heilmittel-Evaluierungs-Kommission (Commission for Evaluation of Drugs)  Decision Maker: Main Association of Austrian Social Security Institutions (Hauptverband der österreichischen Sozialversicherunsträger, HVB) | 1. Pharmacological analysis (comparison with therapeutic alternatives and perceived degree of innovation), 2. Medical-therapeutic evaluation (target patient group, effectiveness, expected duration and treatment frequency) 3. Economic considerations (this includes budget impact and PE evidence). | Unknown / not stated |
| Dutch duel insurance system (Garau & Mestre-Ferrandiz 2009; Vegter et al. 2010) | Non-hospital treatments:  Applicant: drug company  Evaluator / Recommendation-maker: a committee of the Dutch Health Care Reimbursement Board (College voor zorgverzekeringen (CVZ))  Decision-maker: the Minister of Health, Welfare and Sport  Hospital treatments (Policy rule on orphan drugs):  Evaluator / recommendation-maker: CVZ | Non-hospital treatments: clinical and pharmacoeconomic evidence and budget impact analysis  Hospital treatments (Policy rule on orphan drugs): “value” dossier, with the conditional on obtaining additional data on the clinical and cost-effectiveness of the medicines being assessed | Non-hospital treatments: Orphan drug developers can be exempted from providing a full phamacoeconomic evaluation if several other criteria are met, such as a small budget impact and an absence of other treatments for the disease. A cost analysis is required even if an exemption for pharmacoeconomic analysis is granted. |
| Swedish National Health Service (Garau & Mestre-Ferrandiz 2009; Jansson 2007) | Applicant: drug company  Evaluator: Swedish Council on Technology Assessment in Health Care (Statens beredning för medicinsk utvärdering (SBU))  Decision-maker: Tandvårds- och läkemedelsförmånsverket (TLV; Dental and Pharmaceutical Benefits Board), previously the Läkemedelsförmånsnämnden (LFN; Pharmaceutical Benefits Board) | According to the Act on Pharmaceutical benefits, etc., an application for reimbursement should be evaluated based on the following four criterion (in order of importance):   1. The principle of human dignity. 2. The principle of need and solidarity. 3. The principle of cost-effectiveness. 4. Principle of marginal benefits. | Higher cost-effectiveness ratio due to the severity of orphan disease: The TLV in effect has different cost effectiveness thresholds for different characteristics of disease-linked severity. For example, a 2008 study by the LFN showed that “for more severe conditions the LFN has accepted costs per QALY in the area of €90,000”. The report also noted a correlation between disease severity and willingness to pay for a QALY.  Limited evidence base: Based on standard HTA methods, greater uncertainty in clinical and cost effectiveness evidence can be accepted when the target population is small, because the cost of making wrong decisions is lower as compared to treatments for more prevalent diseases. |
| Spanish national Health Service (Garau & Mestre-Ferrandiz 2009; ISPOR 2009d) | Applicant: drug company  Evaluator: National HTA Agency (Instituto de Salud Carlos III (ISCIII)) in collaboration with Regional HTA Agencies  Decision-maker: Inter-Ministerial Pricing Commission CIPM (La Comisión Interministerial de Precios de los Medicamentos) led by the Ministry of Health (MSC) | The following factors determine whether or not a medicine is reimbursed by the Spanish MSC:   * the seriousness of the disease; * the needs of certain groups (egg equity); * the medicine’s therapeutic and social utility; * the limits of public expenditure allocated to pharmaceutical benefits; * the existence of alternative treatments for the same conditions; * the medicine’s degree of innovation; * the price of the product   Pharmacoeconomic evaluations are not mandatory in the pricing and reimbursement process. Overall, pharmacoeconomics currently plays a small role in the Spanish pricing and reimbursement system, although some initiatives exist at the regional level. | The pricing and reimbursement system does not treat orphan drugs any differently relative to conventional medicines but the criteria used are likely to result in approval. |
| Italian National Health Service, National Pharmaceutical Formulary PFN (Prontuario Farmaceutico Nazionale) (Garau & Mestre-Ferrandiz 2009; ISPOR 2008) | Applicant: drugs company  Evaluator: Comitato Scientifico e Tecnico (CTS), Comitato Prezzi e Rimborso (CPR)  Decision-maker: Agenzia Italiana del Farmaco (AIFA) | The reimbursement status is defined by AIFA based on the following criteria, which are employed for both orphan drugs and non-orphan drugs:   * Whether the new product is indicated for a disease with no alternative or adequate therapy; * Whether the new product provides a better benefit risk ratio than existing therapies; * Whether the new product generates socioeconomic benefits, which mainly refers to a lower price relative to the comparator(s). | The pricing and reimbursement system does not treat orphan drugs any differently relative to conventional medicines but the criteria used are likely to result in approval. |
| German Statutory Health Insurance (Garau & Mestre-Ferrandiz 2009) | Most pharmaceuticals approved by the EMA or the German Federal Institute for Drugs and Medical Device (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) are covered by the German statutory sickness funds, except for drugs for minor illnesses and ‘lifestyle’ drugs.  Under certain conditions (egg uncertain effectiveness, prescribing limitations etc.),  Evaluator: Institute for Quality and Efficiency in Healthcare (IQWiG)  Decision-maker: the Joint Federal Committee, G-BA (Gemeinsamer Bundesausschuss) | Reference Pricing system: The G-BA is responsible for identifying drugs and assigning them to one of three reference price groups (egg products with the same active ingredient (group 1), products with therapeutically and pharmacologically similar active ingredients (group 2) and compounds with comparable therapeutic effects (group 3)  Drugs that are innovative and those without any therapeutic equivalent (as is the case with may orphan drugs) are exempt from classification and are generally fully reimbursed.  Otherwise: cost-effectiveness analysis will be conducted by the IQWiG if the drug has a comparator and shows demonstrated therapeutic improvements. | No special consideration for drugs for orphan diseases. However, as there is often no alternative therapeutic option (comparator) existing for a majority of orphan drugs, they will not be assessed in terms of cost-effectiveness. |
| French National Health Insurance (Garau & Mestre-Ferrandiz 2009; ISPOR 2009b) | Applicant: drug company  Evaluator: Commission d’Evaluation des Médicaments (HAS)  Decision-maker: Health Ministry, Union Nationale des Caisses d’Assurance Maladie (UNCAM), Comité Economique des Produits de Santé (CEPS) | Process:   1. HAS assesses the medical value (*Service Médical Rendu* – SMR) and incremental medical value (Amélioration du Service Médical Rendu – ASMR) for each pharmaceutical. 2. The Economic Committee for Healthcare Products *Comité Economique des Produits de Santé* - CEPS) is charged with determining and negotiating the price of the new drug with the manufacturer.   SMR: drugs are classified into three levels (major, moderate or insufficient) of medical value, generally based on efficacy and disease severity considerations.  ASMR: based on the degree of innovation of a new drug relative to existing treatments, ranging from major to no improvement.  Pharmacoeconomics can influence decision-making but it is not an official criterion. However, the role of economic evaluations is expected to increase in the near future. | Lower level evidence allowed |
| National Health Service (NHS), England and Wales (Canadian Agency for Drugs and Technologies in Health 2013; National Institute for Health and Care Excellence 2013) | Applicant: drug company  Evaluator: an external group to NICE (review group) (since 2013); AGNSS (2005 – 2013)  Recommendation/Decision maker: Evaluation Committee, NICE | Highly specialised technologies programme criteria considered:   1. Nature of the condition (including morbidity/clinical disability with current standards of care; effect on caregivers’ quality of life; current treatment options); 2. Impact of the new technology (clinical effectiveness; magnitude of health benefits for patients, and caregivers when appropriate) 3. Cost to the National Health Service and Personal Social Services (including budget impact; robustness of costing and budget impact information; patient access agreements) 4. Value for money (benefit compared to current treatment; other resources needed to use the technology; impact on budget available) 5. Impact beyond direct health benefits (are there any such benefits, are costs/savings incurred outside of the NHS and PSS) 6. Impact on delivery of the specialised service (staffing and infrastructure requirements such as training, planning for expertise).   AGNSS: based on 12 core criteria organised into the following 4 groups: a) health gain; b) societal value; c) reasonable cost; and d) best practice. The AGNSS framework requires that no single criterion should hold sway but a holistic view be taken, balancing how the different criteria work together in reaching a decision. More expensive products will be expected to benefit nearly all patients treated, i.e. have a NNT approaching 1. | Avoids a rigid quality-adjusted life year (QALY) ceiling like NICE. Instead it takes into consideration a broader societal perspective  (Cost-effectiveness a required element of the reimbursement submission for both programmes) |
| NHS Scotland (Canadian Agency for Drugs and Technologies in Health 2013; ISPOR 2007; Vegter et al. 2010) | Applicant: drug company  Evaluator: New Drug Committee of the SMC  Decision-maker: Scottish Medicines Consortium (SMC) | Clinical efficacy and cost-effectiveness. | Allow acceptance of more uncertainty in the economic case or a higher cost per QALY for orphan drugs (cost-effectiveness a required element of the reimbursement submission even for orphan drugs)  Modifiers” may be applied in cases of a relatively high cost per QALY, when the committee finds the clinical and economic case to be robust. The assessment may be modified by giving consideration to evidence relating to other factors including, but not limited to:   * treatment of a life-threatening disease * substantial increase in life expectancy or quality of life * absence of other therapeutic options * targeting of a medicine for a specific sub-group of patients * reversal versus stabilisation of a condition * bridging a gap to a definitive therapy * offering an alternative to an unlicensed drug that is the sole treatment in use for a specific condition.   Clinical expert and patient interest group input are also considered for a specific drug, as well as special issues highlighted by the manufacturer. |
| **North America** |  |  |  |
| Provincial and territorial health authorities (Canadian Agency for Drugs and Technologies in Health 2013);ISPOR, 2011, 1} | Applicant: drug company  Evaluator (for CDR): Canadian Agency for Drugs and Technologies in Health (CADTH)  Recommendation-maker:   * General: Canadian Expert Drug Advisory Committee (CEDAC), Conseil du medicament (Québec) * Oral oncology drugs: Committee to Evaluate Drugs (CED), CED-Cancer Care Ontario (CCO) Subcommittee, Conseil du medicament (Québec) | * CDR: Cost-effectiveness or cost-utility analyses are required if the drug: a) is the first available to treat a disease or disorder or has established a new therapeutic class; or b) has demonstrated differences in safety or efficacy versus comparators. Budget impact analyses are also required for CDR submissions for most of the participating drug plans. * Quebec submission: Economic evaluation according to CADTH guidelines and a detailed price justification required. | NR |
| Ontario health authority (Canadian Agency for Drugs and Technologies in Health 2013) | Applicant: manufacturers or physicians  Evaluator: 5-member DRD Working Group  Decision maker: Executive Officer of the Ontario Public Drug Programs | Budget impact is taken into consideration in formulating the final decision | Cost-effectiveness analysis is not conducted, nor is cost-effectiveness a deciding factor in evaluating a drug. |
| Alberta health authority (Rare Disease Drug Program) (Canadian Agency for Drugs and Technologies in Health 2013) | Applicant: rare disease specialist  Evaluator: Alberta’s Rare Disease Clinical Review Panel  Decision maker: Alberta’s Minister of Health | NR | NR |
| Alberta health authority (Short Term Exceptional Drug Therapy) (Canadian Agency for Drugs and Technologies in Health 2013) | Applicant: specialist physician working at an Alberta Health Services facility and actively treating a patient for a rare clinical condition  Evaluator: NR  Decision maker: NR | NR | NR |
| **Asia** |  |  |  |
| Japanese statutory health insurance (Japan Intractable Diseases Information Center 2014) | Applicants: patients  Evaluator: health centre that has jurisdiction over the area the applicant lives in  Decision-maker: governor of the prefecture | Patients with any of the 56 diseases covered by the Specified Disease Treatment Research Program | NR |
| National health insurance, South Korea (Hong et al. 2014; Soo 2014) | Applicant: Drug company  Evaluator: Drug Benefit Coverage Assessment Committee (DBCAC) of the Heatlh Insurance Review Agency (HIRA)  Decision-maker: Health Insurance Policy Review Committee within the ministry | Positive recommendation for reimbursement is based on the drug’s clinical usefulness, cost-effectiveness, disease severity, financial impacts, and it’s reimbursement status and pricing in foreign countries. | Products for severe diseases or rare diseases were recommended if the new drug:   * has no alternative treatment; * is used for life-threatening disease; * is used for a minority of patients who have rare disease; and * is capable of proving clinically meaningful and substantial improvement such as extended survival,   The NHIC can conduct the negotiation process with the company without data proving cost-effectiveness. |
| Chinese medical insurance system (Ngorsuraches et al. 2012) | Applicant: NR  Evaluator: experts and pharmacoeconomists  Decision-maker: more than 2000 experts (voting) | * Safety, efficacy, and clinical needs * Information of price and pharmacoeconomic evaluation in other countries * Budget impact | None |

AGNSS = Advisory group for National Specialised Services ; AIFA = italian Pharmaceutical Agency ; C BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte; CADTH = Canadian Agency for Drugs and Technologies in Health; CCO = Cancer Care Ontario CED = Committee to Evaluate Drugs; CEDAC = Canadian Expert Drug Advisory Committee; CEM = Commission d’Evaluation des Médicaments ; CEPS = Comité Economique des Produits de Santé; CIPM = Inter-Ministerial Pricing Commission; CVZ = College voor zorgverzekeringen; DBCAC = Drug Benefit Coverage Assessment Committee; DRC = Drug Reimbursement Committee; HAS = Haute Autorité de Santé ; G-BA = Gemeinsamer Bundesausschuss; HIRA = Health Insurance Review Agency; HTA = Health technology assessment; HVB = Hauptverband der österreichischen Sozialversicherunsträger; IQWiG = Institute for Quality and Efficiency in Healthcare; ISCIII = Instituto de Salud Carlos III; ISPOR = International Society for Pharmacoeconomics and Outcomes Research LFN = Läkemedelsförmånsnämnden; NHS = National health Service; NICE = National Institute of Health and Clinical Excellence; NR = not reported; QALY = Quality adjusted life year; SBU = Statens beredning för medicinsk utvärdering; SMC = Scottish Medicines Consortium; TLV = Tandvårds- och läkemedelsförmånsverket; UNCAM = Union Nationale des Caisses d’Assurance Maladie

Table 176 Monitoring outcomes of the decision to reimburse, summary by country.

| Country / funding body (references) | Is there monitoring of areas of uncertainty in drug funding decisions concerning rare/ultra-rare conditions? | If so, what methods are used? | Is there a timetabled programme for the review of decisions or is it *ad hoc*? |
| --- | --- | --- | --- |
| Australia | NR | NR | NR |
| Belgium (Denis et al. 2011) | Yes | Companies need to submit a dossier to the DRC for initial reimbursement, followed by a revised dossier 1.5–3 years after initial reimbursement approval. Since 2008, dossiers need to comply with guidelines for pharmacoeconomic evaluation in Belgium as issued by the Belgian Health Care Knowledge Centre (a state funded  research institution) |  |
| Austria | NR | NR | NR |
| Dutch duel health insurance system (Garau & Mestre-Ferrandiz 2009) | Non-hospital treatments: NR  Hospital treatments (Policy rule on orphan drugs): Yes | Hospital treatments (Policy rule on orphan drugs): after a maximum of 3 years, the CVZ reappraises the evidence that has been collected and on this basis it reviews its decisions on the product listing. | NR |
| Swedish National Health Service | NR | NR | NR |
| Spanish National Health Service | NR | NR | NR |
| Italian National Health Service | NR | NR | NR |
| German Statutory Health Insurance | NR | NR | NR |
| French National Health Insurance (ISPOR 2009b) | Yes (for all drugs). | The registration on the reimbursable list is valid during 5 years. At the end of this period, the Commission d’Evaluation des Médicaments re-evaluates the SMR and ASMR level and the price can be reviewed by the CEPS accordingly. | NR |
| National Health Service (NHS), England and Wales (Canadian Agency for Drugs and Technologies in Health 2013) | Yes (for the AGNSS)  NR (for the Highly Specialised Technologies Programme) | Given the difficulty of collecting data for ‘ultra-orphan’ and rare disorders, AGNSS assumes further data collection will occur in the 5 years after recommendation, and assesses the ability of the applicant to do this (unknown for the Highly Specialised Technologies Programme). | NR |
| NHS, Scotland | NR | NR | NR |
| Ontario health authority | NR | NR | NR |
| Alberta health authority (Rare Disease Drug Program)  (Canadian Agency for Drugs and Technologies in Health 2013) | Yes | Ongoing reimbursement of pharmaceutical for individual patients based on clinical response. | NR |
| Alberta health authority (Short Term Exceptional Drug Therapy) | NR | NR | NR |
| Japanese statutory health insurance | NR | NR | NR |
| South Korea National Health Insurance (Soo 2014) | NR | NR | *Ad hoc* |
| Chinese medical insurance system | NR | NR | NR |

AGNSS = Advisory group for National Specialised Services ; ASMR = Australian Society for Medical Research ; CEPS = Comité Economique des Produits de Santé ; CVZ = College voor zorgverzekeringen; DRC = Drug Research Centre; NR = not reported; SMR = Service Médical Rendu

# Appendix J Quality assurance documentation (ToR 7)

Table 177 Example of quality assurance documentation

| Date | Quality issue identified by (name) | Type of issue:  1: erroneous data  2: missing data  3: duplicated data  4: confidential data breach  5: database / software error  6: efficiency issue  7: other | Description of issue | How did the issue occur | Steps taken to fix the current issue. | How could the system be improved to reduce the likelihood of the issue occurring | Other staff informed? | Please Initial |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 23/11/2014 | Joe Bloggs | 1: erroneous data | The field requesting Haemoglobin was completed yet contained an implausible value (>200 g/L). This was high compared with previous entries. | The treating doctor entered 225 g/L instead of 125 g/L. | The treating doctor was contacted to clarify the actual haemoglobin value. | As 225 g/L is not an impossible value, it cannot be disallowed as an entry value, however, a warning could be built into the data entry form to indicate that the value appears to be inconsistent with previous values and prompt the treating doctor to review the value. | Staff will be informed of possible errors with laboratory values. |  |

# Appendix K Example of patient information and consent form for rare diseases registry (ToR 7)

Australian Government Department of Health

**Participant Information Sheet/Consent Form**

|  |  |
| --- | --- |
| **Title** | *Collection of data for drugs reimbursed through the rare diseases program* |
| **Short Title** | *Rare diseases registry* |
| **Contact** | *Ms xxxxxxx*  Rare diseases registry coordinator  Mail Drop xxxxx  Canberra, ACT, 2600  Ph: 02 xxxxxxxx |

**Part 1 What does my participation involve?**

1. **Introduction**

*The purpose of this section is to state the reason the participant is being invited to take part in the collection of data for the registry and to explain the purpose of the form and the nature of informed consent.*

As part of the Government reimbursement program for Drug A, you are being asked to provide information about your ongoing health and wellbeing.

Disease A is very rare and some information is missing regarding things like the type and seriousness of the symptoms associated with the disease and how much the disease affects your everyday living. The collection of your data may help better describe Disease A as well as provide information about how well Drug A works.

By signing this consent form you are telling us that you:

* Understand what you have read about the data collection
* Consent to the collection of your data
* Consent to the tests that may be in addition to your normal management
* Consent to the use of your personal and health information as described

The collection of this data is a requirement for receiving Drug A. If you feel you cannot consent to the collection of your data, your reasons will be considered by the Department and you may be exempted from some of the data collection.

You will be given a copy of this Participant Information and Consent Form to keep.

**2 What is the purpose of this research?**

This research will improve the understanding of Disease A in Australian patients as well as how patients respond to Drug A. The Rare Disease Registry Committee may use this information to advise Government or treating clinicians how to better use Drug A or better treat patients with Disease A. The Rare Disease Registry Committee may also use this information to help verify whether the drug is achieving the results that the drug manufacturer stated it would. Findings from this data collection may alter the way Drug A is provided, or result in Drug A no longer being funded to safety or effectiveness concerns.

This research is being conducted by the Australian Government Department of Health.

**3 What does participation in this research involve?**

Your participation in this research, after you have signed this consent form, will involve seeing your treating doctor about every 6 to 12 months. You may see your doctor more frequently if required.

As part of the normal monitoring of your condition, you will have blood tests and scans to establish whether your disease is stable and how well you are responding to Drug A. Usually, these tests will be all that is required for the Rare Diseases Registry. Sometimes, you may not have had a particular test for some time and this may have to be scheduled so that this information can be collected. If this is the case, you may have to have an additional blood test or scan (usually no more often than every 6 or 12 months).

You may also be asked to complete a questionnaire every 6 or 12 months. This questionnaire will ask about your general well-being, including things like pain, tiredness and how well you manage to get things done each day.

Your information will be collected for at least as long as you are receiving Drug A, and may be collected even if you stop taking Drug A, however fewer tests may be required. In some cases, data collection may continue through your life and may include the collection of information on causes of death.

**4 What do I have to do?**

The data collection for the Rare Diseases Registry may require you to complete a questionnaire about every 6 to 12 months. It may also require you to see your treating doctor about every 6 to 12 months, although this may have already happened as part of monitoring your condition or your response to Drug A.

**5 Other relevant information about the research project**

Everyone with Disease A who receives Drug A on the Rare Diseases Reimbursement Scheme will be involved in this data collection (unless there is an acceptable reason not to participate). These patients will be all across Australia.

**6 Do I have to take part in this research project?**

While participation in this data collection is voluntary, it is a condition of receiving Drug A on the Rare Diseases Reimbursement Scheme. Should you decide not to take part in this data collection, ordinarily you would not be eligible for reimbursed access to Drug A. If you agree to receive Drug A on the scheme and feel that you have a good reason to not participate in the collection of your data, this will be considered by the Rare Diseases Registry Committee and you may be exempted from some of the data collection.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

**7 What are the possible benefits of taking part?**

You may not receive any benefits from participating in the Rare Diseases Registry. The information collected may provide a better understanding of your disease or of how Drug A works for you and your treatment may be able to be improved. Also, your information may provide a better understanding of Disease A or Drug A for future patients.

**8 What are the possible risks and disadvantages of taking part?**

There are no clear risks associated with taking part in the Rare Diseases Registry. However, if the Registry requires information at a time when you have not had a recent blood test or scan, your treating doctor may be asked to arrange this. The Registry staff will work with your treating doctor to ensure that additional tests, over and above what your treating doctor would ordinarily require for the management of your condition, are entirely avoided or kept to a minimum.

If you are required to have an additional blood test, this will involve a needle and may have some side-effects at where the needle is inserted, such as bruising or bleeding.

If you are required to have an additional scan (which doesn’t involve radiation), this usually will involve no additional risks.

If your scan involves radiation (like an x-ray or CT scan), the level of radiation associated is low. Your treating doctor will explain the risks associated with these types of scans [this may require a specific paragraph addressing the use of ionising radiation – such statements are required by several HRECs].

**9 What if new information arises during this research project?**

If new information arises during the course of your data collection that is relevant to you, Disease A or Drug A, your treating doctor will inform you about it. If the information is identified by the Registry staff and deemed to affect you, they will contact your treating doctor.

If there are substantial changes to the types of data collected, or the use of the data, you may be contacted through your treating doctor and asked to consent to the new process, as required by a government-approved HREC.

**10 What if I withdraw from this research project?**

If you decide to withdraw your consent for data collection relating to Drug A, you may no longer be eligible to receive Drug A through the Rare Diseases Reimbursement Scheme.

**11 What happens when the research project ends?**

At some point there may no longer be a need to collect information about Disease A or Drug A. If this occurs, you will be notified and data collection will no longer happen. However, your treating doctor may still require you to undergo many or all of the tests that are part of this data collection as part of your usual care.

**Part 2 How is the research project being conducted?**

**12 What will happen to information about me?**

Information collected about you, Disease A or your response to Drug A will be kept in a secure database. Only the Rare Diseases Reimbursement Committee and staff working with the database will have access to information such as your name or personal details. The staff have signed confidentiality agreements and access to the database will be strictly controlled according to procedures that are compliant with the Privacy Act 1988, the International Conference on Harmonisation Good Clinical Practice (IHC GCP) and the NHMRC National statement on Ethical Conduct in Human Research.

Information from the database may be accessed for auditing purposes, and may be published. However, no identifying information will be made available in any public reports and, due to the rarity of Disease A, particular care will be taken to aggregate (combine data from many patients) so that no patient’s data can be identified in the report. Data that are reported will be things like average age of patients, average dose of Drug A, the number of people who experience side effects and the types of benefit experienced by patients on Drug A. No one will be able to identify you from these reports.

It is possible that your data may be of value to other researchers who are looking to improve their understanding about Disease A or Drug A. If this is the case, and you consent to your data being used for this research, your data will be provided in a non-identifiable manner (your name, medical numbers, or any identifying information will be removed before these data are provided to another researcher). This researcher may be in Australia, or may be international. The provision of your data for other research purposes may improve our understanding of Disease A or Drug A; however, providing this information is entirely voluntary and you may choose not to participate. If you choose not to allow your non-identifiable information with another research group, it will have no impact upon your eligibility for treatment with Drug A in any way.

If you choose not to have your non-identifiable information given to other researchers, your information will only be used for the purposes of the registry and it will only be disclosed to others with your permission, or when required by law.

Most of your information will be collected from your treating doctor or directly from you (if you complete questionnaires). Sometimes data may need to be collected from your medical records or laboratory results.

Information about your participation in data collection for the registry will be recorded in your health records.

Your data will be stored securely for as long as the reimbursement of Drug A continues and sometimes longer. If data on Drug A is no longer required, the data in this registry will be destroyed after a period of time determined by the central HREC.

**13 Who is organising and funding the research?**

This research is being organised and funded by the Australian Government Department of Health. Some of the funding to support the registry may be recovered from the company that makes Drug A; however the company will have no access to the data. Sometimes companies that make drugs will seek to collect similar data about patients and if this happens, your doctor will ask you to consent for this also.

**14 Who has reviewed the research project?**

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Department of Health. This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

**15 Further information and who to contact**

The person you may need to contact will depend on the nature of your query. If you have questions about Disease A or the effects of Drug A, you should contact your treating doctor. If you wish to discuss anything about the data collection process, your doctor may be able to answer some questions (like exactly what is being collected). If you would like further information about where your information is stored, or how it is used, you may contact the Rare Diseases Registry staff (contact details below).

If you would like to discuss anything about this project with someone who is not involved in the project, or you have complaints about any aspect of the project and would prefer to talk to someone other than your treating doctor or the registry staff, you can call the Department of Health HREC (the ethics committee that approved the project).

**Clinical contact person**

|  |  |
| --- | --- |
| Name | *Treating Doctor* |
| Position |  |
| Telephone |  |
| Email |  |

**Registry contact person**

|  |  |
| --- | --- |
| Name | *Registry personnel* |
| Position |  |
| Telephone |  |
| Email |  |

**Complaints contact person**

|  |  |
| --- | --- |
| Name | *HREC representative* |
| Position |  |
| Telephone |  |
| Email |  |

**Consent Form -** *Adult providing own consent*

|  |  |
| --- | --- |
| **Title** | *Collection of data for drugs reimbursed through the rare diseases program* |
| **Short Title** | *Rare diseases registry* |
| **Contact** | *Ms xxxxxxx*  *Rare diseases registry coordinator*  *Mail Drop xxxxx*  *Canberra, ACT, 2600*  *Ph: 02 xxxxxxxx* |

**Declaration by Participant**

* I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
* I understand the purposes, procedures and risks of the research described in the project.
* I have had an opportunity to ask questions and I am satisfied with the answers I have received.
* I freely agree to participate in this research project as described.
* I understand that I will be given a signed copy of this document to keep.

| ***Optional Consents*** | Yes | No |
| --- | --- | --- |
| I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to the Department of Health Rare Diseases Registryconcerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential. | ***□*** | ***□*** |
| I give permission for my non-identifiable information to be released for the purposes of research related to either Disease A or Drug A. I understand that such information will remain confidential and that I will not be identifiable to any researchers outside of the Rare Diseases Registry. | ***□*** | ***□*** |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | |
|  | Name of Participant (please print) | |  |  |  |  |
|  | | | | | | |
|  | Signature |  | | Date |  |  |
|  | | | | | | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | |
|  | Name of Witness (please print) | |  | | |  |
|  | | | | | | |
|  | Signature |  | | Date |  |  |
|  | | | | | | |

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | |
|  | Name of Study Doctor/  Senior Researcher† (please print) | |  | | |  |
|  | | | | | |  |
|  | Signature |  | | Date |  |  |
|  | | | | | | |

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

1. [PBS Post market reviews LSDP site](http://www.pbs.gov.au/info/reviews/life-saving-drugs) [↑](#footnote-ref-1)
2. [Department of Health LSDP site](http://www.health.gov.au/lsdp) [↑](#footnote-ref-2)
3. [LSDP criteria](http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-criteria) [↑](#footnote-ref-3)
4. Grey literature encompasses multiple document types produced on all levels of government, academia, business, and other organisations that are produced in electronic and print formats and are not controlled by commercial publishing i.e. *where publishing is not the primary activity of the producing body* (Source: http://www.greynet.org/greynethome/aboutgreynet.html) [↑](#footnote-ref-4)
5. Source: [PubMed advice on Searching for Drug Information](http://nnlm.gov/training/pubmedfortrainers/Searching_for_Drug_Information.pptx) [↑](#footnote-ref-5)
6. Bai A, Shukla VK, Bak G, Wells G. *Quality Assessment Tools Project Report*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2012. [↑](#footnote-ref-6)
7. White blood cell count reference range = 4.0 – 11.0 ([QML Pathology 2009](#_ENREF_240)) [↑](#footnote-ref-7)
8. Haemoglobin reference range = Males: 135 - 180 g/L; Females: 115 – 160 g/L ([QML Pathology 2009](#_ENREF_240)) [↑](#footnote-ref-8)
9. Platelets reference range = 150 – 450 x 109/L ([QML Pathology 2009](#_ENREF_240)) [↑](#footnote-ref-9)
10. Haemoglobin reference range: Males = 135 – 180 g/L; Females = 115 – 160 g/L ([QML Pathology 2009](#_ENREF_240)) [↑](#footnote-ref-10)
11. Platelet count reference range = 150 – 450 x 109/L ([QML Pathology 2009](#_ENREF_240)) [↑](#footnote-ref-11)
12. conference and poster abstracts containing data have not been listed [↑](#footnote-ref-12)
13. QRS = combination of three graphical deflections seen on a typical electrocardiogram (i.e. part of the QT interval) [↑](#footnote-ref-13)
14. Minimum clinically important difference on the 6MWT is considered to be 54 metres ([Lachmann & Schoser 2013](#_ENREF_179)) [↑](#footnote-ref-14)
15. For the last 2.5 years of the trial laronidase was administered to 19 European patients without human serum albumin, in accordance with the European product label ([Clarke et al. 2009](#_ENREF_53)) [↑](#footnote-ref-15)
16. The two-component composite score for each patient was calculated by summing the ranks of the two individual components according to the procedure described by O’Brien, 1984. [↑](#footnote-ref-16)
17. One patient does not have a recorded start date or recorded visit. [↑](#footnote-ref-17)
18. Type III PNH cells have a complete deficiency of GPI membrane anchoring proteins([Hillmen et al. 2004](#_ENREF_131)) [↑](#footnote-ref-18)
19. Based on 94 patients with baseline values [↑](#footnote-ref-19)
20. An individualised transfusion algorithm was calculated for each patient on the basis of the history of transfusions during the previous 12 months; the algorithm documented the number of units of packed RBCs to be transfused for given haemoglobin values and served as a prospectively determined guide for transfusion during the observation and treatment periods. [↑](#footnote-ref-20)
21. Defined as those who did not require a blood transfusion during the previous 6 months [↑](#footnote-ref-21)
22. Calculated during the review [↑](#footnote-ref-22)
23. FACIT-Fatigue instrument: scores can range from 0 to 52. A positive change from baseline indicates an improvement in fatigue and a negative change indicates a worsening in fatigue. [↑](#footnote-ref-23)
24. http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-criteria [↑](#footnote-ref-24)
25. http://checkorphan.org/grid/news/treatment/ema-approves-eisai-s-lenvatinib-for-accelerated-assessment-in-radioiodine-refractory-differentiated-thyroid-cancer [↑](#footnote-ref-25)
26. http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-criteria [↑](#footnote-ref-26)
27. Health Technology Assessment international [↑](#footnote-ref-27)
28. International Society for Pharmacoeconomic Outcomes Research [↑](#footnote-ref-28)
29. A medication, vaccine or in vivo diagnostic agent is designate as an orphan drug by the TGA if it intended to treat, prevent or diagnose a rare disease or is not commercially viable to treat, prevent or diagnose another disease or condition ([Australian Government 1990](#_ENREF_16)). [↑](#footnote-ref-29)
30. http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-criteria [↑](#footnote-ref-30)
31. International Health Economics Association [↑](#footnote-ref-31)
32. Society of Medical Decision Making [↑](#footnote-ref-32)
33. Health Technology Assessment international [↑](#footnote-ref-33)
34. International Society of Pharmacoeconomics Research [↑](#footnote-ref-34)
35. Department of Health, *Patient Conditions for Initial and Ongoing Subsidy Through the LSDP*, available at: [Criteria for LSDP](http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-criteria). Accessed 16/09/2014. [↑](#footnote-ref-35)
36. http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-criteria [↑](#footnote-ref-36)
37. http://www.health.gov.au/internet/main/publishing.nsf/Content/privacy-policy [↑](#footnote-ref-37)
38. http://www.protectivesecurity.gov.au/pspf/Pages/default.aspx [↑](#footnote-ref-38)
39. http://www.health.gov.au/internet/main/publishing.nsf/Content/health-ethics-index.htm [↑](#footnote-ref-39)
40. http://www.australianclinicaltrials.gov.au/node/23 [↑](#footnote-ref-40)
41. Systematic reviews were excluded if they did not report results for RCTs separately, if only one database was included in the literature search, or if they were outdated by a more recent review. [↑](#footnote-ref-41)
42. Systematic reviews were excluded as they contained only one RCT. It was decided to include the original study in place of the systematic reviews. [↑](#footnote-ref-42)