5.13 SEBELIPASE ALFA, Solution for injection, 20 mg in 10 mL vial, Kanuma®, ALEXION PHARMACEUTICALS PTY LIMITED.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) PBS listing of sebelipase alfa for the treatment of children and adults with late-onset lysosomal acid lipase deficiency (LAL-D).

1.2 Listing was requested on the basis of a cost-utility analysis (CUA) of sebelipase alfa plus best supportive care (BSC) versus BSC in patients with late-onset LAL-D (Table 1). It is implied that patients treated with sebelipase alfa will also receive BSC from herein unless otherwise stated.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients diagnosed with late-onset LAL-D.
Intervention	Sebelipase alfa administered at 1 mg/kg every 2 weeks as an IV infusion, with the option of dose escalation to 3 mg/kg once every 2 weeks based on suboptimal response to clinical and biochemical criteria. Sebelipase alfa is administered either as monotherapy or in combination with BSC.
Comparator	Placebo ± BSC. BSC compromised of nutritional support, lifestyle modifications, and/or lipid-lowering medications, as clinically indicated.
Outcomes	Primary: ALT normalisation Secondary: LDL-c, HDL-c, AST normalisation, TG, liver fat content, liver histopathology and liver volume.
Clinical claim	Sebelipase alfa ± BSC is superior to placebo ± BSC in achieving primary and secondary efficacy outcomes. Sebelipase alfa ± BSC has a manageable safety profile compared with placebo ± BSC.

Source: Table 1-2, p31 of the submission.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSC = best supportive care; HDL-c = high-density lipoprotein cholesterol; IV = intravenous; LAL-D = lysosomal acid lipase deficiency; LDL-c = low-density lipoprotein cholesterol; TG = triglyceride.

2 Background

Registration status

2.1 Sebelipase alfa was approved by the TGA on 18 May 2017 for the following indication: "Kanuma (sebelipase alfa rce) is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D)."

Previous PBAC consideration

2.2 The PBAC did not recommend the listing of sebelipase alfa for the treatment of infantile onset LAL-D in March 2022. The PBAC considered sebelipase alfa an effective treatment for infantile-onset LAL-D; however, the incremental cost-effectiveness ratio

(ICER) for sebelipase alfa compared with best supportive care was extremely high and uncertain (paragraph 7.1, sebelipase alfa, Public Summary Document [PSD], March 2022 PBAC Meeting). Sebelipase alfa is funded through the Life Saving Drugs Program (LSDP)[1] for the treatment of infantile-onset LAL-D.

3 Requested listing

3.1 Secretariat suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price[a] for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SEBELIPASE ALFA					
Initial					
Sebelipase alfa, 20 mg/10 mL injection, 10 mL vial	Public hospital: Published price: $[redacted] Effective price: $[redacted] Private hospital: Published price: $[redacted] Effective price: $[redacted]	1	1	5	Kanuma
Continuing					
Sebelipase alfa, 20 mg/10 mL injection, 10 mL vial	As above	1	1	5	Kanuma

per vial (i.e. $[redacted]/mg) in the economic model. Dispensed prices could not be verified during the evaluation.

Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public / Private
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
Authority type: ☒ Complex Authority Required (CAR)
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice:

[1] https://www.health.gov.au/sites/default/files/2023-04/life-saving-drugs-program-sebelipase-alfa-kanuma-outcome-statement.pdf

No increase in the maximum number of repeats may be authorised

Episodicity: ~~blank~~ *Late-onset*
Severity: blank
Condition: ~~Late-onset~~ lysosomal acid lipase deficiency (LAL-D)
Indication: Late-onset lysosomal acid lipase deficiency (LAL-D)
Treatment Phase: Initial treatment
Clinical criteria:
Patient must have a confirmed diagnosis of late-onset LAL-D *demonstrated by the deficiency in LAL enzyme activity when tested at the National Referral Laboratory*. ~~Diagnosis of LAL-D must be confirmed by evidence demonstrating deficiency in LAL enzyme activity when tested at the National Referral Laboratory~~
AND
Clinical criteria:
Patient must be *either (i)* receiving, ~~or~~ (*ii)* enrolled to receive, professional nutritional support including dietetic and weight management advice.
AND
Clinical criteria:
Patient must have persistent elevated transaminases ~~D~~ *d*efined as *alanine transaminase* (ALT) level *of* 1.5 ~~x~~ *times the* upper limit of normal (ULN) based on the age- and gender-specific normal ranges on 2 consecutive ALT measurements obtained at least 1 week apart; OR
Patient must have persistent dyslipidaemia ~~D~~ *d*efined as LDL-C ~~>~~ *of more than* 130mg/dL and/or triglycerides (TG) ~~>~~ *of more than* 200mg/dL and/or HDL-C ~~<~~ *of less than* 50mg/dL on 2 consecutive measurements obtained at least 1 week apart; OR
Patient must have evidence of hepatomegaly ~~D~~ *d*efined as 1.25 ~~x~~ *times* normal volume; OR
Patient must have evidence of splenomegaly ~~D~~ *d*efined as 4 ~~x~~ *times* normal volume; OR
Patient must have evidence of *liver* fibrosis *confirmed* by liver biopsy *with* Ishak score ~~≥~~ of at least 1 OR
~~Patient must have impaired growth~~ ~~Defined as:~~ ~~i. Weight-for-age (WFA) or stature-for-age (SFA) less than the age- and gender- appropriate 5th percentile on a standard World Health Organization (WHO) (subjects ≤ 24 months of age) or Centers for Disease Control and Prevention (CDC) (subjects > 24 months and < 4 years of age) WFA or SFA chart for at least 3 months prior to treatment initiation; OR~~ ~~ii. Poor weight gain as evidenced by calculated weight percentile decreasing across 2 major percentile (99th, 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, 3rd, and 1st) lines on a standard WHO (subjects ≤24 months of age) or CDC (subjects > 24 months and <4 years of age) WFA chart over a period of 6 months prior to treatment initiation~~ *Patient must have impaired growth defined as low growth measures demonstrated by weight-for-age (WFA) or stature-for-age (SFA) less than the age- and gender- appropriate 5th percentile on a standard World Health Organization (WHO) charts for children up to 24 months old; or Centers for Disease Control and Prevention (CDC) charts for children between 24 months and 4 years of age, for at least 3 months prior to treatment initiation; OR*
Patient must have impaired growth defined as poor weight gain demonstrated by calculated weight percentile decreasing across 2 major percentile (99th, 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, 3rd, and 1st) lines on a standard WHO WFA charts for children up to 24 months old or CDC WFA Charts for children between 24 months and 4 years of age over the 6 months prior to treatment initiation; OR

~~Patient must have suspected malabsorption with:~~ ~~i. Persistent unexplained gastrointestinal symptoms such as nausea, diarrhea, abdominal pain, and bloating; OR~~ ~~ii. Unexplained anaemia, or other abnormalities suggestive of malabsorption (e.g., osteomalacia, hypoalbuminaemia, prolonged bleeding time due to vitamin K deficiency); AND~~ ~~iii. Documented small intestinal disease involvement on a small bowel biopsy performed within 1 year of treatment initiation~~ *Patient must have suspected malabsorption with either (i) persistent unexplained gastrointestinal symptoms or (ii) Unexplained anaemia, or other abnormalities suggestive of malabsorption* *with small intestinal involvement confirmed on a biopsy within 1 year prior to treatment initiation.*
Treatment criteria:
Must be treated by a specialist with experience in the diagnosis and management of metabolic disease.
Prescribing Instructions: ~~At the time of the authority application, medical practitioners must request the appropriate number of vials, to provide sufficient drug for 6 months of treatment, according to the specified dosage in the approved Product Information (PI).~~ *At the time of the authority application, prescribers must request the appropriate number of vials to provide sufficient drug, based on the weight of the patient, for 4 weeks of treatment, according to the recommended dosing regimen in the Therapeutic Goods Administration (TGA) approved Product information (PI). Up to a maximum of 5 repeats will be authorised.*
Prescribing Instructions: *Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.*
Prescribing Instructions: *Persistent unexplained gastrointestinal symptoms include but not limited to nausea, diarrhea, abdominal pain, and bloating.*
Prescribing Instructions: *Other abnormalities suggestive of malabsorption include but not limited to osteomalacia, hypoalbuminaemia, prolonged bleeding time due to vitamin K deficiency.*
Prescribing Instructions: *The authority application must be made in writing and must include:* *(1) details of the proposed prescription; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)*
Indication: Late-onset lysosomal acid lipase deficiency (LAL-D)
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must be *either (i)* receiving, ~~or~~ (*ii)* enrolled to receive, professional nutritional support including dietetic and weight management advice.
AND
Clinical criteria:
~~Subsidised treatment may continue unless one or more of the following situations apply:~~ ~~• failure to comply adequately with treatment or measures~~ ~~• therapy fails to prevent significant morbidity due to late-onset LAL-D~~ ~~Significant morbidity may include (but is not limited to) multi-organ failure, liver failure, and severe nutritional deficiency~~ ~~• the patient experiences unresolved severe injection site or severe hypersensitivity reactions, which cannot be managed with standard treatment or are life-threatening~~ *Patient must not have developed significant morbidity associated with late-onset LAL-D (including, but not limited to, multi-organ failure, liver failure, or severe nutritional deficiency);*
Treatment criteria:
Must be treated by a specialist with experience in the diagnosis and management of metabolic disease.

Prescribing Instructions: ~~At the time of the authority application, medical practitioners must request the appropriate number of vials, to provide sufficient drug for 6 months of treatment, according to the specified dosage in the approved Product Information (PI).~~ *At the time of the authority application, prescribers must request the appropriate number of vials to provide sufficient drug, based on the weight of the patient, for 4 weeks of treatment, according to the recommended dosing regimen in the Therapeutic Goods Administration (TGA) approved Product information (PI). Up to a maximum of 5 repeats will be authorised.*
Prescribing Instructions: *The authority application must be made in writing and must include:* *(1) details of the proposed prescription; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)*
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public / Private
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
Authority type: ☒ Complex Authority Required (CAR)
Indication: Late-onset lysosomal acid lipase deficiency (LAL-D)
Treatment Phase: Transitioning from non-PBS subsidised to PBS-subsidised treatment - Grandfather arrangements
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [date of PBS listing]
AND
Clinical criteria:
Patient must have a confirmed diagnosis of late-onset LAL-D *demonstrated by the deficiency in LAL enzyme activity when tested at the National Referral Laboratory*. ~~Diagnosis of LAL-D must be confirmed by evidence demonstrating deficiency in LAL enzyme activity when tested at the National Referral Laboratory~~
AND
Clinical criteria:
Patient must be *either (i)* receiving, ~~or~~ (*ii)* enrolled to receive, professional nutritional support including dietetic and weight management advice.
AND
Clinical criteria:
Patient must have had persistent elevated transaminases defined as alanine transaminase (ALT) level of 1.5 times the upper limit of normal (ULN) based on the age- and gender-specific normal ranges on 2 consecutive ALT measurements obtained at least 1 week apart, prior to treatment initiation with this drug for this PBS indication; OR
Patient must have *had* persistent dyslipidaemia ~~D~~ *d*efined as LDL-C ~~>~~ *of more than* 130mg/dL and/or triglycerides (TG) ~~>~~ *of more than* 200mg/dL and/or HDL-C ~~<~~ *of less than* 50mg/dL on 2 consecutive measurements obtained at least 1 week apart, *prior to treatment initiation with this drug for this PBS indication; OR*
Patient must have *had* evidence of hepatomegaly ~~D~~ *d*efined as 1.25 ~~x~~ *times* normal volume, *prior to treatment initiation with this drug for this this PBS indication;* OR
Patient must have *had* evidence of splenomegaly ~~D~~ *d*efined as 4 ~~x~~ *times* normal volume, *prior to treatment initiation with this drug for this this PBS indication*; OR
Patient must have *had* evidence of *liver* fibrosis *confirmed* by liver biopsy *with* Ishak score ~~≥~~ of at least 1, *prior to treatment initiation this drug for this PBS indication;* OR
Patient must have had impaired growth defined as low growth measures demonstrated by weight-for-age (WFA) or stature-for-age (SFA) less than the age- and gender- appropriate 5th percentile on a standard World Health Organization (WHO) charts for children up to 24 months old; or Centers for Disease Control and Prevention (CDC) charts for children between 24 months and 4 years of age, for at least 3 months prior to treatment initiation with this drug for this PBS indication; OR
Patient must have had impaired growth defined as poor weight gain demonstrated by calculated weight percentile decreasing across 2 major percentile (99th, 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, 3rd, and 1st) lines on a standard WHO WFA charts for children up to 24 months old or CDC WFA Charts for children between 24 months and 4 years of age over the 6 months prior to treatment initiation with this drug for this PBS indication; OR

Patient must have had suspected malabsorption with either (i) persistent unexplained gastrointestinal symptoms or (ii) Unexplained anaemia, or other abnormalities suggestive of malabsorption *with small intestinal involvement confirmed on a biopsy within 1 year prior to treatment initiation with this drug for this PBS indication.*
AND
Clinical criteria:
~~Subsidised treatment may continue unless one or more of the following situations apply:~~ ~~• failure to comply adequately with treatment or measures~~ ~~• therapy fails to prevent significant morbidity due to late-onset LAL-D~~ ~~Significant morbidity may include (but is not limited to) multi-organ failure, liver failure, and severe nutritional deficiency~~ ~~• the patient experiences unresolved severe injection site or severe hypersensitivity reactions, which cannot be managed with standard treatment or are life-threatening~~ Patient must not have developed significant morbidity associated with late-onset LAL-D (including, but not limited to, multi-organ failure, liver failure, or severe nutritional deficiency);
Treatment criteria:
Must be treated by a specialist with experience in the diagnosis and management of metabolic disease.
Prescribing Instructions: ~~At the time of the authority application, medical practitioners must request the appropriate number of vials, to provide sufficient drug for 6 months of treatment, according to the specified dosage in the approved Product Information (PI).~~ *At the time of the authority application, prescribers must request the appropriate number of vials to provide sufficient drug, based on the weight of the patient, for 4 weeks of treatment per dispensing, according to the recommended dosing regimen in the Therapeutic Goods Administration (TGA) approved Product information (PI). Up to a maximum of 5 repeats will be authorised.*
Prescribing Instructions: *Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.*
Prescribing Instructions: *Persistent unexplained gastrointestinal symptoms include but not limited to nausea, diarrhea, abdominal pain, and bloating.*
Prescribing Instructions: *Other abnormalities suggestive of malabsorption include but not limited to osteomalacia, hypoalbuminaemia, prolonged bleeding time due to vitamin K deficiency.*
Prescribing Instructions: *The authority application must be made in writing and must include:* *(1) details of the proposed prescription; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)*

3.2 The submission proposed 5 repeats for initial and continuing scripts, which would provide a total of 6 infusions. The submission stated that 6 infusions would cover 6 months of treatment; however, with fortnightly dosing, 6 infusions equate to 12 weeks (3 months) of treatment. The PSCR clarified that it had based the listed quantity corresponding to monthly supply rather than a single infusion, but confirmed that the intention was to align prescribing with a six month treatment period.

3.3 The defined population in the proposed restriction was children and adults diagnosed with late-onset LAL-D, with no minimum and maximum age specified. The pivotal LAL-CL02 trial included patients ≥4 years old (range: 4-58 years), with 29% ≥ 18 years, and the LAL-CL06 study used in the supplementary analysis also included younger patients aged ≥8 months old. The sebelipase alfa TGA product information (PI) stated that "safety and efficacy of sebelipase alfa rce in patients older than 65 years have not been

established. Therefore, no information was available to determine whether patients aged 65 years and over respond differently from younger patients." (p5 of the sebelipase alfa TGA PI). The PSCR argued for a broad age range in the proposed restriction to ensure equitable access, highlighting feasibility constraints in ultra-rare disease trials.

3.4 The requested restriction stated that patients must have a diagnosis of late-onset LAL-D, confirmed by demonstrating deficient LAL enzyme activity at the National Referral Laboratory. The Secretariat noted this was consistent with the LSDP criteria for infantile-onset LAL-D. The evaluation considered it would be appropriate to specify the type of test required to diagnose late-onset LAL-D (e.g. a leukocyte-based assay), and/or specify the range of LAL activity required. The PSCR noted that the proposed restriction in the submission aligned with current LSDP eligibility criteria and stated that the assay type or enzyme activity threshold was not specified in order to maintain flexibility across evolving testing methods.

3.5 The Secretariat noted that the LSDP listing for infantile-onset LAL-D also requires confirmation via genetic testing, however the submission noted that a negative result cannot reliably exclude late-onset LAL-D, as mutations in deep intronic or regulatory regions may go undetected, and newly identified pathogenic variants may not yet feature in existing databases.

3.6 The initial eligibility restriction further limits access to patients demonstrating one or more specified disease manifestations (i.e. persistent elevated transaminases, dyslipidaemia, hepatomegaly, splenomegaly, liver fibrosis, impaired growth, OR gastrointestinal manifestations of malabsorption), in line with the submission's proposed target population. Although the proposed definition for persistent elevated transaminases (i.e. ALT level 1.5 x ULN on 2 consecutive ALT measurements obtained at least 1 week apart) was consistent with the LAL-CL02 trial, patients without elevated transaminases may be eligible under the proposed restriction if they demonstrate another listed manifestation. This was inconsistent with the LAL-CL02 trial, which required elevated ALT for all patients. Additionally, LAL-CL02 excluded patients with severe hepatic dysfunction (Child-Pugh C), other active liver diseases or comorbidities likely to confound outcomes, and those with a prior liver or haematopoietic stem cell transplant. LSDP listing for infantile onset LAL-D excludes patients "with another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by therapy"; "with another medical condition that might reasonably be expected to compromise a response to therapy"; or "requiring liver transplantation". Given the substantial under-diagnosis rate of late-onset LAL-D and variable clinical presentation (see paragraph 4.2 and Table 12), it is unclear what proportion of the late-onset LAL-D population, including patients who may be diagnosed following increased testing, would meet the proposed restriction criteria.

3.7 The proposed continuing restriction requires stopping PBS subsidised treatment if any of the following occur: hypersensitivity or severe injection site reactions, non-compliance, or if treatment failed to prevent significant morbidity. The Secretariat noted that stopping treatment due to adverse events is standard in clinical practice,

and ongoing treatment is generally contingent on patient compliance (i.e. these requirements are not unique). Therefore, the Secretariat suggested amending the clinical criterion to: 'Patient must not have developed significant morbidity associated with late-onset LAL-D (including, but not limited to, multi-organ failure, liver failure, or severe nutritional deficiency)'.

3.8 A special pricing arrangement (SPA) was proposed for sebelipase alfa. The proposed effective ex-manufacturer price (EMP) was $[redacted] per 100 mg vial. The submission stated the proposed effective EMP represents a [redacted]% discount relative to the LSDP price for the treatment of infantile-onset LAL-D. The March 2022 submission for infantile-onset LAL-D proposed a published AEMP of $[redacted] and did not propose a SPA.

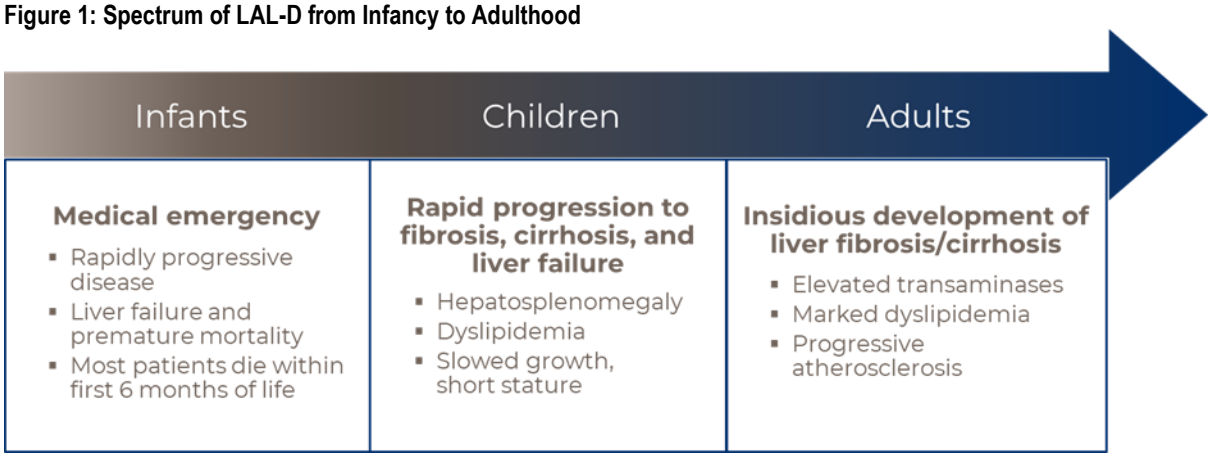
3.9 A separate grandfathering restriction was proposed to permit patients who may have received sebelipase alfa for late-onset LAL-D prior to reimbursement to transition to PBS-funded treatment. The Secretariat noted that eligibility under the grandfather restriction should be similar to the initial treatment including any response/stopping criteria. The submission included < 500 grandfathered patients in the financial estimates,< 500 of whom were accessing treatment through an early access program.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 LAL-D is an ultra-rare, heterogeneous disease associated with significant morbidity and mortality affecting individuals from infancy through to adulthood. LAL-D is an autosomal recessive metabolic disorder involving continuous lysosomal accumulation of cholesteryl esters (CEs) and triglycerides (TGs) resulting from reduced or absent lysosomal acid lipase (LAL) activity. LAL-D is classified according to clinical presentation as 2 broad subtypes: 1) infantile onset LAL-D (historically known as rapidly progressive LAL-D or Wolman disease) that presents in infants, and 2) late-onset LAL-D or cholesteryl ester storage disease (CESD) that presents in children and adults (see Figure 1). The main distinction between the subtypes is defined through LAL activity level. Patients with infantile-onset LAL-D present with <1% or absent LAL activity, whereas patients with CESD demonstrate LAL activity of 1-10% (paragraph 4.2, sebelipase alfa, PSD, March 2022 PBAC Meeting). The extent of tissue deposition of CEs and TGs is directly proportional to disease severity and inversely proportional to age at presentation.

Figure 1: Spectrum of LAL-D from Infancy to Adulthood



Source: Figure 1-2, p35 of the submission

4.2 Late-onset LAL-D demonstrates marked clinical heterogeneity in both presentation and disease progression. Children and adults with late-onset LAL-D commonly present with dyslipidaemia (i.e. elevated low-density lipoprotein cholesterol [LDL-c or bad cholesterol] and reduced high-density lipoprotein cholesterol [HDL-c or good cholesterol]), accelerated atherosclerosis, hepatomegaly, elevated transaminases, and progressive liver disease ranging from fibrosis to liver cirrhosis. These hepatic and systemic manifestations result in significant morbidity and premature mortality from liver failure and/or accelerated atherosclerotic disease secondary to chronic dyslipidaemia. Disease severity appears to be influenced by the efficiency of compensatory metabolic pathways rather than residual enzyme activity levels (Tebani et al. 2021; Wilson DP 2020). Patients across all age groups may remain asymptomatic or present with non-specific gastrointestinal symptoms, including abdominal pain, nausea, and constipation (Bernstein et al. 2013a; Reiner et al. 2014). The disease trajectory varies considerably: some patients exhibit rapidly progressive disease during early childhood, whereas others display an attenuated phenotype that may remain undiagnosed until adolescence or adulthood (Bernstein et al. 2013b; Bernstein et al. 2013a).

4.3 The reported prevalence of LAL-D in European-ancestry cohorts ranged from one in 406,193 in a Slovenian paediatric population to one in 40,000 in a German population. Of these, del Angel et al. (2019)[2] provided the most robust estimate for late-onset LAL-D, reporting a birth prevalence of 3.45-5.97 per million (average prevalence rate of 4.71 per million). The total number of individuals with LAL-D in Australia was previously estimated to be 142 to 297 (infantile-onset and late-onset) (paragraph 4.4, sebelipase alfa, PSD, March 2022 PBAC Meeting). Late-onset LAL-D is currently under-recognised, likely due to the ultra-rare nature of the disease, limited disease awareness, and because of its large variation in clinical presentation which can

[2] del Angel, G., A. T. Hutchinson, N. K. Jain, C. D. Forbes, and J. Reynders. 2019. "Large-scale functional LIPA variant characterization to improve birth prevalence estimates of lysosomal acid lipase deficiency." Hum Mutat 40 (11):2007-2020. doi: 10.1002/humu.23837.

resemble a variety of more commonly diagnosed conditions (Nascimbeni et al. 2020[3]). However, the submission stated that although the disease may be under-recognised and diagnosis delayed (Bernstein et al. 2013b[4]; Reiner et al. 2014[5]), the diagnostic process is clear.

4.4 Sebelipase alfa is a recombinant human lysosomal acid lipase enzyme that acts as enzyme replacement therapy in patients with LAL-D. It hydrolyses accumulated cholesteryl esters and triglycerides in LAL-deficient cells, thereby reducing the pathological effects in affected tissues. The Pre-PBAC response noted that sebelipase alfa is the currently the only therapy that addresses the underlying enzymatic deficiency in late-onset LAL-D.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated placebo plus BSC, defined as nutritional support, lifestyle modifications, and/or lipid-lowering medications (e.g. hydroxymethylglutaryl-coenzyme A reductase inhibitors, bile acid sequestrants and fibrates), as clinically indicated, as the main comparator to sebelipase alfa plus BSC. The evaluation and the ESC considered that BSC was an appropriate comparator.

5.2 The submission did not consider liver transplantation or haematopoietic stem cell transplantation (HSCT) as part of BSC. However, liver transplantation was included as a health state in the economic model. The evaluation and the ESC considered that the exclusion of HSCT as part of BSC was reasonable, noting that for children and adults with late-onset LAL-D, the procedural risks and risk of graft-vs-host disease outweigh the benefits (sebelipase alfa TGA AusPAR). Because older patients experience slower disease progression, clinicians are more likely to prioritise liver transplantation for end-stage organ failure over experimental HSCT, especially when other treatments (e.g., sebelipase alfa) fail.

For more detail on PBAC's view, see section 7 PBAC outcome.

[3] Nascimbeni, F., C. Dionisi Vici, U. Vespasiani Gentilucci, F. Angelico, V. Nobili, S. Petta, and L. Valenti. 2020. "AISF update on the diagnosis and management of adult-onset lysosomal storage diseases with hepatic involvement." Dig Liver Dis 52 (4):359-367. doi: 10.1016/j.dld.2019.12.005

[4] Bernstein, Donna, and Robert Desnick. 2013b. "Cholesteryl ester storage disease (CESD): An under-recognized and treatable LSD with liver dysfunction/failure and dyslipidemia." Molecular Genetics and Metabolism 108 (2):S24. doi: https://doi.org/10.1016/j.ymgme.2012.11.036.

[5] Reiner, Ž, O. Guardamagna, D. Nair, H. Soran, K. Hovingh, S. Bertolini, S. Jones, M. Ćorić, S. Calandra, J. Hamilton, T. Eagleton, and E. Ros. 2014. "Lysosomal acid lipase deficiency--an under-recognized cause of dyslipidaemia and liver dysfunction." Atherosclerosis 235 (1):21-30. doi: 10.1016/j.atherosclerosis.2014.04.003.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinicians discussed the natural history of the disease and clinical management of late-onset LAL-D, describing it as a multisystem disorder with manifestations including dyslipidaemia, progressive liver disease and premature cardiovascular disease, and considered that it is associated with approximately 15 years reduction in life expectancy. The clinicians considered that current management options including dietary measures, lipid-lowering therapy and supportive hepatology care, have an impact on the disease, but are insufficient as they do not address the underlying enzyme deficiency. The clinicians stated that enzyme replacement therapy with sebelipase alfa addresses the underlying disease mechanism. The clinicians considered that the therapy is considered safe and effective, with substantial benefits for young patients facing lifelong disease burden.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (11) and health care professionals (5) via the Office of Health Technology Assessment Consultation Hub. The inputs described the substantial burden of late-onset LAL-D on affected children and families, including fatigue, liver disease, cardiovascular disease, and impacts on participation in school, sport and social activities, and anxiety associated with progressive disease. Input described current care as ineffective, and that treatment with sebelipase alfa was associated with improvements in daily functioning and participation in family, school and community life. Health professionals emphasised the lack of disease-modifying treatments and the importance of equitable and reliable access to therapy for this rare condition.

Clinical trial

6.3 The submission was based on one direct randomised controlled trial:

- The LAL-CL02 (ARISE) trial enrolled children and adults (aged ≥4 years) with late-onset LAL-D, comparing sebelipase alfa 1 mg/kg intravenous infusion (n=36) to placebo (n=30) every other week over a 20-week double-blind period, with normalisation of alanine aminotransferase (ALT) as the primary endpoint (full analysis set (FAS): 66).

6.4 The submission identified one open-label study:

- LAL-CL06 (N=31) was an open-label study in a broad population of children and adults, including those previously excluded from other trials on the basis of age (i.e. ≥8 months and <4 years old), disease progression, or prior transplantation. It was included as a supplemental analysis of safety and efficacy. It was excluded from the main analyses because it was not randomised and lacked a control arm, but provided broader evidence for sebelipase alfa beyond the pivotal LAL-CL02 trial. The primary objective of LAL-CL06 was safety assessment, while secondary endpoints focused on liver histopathology and biochemical markers, including ALT, aspartate aminotransferase (AST), and lipid parameters such as LDL, HDL, and non-HDL.

6.5 The submission also presented supportive evidence from the LAL-D registry:

- an observational, multicentre, international registry designed to collect longitudinal data in patients with a confirmed diagnosis of LAL-D. The analysis included 266 patients (of 315 enrolled), of whom 205 received sebelipase alfa (181 with late-onset LAL-D).

6.6 Details of the randomised trial and single arm study presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Sebelipase alfa ± BSC vs Placebo ± BSC		
LAL-CL02 NCT01757184	Clinical Study Report: A multicenter, randomized, placebo controlled study of sbc-102 in patients with lysosomal acid lipase deficiency.	CSR, May 2014
	Burton et al. (2015c) "A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency."	New England Journal of Medicine; 373(11): 1010-1020.
	Burton et al. (2022) "Sebelipase alfa in children and adults with lysosomal acid lipase deficiency: Final results of the ARISE study."	J Hepatol; 76(3): 577-587.
	Wilson et al. (2018) "Sebelipase alfa improves atherogenic biomarkers in adults and children with lysosomal acid lipase deficiency."	J Clin Lipidol; 12(3): 604-614.
LAL-CL06 NCT02112994	Clinical Study Report: Sebelipase Alfa (Kanuma) Lal-Cl06, A Multi-Center, Open-Label Study Of Sebelipase Alfa In Patients With Lysosomal Acid Lipase Deficiency. 144-Week Clinical Study Report	CSR, Oct 2018

Source: Table 2-3, pp73-74 of the submission.
BSC = Best supportive care; CSR = Clinical study report
Note: Poster or conference presentations or abstract-only publications presented by the submission are excluded from the Table above.

6.7 The key features of the direct randomised trial and single arm study are summarised in Table 3.

Table 3: Key features of the included evidence

Trial/ Study	N	Design/ duration	Bias	Population	Relevant Outcomes	Used in economic model
LAL-CL02 (Trial)[a]	66 (sebelipase alfa: 36, placebo: 30)	R, DB, PC, MC 20 Week induction period followed by 130-week OL extension and 104-week OL expanded treatment period	Low	≥4 years old of age with a confirmed enzyme activity–based diagnosis of LAL-D and a baseline ALT level ≥1.5x the ULN on 2 consecutive screening measurements ≥1 week apart.	Primary: ALT normalisation Secondary: LDL-c, HDL-c, AST normalisation, TG, liver fat content, liver histopathology and liver volume. Others: safety, HRQoL (FACIT-fatigue, CLDQ, PedsQL)	Paired-biopsy data[b] converted from Ishak scoring scale[c] to METAVIR scores[c] to inform FPR (transition probabilities) in the model.
LAL-CL06 (study)	31	OL, MC, phase 2	High	> 8 months of age with confirmed diagnosis of LAL-D and predefined clinical manifestations[d].	Primary: Safety of IV infusions of sebelipase alfa Secondary: serum transaminases (ALT, AST), lipid parameters (LDL-c, HDL-c, non-HDL-c, TGs), liver histopathology. Others: HRQoL and anthropometric growth parameters for paediatric patients.	

Source: pp75-82 of the submission; p134 of the submission

ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; CLDQ = Chronic Liver Disease Questionnaire; DB = Double Blind; FACIT = Functional Assessment of Chronic Illness Therapy; FPR = Fibrosis progression rate; HDL-c = High-Density Lipoprotein cholesterol; HRQOL = Health-related quality of life; IV = Intravenous; LAL-D = Lysosomal Acid Lipase Deficiency; LDL-c = Low-Density Lipoprotein cholesterol; MC = Multicentre; METAVIR = Meta-analysis of histological data in viral hepatitis; OL = Open-Label; PC = Placebo-Controlled; PedsQL = Paediatric Quality of Life Inventory; R = Randomised; TG = Triglycerides; ULN = Upper Limit of Normal.

[a] The LAL-CL02 trial included a screening period of up to 6 weeks and randomisation was stratified by the following parameters: age at randomisation (< 12 years, ≥ 12 years); average screening ALT level (< 3 × ULN, ≥ 3 × ULN); and use of lipid-lowering medications (LLM) (yes, no).

[b] Pooled across LAL-CL02 and LAL-CL06 to inform transition/progression related to treatment with sebelipase alfa. Pooled LAL-CL02 trial data and natural history data (based on Bernstein et al. 2013; Burton et al. 2015) to inform transition/progression under BSC.

[c] Ishak and METAVIR systems classify liver fibrosis stages from no scarring to cirrhosis, with METAVIR (F0-F4) providing a simpler 5-stage scale compared to the more detailed 7-stage Ishak (0-6) scale. Both align with F0/Stage 0 representing no fibrosis. METAVIR's F1-F2 (portal tract fibrosis with minimal/rare septa) roughly corresponds to Ishak Stages 1-3, while F3 (marked bridging/numerous septa) matches Ishak Stages 4-5 (marked bridging/incomplete cirrhosis). Both define advanced cirrhosis as F4 or Ishak Stage 6 respectively.

[d] For patients aged > 8 months to <4 years, inclusion required clinical manifestations such as dyslipidaemia, elevated liver enzymes, impaired growth, or suspected malabsorption. For those ≥4 years or older, eligibility included evidence of advanced liver disease, histological disease recurrence, persistent dyslipidaemia, or malabsorption.

Comparative effectiveness

6.8 Table 4 summarises the primary and key secondary efficacy outcomes from the LAL-CL02 trial (week 20 results).

Table 4: Results of key primary and secondary endpoints in the LAL-CL02 trial

Outcome at Week 20	N	Sebelipase alfa	PBO	RD (95% CI)[g]	P-value
Primary efficacy endpoint					
ALT normalisation, n/N (%)	66	11/36 (31)	2/30 (7)	**24% (6.40, 41.38)**	**0.0271**
Secondary efficacy endpoints					
Percentage change from baseline in LDL-c, mean (SD)	66	-28.42 (22.30)	-6.25 (13.02)	**-22.174 (-31.40, -12.95)**	**<0.0001**
Percentage change from baseline in non-HDL-c, mean (SD)	66	-27.97 (18.61)	-6.94 (10.92)	**-21.04 (-28.75, -13.32)**	**<0.0001**
AST normalisation, n/N (%)	65[a]	15/36 (42)	1/29 (3)	**39% (20.80, 55.64)**	**0.0003**
Percentage change from baseline in TG, mean (SD)	66	-25.45 (29.41)	-11.14 (28.83)	**-14.30 (-28.70, 0.08)**	**0.0375**
Percentage change from baseline in HDL-c, mean (SD)	66	19.57 (16.83)	-0.29 (12.36)	**19.86 (12.47, 27.25)**	**<0.0001**
Percentage change from baseline in liver fat content, mean (SD)[b]	57[c]	-31.98 (26.76)	-4.21 (15.56)	**-27.77 (-39.84, -15.70)**	**<0.0001**
Improvement in liver histopathology, n/N (%)[d]	26[e]	10/16 (63)	4/10 (40)	23% (-16.03, 61.03)	0.4216
Percentage change from baseline in liver volume, mean (SD)	60[f]	-10.28 (10.51)	-2.66 (10.11)	**-7.62% (-13.00, -2.25)**	**0.0068**[h]

Source: Compiled during the evaluation based on Tables 2-13, p102; 2-14, p109; 2-15, p111; 2-16, p112; 2-17, p115; 2-18, p116; 2-19, p118; 2-21, p120; 2-23, p120 of the submission.

ALT = alanine aminotransaminase; AST = aspartate aminotransaminase; CI = confidence interval; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; MRI = Magnetic resonance imaging; PBO = Placebo; RD = risk difference; SD = standard deviation; TG = triglyceride.

Bold indicates statistically significant results.

For categorical outcomes, 95% confidence intervals for RD were estimated using Fisher's exact test (https://www.openepi.com/TwobyTwo/TwobyTwo.htm); for continuous outcomes, 95% CIs for RD were estimated using an unpaired t-test (*https://www.graphpad.com/quickcalcs/ttest1/?format=sd*).

Note: The primary and secondary endpoint results were presented in the prespecified fixed-sequence hypothesis-testing sequence for statistical significance. Fisher's exact test was used to analyse normalisation of ALT/AST levels and liver histologic endpoints, and the Wilcoxon rank-sum test was used for all other endpoints. The central laboratory defined normalisation of ALT/AST levels. The double-blind statistical analysis plan defined "normal" as < ULN and "abnormal" as > ULN but did not specify how a patient with an ALT at the ULN would be classified. For the purposes of the primary analysis, the submission defined "normal" as ≤ ULN and "abnormal" as > ULN.

[a] 1 patient in the placebo arm had a normal AST level at baseline.

[b] Hepatic fat content was measured by means of multi-echo gradient echo MRI.

[c] Data were missing for 4 patients in the sebelipase alfa arm and for 5 in the placebo arm. MRI was not performed in patients with medical implants or in children requiring sedation.

[d] Reduction in steatosis was defined as an absolute decrease of ≥5% points from baseline in the morphometric assessment of the hepatic fat content.

[e] Paired biopsy samples were required in patients ≥18 years unless contraindicated and were optional in patients <18 years of age. The LAL-CL02 trial included only 26 paired liver histopathology results (biopsies) for analysis, as liver biopsy is an invasive procedure and was not mandatory for all 66 participants. Many patients or guardians opted out, particularly in the paediatric population.

[f] Data were missing for 3 patients in the sebelipase alfa arm and for 3 in the placebo arm.

[g] RD>0 favours sebelipase alfa for ALT normalisation, AST normalisation, % change from baseline in HDL-c and improvement in liver histopathology. RD<0 favours sebelipase alfa for % change from baseline in LDL-c, non-HDL-c, TG, liver fat content, and liver volume.

[h] Nominal p value.

6.9 A statistically significantly greater proportion of patients in the sebelipase alfa arm than in the placebo arm in the LAL-CL02 trial achieved normalisation in ALT at Week 20 (31% vs 7%, p = 0.0271).

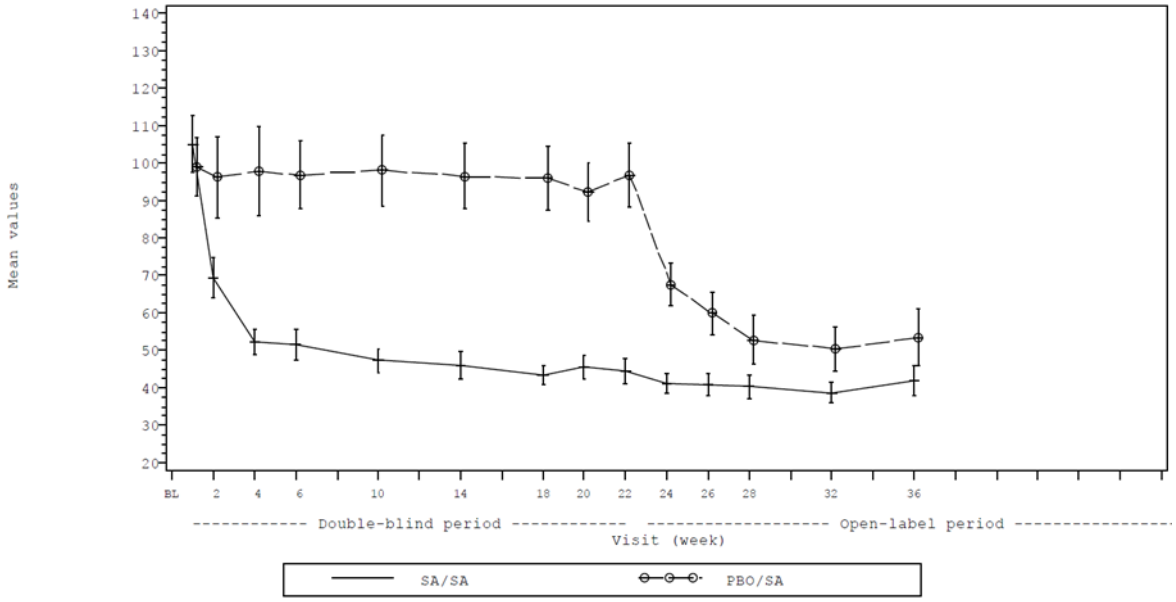
6.10 ALT normalisation was observed as early as Week 2 in the treatment arm of the LAL-CL02 trial, with a statistically significant difference in favour of treatment over placebo

from Week 6 onwards. The proportion of patients achieving ALT normalisation remained relatively consistent (29%) from Week 6 through to Week 20, whereas no more than 7% of placebo patients achieved ALT normalisation at any time point.

6.11 The reductions in mean ALT over time were significantly greater with sebelipase alfa vs placebo (p<0.0001), with lower values at every post-baseline timepoint. In the sebelipase alfa arm, mean ALT decreased from 105.1 U/L at baseline to the lowest mean ALT value of 43.4 U/L at Week 18 (-55%), and was 47.2 U/L at Week 20. In the placebo arm, mean ALT was 99.0 U/L at baseline, reaching a low of 92.4 U/L at Week 20 (-6%), with no further change.

6.12 During the open-label treatment period of the LAL-CL02 trial, a similar pattern of response was observed in patients switched from placebo to 1 mg/kg Q2W sebelipase alfa, with sustained normalisation of transaminases, further reduction in fat fraction in the liver, and further reductions in total cholesterol, LDL-c, and TGs, with increases in HDL-c (sebelipase alfa TGA AusPAR). Figure 2 presents mean (±SE) ALT values over time during the double-blind period (until week 20) and open-label period (weeks 22–36) in the LAL-CL02 trial.

Figure 2: Mean (±SE) ALT values over time by treatment arms in the LAL-CL02 trial



Source: Figure 2-12, p108 of the submission.
ALT = Alanine aminotransferase; BL = Baseline; ES = Extension set; PBO/SA: Placebo/sebelipase alfa; SA/SA = Sebelipase alfa/sebelipase alfa; SE = Standard error.

6.13 Health-related quality of life (HRQoL) assessments in the LAL-CL02 trial revealed no clear treatment effect for sebelipase alfa during either the double-blind or open-label periods. The evaluation considered that these findings are subject to methodological limitations, as the generic instruments used may not have been sufficiently sensitive to detect disease-specific changes. Furthermore, the evaluation noted that the trial was not powered for HRQoL as an exploratory endpoint.

6.14 Overall, the evaluation considered that the subgroup analyses based on the LAL-CL02 trial suggested that the treatment effect of sebelipase alfa was generally consistent

across most baseline characteristics, though small sample sizes limited the ability to reach definitive conclusions for many outcomes. A notably higher efficacy response in the sebelipase alfa arm, particularly for ALT and AST normalisation, was observed in patients already receiving background lipid-lowering medications, which were used by 42% of patients in the sebelipase alfa arm and 37% of patients in the placebo arm (39% overall). While patients with more severe baseline disease, characterised by higher ALT or LDL-c levels, showed lower rates of biochemical normalisation, they experienced significantly greater absolute reductions in liver enzymes and fat content compared to those with lower baseline values.

6.15 In the open-label LAL-CL06 study, both mean ALT and mean AST levels decreased by approximately 25% from baseline within 4 weeks of treatment initiation. These reductions were maintained through Week 144 (around 32% decline each). While a temporary increase in lipids occurred at Week 4, this was attributed to the mobilisation of accumulated substrates.

6.16 Evidence presented for survival and cardiovascular outcomes was indirect, and no treatment effect on survival or quality of life was demonstrated for late-onset LAL-D. The PSCR referred to natural history evidence showing high premature mortality in untreated patients, including deaths from liver and atherosclerotic disease, and contrasted this with treated cohorts from LAL-CL02, LAL-CL06, the International LAL-D Registry, and a French cohort study (Lacaille et. al. 2026)[6] where no deaths were observed among sebelipase alfa-treated patients compared with 4 deaths in untreated patients. However, the ESC noted that these findings were derived from heterogeneous natural history data and were not directly comparable with trial or registry populations, and did not establish a causal treatment effect.

6.17 The PBAC noted that the benefit of sebelipase alfa in late-onset LAD-D was modest compared to the benefit previously noted in infantile-onset LAL-D, where 79% of patients with treated with sebelipase alfa survived to 12 months and 68% of patients survived to 24 months, compared to none in the natural history study (paragraph 7.4, sebelipase alfa, PSD, March 2022 PBAC Meeting).

Comparative harms

6.18 Table 5 presents the results of the safety comparison for sebelipase alfa and placebo based on the pivotal LAL-CL02 trial.

[6] Lacaille, F., Marguet, S., Rascon Velasco, V. et al. Real-World Study of Management and Outcomes of Patients with Lysosomal Acid Lipase Deficiency (LAL-D) in France. Adv Ther 43, 2268–2282 (2026). https://doi.org/10.1007/s12325-026-03510-w

Table 5: Summary of TEAEs in the LAL-CL02 trial (FAS, double-blind period)

Patients with ≥1	Sebelipase alfa (N=36) n (%)	Placebo (N=30) n (%)	RD (95% CI)
TEAE	31 (86)	28 (93)	-0.07 (-0.22, 0.07)
Drug-related TEAE[a]	5 (14)	6 (20)	-0.06 (-0.24, 0.12)
Severe TEAE	3 (8)	1 (3)	0.05 (-0.06, 0.16)
IAR	2 (6)	4 (13)	-0.08 (-0.22, 0.07)
TEAE leading to withdrawal from double-blind period	1 (3)[b]	0	0.03 (-0.03, 0.08)
Serious TEAE	2 (6)	1 (3)	0.02 (-0.08, 0.12)
Drug-related serious TEAE[a]	1 (3)	0	0.03 (-0.03, 0.08)
TEAE leading to death	0	0	NA

Source: Table 2-27, p126 of the submission.

AE = Adverse event; CI = confidence interval; FAS = full analysis set; IAR = Infusion-associated reaction; N = Number of patients in specified treatment arm; n = Number of patients with at least one event in the category; % = Percentage based on N; RD = Risk Difference; TEAE = treatment-emergent adverse event.

Note: RD<0 favours sebelipase alfa over placebo.

[a] AEs the investigators considered to be related, possibly related or AEs with a missing relationship to the study drug.

A patient may have findings in more than one category.

[b] Although not indicated as leading to study drug withdrawal, the study drug was initially held but then not resumed for one patient due to an infusion-related reaction and associated symptomology; the patient was discontinued from the double-blind Period following their second infusion due to this event and could enter the open-label period upon rechallenge.

6.19 During the double-blind period in the LAL-CL02 trial, in the sebelipase alfa arm, common treatment-emergent adverse events (TEAEs) (>10% incidence) were headache (28%), pyrexia (19%), diarrhoea, oropharyngeal pain, and upper respiratory infection (17% each), and epistaxis and nasopharyngitis (11% each). Events with notably higher incidence (>5% difference) in sebelipase alfa vs placebo were headache (28% vs 20%) and oropharyngeal pain (17% vs 3%). Overall, 14% of patients in the sebelipase alfa arm and 20% of patients in the placebo arm experienced at least one drug-related TEAE.

6.20 In the open-label period of the LAL-CL02 trial, 97% of patients reported at least one TEAE, most of which were noted to be mild and unrelated to the study drug. Serious adverse events (SAEs) remained infrequent, occurring in 17% of patients; notably, only one treatment-related serious adverse event (SAE) was recorded across the entire study population. Zero deaths occurred, and while 2 patients discontinued treatment following infusion-associated reactions, no patients withdrew from the study due to adverse events.

6.21 In the LAL-CL02 trial, 5 out of 35 patients (14%) developed anti-drug antibodies (ADAs), with generally low and transient titres observed, with no neutralising antibodies detected. The TGA PI noted that "… there is no clear relationship between either development of ADAs/inhibitory antibody activity and associated hypersensitivity reactions or suboptimal clinical response." (p4 of the sebelipase alfa TGA PI).

6.22 The evaluation considered that due to the limitations inherent to the LAL-CL02 trial's extension period (open-label without a control arm), no definitive conclusions can be made regarding the long-term safety of sebelipase alfa.

Benefits/harms

6.23 A summary of the comparative benefits and harms for sebelipase alfa vs placebo (BSC) is presented in Table 6.

Table 6: Summary of comparative benefits and harms for sebelipase alfa and placebo (BSC)

	Sebelipase alfa n/N (%)	PBO n/N (%)	Event rate/100 patients		RD (95% CI)
			Sebelipase alfa	PBO	
Benefits					
ALT normalisation	11/36	2/30	31	7	24 (6.40, 41.40)
HARMS					
Adverse events	**Sebelipase alfa n/N (%)**	**PBO n/N (%)**	**Event rate/100 patients**		**RD (95% CI)**
			Sebelipase alfa	**PBO**	
TEAEs	31/36	28/30	86	93	-0.07 (-0.22, 0.07)
Severe TEAE	3/36	1/30	8	3	0.05 (-0.06, 0.16)
IAR	2/36	4/30	6	13	-0.08 (-0.22, 0.07)

Source: Table 2-13, p102 of the submission; Table 2-27, p126 of the submission.
ALT = Alanine Aminotransferase; BSC = Best supportive care; CI = Confidence Interval; IAR = Infusion-associated reaction; N = Number of patients in specified treatment arm; n = Number of patients with at least one event in the category; PBO = Placebo; RD = Risk Difference; TEAEs = Treatment-Emergent Adverse Events.
Note: Maximum follow-up duration (blind period): 20 Weeks.

6.24 On the basis of direct comparative evidence presented by the submission, for every 100 patients treated with sebelipase alfa in comparison with placebo over a treatment duration of 20 weeks:

- Approximately 24 more patients would achieve normalisation of ALT.
- There would be no significant differences in overall TEAEs, severe AEs or infusion-associated reactions.

Clinical claim

6.25 The submission described sebelipase alfa as superior in terms of efficacy compared with BSC.

6.26 The evaluation and the ESC considered that the claim of superior effectiveness was reasonably supported by the evidence presented in the submission, and it was likely that patients with late-onset LAL-D treated with sebelipase alfa would derive an improvement in liver biomarkers (including ALT, AST, cholesterol, liver fat and liver volume) compared to BSC alone. The evaluation and the ESC considered that the comparative efficacy results should be interpreted in the context of the following limitations:

- The 20-week comparative trial duration in the LAL-CL02 trial and the small sample size (N=66) were likely inadequate for a chronic, progressive disease like LAL-D. Short-term relevance was limited to biochemical response, and no data was available for durability, fibrosis regression, cardiovascular event reduction, long-term safety or survival. The PSCR noted the broader evidence base also included the international

LAL-D registry and a French cohort study, which had 4.65 years and >6 years median follow-up, respectively.

- The primary endpoint in the LAL-CL02 trial, i.e., ALT normalisation, was a biomarker rather than a clinical endpoint. "Normal" ALT does not necessarily exclude the presence or progression of liver disease.
- The LAL-CL02 trial included stratification based on age, ALT level, and lipid lowering medications. However, the small trial sample limited constrained statistical power and subgroup analysis.
- Functional assessment of chronic illness therapy (FACIT-Fatigue), chronic liver disease questionnaire (CLDQ), and PedsQL showed no obvious treatment effect, and there was no obvious treatment effect overall in fatigue or HRQoL.

6.27 The submission described sebelipase alfa as non-inferior in terms of safety compared with placebo. The evaluation and the ESC considered that this claim was plausible, but uncertain.

6.28 The PBAC considered that the claim of superior comparative effectiveness was likely reasonable for the population of patients represented by the LAL-CL02 trial, as supported by evidence of improvement in lipid and liver biomarkers compared to BSC alone.

6.29 The PBAC considered that the claim of non-inferior comparative safety was likely reasonable.

Economic analysis

6.30 The submission presented a cost-utility analysis comparing sebelipase alfa plus BSC with BSC alone in patients with LAL-D. The economic evaluation used a cohort Markov state-transition model over a 100-year horizon, with nine health states, defined by fibrosis stage (F0-F4), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT) and death. The model applied annual cycles and accrued costs and outcomes using half-cycle corrected Markov traces. The evaluation considered that the general modelling approach was reasonable for a chronic progressive condition, although the available clinical evidence was limited to relatively short-term trial follow-up, so the model relied heavily on extrapolation beyond the observed trial period.

6.31 The ESC considered that the model presented had important structural limitations. It is essentially a simplified hepatic disease progression model whereas LAL-D is a multisystem disorder. As such, the model did not capture important non-hepatic manifestations, for example cardiovascular morbidity and mortality. The ESC considered that the considerable cardiovascular disease in sebelipase alfa treated patients in the French cohort study demonstrated that it may not be reasonable to focus only on hepatic components of the disease. The Pre-PBAC response acknowledged that cardiovascular disease is an important contributor to morbidity and mortality; however considered that the available data are not sufficiently robust

to quantify cardiovascular event rates, mortality benefits or utility impacts for economic modelling.

6.32 Table 7 presents a summary of the model structure and rationale.

Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Type of analysis	Cost-utility analysis
Outcomes	Cost per QALY gained; Cost per LYs gained
Time horizon	Lifetime (100-year time horizon)
Methods used to generate results	Markov state transition model
Health states	9 health states: METAVIR Fibrosis stages F0, F1, F2, F3 and F4; DCC; HCC; LT and Death.
Cycle length	Annual cycle length
Transition probabilities	Derived from multiple sources to model disease progression. Untreated patients: constant fibrosis progression rate of 0.19 stages/year (17.1% annual probability of progression). Advanced liver outcomes informed by Mahady et al. (2012), Zhang et al. (2015) and Younossi et al. (2016). Sebelipase alfa-treated patients: derived from paired-biopsy data from LAL-CL02 and LAL-CL06, converted from Ishak to METAVIR scores, assuming fibrosis regression of 43.0% in Year 1 (based on pooled paired-biopsy data from 12 patients in LAL-CL02 and 24 patients in LAL-CL06), 19.5% in Year 2 (based on 11 patients in LAL-CL06) and conservatively assumes no further regression beyond Year 2. Background mortality: based on age-specific ABS Life Tables, averaged for males and females.
Utility weights	Population-based utilities from McCaffrey et al. (2016) using EQ-5D-5L data. Age- and sex-adjusted baseline utilities applied multiplicatively with disease-specific decrements; supplemented with literature for health-state-specific utilities.
Software package	Microsoft® Excel 365

Source: Table 3-1, p149 of the submission.

ABS = Australian Bureau of Statistics: DCC = Decompensated Cirrhosis; EQ-5D-5L = EuroQol-5 Dimension-5 Level; HCC = Hepatocellular Carcinoma; ICER = Incremental Cost Effectiveness Ratio; LAL-D = Lysosomal acid lipase deficiency; LT = liver transplant; LYs = life years; METAVIR = Meta-analysis of histological data in viral hepatitis; QALYs = Quality-adjusted life years.

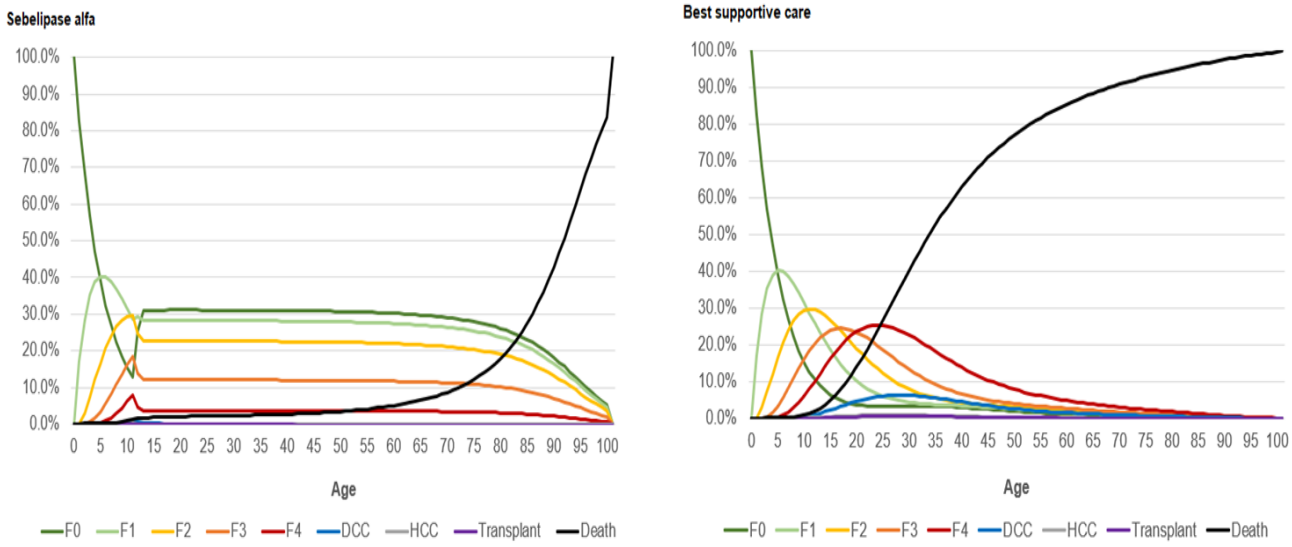
6.33 The evaluation considered that the main uncertainty in the economic model was that the magnitude of benefit depended heavily on structural assumptions and long-term extrapolation. In particular, the untreated disease/fibrosis progression rate was derived indirectly from biopsy stage and age, the treatment effect was based on short-term biopsy data and translated into fibrosis regression in Years 1-2, and the benefit was assumed to continue over the lifetime horizon. Therefore, the large projected gains in life years and quality adjusted life years (QALYs) were not directly observed in the clinical studies but were generated by the model structure. The Pre-PBAC response acknowledged that the model extrapolated observed fibrosis regression beyond the trial period to estimate long-term outcome, which it suggested was unavoidable given the ultra-rare nature of the disease and the infeasibility of generating long-term comparative data for survival, liver transplantation or end-stage liver disease. However, this uncertainty was not fully characterised (e.g. limited model diagnostics or external validation of results, see paragraph 6.44).

6.34 The economic model generated the baseline fibrosis distribution by assuming patients were in F0 (i.e., no fibrosis) at birth and then applied a constant untreated fibrosis progression rate of 0.19 stages/year up to the model baseline age of 11 years, from which point treatment effects, costs and health outcomes were modelled. This was a strong structural assumption, which the ESC considered was unlikely to have reflected

the heterogeneity of the proposed PBS population, including variation in age at diagnosis, fibrosis severity, and liver involvement at treatment initiation.[7]The resulting Markov traces (Figure 3) illustrate how the model translated early fibrosis regression/stabilisation in the sebelipase alfa arm into delayed progression to advanced liver disease and projected survival differences over the lifetime horizon. The ESC considered that the application of a constant rate of fibrosis progression to the BSC arm, whilst pragmatic and transparent, is likely a key driver of modelled results. The ESC considered that model entry in the F0 health state from birth and a return to the F0 state following liver transplantation were highly uncertain.

6.35 The ESC noted that, based on the Markov traces, at an age of 75 years, approximately 88% of patients in the sebelipase alfa arm remained alive compared with approximately 7% in the BSC arm. The ESC considered these estimates to be uncertain and optimistic.

Figure 3: Modelled Markov traces for sebelipase alfa and BSC



Source: Figures 3-5 and 3-6, pp173-174 of the submission.
BSC = best supportive care; F0-F4 = METAVIR fibrosis stages; DCC = Decompensated cirrhosis; HCC = Hepatocellular carcinoma.
Note: Years 0 to 11 were used to generate the modelled baseline fibrosis distribution; treatment effects and economic outcomes were applied from age 11 onwards.

6.36 Table 8 presents the key drivers of the model.

[7] Wilson DP, Patni N. Lysosomal Acid Lipase Deficiency. [Updated 2023 Mar 15]. In: Feingold KR, Adler RA, Ahmed SF, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395569/
Burton BK, Deegan PB, Enns GM, et al. Clinical Features of Lysosomal Acid Lipase Deficiency. J Pediatr Gastroenterol Nutr. 2015;61(6):619-625. doi:10.1097/MPG.0000000000000935

Table 8: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/ QALY gained
Untreated fibrosis progression rate	Base case used a pooled FPR = 0.19 stages/year derived from LAL-CL02, Bernstein et al. (2013) and Burton et al. (2015). Alternative source-specific FPRs were tested: Bernstein et al., LAL-CL02, and Burton et al.	High. - Using Bernstein et al. alone increased the ICER by [redacted]% to $[redacted][1]/ QALY gained. - Using LAL-CL02 alone decreased the ICER by [redacted]% to $[redacted][1]/ QALY gained. - Using Burton et al. alone decreased the ICER by [redacted]% to $[redacted][1]/ QALY gained.
Vial use assumption	The submission base case assumed vial optimisation/sharing between patients for sebelipase alfa. During the evaluation, this assumption was removed so that drug costs were based on single-use vials, with unused product discarded, consistent with the sebelipase alfa PI.	High, favours sebelipase alfa. Removing vial optimisation/sharing increased the ICER by [redacted]% to $[redacted][1]/ QALY gained.
Dose escalation assumption	Base case assumed all patients initiated sebelipase alfa at 1 mg/kg Q2W, with 20.62% escalating to 3 mg/kg Q2W from Year 2 onwards. Additional scenarios were tested: no dose escalation, where all patients remained at 1 mg/kg Q2W; 40% escalation to 3 mg/kg Q2W; and 60% escalation to 3 mg/kg Q2W.	High. Assuming no dose escalation decreased the ICER by [redacted]% to $[redacted][1]/QALY gained. Assuming 40% and 60% escalation to 3 mg/kg Q2W increased the ICER by [redacted]% to $[redacted][1]/QALY gained and by [redacted]% to $[redacted][1]/QALY gained, respectively.

Source: Table 3-24, p178, and economic evaluation workbook of the submission.
BSC= best supportive care; FPR = fibrosis progression rate; ICER = incremental cost-effectiveness ratio; kg = kilograms; mg = milligrams; PI = Product Information; Q2W = every 2 weeks; QALY = quality-adjusted life year.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*

6.37 The model was sensitive to the assumed untreated fibrosis progression rate, vial use assumption (i.e., vial sharing between patients) and dose escalation assumption. The evaluation considered that this reflected the importance of both the comparator progression assumptions and the cost of lifelong sebelipase alfa treatment in the model. The ESC noted that from Year 3 onwards, the model structure appeared to hold sebelipase alfa treated patients within fibrosis states rather than allowing continued fibrosis progression. The ESC considered this was likely to be a major driver of the large projected long-term survival benefit. As such, the ESC considered that model's long-term outcomes were driven less by observed clinical data and more by the structural way in which treatment benefit was carried forward over the lifetime horizon.

6.38 The evaluation considered that a key issue was the assumption of vial use/optimisation. In the economic model, the submission stated that vial optimisation meant that a vial could be 'virtually shared', so the cost was based only on the amount of drug used by the patient and any unused remainder was effectively allocated to another patient. This did not appear consistent with the sebelipase alfa's PI, which states that the product is supplied as a single-use vial and that any unused portion must be discarded because it contains no preservatives. It was also inconsistent with the PBAC guidelines (p81), which state that wastage should be incorporated in the model because it is a consumption and therefore an incurred cost. As a result, the evaluation considered that the vial optimisation assumption underestimated drug

acquisition costs. Removing vial optimisation increased the ICER by [redacted]% to > $1,055,000/QALY gained.

6.39 The ESC noted that utilities were derived indirectly, using Australian age- and sex-specific population norms from McCaffrey et al. (2016), with health-state-specific utility decrements for fibrosis and advanced liver disease applied from the literature. In the absence of late-onset LAL-D-specific utility data, the submission used proxy decrement values from Crossan et al. (2015) in the base case. The ESC considered that with the assumption that patients in F0-F1 had general population utility values, this meant that any symptoms (e.g. CVD related events) present before progression to F2-F3 were not captured, and therefore lacked face validity. The ESC noted alternative utility values were not tested in sensitivity analyses.

6.40 Table 9 presents the results of the economic evaluation. A trial-based or stepped economic evaluation was not presented in the submission.

Table 9: Results of the economic evaluation, as presented in the submission (effective price)

Component	Sebelipase alfa	BSC	Increment
Costs	$[redacted]	$120,404	$[redacted]
Outcomes			
QALYs (discounted)	17.85	11.47	6.38
QALYs (undiscounted)	66.51	23.17	43.34
LYs (undiscounted)	77.10	28.21	48.89
Incremental cost per QALY gained (discounted)			$[redacted][1]
Incremental cost/LY gained (undiscounted)			$[redacted][1]

Source: Table 3-19, p176 of the submission.
BSC = best supportive care; LYs = life years; QALYs = quality adjusted life years.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*

6.41 The base-case results suggested very large, modelled survival and QALY gains, and a very high incremental cost. Sebelipase alfa was associated with an incremental gain of 49 undiscounted LYs compared with BSC. The evaluation and the ESC noted that the magnitude of the LY gain reflected the modelled delay in progression to advanced liver disease and death over the lifetime horizon, rather than the real world long-term comparative survival data. Incremental cost was driven primarily by drug acquisition cost. The ESC noted that there were cost offsets associated with reduced time spent in advanced liver disease states, particularly DCC, HCC and LT.

6.42 The results of key sensitivity analyses are summarised in Table 10.

Table 10: Results of the sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Base case	$[redacted]	6.38	$[redacted][1]	-
Discount rate (base case 5% costs and outcomes)				
0% costs and outcomes	$[redacted]	43.34	$[redacted][1]	[redacted]%
3.5% costs and outcomes	$[redacted]	10.22	$[redacted][1]	[redacted]%
FPR (base case: average of all 3 sources)				
FPR = LAL-CL02	$[redacted]	6.74	$[redacted][1]	[redacted]%
FPR = Bernstein et al.	$[redacted]	4.42	$[redacted][1]	[redacted]%
FPR = Burton et al.	$[redacted]	7.41	$[redacted][1]	[redacted]%
Uncertainty analysis conducted during the evaluation				
Dose escalation (base case 20.62% escalate to 3 mg/kg Q2W from Year 2 onwards)				
No dose escalation: 100% remain on 1 mg/kg Q2W	$[redacted]	6.38	$[redacted][1]	[redacted]%
40% escalate to 3 mg/kg Q2W	$[redacted]	6.38	$[redacted][1]	[redacted]%
60% escalate to 3 mg/kg Q2W	$[redacted]	6.38	$[redacted][1]	[redacted]%
Background mortality correction [a]	$[redacted]	6.21	$[redacted][1]	[redacted]%
Half-cycle correction [b]	$[redacted]	6.38	$[redacted][1]	
Compliance rate correction [c]	$[redacted]	6.38	$[redacted][1]	[redacted]%
All 3 errors corrected (i.e., mortality + half cycle + compliance rate) [d]	$[redacted]	6.21	$[redacted][1]	[redacted]%
Vial optimisation (base case: vial optimisation applied) [e]				
Vial optimisation not applied	$[redacted]	6.38	$[redacted][1]	[redacted]%
All 3 errors corrected [d] + vial optimisation not applied [e]	$[redacted]	6.21	$[redacted][1]	[redacted]%

Source: Table 3-24, p178, and economic evaluation workbook of the submission.

BSC = best supportive care; FPR = fibrosis progression rate; ICER = incremental cost-effectiveness ratio; kg = kilogram; mg = milligram; PI = Product Information; Q2W = every 2 weeks; QALY = quality-adjusted life year; TTO= time trade off; VAS = visual analogue scale.

[a] In the economic evaluation workbook, the model initially combined male and female background mortality incorrectly. Rather than applying a weighted sum using the proportion of males and females in the cohort, the formula took an average of the weighted values. This understated the combined background mortality rate and therefore reduced general population mortality in the model. During the evaluation workbook review, this formula was corrected on the Background Mort. Data worksheet (cells N11 to N111), so that male and female mortality were combined using a weighted sum.

[b] A minor formula inconsistency was identified in the Costs worksheet for BSC F0 non-drug costs (cells P16:P116), where half-cycle correction was not applied consistently with the other health states. This was corrected during the evaluation workbook review.

[c] The economic model workbook applied a 96% compliance rate (cell V65, 'Inputs' worksheet) for sebelipase alfa. This was inconsistent with the accompanying assumption of 2 missed doses per year, which would imply compliance of approximately 92.3% (24/26 doses). The compliance input was therefore corrected in the evaluation for consistency with the modelled dosing schedule.

[d] The evaluation results incorporated correction of the three workbook implementation issues identified during review: (i) background mortality was corrected so that male and female mortality were combined using a weighted sum rather than an average of weighted values; (ii) half-cycle correction was applied consistently to the BSC F0 non-drug cost formulas in the Costs worksheet; and (iii) the compliance rate for sebelipase alfa was reduced from 96% to approximately 92.3%, consistent with the assumption of 2 missed doses per year.

[e] The evaluation results were generated without vial optimisation assumption. Drug costs were therefore calculated on the basis of whole single-use vials, with any unused portion assumed to be discarded, consistent with the sebelipase alfa PI.

The redacted values correspond to the following ranges:

[1] > $1,055,000

6.43 Use of alternative fibrosis progression rate (FPR) sources and discount rates materially influenced the ICER. However, the evaluation considered that the submission's sensitivity analysis did not explore all important sources of uncertainty, including vial optimisation, alternative dose-escalation assumptions (which were tested during the evaluation), alternative sources for the utility values, time horizon, underlying mortality and discontinuation assumptions. In addition, errors relating to background

mortality, half-cycle correction in BSC F0 non-drug costs, and compliance rate, were corrected in the evaluation's sensitivity analyses.

6.44 The ESC noted that the base case ICER (> $1,055,000 per QALY gained) was very high and highly uncertain. It was further noted that the gains in life years and QALYs appeared implausibly large. Overall, the ESC considered that the model was of limited use for decision making, noting key concerns including:

- the model was a simplified hepatic disease progression model and did not adequately represent LAL-D as a multisystem disease (paragraph 6.31);
- the limited data supporting the natural disease course (paragraph 6.16);
- limited model diagnostics were presented, for example health state occupation diagnostics;
- no external validation of the model results;
- time horizon, reduced underlying mortality rates and discontinuation assumptions were not able to be tested in sensitivity analyses but were likely to be key drivers; and mortality estimates and utility values lacked face validity.

Drug cost/patient/year

6.45 Treatment with sebelipase alfa was expected to be long term. The submission's economic evaluation estimated annual drug cost varied from $[redacted] at age 11 years to $[redacted] at ages 55+ years (drug cost only). By contrast, the financial estimates used a fixed mean body weight of 49.13 kg, equating to an annual drug cost of approximately $[redacted] in Year 1 and $[redacted] from Year 2 onwards. The estimates in economic and financial analyses were not directly comparable because drug costs were calculated differently. The economic model followed a single hypothetical cohort over time and applied dosing to an age-specific weight trajectory as patients aged; the base case also, inappropriately, assumed vial optimisation. The financial model estimated the budget impact used a fixed mean body weight based on LAL-CL02 trial patients. The financial model also did not apply vial optimisation; instead, it converted fixed mean body weight into fixed whole-vial counts per dose (3 vials at 1 mg/kg Q2W and 8 vials at 3 mg/kg Q2W) and then estimated cost over the first 6 years of listing using the weighted dispensed cost per script.

6.46 Table 11 presents the drug cost per patient per year for sebelipase alfa.

Table 11: Drug cost per patient for sebelipase alfa

	Trial dose and duration	Model	Financial estimates
Mean dose	1 mg/kg Q2W; escalation to 3 mg/kg Q2W possible	Year 1: 1 mg/kg Q2W; Year 2+: 79.38% at 1 mg/kg Q2W, 20.62% at 3 mg/kg Q2W	Same dose structure as model
Duration	LAL-CL02: 20 weeks double blind, with open-label follow-up of approximately 5 years. LAL-CL06: follow-up up to 144 weeks	Lifetime (100-year horizon)	6 years
Body weight basis	Trial patients	Age-specific weight trajectory: 42.41 kg (age 11), 45.77 kg (12), 48.89 kg (13), 61.27 kg (18), 67.56 kg (20-24), 72.81 kg (25-34), 71.70 kg (35-44), 67.19 kg (45-54), 66.51 kg (55+)	Fixed mean weight 49.13 kg (based on baseline LAL-CL02 patients (mean age approx. 17 years; median ~13 years; range approx. 5-59 years)
Total vials/patient/year	NR	Not separately reported; varied by age and dose	Year 1: 78 vials/year Year 2+: weighted average 104.81 vials/year [a]
Cost per vial	NR	$[redacted] per 20 mg vial	
Drug cost/patient/year	NR	Age-dependent annual drug cost: $[redacted] (age 11); $[redacted] (12); $[redacted] (13); $689,372 (18); $[redacted] (20-24); $[redacted] (25-34); $[redacted] (35-44); $[redacted] (45-54); $[redacted] (55+)	Year 1: $[redacted] Year 2+: $[redacted]

Source: Compiled during the evaluation based on the clinical section and information gleaned from economic and financial workbooks of the submission; Tables 14.1.2.1.3 and 14.1.3.1.3, pp3,6, LAL-CL02 CSR Tables and Figures.
IV = intravenous; kg = kilograms; mg = milligram; NR = not reported; Q2W = every 2 weeks.
[a] In the financial estimates, Year 1 assumed 1 mg/kg Q2W for all patients at a fixed mean weight of 49.13 kg, equivalent to 3 vials per dose and 78 vials/year (3 x 26). From Year 2 onwards, the model applied a dose split of 79.38% at 1 mg/kg Q2W and 20.62% at 3 mg/kg Q2W, resulting in a weighted average of 104.81 vials/year (78 × 79.38% + 208 × 20.62%). Source: '3c. Impact - proposed (eff)' worksheet of the submission's Section 4 financial workbook.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC.

6.48 The submission used an epidemiological approach together with data from the compassionate access program to estimate the financial impact of listing sebelipase alfa. Table 12 presents the key inputs and data sources used in these estimates.

Table 12: Key inputs for financial estimates, epidemiological approach

Parameter	Value	Source	Comment
Population: late-onset LAL-D			
Prevalent	4.71 per million late-onset LAL-D birth prevalence applied to ABS population counts	Midpoint of del Angel et al. (2019); ABS population data	Uncertain as a European descent genetic prevalence estimate was applied to the Australian population as a proxy for prevalent late-onset LAL-D cases. Alternative values from the same source (3.45 and 5.97 per million) changed the 6-year PBS/RPBS cost by -25% to +26%.
Diagnosed rate	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Submission estimate	Uncertain. The submission noted that late-onset LAL-D is under-recognised, with diagnostic delays, particularly in adults, due to disease rarity, low awareness and variable clinical presentation. The diagnosed rate was informed by published evidence reporting on under-diagnosis and diagnostic delay and by Australian early access experience, rather than based on observed Australian diagnostic data. This was one of the main drivers of treated patient numbers and budget impact; a [redacted]% (Yr 1) to [redacted]% (Years 5 & 6) scenario increased the 6-year budget impact by 23%.
% Treatment Uptake Rate	Years 1 to 6: [redacted]% every year	Submission assumption	Likely optimistic, as it assumed [redacted].
Sebelipase alfa [a]			
% Compliance	96%	LAL-CL02 trial + assumption of 2 missed doses annually	The submission applied a 96% compliance rate but also stated that 2 doses would be missed each year. Under a Q2W schedule (26 doses/year), 2 missed doses would imply compliance of approximately 92.3%, not 96%. The submission assumption slightly overstated script volumes and budget impact.
Discontinuation rate	Years 1 to 6: 0% every year	Submission assumption	Likely optimistic, although plausible given severe disease and lack of alternatives. It increased cumulative budget impact.
Dosage Regimen & Relative Dose Intensity	Year 1: 1 mg/kg Q2W (100% of patients) Year 2+: 79.38% at 1 mg/kg Q2W, 20.62% at 3 mg/kg Q2W	PI and international LAL-D registry	Within the approved label, but uncertain. The base case assumed all patients initiated at 1 mg/kg Q2W, with 20.62% escalating to 3 mg/kg Q2W from Year 2 onwards. This represented the approved dosing regimen and available registry dosing data, but the one-time dose-adjustment rule (from year 2 onwards) may not fully reflect longer-term dose changes.
Mean body weight	49.13 kg	Mean weight in LAL-CL02 trial	This was a simplifying assumption. The financial model costed treatment-naïve patients using a fixed mean body weight of 49.13 kg from LAL-CL02, whereas the proposed PBS population included both children and adults and the expected treated age mix was uncertain. For a mg/kg therapy, a body weight estimate based on the expected treated population would have been preferable. Increasing mean body weight to 68.92 kg (49.13 kg plus 1 SD from LAL-CL02) increased the 6-year PBS/RPBS cost by 22%.
MBS Impacts	MBS item 14245; one administration per dose	PI, existing use in infantile LAL-D	One administration per dose was consistent with the IV treatment schedule. However, the financial model workbook applied 26 services per patient annually and excluded grandfathered patients from the MBS IV cost calculation. This did not reflect the submission's assumption of 2 missed doses annually and therefore underestimated the MBS impact. Corrected MBS costs slightly increased the net health budget impact in the sensitivity analysis.

Source: Tables 4-1, 4-3, 4-4,4-7,4-9, pp184,188,189,191,192 of the submission; Section 4 financial workbook of the submission. Italicised text was added during the evaluation.

ABS = Australian Bureau of Statistics; BSC = best supportive care; IV = intravenous; LAL-D = lysosomal acid lipase deficiency; MBS = Medicare Benefits Schedule; PI = Product Information; Q2W = every 2 weeks; SD = standard deviation; Yr = year.
[a] BSC was not shown separately in this table because no specific displaced PBS-listed medicine was modelled, and supportive care costs were assumed to remain unchanged in the financial analysis. This was a conservative approach but was reasonable in the current context.

6.49 Table 13 summarises the estimated use and financial implications.

Table 13: Estimated use and financial implications of sebelipase alfa (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Prevalent number of patients with late-onset LAL-D	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients treated [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][4]	[redacted][4]
Estimated financial implications of sebelipase alfa						
Net cost to PBS/RPBS less copayments	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to health budget	**$**[redacted][2]	**$**[redacted][2]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]

Source: Tables 4-3, 4-8, 4-14 and 4-16, pp188, 191, 195, 197-198 of the submission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
[a] Includes < 500 grandfathered patients per year.
[b] Total PBS scripts were estimated in the submission by multiplying the number of treated patients in each year (including initiating, continuing and grandfathered patients) by the assumed 26 infusions per patient per year and the 96% compliance rate. This gave an average of 24.96 scripts per patient per year (26 × 0.96), which was equivalent to approximately < 500 scripts in Year 1 and 500 to < 5,000 scripts in Year 6. The accompanying assumption of 2 missed doses annually would imply a compliance rate of 92.31% (24/26) rather than 96%. The results with 92.31% compliance rate have been presented in the sensitivity analysis (Table 14).
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *$0 to < $10 million*
[3] *$10 million to < $20 million*
[4] *500 to < 5,000*

6.50 The total cost to the PBS/RPBS of listing sebelipase alfa was estimated to be $0 to < $10 million in Year 1, increasing to $10 million to < $20 million in Year 6, and a total of $60 million to < $70 million in the first 6 years of listing.

6.51 The submission included < 500 grandfathered patients who were stated to be receiving sebelipase alfa through an existing compassionate access program, of whom < 500 had previously participated in the LAL-CL02 (n=< 500) and LAL-CL06 (n=< 500) trials. These patients were assumed to meet the proposed PBS eligibility criteria and, because the financial model used a prevalence-based approach, were stated to have been removed from the prevalent population and then added back separately to avoid double counting. Grandfathered patients were costed using their current prescribed dosing and were treated as continuing patients.

6.52 The evaluation and the ESC considered that estimated treated patient numbers were uncertain:

- The base case applied a prevalence 4.71 per million from del Angel et al. (2019) to the Australian population as a proxy for prevalent late-onset LAL-D cases. This was pragmatic but uncertain because it applied a genetic/birth prevalence estimate from a European-descent population to the Australian population and did not specifically account for age-specific survival, or diagnosis.

- The diagnosis rate was based on a submission estimate informed by published evidence of under-diagnosis and diagnostic delay and by Australian early access experience, rather than observed Australian diagnostic data. The PSCR maintained that in the absence of Australian diagnostic data, the submission estimate was a reasonable basis for estimation, and noted that the absolute number of treated patients was expected to remain small under plausible scenarios. However, the evaluation considered it is unclear how many additional patients would seek treatment if sebelipase alfa were funded for late-onset LAL-D. It is possible that, on average, additional diagnosed patients would be older and therefore heavier than patients already diagnosed due to the more severe disease trajectory for patients diagnosed at younger ages.

6.53 Body weight was also a major driver because sebelipase alfa is dosed on a mg/kg basis. The financial model used a fixed mean body weight (49.13 kg) based on the mean weight of LAL-CL02 trial patients, which the submission considered to be representative of the treatment naïve late-onset LAL-D population. This method was inconsistent with the economic model (see paragraph 6.45) and was a simplifying assumption for a proposed PBS population that included both children and adults. Its direction of bias was uncertain, although it may be underestimated if the treated population includes a higher proportion of adults.

6.54 Sensitivity analyses performed on the financial estimates are presented in Table 14 below. The sensitivity analysis showed that the estimated budget impact was driven mainly by the prevalence rate (from 4.71 to 5.97 per million), diagnosed rate (from [redacted]% to [redacted]%), and body-weight assumptions (from 49.13 kg to 68.92 kg).

Table 14: Sensitivity analyses on the net financial impact to the PBS/RPBS (effective price)

Net cost to PBS/ RPBS	2027	2028	2029	2030	2031	2032	Total over 6 years	% change from base case
Base case	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][4]	-
Prevalence rate (base case: 4.71 per million)								
3.45 per million	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]	-[redacted]%
5.97 per million	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][5]	[redacted]%
Body weight (base case: 49.13 kg)								
29.34 kg (- 1 SD)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	[redacted][1]	$[redacted][1]	$[redacted][3]	-[redacted]%
68.92 kg (+ 1 SD)	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][5]	[redacted]%
Diagnosed rate (base case: [redacted]%-[redacted]%)								
[redacted]%-[redacted]%	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][6]	-[redacted]%
[redacted]%-[redacted]%	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][5]	[redacted]%
Uptake rate (base case: [redacted]%)								
[redacted]%	$[redacted]	$[redacted][1]	$[redacted][1]	$[redacted]	$[redacted][2]	$[redacted][2]	$[redacted][6]	-[redacted]%
Compliance rate (base case: 96%)								
92.31%[a]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][4]	-[redacted]%

Source: Table 4-17, p199 and Section 4 financial workbook of the submission.
Kg = kilograms; PBS = Pharmaceutical Benefits Scheme; Q2W = every 2 weeks; RPBS = Repatriation Pharmaceutical Benefits Scheme; SD = standard deviation.
[a] The Section 4 workbook applied a 96% compliance rate to sebelipase alfa scripts (worksheet 3a. Scripts – proposed, cells J117:J124). This was inconsistent with the submission's assumption of 2 missed Q2W doses per year, which implies compliance of approximately 92.31% (24/26 doses). The compliance input was therefore corrected in the evaluation for consistency with the modelled dosing schedule.
The redacted values correspond to the following ranges:
[1] *$0 to < $10 million*
[2] *$10 million to < $20 million*
[3] *$40 million to < $50 million*
[4] *$60 million to < $70 million*
[5] *$70 million to < $80 million*
[6] *$50 million to < $60 million*

Quality Use of Medicines

6.55 The submission stated that quality use of medicines would be supported through TGA-approved prescribing information, consumer medicines information, specialist prescribing and administration arrangements, and ongoing post-marketing surveillance through the international LAL-D Registry.

Financial Management – Risk Sharing Arrangements

6.56 The submission proposed a risk-sharing arrangement, with Commonwealth Payment Thresholds based on the agreed financial estimates. This was intended to provide the Government with greater certainty over expenditure on sebelipase alfa.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the PBS listing of sebelipase alfa for the treatment of children and adults with late-onset lysosomal acid lipase deficiency (LAL-D). The PBAC noted there was a clinical need for disease modifying treatments for this ultra rare disease. The PBAC noted that late-onset disease represents a more heterogeneous phenotype than infantile-onset LAL-D, including substantial variability in age of onset, disease severity and progression. The PBAC considered that although sebelipase alfa treatment improves biomarkers (including liver enzymes and cholesterol), the magnitude of clinical benefit, cost-effectiveness and financial impact remain highly uncertain because it will vary substantially depending on which patients with late-onset LAL-D are treated.

7.2 The PBAC considered the primary reason for this outcome was due to uncertain place in therapy.

7.3 The PBAC acknowledged the input from consumers and healthcare professionals describing the severe impact of late-onset LAL-D, and the lack of available disease-modifying treatments. The PBAC considered that there was clinical need for additional treatments for this ultra-rare disease.

7.4 The PBAC noted that the disease trajectory for late-onset LAL-D varies considerably, with some patients exhibiting rapidly progressive disease during early childhood, whereas others display an attenuated phenotype (see paragraph 4.2). The PBAC considered that the low diagnosis rate of late-onset LAL-D, at least in part, reflects the variable phenotype, and noted that the extent of benefit from treatment will likely be less in patients with a mild phenotype. As such, given the high proposed price for sebelipase alfa, the PBAC considered that it was unclear if this treatment should be available for all patients or if it should be restricted to those with a more severe phenotype.

7.5 In terms of the proposed restriction, the PBAC considered it appropriate to limit treatment to patients with confirmed late-onset LAL-D and noted that the submission sought to further limit eligibility to patients demonstrating one or more disease manifestations (see paragraph 3.6). However, the PBAC considered that it was unclear which patients with late-onset LAL-D would be eligible for treatment under the proposed restriction and whether the proposed restriction adequately defined the population expected to derive substantial clinical benefit. In particular, patients would only need to meet one of the listed disease manifestation criterion, which was less restrictive than the inclusion criteria for the key LAL-CL02 trial, which required evidence of persistent elevated transaminases.

7.6 The PBAC considered that the proposed comparator of placebo plus best supportive care (BSC, defined as nutritional support, lifestyle modifications, and/or lipid-lowering medications) was appropriate.

7.7 The PBAC noted that the submission was based on one randomised double-blind trial, LAL-CL02 (N=66), comparing sebelipase alfa plus BSC to placebo plus BSC over a 20-week period (paragraph 6.3), and supported by the single-arm LAL-CL06 study (paragraph 6.4) and evidence from the LAL-D registry (paragraph 6.5).

7.8 The PBAC considered that it was likely that patients with late-onset LAL-D treated with sebelipase alfa plus BSC would derive an improvement in liver biomarkers (e.g. 31% vs 7% ALT normalisation in sebelipase alfa vs placebo group at week 20) compared to BSC alone. The PBAC considered that the clinical evidence was limited by the small sample size, limited comparative follow-up, reliance on surrogate endpoints and lack of demonstrated benefit in fatigue, health-related quality of life or survival (see paragraph 6.26). The PBAC noted that patients with more severe disease at study entry, characterised by higher ALT or LDL-c levels, showed lower rates of biochemical normalisation, but experienced significantly greater absolute reductions in liver enzymes and fat content compared to those with lower baseline values. However the PBAC noted the sub-group analyses were limited by the small sample size (see paragraph 6.14). The PBAC considered the applicability of the trial population to the proposed broader PBS population was unclear (see paragraph 7.5). As such, the PBAC considered that the magnitude and clinical meaningfulness of benefit in the proposed PBS population to be uncertain.

7.9 The PBAC considered that the submission's claim of non-inferior safety was likely reasonable, based on the available comparative evidence from LAL-CL02. However, the PBAC noted limitations in regard to small sample size and short duration of follow-up.

7.10 The PBAC noted the important structural limitations of the economic model and optimistic assumptions and inputs, and agreed with the ESC that the model was of limited use for decision making (paragraph 6.44). As such the PBAC considered that the estimated incremental cost effectiveness ratio (ICER, > $1,055,000 to > $1,055,000 per QALY gained), was highly uncertain and unacceptably high. The PBAC noted that the model used a simplified hepatic disease progression structure for a multisystem disease, but acknowledged that this may have been a pragmatic approach given the limited evidence available to quantify non-hepatic outcomes. However, the PBAC considered that the model did not adequately address the variable presentation and disease trajectory (see paragraphs 7.4 and 7.8). The PBAC also noted the model limitations identified by the ESC, including the limited data supporting the natural disease course, limited model diagnostics, lack of external validation, and inability to test key assumptions such as time horizon, underlying mortality and discontinuation.

7.11 The PBAC noted the submission estimated a net cost to the PBS of $60 million to < $70 million in the first 6 years of listing, based on < 500 treated patients, including < 500 grandfathered patients. The PBAC considered the financial estimates were uncertain, primarily due to the uncertainty in the treated patient numbers (paragraph 6.52) and

body weight (paragraph 6.53). The PBAC noted that the estimated treated population was based on only [redacted]% of the prevalent late-onset LAL-D population being diagnosed, and given the variable disease course considered it was unclear how many additional patients would be diagnosed if sebelipase alfa were PBS listed.

7.12 The PBAC considered any resubmission should more clearly define the population to be treated with sebelipase alfa, and account for the variation in the disease course and expected treatment benefit for this population. This should inform estimates of the magnitude and clinical meaningfulness of benefit, cost-effectiveness and financial estimates. The PBAC considered the issues outlined in these minutes regarding the economic model should also be addressed (paragraph 6.44). The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.