

# **Post-Market Review of Products Used in the Management of Diabetes**

## **Part 3: Type 2 Diabetes Medicines**

**Draft Report to PBAC**

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## STRUCTURE OF THE REPORT

This Report is presented in seven parts, as briefly outlined below.

**Executive Summary** – Summarises the key findings of the Review, including the Reference Group’s consideration of the evidence and stakeholder input.

**Part 1** – Provides the background, context and process for the Review.

**Part 2** – Provides background information on type 2 diabetes, including its prevalence and impact in Australia. This part also provides a summary of Australian and international guidelines for the treatment of type 2 diabetes, focussing on pharmacotherapy algorithms.

**Part 3** – Provides summaries of the key points raised by stakeholders in submissions and at the Stakeholder Forum, and advice used to guide the Review provided by the Internal Working Group and Diabetes Review Reference Group.

**Part 4** – Describes the use of type 2 diabetes medicines and patterns of treatment in Australia based on Pharmaceutical Benefits Scheme (PBS) data. This is considered in the context of the PBS restrictions to determine if current use represents expected cost-effective use.

**Part 5** – Summarises the clinical trial evidence used to support PBS listing of type 2 diabetes medicines from January 2002 to November 2013.

**Part 6** – Collates new trial evidence published since 2002 on the safety and efficacy of type 2 diabetes medicines, including network meta-analyses of the triple therapy trials.

## ABBREVIATIONS

ACRRM	Australian College of Rural and Remote Medicine
ADEA	Australian Diabetes Educators Association
ADS	Australian Diabetes Society
AHQR	Agency for Healthcare Research and Quality (USA)
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
BGTS	Blood Glucose Test Strips
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CHD	Coronary Heart Disease
CVD	Cardiovascular disease
DHS	Department of Human Services
Diabetes medicines	Medicines indicated for glucose-lowering therapy (ATC-A10)
DoH	Department of Health
DPP-4 inhibitors	Dipeptidyl peptidase 4 inhibitors (also known as ‘gliptins’)
DUSC	Drug Utilisation Sub-Committee
DVA	Department of Veterans’ Affairs
ESC	Economics Sub-Committee (of the PBAC)
FDC	Fixed dose combination
GLP-1 agonist	Glucagon-like peptide-1 agonist (also known as incretin analogues)
HbA <sub>1c</sub>	Haemoglobin A <sub>1c</sub> or glycated haemoglobin
HR	Hazard ratio
IDF	International Diabetes Federation
MBS	Medical Benefits Scheme
MCID	Minimum clinically important difference
MD	Mean difference
MI	Myocardial infarction
MSAC	Medical Services Advisory Committee

NDSS	National Diabetes Services Scheme
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research (United Kingdom)
NHMRC	National Health and Medical Research Council
NMP	National Medicines Policy
NPS MedicineWise	National Prescribing Service MedicineWise
NZGG	New Zealand Guidelines Group
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PBD	Pharmaceutical Benefits Division
PIN	Patient Identifier
PVD	Peripheral Vascular Disease
QUM	Quality Use of Medicines
RACGP	Royal Australian College of General Practitioners
RCT	Randomised Control Trial
Reference Group	Diabetes Review Reference Group
RPBS	Repatriation Pharmaceutical Benefits Scheme
SGLT2	Sodium-glucose linked transporter protein 2
SIGN	Scottish Intercollegiate Guidelines Network
TGA	Therapeutic Goods Administration
The Department	The Department of Health
ToR	Terms of Reference
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization

## EXECUTIVE SUMMARY

### *Background and context*

Diabetes is a major health issue, as recognised by its status as a National Health Priority Area. Due to the considerable recent changes in diabetes management, including the Pharmaceutical Benefits Scheme (PBS) listing of a number of new medicines for the treatment of diabetes, the Pharmaceutical Benefits Advisory Committee (PBAC) agreed to a Post-market Review of Products used in the Management of Diabetes (Diabetes Review) in August 2012. This Review aims to ensure that patients are using the most appropriate medicines and products, effectively and safely, to achieve optimal health outcomes and support quality use of medicines.

The Diabetes Review has been undertaken in three stages. This draft Report contains the findings for Stage 3, which focused on type 2 diabetes medicines. The objectives of the Medicines Review, in line with Terms of Reference (ToR) 1–4, were to:

1. Describe the utilisation and patterns of treatment of PBS listed drugs for type 2 diabetes, and compare these with PBS restrictions.
2. Consider if the utilisation of PBS listed drugs in current clinical practice represents expected cost effective use.
3. Consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002.
4. Collate and evaluate any additional clinical studies or meta-analyses for drugs currently PBS listed for type 2 diabetes that the PBAC has not seen and that would inform their consideration.

The Medicines Review has been conducted according to the Post-market Review Framework. An Internal Working Group and an expert Reference Group provided guidance and input to the Review.

Under the PBS, all of the newer type 2 diabetes medicines (thiazolidinediones - TZDs, DPP-4 inhibitors - gliptins, SGLT2 inhibitors, and GLP-1 receptor agonists) are subsidised for use in dual combination therapy with metformin or a sulfonylurea in patients meeting certain criteria. Only pioglitazone and exenatide are currently PBS-listed for use in triple combination therapy with metformin + sulfonylurea, and only pioglitazone is currently listed for use in combination with insulin. Insulin was considered out of scope of the Review, except as a comparator.

Table 1 shows the prices of the newer type 2 diabetes medicines listed on the PBS.

**Table 1. Prices of newer type 2 diabetes medicines on the PBS (1 August 2014 PBS Schedule).**

Drug Name	Form & Strength	Item No.	MQ packs/ MQ units/ No. of Repeats.	DPMQ (Price)
<b><i>TZDs</i></b>				
Pioglitazone	15 mg tablet	8694N	1/28/5	\$32.13
	30 mg tablet	8695P	1/28/5	\$45.19
	45 mg tablet	8696Q	1/28/5	\$55.39
Rosiglitazone	4 mg tablet	8689H	1/28/5	\$61.49
	8 mg tablet	8690J	1/28/5	\$90.94
<b><i>TZD + metformin combinations</i></b>				
Rosiglitazone + metformin	2 mg + 500 mg tablet	9059T	1/56/5	\$63.58
	2 mg + 1 g tablet	9060W	1/56/5	\$65.54
	4 mg + 500 mg tablet	9061X	1/56/5	\$93.04
	4 mg + 1 g tablet	9062Y	1/56/5	\$95.00
<b><i>DPP-4 inhibitors</i></b>				
Alogliptin	6.25 mg tablet	2944Y	1/28/5	\$59.20
	12.5 mg tablet	2933J	1/28/5	\$59.20
	25 mg tablet	2986E	1/28/5	\$59.20
Linagliptin	5 mg tablet	3387G	1/30/5	\$62.95
Saxagliptin	2.5 mg tablet	10128C	1/28/5	\$59.20
	5 mg tablet	8983T	1/28/5	\$59.20
Sitagliptin	25 mg tablet	9180E	1/28/5	\$59.20
	50 mg tablet	9181F	1/28/5	\$59.20
	100 mg tablet	9182G	1/28/5	\$59.20
Vildagliptin	50 mg tablet	3415R	1/60/5	\$62.95
<b><i>DPP-4 inhibitor + metformin combinations</i></b>				
Alogliptin + metformin	12.5 mg + 500 mg tablet	10033C	1/56/5	\$61.30
	12.5 mg + 850 mg tablet	10032B	1/56/5	\$62.70
	12.5 mg + 1 g tablet	10035E	1/56/5	\$63.26
Linagliptin + metformin	2.5 mg + 500 mg tablet	10038H	1/60/5	\$65.20
	2.5 mg + 850 mg tablet	10045Q	1/60/5	\$66.69
	2.5 mg + 1 g tablet	10044P	1/60/5	\$67.29
Saxagliptin + metformin	2.5 mg + 1 g tablet: MR	10048W	1/56/5	\$63.26
	5 mg + 500 mg tablet: MR	10055F	1/28/5	\$60.25
	5 mg + 1 g tablet: MR	10051B	1/28/5	\$61.30
Sitagliptin + metformin	50 mg + 500 mg tablet	9449H	1/56/5	\$61.30
	50 mg + 850 mg tablet	9450J	1/56/5	\$62.70
	50 mg + 1 g tablet	9451K	1/56/5	\$63.26
	50 mg + 1 g tablet: MR	10090C	1/56/5	\$63.26
	100 mg + 1 g tablet: MR	10089B	1/28/5	\$61.30
Vildagliptin +	50 mg + 500 mg tablet	5474D	1/60/5	\$62.12

Drug Name	Form & Strength	Item No.	MQ packs/ MQ units/ No. of Repeats.	DPMQ (Price)
metformin	50 mg + 850 mg tablet	5475E	1/60/5	\$63.61
	50 mg + 1 g tablet	5476F	1/60/5	\$64.21
<b><i>SGLT2 inhibitors</i></b>				
Canagliflozin	100 mg tablet	2873F	1/30/5	\$96.61
	300 mg tablet	2987F	1/30/5	\$96.61
Dapagliflozin	10 mg tablet	10011X	1/28/5	\$90.40
<b><i>GLP-1 receptor agonists</i></b>				
Exenatide	5 µg/0.02 mL injection, 60 unit doses	3423E	1/1/5	\$122.79
	10 µg/0.04 mL injection, 60 unit doses	3424F	1/1/5	\$131.65

Abbreviations: DPMQ = Dispensed price for maximum quantity, MQ = Maximum quantity, MR = Modified release.

### ***Review of clinical guidelines***

A brief review of Australian and international clinical guidelines for the management of type 2 diabetes was commissioned from Griffith University. Most guidelines recommend an individualised approach to the treatment of type 2 diabetes, including patient HbA<sub>1c</sub> targets. With regard to pharmacotherapy, the aim is to prevent microvascular events, whilst reducing the risk of severe hypoglycaemia and adverse events from treatment. Other considerations in medicine choice are efficacy, potential side effects, cost, effects on body weight, comorbidities, life expectancy, patient preferences for oral or injectable medicines, and ability to manage medicine administration.

Metformin is most commonly recommended as the first line medicine for the management of blood glucose levels (unless contraindicated or the patient is intolerant). Many guidelines recommend sulfonylureas as the preferred or usual second line therapy (unless contraindicated or the patient is intolerant), either in combination with metformin or as an alternative in the case of intolerance or contraindications. The arguments in favour of sulfonylureas raised in the guidelines are long term clinical experience, evidence supporting a reduction in microvascular complications, and low cost.

Most guidelines note that all classes of type 2 diabetes medicines are equally effective in reducing HbA<sub>1c</sub> in second line therapy. For this reason, some guidelines do not favour any specific second line therapy and recommend that the choice is based on individual patient factors.

If dual therapy is ineffective in controlling blood glucose, guidelines commonly recommend triple therapy, with insulin as the preferred third line option in combination with metformin + sulfonylurea. The evidence base and cost are important factors in this recommendation. Other treatments can be used if the preferred option is not suitable due to contraindications or intolerances, and it is generally recommended

that the medicine selected is tailored to the individual patient. More complex insulin regimens are usually recommended for those not controlled by initial triple therapy.

### ***Stakeholder consultation***

Stakeholders were consulted through a public submission process and an invited Stakeholder Forum, and were provided with an opportunity to comment on the draft Report. Stakeholders highlighted the need for a patient-centred approach to treatment, including individualisation of HbA<sub>1c</sub> targets. Stakeholders recommended that choice of therapy be determined for an individual taking account of factors such as: age, time since diagnosis, symptoms, cardiovascular profile, weight, risk of hypoglycaemia, side effects, comorbidities, and features that may facilitate patient compliance.

Most newer medicines, such as DPP-4 inhibitors and GLP-1 receptor agonists, were considered comparable to sulfonylureas in terms of HbA<sub>1c</sub> lowering. However, stakeholders considered that other important outcomes included avoidance of hypoglycaemia, body weight change, side effects, hospitalisations, long term health outcomes and development of microvascular and macrovascular complications. Stakeholders considered it particularly important to try to minimise hypoglycaemic events due to their multi-dimensional effect on patients, including quality of life, productivity, risk of falls in the elderly, and for severe hypoglycaemia, limiting expensive hospital admissions.

Stakeholders noted that the PBS restrictions were complex and required updating. Similarly, stakeholders highlighted that the proliferation of available clinical guidelines may be causing prescriber confusion, and recommended that the guidelines should be updated and consolidated.

Stakeholders emphasised that treatment pathways need to consider prevention, education and lifestyle factors, and that community and school based education programmes were important to motivate people to address lifestyle factors.

### ***Medicines use (ToR 1 and 2)***

The Department's Drug Utilisation Sub-Committee (DUSC) Secretariat, the PBS Information Management Section and the University of Adelaide undertook analyses of the patterns of use of type 2 diabetes medicines. Government expenditure on diabetes medicines increased from almost \$130 million in 2000 to about \$500 million in 2013. In 2013, the highest expenditure was on insulins, followed by fixed dose combinations and DPP-4 inhibitors, while the lower cost metformin and sulfonylureas were the most commonly prescribed oral type 2 diabetes medicines.

In patients initiating type 2 diabetes pharmacotherapy between 2003–04 and 2009–10, metformin was the most common first line medicine, in line with clinical guidelines. In the first 3.5 years after starting therapy, more than 60% of patients did not add or switch medicines and fewer than 5% of patients added or switched medicines outside of the PBS restrictions for subsidy.

For patients initiating a newer type 2 diabetes medicine (a DPP-4 inhibitor, TZD or exenatide) between July and December 2011, 47.7% had not received a supply of both metformin and a sulfonylurea in the two years prior. The PBS restrictions at the time required prior use of metformin and a sulfonylurea (except where treatment with these medicines was contraindicated). This use outside the restrictions was highest for those initiating a DPP-4 inhibitor + metformin fixed dose combination (55%) and the DUSC considered that the availability of combination products may be contributing to use outside of the PBS restrictions.

In April and July 2013, as a result of these findings, the PBAC recommended the listings of saxagliptin with metformin, linagliptin with metformin and alogliptin for the treatment of type 2 diabetes, the latter in combination with metformin or a sulfonylurea, without the requirement for contraindication or intolerance to metformin + sulfonylurea. The PBAC recommended the listings at a reduced price, where the likely proportion of use in patients who have not trialled a sulfonylurea was cost-minimised to the average daily dose of a sulfonylurea in combination with metformin. Alogliptin was subsequently listed on the PBS on 1 December 2013 with the reduced price and revised restriction. Due to the application of the reference pricing policy, the sponsors of the other listed DPP-4 inhibitors agreed to reduced PBS prices. The restrictions for the other DPP-4 inhibitors were similarly revised at the same time.

In July 2014, the PBAC recommended the listing of a fixed dose combination of dapagliflozin + metformin XR, and that the PBS listings for dapagliflozin and the fixed dose combination be aligned with that of the DPP-4 inhibitors. The PBAC considered that such an alignment of restrictions would be cost-effective if the prices were also aligned with the DPP-4 inhibitors, noting the current dapagliflozin cost offset for adverse events.

Of patients prescribed a newer type 2 diabetes medicine between February 2011 and May 2012, 27.9% were co-prescribed a regimen of medicines that did not comply with PBS subsidy criteria. Triple oral therapy with DPP-4 inhibitor + metformin + sulfonylurea contributed the most to this use outside PBS restrictions. Some use of DPP-4 inhibitor monotherapy, exenatide with insulin, and pioglitazone either alone or with another newer type 2 diabetes medicine, was also evident. The DUSC considered that the overall rate of use beyond the PBS restrictions in relation to newer type 2 diabetes medicines is at least 30%, and that this is a conservative estimate of non-cost-effective use.

### ***Evidence used to supporting PBS listings (ToR 3)***

The University of Newcastle developed a report consolidating the clinical trial evidence used to support PBS listings of diabetes medicines listed between 2002 and 2013. Earlier submissions for TZDs were also reviewed.

A total of 177 clinical studies/systematic reviews assessing the newer type 2 diabetes medicines and nominated comparators were identified from 47 submissions considered

by the PBAC. Twenty-six (55%) of these submissions received positive recommendations. Only 17 submissions (36%) presented some direct head-to-head evidence against the main comparator. The newer type 2 diabetes medicines have been positioned after the use of metformin and/or a sulfonylurea based on a series of non-inferiority comparisons originating from insulin.

Superiority claims in terms of comparative efficacy were made in 14 submissions. No submission has received a positive recommendation on the basis of a clinical claim of superiority. The PBAC has noted marginal differences in change in HbA<sub>1c</sub> between medicines, but has never accepted a claim of superiority due to the difficulty in translating these differences to clinical outcomes. When presented, the nominated non-inferiority margin for change in HbA<sub>1c</sub> from baseline generally ranged from 0.3% to 0.4% (3–4 mmol/mol). The PBAC has acknowledged that there may be differences between treatments in regards to weight management and hypoglycaemia, but the magnitude and clinical importance of these differences has not been adequately demonstrated.

None of the newer type 2 diabetes medicine submissions have presented microvascular or macrovascular events as a key outcome. Cardiovascular safety data has been considered for two DPP-4 inhibitors. Other limitations of the clinical evidence include the lack of long term safety data and uncertain applicability of the clinical evidence (e.g. duration of treatment, background therapies, treatment details).

PBS restrictions and Therapeutic Goods Administration (TGA) indications for the medicines were also compared. The following combinations of therapies for the newer type 2 diabetes medicines are TGA-approved, but not subsidised by the PBS:

- monotherapy
- TZD + DPP-4 inhibitor/SGLT2 inhibitor
- triple therapy with metformin + sulfonylurea + DPP-4 inhibitor/SGLT2 inhibitor
- insulin in combination with a DPP-4 inhibitor/SGLT2 inhibitor/GLP-1 receptor agonist
- initial use of a DPP-4 inhibitor or SGLT2 inhibitor with metformin.

Conversely, the current PBS listing for pioglitazone allows use in any combination with insulin, while the TGA indication specifies dual therapy with insulin only.

### ***New evidence (ToR 4)***

Griffith University undertook a systematic literature review of the safety and efficacy of type 2 diabetes medicines, including a network meta-analysis of triple therapy trials. A total of 87 publications published between January 2003 and March 2014, covering 72 RCTs (43 not seen by the PBAC previously) were identified. No long term macrovascular or microvascular outcome data for acarbose, insulin, SGLT2 inhibitors and GLP-1 receptor agonists was identified. Limited trial data were available with a duration of

over six months and many trials were underpowered to detect differences in adverse events.

The monotherapy trials and the majority of dual therapy trials were not analysed further on the advice of the expert Reference Group, as it was considered that the PBAC had already considered the comparisons in these trials. However, one dual therapy trial considered a combination not yet seen by the PBAC (TZD + DPP-4 inhibitor). Compared to TZD monotherapy, TZD + DPP-4 inhibitor reduced HbA<sub>1c</sub> (-0.9%; 95% CI: -1.1, -0.7) and increased weight (1.1 kg; p-value not reported).<sup>1</sup> The results may not be applicable to Australian practice as the patients were treatment naïve.

Table 2 provides a summary of the triple therapy trial evidence for the different therapeutic groups. Twenty-one triple therapy RCTs were identified and assessed for risk of bias: high – 4 trials, unclear – 12 trials, and low – 5 trials.

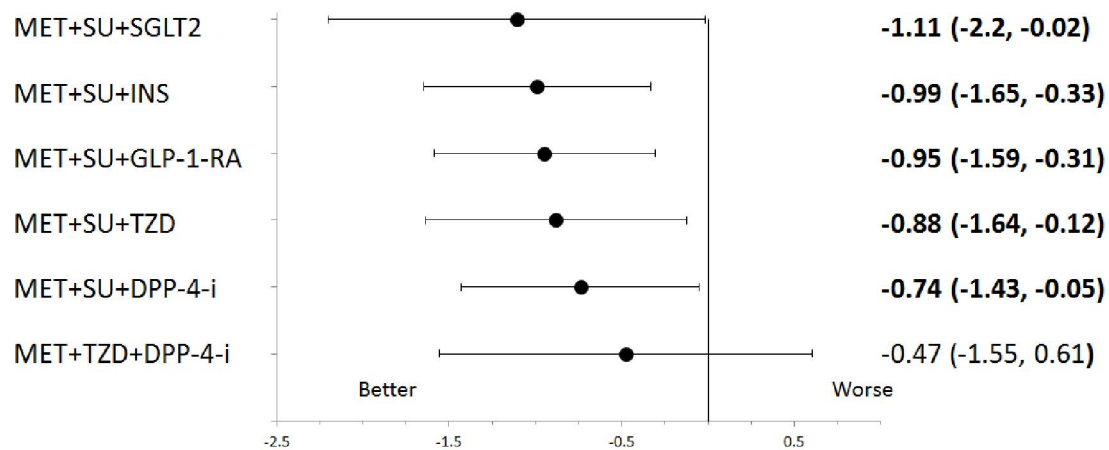
**Table 2. Available evidence for triple therapy.**

Triple therapy	Evidence available	No. of trials	No. of trials seen by PBAC*
<b>DPP-4 inhibitors</b>			
+ Metformin + Sulfonylurea	Yes	3	2
+ Metformin + TZD	Yes	3	0
+ Metformin + Insulin	Yes	1	0
<b>TZD</b>			
+ Metformin + Sulfonylurea	Yes	3	2
+ Metformin + DPP-4 inhibitor	Yes	3	0
<b>Insulin</b>			
+ Metformin + DPP-4 inhibitor	Yes	1	0
+ Metformin + Sulfonylurea	Yes	11	3
+ Metformin + GLP-1 receptor agonist	Yes	1	0
<b>GLP-1 RA</b>			
+ Metformin + Sulfonylurea	Yes	5	3
+ Metformin + Insulin	Yes	1	0
<b>SGLT2 inhibitors</b>			
+ Metformin + Sulfonylurea	Yes	1	1
<b>Acarbose</b>	No	0	0

\* Trials included in submissions from 2002 to November 2013.

HbA<sub>1c</sub>, body mass index (BMI) and age at baseline were similar in the analysed trials. All triple therapy combinations of medicines provided a significantly better reduction in HbA<sub>1c</sub> at six months compared to metformin + sulfonylurea dual therapy, in the range of 0.7–1.1%, except for metformin + TZD + DPP-4 inhibitor (Figure 1). None of the triple therapy combinations demonstrated clinically relevant differences in HbA<sub>1c</sub> compared with other triple therapies.

**Figure 1. Forest plot of mean difference in HbA<sub>1c</sub> (%) (95% CI) at six months for triple therapy combinations compared to metformin + sulfonylurea dual therapy – network analysis.**

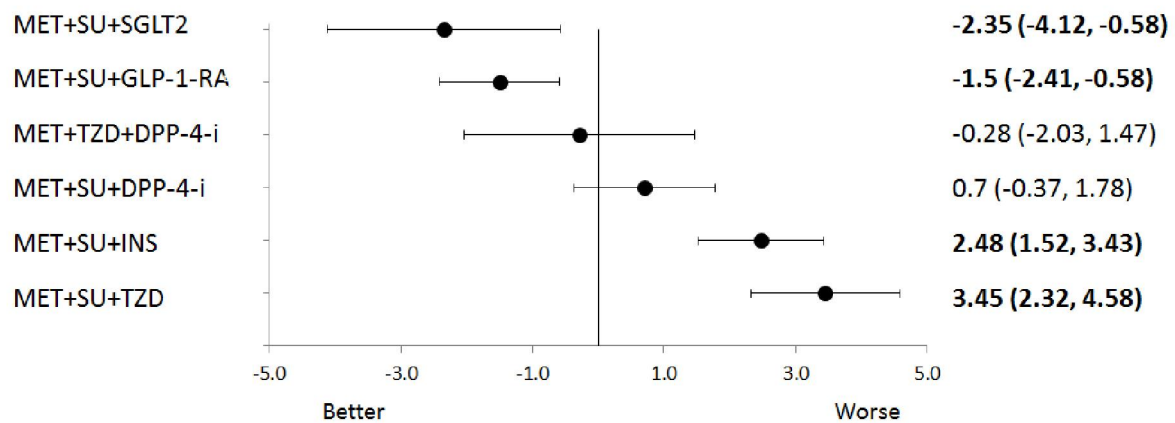


Statistically significant difference are marked in **bold**.

Abbreviations: CI = confidence interval; DPP-4-i = DPP4 inhibitor; GLP-1-RA = GLP-1 receptor agonist; INS = insulin; MET = metformin; SGLT2-i = sodium glucose co-transporter 2 inhibitor; and SU = sulfonylurea.

Triple therapy regimens were often weight neutral or resulted in weight gain after six months of treatment compared to metformin + sulfonylurea in the range of -0.3 to 3.5 kg (Figure 2). The combination of SGLT2 inhibitor + metformin + sulfonylurea showed a significant reduction with a mean difference of -2.4 kg, and the combination of GLP-1 receptor agonist + metformin + sulfonylurea showed a significant reduction with a mean difference of -1.5 kg. In terms of body weight change, when used in combination with metformin + sulfonylurea: SGLT2 inhibitors and GLP-1 receptor agonists were superior to insulin, TZDs, and DPP-4 inhibitors; and insulin was superior to TZDs.

**Figure 2. Forest plot of mean difference in change in body weight (kg) (95% CI) at six months for triple therapy combinations compared to metformin + sulfonylurea dual therapy – network analysis.**



Statistically significant difference are marked in **bold**.

Abbreviations: CI = confidence interval; DPP-4-i = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 receptor agonist; INS = insulin; MET = metformin; SGLT2 = sodium glucose co-transporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

Four trials were identified that examined long term outcomes when a sulfonylurea, TZD or DPP-4 inhibitor was added to existing therapy (Table 3). Existing medications varied within and between the trials. No trials examining long term macrovascular or microvascular outcomes were identified for insulins, GLP-1 receptor agonists, SGLT2 inhibitors or acarbose.

Sulfonylureas, TZDs and DPP-4 inhibitors added to existing therapy all provided a statistically significant reduction in HbA<sub>1c</sub>, but increased the risk of hypoglycaemia compared to existing medication in trials of greater than two years duration. Only sulfonylureas when added to existing medication reduced major microvascular events (HR: 0.86; 95% CI: 0.77, 0.97). The addition of TZDs to existing medication reduced major macrovascular events (HR: 0.84; 95% CI: 0.72, 0.98), while DPP-4 inhibitors had no effect on this outcome. TZDs increased the risk of heart failure, and TZDs and DPP-4 inhibitors increased the risk of hospitalisation due to heart failure.

**Table 3. Primary and key secondary cardiovascular outcome results from trials (trials with a duration of greater than 1 year).**

Comparison	EM vs. EM + SU	EM vs. EM + TZD	EM vs. EM + DPP-4 inhibitors	
Trial publication	Advance 2008 <sup>2</sup>	Dormandy 2005 <sup>3</sup>	Scirica 2013 <sup>4</sup>	White 2013 <sup>5</sup>
Trial duration	5 years (median)	34.5 months	2.1 years	18 months
N	EM + SU: 5,571 EM: 5,569	EM + TZD: 2,605 EM: 2,633	EM + DPP-4: 8,280 EM + PBO: 8,212	EM + DPP-4: 2,701 EM + PBO: 2,679
Death from any cause	0.93 (0.83, 1.06) <sup>a</sup>	0.96 (0.78, 1.18) <sup>a</sup>	NR	NR
Heart failure	5 (-14 to 21) <sup>d</sup>	<b>1.49 (1.23, 1.8)<sup>b</sup></b>	NR	NR
Hospitalisation due to heart failure	NR	<b>1.42 (1.1, 1.83)<sup>b</sup></b>	<b>1.27 (1.07, 1.51)<sup>a</sup></b>	NR
Major microvascular events: new or worsening nephropathy or retinopathy	<b>0.86 (0.77, 0.97)<sup>a</sup></b>	NR	NR	NR
Major macrovascular events: CV death, non-fatal MI and non-fatal stroke.	0.94 (0.84, 1.06) <sup>a</sup>	<b>0.84 (0.72, 0.98)<sup>a</sup></b>	1.00 (0.89, 1.12) <sup>a</sup>	0.96 ( $\leq$ 1.16) <sup>c</sup>
Death from any cause, non-fatal MI, stroke, acute coronary syndrome, leg amputation/revascularisation and coronary revascularisation	NR	0.90 (0.80, 1.02) <sup>a</sup>	NR	NR
Combined major macrovascular and microvascular events	<b>0.90 (0.82, 0.98)<sup>a</sup></b>	NR	NR	NR
CV death, MI, stroke, hospitalisation for unstable angina, HF, or coronary revascularisation: secondary efficacy end point	NR	NR	1.02 (0.94, 1.11) <sup>a</sup>	NR
CV death, MI, stroke or urgent revascularization due to unstable angina: secondary efficacy end point	NR	NR	NR	0.95 ( $\leq$ 1.14) <sup>c</sup>

Statistically significant difference are marked in **bold**.

Abbreviations: CV = cardiovascular, MI = myocardial infarction; EM = Existing medication; DPP-4 = DPP-4 inhibitor; N = Number of patients; NR = Not reported; and SU = sulfonylurea.

Notes: <sup>a</sup> Hazard ratio (95% confidence interval); <sup>b</sup> Odds ratio (95% CI); <sup>c</sup> Hazard ratio (the upper boundary of the one-sided repeated CI, at an alpha level of 0.01); <sup>d</sup> Relative risk reduction (95% CI).

### **Reference Group consideration**

The expert Reference Group considered the draft Medicines Review Report, including the reports addressing ToR 1–4 and stakeholder input, on 20 August 2014. The members noted that patients and clinicians wanted access to a wider range of triple therapies and that triple therapy combinations recommended in some clinical guidelines are not currently subsidised under the PBS. Members considered that there was clinical need for access to triple therapy with metformin + sulfonylurea + DPP-4 inhibitors/SGLT2 inhibitors/GLP-1 receptor agonists (noting that exenatide is available for use in triple therapy). The currently available triple oral therapy combinations of metformin +

sulfonylurea + pioglitazone/acarbose, were deemed either unpopular due to side effects or only appropriate for small, select groups of patients. Members also noted that many patients disliked injections, and that patient-specific factors and consumer choice around side effects were important in the prescribing of type 2 diabetes medicines.

Reference Group members considered that the triple therapy use outside of the restrictions seen in the utilisation review was an accurate reflection of Australian practice. Members regarded the 0.7–1.1% improvement in HbA<sub>1c</sub> seen with the triple therapy combinations at six months treatment as clinically meaningful. Although there were few studies longer than six months to demonstrate durability of response, the members considered that the few trials available did demonstrate a durable response, as did open label trials. However, members queried whether the use of DPP-4 inhibitors and SGLT2 inhibitors in triple therapy would be cost-effective at the current prices.

Members noted that newer medicines were being heavily marketed, driving a reduction in sulfonylurea prescribing. Members observed that in evidence-based guidelines sulfonylureas were still considered the usual second line medicine, and that the Department should consider prescriber education around the role of sulfonylureas.

Members noted that stakeholders had requested that the 2009 'National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes'<sup>6</sup> be updated, but that these guidelines were developed by a third party, not the Department.

Some members considered that it would be useful to have the option to use medicines in patients with a HbA<sub>1c</sub> below 7%, in line with some clinical guidelines. However, the majority of members judged that this use would not improve cost-effectiveness, and that long term outcome data was needed to support this practice. Members stated that some data indicated that lower targets did not improve clinical outcomes and may increase the risk of hypoglycaemic events.

The Reference Group members deemed that the inclusion of a 'General statement on blood glucose-lowering medicines for the management of type 2 diabetes' in the PBS, to summarise the restrictions on type 2 diabetes medicines, would be useful to prescribers. Members also generally supported the inclusion of a 'stopping rule' in the statement, so that if a clinically meaningful change in blood glucose levels (i.e. 0.5% reduction in HbA<sub>1c</sub> or equivalent) had not occurred after a specified period of time (after addressing any adherence issues), then the medicine should be ceased and a new medicine trialled. Members felt that this was in line with a number of clinical guidelines and would improve cost-effectiveness, but noted that prescriber education would be required to promote this practice.

# **PART 1 – REVIEW BACKGROUND, PROCESS AND CONTEXT**

## **1.1 Diabetes Post-market Review**

Appropriate medication and treatment management is an important objective of Australia's National Medicines Policy (NMP). The Post-market Review of Products used in the Management of Diabetes (Diabetes Review) aims to ensure that patients are using the most appropriate medicines and products, effectively, and safely, to achieve optimal health outcomes and support quality use of medicines.

The Diabetes Review is divided into three stages:

1. Blood glucose test strips use in people with type 2 diabetes not using insulin.
2. Insulin pumps for people with type 1 diabetes, and the Insulin Pump Programme.
3. Medicines used in the management of type 2 diabetes.

Each stage is being progressed separately with the findings presented in an associated report. Each report is designed to be read as a stand-alone document and may contain some shared information with previous reports. Reports will be provided to the Pharmaceutical Benefits Advisory Committee (PBAC), where appropriate, and to the Government for consideration in a staged approach. The findings will be published on the Diabetes Review website.

Each stage will be progressed in line with work being undertaken across other NMP partners including the Therapeutic Goods Administration (TGA), the National Health and Medical Research Council (NHMRC), and the National Prescribing Service Medicinewise (NPS MedicineWise).

Further information on the NMP, the Post-Market Monitoring Programme, and the role of the PBAC, is in [Appendix A](#).

## **1.2 Medicines Review**

### **1.2.1 Background**

In February 2012, the Drug Utilisation Sub-Committee (DUSC) of the PBAC requested a complete review of type 2 diabetes medicines, following its consideration of a number of changes to diabetes products listed on the PBS. These included amended restrictions, additional indications for existing medicines, and the listing of new medicines. The DUSC noted use of medicines outside the PBS restrictions, that the PBS restrictions have become complex over time and that safety concerns have arisen for some medicines. The PBAC considered the DUSC advice and recommended a review of the utilisation and cost-effectiveness of type 2 diabetes medicines in March 2012.

### 1.2.2 Terms of Reference (ToR)

In August 2012, the PBAC endorsed the Terms of Reference (ToR) for the Diabetes Review. The Medicines Review (Stage 3) comprises ToR 1–4 of the Diabetes Review, provided below.

Purpose: to examine and characterise the complexity and heterogeneity of PBS listings for medicines used in type 2 diabetes to inform an assessment of their effectiveness in terms of clinical outcomes and cost.

1. Describe the utilisation and patterns of treatment of PBS listed drugs for type 2 diabetes, and compare these with PBS restrictions.
2. Consider if the utilisation of PBS listed drugs in current clinical practice represents expected cost-effective use.
3. Consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002.
4. Collate and evaluate any additional clinical studies or meta-analyses for drugs currently PBS listed for type 2 diabetes that the PBAC has not seen and that would inform their consideration.

### 1.2.3 Scope

The Medicines Review aims to analyse the use, patterns of treatment, and evidence of clinical benefit of PBS listed type 2 diabetes medicines. This includes a review of the listing of type 2 diabetes medicines on the PBS, and the associated restrictions; and a review of Australian and international pharmacotherapy algorithms for the treatment of type 2 diabetes.

Table 1.1 lists the medicines that have been registered on the Australian Register of Therapeutic Goods (ARTG) and listed on the PBS and Repatriation PBS (RPBS) for the management of type 2 diabetes, that are in scope of the Medicines Review. Although insulin is used in the management of type 2 diabetes, it is not a focus of this Review. However, the utilisation data and information on the comparative safety and efficacy of insulin may be used to provide context.

**Table 1.1. Medicines in scope of the Review: Medicines subsidised by the PBS and RPBS for the treatment of type 2 diabetes at 1 August 2014, or considered for listing to November 2013.**

Drug Class	Description/Main action	Drug(s)	First PBS listing
Biguanides	Decrease glucose production in the liver.	Metformin and Metformin XR	May 1963
Sulfonamides (sulfonylureas)	Stimulate insulin secretion by the pancreas.	Glibenclamide <sup>a</sup>	Aug 1993
		Glicazide	Aug 1993
		Glimepiride	Nov 2000

		Glipizide	Aug 1993
Alpha glucosidase inhibitors	Inhibit uptake of simple carbohydrates in the small intestine.	Acarbose	Nov 1997
Thiazolidinediones (TZDs or glitazones)	Increase the response of cells to insulin.	Pioglitazone	Nov 2003
		Rosiglitazone <sup>a</sup>	Nov 2003
Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins)	Increase insulin synthesis and release by the pancreas.	Alogliptin <sup>a</sup>	Oct 2013
		Linagliptin <sup>a</sup>	Mar 2012
		Saxagliptin <sup>b</sup>	Jun 2011
		Sitagliptin <sup>a,b</sup>	Aug 2008
		Vildagliptin <sup>a</sup>	Aug 2010
Sodium-glucose linked transporter protein 2 (SGLT2) inhibitors	Block glucose reabsorption in the kidney.	Canagliflozin	Dec 2013
		Dapagliflozin	Dec 2013
GLP-1 receptor agonists (incretin analogues)	Increase insulin synthesis and release by the pancreas.	Exenatide	Aug 2010
		Liraglutide	Not listed (Recommended: March 2013)

<sup>a</sup> Metformin FDC available.

<sup>b</sup> Metformin XR (extended release) FDC available.

#### 1.2.4 Changes to PBS listings during the Review

The following major changes to PBS listed medicines for the management of type 2 diabetes occurred in parallel with the Diabetes Review as a result of sponsor submissions:

- Alogliptin, canagliflozin and dapagliflozin were listed on 1 December 2013.
- Sitagliptin + simvastatin FDC was deleted on 1 April 2014.
- Metformin XR FDCs with saxagliptin and sitagliptin were listed on 1 March 2014 and 1 May 2014, respectively.

In April and July 2013, the PBAC recommended the listings of saxagliptin with metformin, linagliptin with metformin and alogliptin for the treatment of type 2 diabetes, the latter in combination with metformin or a sulfonylurea. At the time, the restrictions on other listed DPP-4 inhibitors allowed use of these medicines with metformin or a sulfonylurea only in patients whose condition was not controlled with metformin + sulfonylurea or with a contraindication to, or intolerant of, a combination of metformin + sulfonylurea. The PBAC recalled that the DUSC Analysis of Medicines for Type 2 Diabetes showed that a high percentage of patients (41%) started a DPP-4 inhibitor, TZD or exenatide without a trial of a sulfonylurea (a population in which cost-

effectiveness has not been demonstrated). Therefore, the PBAC recommended the listing of these medicines at a reduced price, where the likely proportion of use in patients who have not trialled a sulfonylurea was cost-minimised to the average daily dose of a sulfonylurea in combination with metformin.

Due to the application of the reference pricing policy, the sponsors of the other listed DPP-4 inhibitors agreed to reduced PBS prices. The PBS prices of metformin + DPP-4 inhibitor fixed dose combination products were also reduced, as these are cost-minimised against the prices of the component medicines, or against other metformin + DPP-4 inhibitor fixed dose combinations. Revised restrictions that removed the requirement for patients to be contraindicated to, or intolerant of, a combination of metformin + sulfonylurea were implemented in parallel with the price reduction.

In July 2014, the PBAC recommended the listing of a dapagliflozin + metformin XR FDC. As proposed by the sponsor, the PBAC recommended that the PBS listings for dapagliflozin and dapagliflozin + metformin XR FDC be aligned with that of the DPP-4 inhibitors. The PBAC considered that such an alignment of restrictions would be cost-effective if the prices were also aligned with the DPP-4 inhibitors, noting that the price would require adjustment to take into account the current dapagliflozin cost offset for adverse events. Also in July 2014, the PBAC recommended the listing of another SGLT2 inhibitor, empagliflozin, on a cost-minimisation basis with dapagliflozin and canagliflozin, with restrictions based on the current listing of these two medicines.

The PBAC rejected the request to list lixisenatide for use in triple combination therapy with basal insulin and either metformin or a sulfonylurea in July 2014, on the basis of uncertain clinical place and inappropriate comparator (up-titrated insulin). The request to list lixisenatide for dual therapy in combination with metformin, and triple therapy in combination with metformin + sulfonylurea, was also rejected on the basis that non-inferiority to exenatide had not been adequately established.

### **1.3 Medicines Review Process**

This post-market review followed the standard process detailed on the [Post-Market Review website](#) (at the time), and involved the following key steps:

- Identification of issues by the DUSC.
- The PBAC recommended the Review and endorsed the ToR.
- The Minister approved commencement of the Review.
- A Reference Group of experts was established to guide the Review.
- Public input was sought through a written submission process.
- A Stakeholder Forum was held to further gather public input.
- Analyses were conducted, e.g. literature reviews.

- A draft report was released for public comment.

The final Report, public submissions, and public comments on the draft Report, will be provided to the PBAC for consideration and recommendation, before the final Report is provided to the Minister.

### **1.3.1 Written submissions addressing the ToRs**

Initial information about the Diabetes Review, including the complete ToR, were first published on the Diabetes Review website on 16 October 2012. Stakeholders were encouraged to join the PBS subscription service to receive alerts relating to the Review.

Input from identified stakeholders and the public was sought by announcing a call for submissions to address ToR 1–4 on the [PBS website](#) on 20 May 2013. Pharmaceutical sponsor companies and key diabetes and health professional organisations were also directly contacted two weeks prior on 6 May 2013, to inform them of the upcoming submission process. The call for submissions was open for six weeks to 2 July 2013.

Twenty-five submissions were received from a range of stakeholders including: industry organisations (10), professional peak bodies (6), non-Government organisations (4), individual professionals (4) and a Government organisation (1). No individual consumers made a submission.

The submissions were published on the Medicines Review public consultation website on 26 August 2013, unless the author requested confidentiality. A summary of key issues raised by stakeholders is in [Part 3.1.1](#). The expert Reference Group (see [Part 1.3.4](#)) was provided with the submissions for consideration.

### **1.3.2 Stakeholder Forum**

A Stakeholder Forum was held in Canberra on 12 September 2013, to provide a further opportunity for stakeholders to contribute to the Medicines Review.

Individuals and organisations that had made a written submission to the Medicines Review were invited to attend. Relevant pharmaceutical sponsor companies and key diabetes and health professional organisations were also directly invited. [Appendix B](#) provides the list of organisations invited. The Forum was announced on the PBS website and via the subscription service on 8 August 2013, and individuals/organisations could nominate to attend. In addition, the Department contacted the Consumers' Health Forum to request that they extend an invitation to consumers and consumer advocates through their networks.

Prior to the Forum, attendees were provided with an agenda and discussion paper that included background information on the Review, the ToR, a summary of the DUSC utilisation analyses, and issues and themes raised by stakeholders through the public submission process. The agenda included group discussion on six questions prepared by the Department with opportunities for additional comments and views to be expressed.

Discussion at the Forum focussed on:

- appropriate treatment pathways for type 2 diabetes, particularly the role of newer medicines
- clinical benefits and safety profiles associated with type 2 diabetes medicines
- the appropriateness and ease of use of the guidelines and PBS restrictions.

There were 37 attendees, including: industry organisations (16), non-Government organisations (7), professional peak bodies (6), individual consumers (5), Government organisations (2), and an individual health professional.

A draft Forum Summary was circulated to attendees, from 18–25 October 2013, to identify any key points that had been missed. Only comments reflecting key discussion points at the Forum were incorporated into the Forum Summary. The Forum Summary was published on the Medicines Review public consultation website on 9 May 2014. A summary of key issues raised by stakeholders is in [Part 3.1.2](#).

### **1.3.3 Internal Working Group**

An Internal Working Group consisting of key government agencies and relevant divisions of the Department was formed to facilitate discussion of potential interactions between the Review and other Government programmes and priorities. The Working Group has assisted in steering the Review and worked in parallel to the Reference Group. The Group convened three times to consider the Medicines Review on 23 October 2012, 10 April 2013, and 10 October 2013; and provided out-of-session comments of the draft Report.

A summary of key issues raised by Working Group members is in [Part 3.2](#).

### **1.3.4 Reference Group**

A Reference Group was formed to provide expert advice on issues raised during the Diabetes Review. The Reference Group included experts from a range of fields including endocrinology, diabetes education, general practice, consumer advocacy, clinical epidemiology, pharmacy, health economics, nutrition, and psychology. The full Reference Group membership will be published on the Diabetes Review website, once all stages of the Review have been finalised.

Reference Group advice has been used to guide the development of the Medicines Review and this Report. Reference Group meetings at which the Medicines Review was discussed, were held on: 17 July 2013, 24 May 2014 and 20 August 2014.

A summary of key issues raised by the Reference Group is in [Part 3.3](#), while the Executive Summary contains the Reference Group's consideration of the evidence and stakeholder input.

### **1.3.5 Utilisation reviews and DUSC consideration (ToR 1 & 2)**

Two utilisation reviews were conducted into the use of type 2 diabetes medicines. The first review was conducted by the Adelaide Health Technology Assessment, School of Population Health and Clinical Practice, University of Adelaide, and analysed overall utilisation of diabetes medicines and the patterns of use of type 2 diabetes medicines when patients initiate pharmacotherapy. The analysis of overall utilisation of diabetes medicines was updated by the Department's PBS Information Management Section in 2014, to provide more current data.

The Department's DUSC Secretariat undertook the second review which analysed the patterns of use of type 2 diabetes medicines after initiation, including use of diabetes medicines prior to initiating a third line agent (a DPP-4 inhibitor, TZD or exenatide), and patterns of diabetes medicines co-administration. A summary of these analyses are included in [Part 4](#).

The utilisation reports on type 2 diabetes medicines were discussed by the DUSC at the October 2012 and February 2013 meetings. The public summaries were made available online.

### **1.3.6 Review of PBS listings of type 2 diabetes medicines (ToR 3)**

The Department engaged the Newcastle Evaluation Group, School of Medicine and Public Health, University of Newcastle, to prepare a report consolidating the clinical trial evidence used to support PBS listings of type 2 diabetes medicines for submissions between 2002 and January 2014. A summary of the report is included in [Part 5](#).

### **1.3.7 Literature reviews (ToR 4)**

The Department engaged the Centre for Applied Health Economics, Griffith University, to prepare a report including:

- A review of the current Australian and international guidelines for the management of type 2 diabetes, focussing on pharmacotherapy algorithms. A summary of this part of the report is included in [Part 2.7](#).
- A literature review and meta-analysis of the comparative safety and efficacy of PBS listed type 2 diabetes medicines, including trial evidence published between 2002 and 2013 (inclusive). A summary of this part of the report is included in [Part 6](#).

### **1.3.8 Public consultation on the draft Report**

Public consultation on the draft Medicines Review Report will be open for two weeks in early October 2014. Public submissions will be provided to the PBAC.

## **PART 2 – TYPE 2 DIABETES MELLITUS**

### **2.1 Diabetes mellitus**

Blood glucose levels are controlled by insulin, a hormone produced by the pancreas. In general, insulin is secreted proportionately to the amount of excess glucose in the blood. It inhibits the use of fat as an energy source and causes fat and skeletal muscle cells to absorb glucose from the blood, lowering blood glucose levels.<sup>7</sup>

Diabetes mellitus (diabetes) is a chronic disease characterised by high levels of glucose in the blood (hyperglycaemia). Diabetes occurs when the pancreas is unable to produce enough insulin, or the body becomes resistant to insulin, or both. Hyperglycaemia can result in a number of complications, including serious damage to the nerves and blood vessels. There are three main types of diabetes: type 1 diabetes, type 2 diabetes, and gestational diabetes.<sup>7</sup> This report focuses on medicines for the treatment of type 2 diabetes.

Diabetes was endorsed as a National Health Priority Area at the Australian Health Minister's Conference in 1996 in recognition of the high prevalence of the disease in Australia, its impact on morbidity and mortality, and its potential for health improvements through prevention and treatment programmes.

#### **2.1.1 Type 1 diabetes**

Type 1 diabetes is an autoimmune disease characterised by the progressive destruction of the insulin producing beta-cells of the pancreas. People with type 1 diabetes cannot produce insulin and require lifelong insulin injections for survival.<sup>7</sup> Type 1 diabetes can occur at any age, but predominantly occurs in children and young adults and is sometimes referred to as juvenile onset diabetes or insulin-dependent diabetes. Type 1 diabetes affects about 10% of people with diabetes.<sup>8</sup> The cause of type 1 diabetes is not known and it is not preventable with current knowledge.<sup>7</sup>

#### **2.1.2 Type 2 diabetes**

Type 2 diabetes is a metabolic disorder associated with hereditary factors and lifestyle risk factors, including poor diet, insufficient physical activity and being overweight or obese.<sup>9</sup> People with type 2 diabetes produce insulin, but may not produce enough of it (insulin deficiency caused by beta cell dysfunction) or cannot use it effectively (insulin resistance). Insulin acts in the liver to suppress the release of glucose into the blood. Insulin resistance causes the liver to inappropriately release glucose, causing hyperglycaemia. Some people with type 2 diabetes may be able to manage their condition through lifestyle changes, others may require diabetes medications or insulin injections to control blood glucose levels.<sup>7</sup>

### 2.1.3 Gestational diabetes

Gestational diabetes occurs during pregnancy and usually resolves after birth. However, a history of gestational diabetes increases a woman's risk of developing type 2 diabetes later in life. It is estimated that gestational diabetes affects women in about 3–8% of pregnancies, usually between the 24<sup>th</sup> and 28<sup>th</sup> week of pregnancy. Additionally, certain populations including Aboriginal or Torres Strait Islander, Indian, Vietnamese, Chinese, Middle Eastern and Polynesian populations, are at increased risk of gestational diabetes.<sup>10</sup>

## 2.2 Prevention

Following a healthy lifestyle can prevent or delay the onset of type 2 diabetes. It is estimated that up to 60–80% of cases are preventable.<sup>11; 12</sup> People at high risk of developing diabetes may be identified through the use of risk assessment tools, such as the Australian type 2 diabetes risk assessment tool (AUSDRISK). The *National Evidence Based Guideline for the Primary Prevention of Type 2 Diabetes*, endorsed by the National Health and Medical Research Council (NHMRC) recommends that risk assessment should begin at age 40 or age 18 for Aboriginal and Torres Strait Islander peoples, and be repeated every three years. Those at high risk of developing type 2 diabetes should be offered lifestyle modifications focussing on increased physical activity, dietary change, and weight loss, through routine clinical practice. Pharmacological interventions may be considered in some people at high risk of developing diabetes, but the potential benefits and harms (e.g. side-effects) should be considered before commencing pharmacotherapy for prevention. Bariatric surgery may be considered in those who are morbidly obese.<sup>11</sup>

Lifestyle intervention programmes have been shown to decrease the incidence of type 2 diabetes developing in those at high risk,<sup>13</sup> and are at least as effective as pharmacological interventions.<sup>14</sup> One large randomised controlled trial (RCT), the Diabetes Prevention Program, which followed 3200 high risk people for an average of 2.8 years, showed a lifestyle intervention programme to be significantly more effective than metformin in delaying the development of type 2 diabetes, reducing the risk by 39% (95% CI: 24, 51).<sup>15</sup>

A Cochrane systematic review found that exercise plus diet interventions significantly reduced the risk of diabetes compared with standard recommendations in high risk groups (RR 0.63; 95% CI: 0.49, 0.79).<sup>16</sup> Another Cochrane review assessing the effect of counselling or education to modify cardiovascular risk factors, showed a reduced risk of total mortality and combined fatal and non-fatal cardiovascular events in diabetes patients with the intervention (OR 0.71; 95% CI: 0.61, 0.83).<sup>17</sup> Long term follow-up studies of people who have undertaken a lifestyle intervention programme indicate that the effects on risk factors and development of type 2 diabetes can be long lasting.<sup>12; 18</sup>

A systematic review of the literature on the cost-effectiveness of diabetes interventions recommended by the American Diabetes Association (ADA), identified intensive

lifestyle interventions in people with impaired glucose tolerance to be very cost-effective compared to standard lifestyle recommendations or no intervention. The intervention had a median cost-effectiveness ratio of USD \$1500 per Quality Adjusted Life Year (QALY) in 2007 based on eight studies.<sup>19</sup> The effectiveness and cost-effectiveness of intensive lifestyle interventions in those at high risk of developing type 2 diabetes, has led many countries to implement population-based diabetes prevention programmes.

### **2.2.1 Australian Government prevention programmes**

The Australian Government recognises that chronic disease is a long term public health problem that requires investment in sustained preventive health activities. As such, the Australian Government is focused on activities targeted to address specific needs in the population, including research and the development and promotion of national evidence-based guidelines for physical activity, nutrition and obesity. A list of Australian Government funded activities to promote healthy living are available at [Appendix C](#).

Prevention initiatives include programmes and resources to educate children in schools about the benefits of healthy eating and regular participation in physical activity through the provision of evidence-based guidelines and initiatives such as the *Sporting Schools Initiative*. The Government has also committed to developing a new National Diabetes Strategy to prioritise the national response to diabetes within the broader context of prevention and primary health care.

The new Indigenous Australians' Health Programme commenced on 1 July 2014 and includes support for healthy lifestyles and reducing tobacco use. The Government is committed to continuing efforts to address the burden of chronic disease in Indigenous people and is undertaking a review of activities under the Tackling Indigenous Smoking and Healthy Lifestyle programme in 2014 to ensure they are informed by the best available evidence.

### **2.2.2 State and territory government prevention programmes**

States and territories have a range of initiatives to promote healthy living throughout the community. The Victorian Government funded 'Life!' programme is an intensive community based lifestyle behaviour change programme managed by Diabetes Australia – Victoria. It is based on the Finnish Prevention Program<sup>20</sup> and the Greater Green Triangle Diabetes Prevention Program<sup>21</sup> and aims to help participants improve their diet, increase physical activity and achieve weight loss. Participants receive access to group and individual coaching and help developing a tailored eating and exercise plan.<sup>22</sup>

Under the '[Pharmacy Health Checks: Know Your Numbers®](#)' programme, people receive a free blood pressure test and are assisted by a pharmacist to complete the Australian type 2 diabetes risk assessment tool (AUSDRISK). Those at high risk of developing type 2 diabetes are provided with lifestyle advice by the pharmacist and

referred to a general practitioner or lifestyle modification programme. The programme was first piloted in Victoria and is currently running in Queensland and New South Wales.

### 2.2.3 Local council and not-for-profit prevention programmes

A number of not-for-profit organisations and local councils also provide healthy lifestyle programmes. Examples include:

- National Heart Foundation of Australia: [Heart Foundation Walking](#).
- Australian Diabetes Council: [BEAT IT Physical Activity and Lifestyle Program](#).
- Fitness Australia (with Baker IDI Heart and Diabetes Institute): [Lift for Life](#).
- Cycling Australia (with Amy Gillett Foundation): [AustCycle](#).
- South Western Sydney Medicare Local Ltd. and Exercise and Sports Science Australia: [Healthy Eating, Activity and Lifestyle \(HEAL\) Program](#).
- National Heart Foundation of Australia (NSW Division): [Heartmoves](#).

## 2.3 Diagnosis

The current World Health Organization (WHO) diagnostic criteria for diabetes include:

- fasting plasma glucose  $\geq 7.0\text{mmol/l}$  ( $126\text{mg/dl}$ ); or
- 2-hour plasma glucose  $\geq 11.1\text{mmol/l}$  ( $200\text{mg/dl}$ ); or
- HbA<sub>1c</sub> (glycated haemoglobin)  $\geq 6.5\%$  ( $48\text{ mmol/mol}$ ).<sup>23; 24</sup>

HbA<sub>1c</sub> is able to show a person's average level of blood glucose over the previous three months. Laboratory testing of HbA<sub>1c</sub> was accepted by the WHO in 2011 as an additional test to diagnose diabetes. In Australia, the Medical Services Advisory Committee (MSAC) recommended in April 2014, the public funding of a new Medical Benefits Scheme (MBS) item for quantitation of HbA<sub>1c</sub> for the diagnosis of diabetes in asymptomatic patients.<sup>25</sup>

Australian clinical guidelines recommend that individuals identified at high risk of developing type 2 diabetes (e.g. through the use of the AUSDRISK Tool) should have a fasting plasma glucose test every three years.<sup>26</sup> The oral glucose tolerance test is also routinely used for the diagnosis of diabetes in Australia.

## 2.4 Prevalence in Australia

The *Australian Health Survey: Updated Results (2011–12)* indicates that the total number of people in Australia aged over two years that have been diagnosed with diabetes

(excluding gestational diabetes) is 999,000, or around 4.6% of the population. This figure has increased by 9.8% since the 2007–08 survey, but has remained stable relative to the population (4.5% in 2007–08).<sup>27</sup> However, the true prevalence of diabetes in Australia is likely to be higher, as the biomedical results from the 2011–12 survey identified around one new case of diabetes for every four diagnosed cases.<sup>28</sup>

The Australian Health Survey (2011–12) showed that, of persons who reported having diabetes, 84.8% had type 2 diabetes, 11.8% had type 1 diabetes and 3.4% had an unspecified type of diabetes. More men reported having diabetes than women (5.1% of all men compared with 4.2% of all women) and the rate of diabetes increased with age and level of disadvantage. People aged 75–84 years had the highest rate of diabetes (17.0%), while people living in areas of most disadvantage were more than twice as likely to report that they had diabetes than people living in areas of least disadvantage (6.8 % versus 3.1%).<sup>27</sup> Other risk factors identified were obesity/overweight and family history.<sup>28</sup> The prevalence of type 2 diabetes is rising in youth globally; however, the rate of new cases of type 2 diabetes in people aged 10–39 in Australia remained relatively stable between 2002–03 and 2011–12. At June 2012, there was an estimated 31,000 people aged 10–39 in Australia with type 2 diabetes (0.3% of this age group).<sup>29</sup>

Type 2 diabetes is over-represented among people of Aboriginal and/or Torres Strait Islander descent and a number of other populations including people of Chinese, Vietnamese, Indian, and Maltese heritage.<sup>30</sup> In the 2012–13 Australian Aboriginal and Torres Strait Islander Health Survey, the self-reported prevalence of diabetes and/or high glucose levels in blood or urine was 8%, or around one in twelve people. Aboriginal and Torres Strait Islander females were more likely than males to report diabetes/high sugar levels (10% versus 7%), and those living in very remote areas were more likely to report diabetes/high sugar levels than those living in major cities (12% versus 7%). After adjusting for differences in age structure, Aboriginal and Torres Strait Islander people were more than three times as likely as other Australians to report diabetes/high sugar levels.<sup>31</sup>

There are also a significant number of Australians at high risk of developing type 2 diabetes. The biomedical results from the Australian Health Survey (2011–12) found that there were three people at high risk of diabetes for every diagnosed case, or around 15% of the population.<sup>28</sup> The WorkHealth programme in Victoria has screened 500,000 workers using the Australian type 2 diabetes risk assessment tool (AUSDRISK) and identified that 24% of workers were at high risk of developing type 2 diabetes (score  $\geq 12$ ). While this survey had disproportionate representation of workers in white collar industries, blue collar workers were more likely to have a high risk of developing type 2 diabetes.<sup>32</sup>

## 2.5 Complications and Impact of Diabetes in Australia

Diabetes significantly affects the health of many Australians and can result in a range of complications. Untreated or poorly managed diabetes can lead to complications including coronary heart disease, stroke, kidney failure, limb amputations and blindness. In 2011, diabetes was the sixth leading cause of death in Australia.<sup>33</sup> Cardiovascular disease is the major cause of death in people with diabetes, accounting for approximately 50% of all fatalities.<sup>34</sup> Hypertensive and cerebrovascular diseases (e.g. stroke), and kidney failure, are also common causes of death.<sup>35</sup>

As the disease progresses, diabetes macrovascular and microvascular complications can damage the heart, blood vessels, eyes, kidneys and nerves, as well as diminishing quality of life. Diabetes increases the risk of:

- heart disease and stroke
- diabetic neuropathy (nerve damage), and reduced blood flow and blood vessel damage, resulting in foot ulcers and limb amputation
- diabetic retinopathy, which can cause blindness resulting from long term accumulated damage to the small blood vessels in the retina (microaneurysms)
- nephropathy (kidney disease), which can lead to kidney failure
- death.<sup>7</sup>

After 15 years of having the disease, approximately 2% of people become blind and 10% develop severe visual impairment. Diabetes is one of the leading causes of kidney failure and this condition is the cause of death in 10–20% of people with diabetes. Diabetic neuropathy affects up to 50% of people with diabetes with common symptoms including tingling, pain, numbness, or weakness in the feet and hands.<sup>7</sup>

There were 8.4 million PBS and RPBS prescriptions supplied for diabetes medicines in 2013, at a cost to government of \$501 million (refer to [Part 4.3.1](#)). In 2008-09, the Australian Government spent \$1.66 billion on all diabetes treatment, including hospital admissions, pharmaceutical prescriptions and items supplied through the National Diabetes Services Scheme.<sup>36</sup>

## 2.6 Monitoring Glycaemic Control

### 2.6.1 HbA<sub>1c</sub>

In addition to its use as a diagnostic tool, HbA<sub>1c</sub> testing is also used to provide an indication of how well a patient's diabetes is being controlled. High levels of HbA<sub>1c</sub> indicate poor glycaemic control. The UK Prospective Diabetes Study (UKPDS) in type 2 diabetes patients showed that intensive glucose control (with a sulfonylurea or insulin) reduced and delayed progression of microvascular complications of diabetes, such as retinopathy, nephropathy and neuropathy, compared to conventional treatment. Over 10 years, the conventional treatment group had a median HbA<sub>1c</sub> of 7.8%, while the

intensive treatment group had a median HbA<sub>1c</sub> of 7.0%, and a 25% risk reduction in microvascular endpoints. However, improving glycaemic control has not been shown to have an independent impact on the development of macrovascular complications.<sup>37</sup>

HbA<sub>1c</sub> testing provides clinicians with an indication that therapy is working and the risk of long term complications is reduced.<sup>38</sup> The guidelines produced by Diabetes Australia and the Royal Australian College of General Practitioners (RACGP) recommend that patients with type 2 diabetes receive a HbA<sub>1c</sub> test as needed on an individual basis, but not more than once every three months.<sup>26</sup>

Australian guidelines recommend a general target HbA<sub>1c</sub> of ≤53 mmol/mol (7.0%) for most patients.<sup>6; 26; 39</sup> However, the guidelines also note that HbA<sub>1c</sub> targets should be individualised based on patient-specific factors, including: patient attitude, risks associated with hypoglycaemia, disease duration, life expectancy, comorbidities, vascular complications and, resources and support systems available. HbA<sub>1c</sub> targets may be lower for those who are recently diagnosed with long life expectancy, and may be higher for those with limited life expectancy or who have a history of severe hypoglycaemia (e.g. ≤64 mmol/mol, 8%).<sup>26</sup> The PBS restrictions generally require a patient to have an HbA<sub>1c</sub> of >53 mmol/mol (7%) before the more expensive oral agents and GLP-1 receptor agonists are added to their treatment regimen.

It should be noted that in people with conditions associated with altered erythrocyte survival (e.g. thalassaemia, portal hypertension, haemolytic anaemia), HbA<sub>1c</sub> is less reliable and self-monitoring of blood glucose or fructosamine testing, which measures the glycation of all serum proteins, may be of more value.<sup>38</sup>

### **2.6.2 Self-monitoring of blood glucose**

Self-monitoring of blood glucose is recommended for patients with type 2 diabetes who are using insulin where patients have been educated in appropriate alterations in insulin dose. Self-monitoring is also normally recommended for patients who are pregnant, experiencing a concomitant illness, or are undergoing changes in treatment, including lifestyle changes. Routine self-monitoring of blood glucose in low-risk patients using oral glucose-lowering medicines (with the exception of sulfonylureas) is not recommended. The frequency of testing should reflect individual circumstances and therapeutic aims.<sup>26</sup>

## **2.7 Pharmacotherapy and Review of Clinical Guidelines**

### **2.7.1 Summary**

The Department contracted Griffith University to undertake a review of Australian and international clinical guidelines for the treatment of type 2 diabetes, with a focus on pharmacotherapy.

Most Australian and international clinical guidelines recommend an individualised approach to the treatment of type 2 diabetes and the optimal HbA<sub>1c</sub> target. The balance is between optimal management of the disease, including the prevention of microvascular events, whilst reducing the risk of severe hypoglycaemia and adverse events. Other considerations are cost, efficacy, potential side effects, effects on body weight, comorbidities, life expectancy, and patient preferences and abilities (e.g. oral or injectable medicines).

Across the guidelines reviewed, metformin is considered the first line of pharmacotherapy unless the patient is contraindicated or intolerant. In this case, sulfonylureas are usually considered the most appropriate alternative to metformin. The main arguments in favour of metformin as first line therapy are long term clinical experience with this agent and low cost compared to other medicines.

The guidelines advise that if treatment with monotherapy does not result in optimal blood glucose levels then dual therapy should be initiated. The recommended dual therapy combination is usually metformin + sulfonylurea, unless contraindicated for the individual patient. In this scenario, other oral medications such as DPP-4 inhibitors (gliptins) and TZDs (glitazones) are generally recommended. The main arguments in favour of sulfonylureas raised in the different guidelines are long term clinical experience, low cost, and equal effectiveness with other agents in reducing HbA<sub>1c</sub>. Some guidelines do not favour any specific second line medicine.

If dual therapy is ineffective in controlling blood glucose, a third agent can be used to assist treatment. Guidelines commonly recommend insulin as the preferred third line option in combination with metformin + sulfonylurea. The evidence base and cost are important factors in this selection for most guidelines. Again, other treatments can be used if the preferred option is not suitable for the patient due to contraindications or intolerances, and it is generally recommended that the medicine selected is tailored to the individual patient. More complex insulin regimens are usually recommended for those not controlled by initial triple therapy.

### **2.7.2 Australian Guidelines**

The 'National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes' was published by the National Health and Medical Research Council (NHMRC) and Diabetes Australia in 2009.<sup>6</sup> The pharmacotherapy algorithm in this guideline was based partly on PBS subsidy arrangements and it does not include SGLT2 inhibitors, as they were not available at that time. Therefore, it is not discussed further in this report.

The Australian Diabetes Society is developing a new guideline on blood glucose management in type 2 diabetes. The draft pharmacotherapy algorithm was provided in-confidence for consideration by the expert Reference Group and the PBAC.

### **2.7.2.1 RACGP and Diabetes Australia**

Figure 2.1 presents the algorithm for pharmacotherapy in the management of type 2 diabetes in the 'General practice management of type 2 diabetes – 2014-15' guideline published by the Royal Australian College of General Practitioners (RACGP) and Diabetes Australia.<sup>26</sup>

The algorithm is adapted from the Scottish Intercollegiate Guidelines Network (SIGN), 'Management of diabetes; A national clinical guideline: 2010',<sup>40</sup> with additional advice and agents added, while some advice was removed. The target for optimal management is to achieve an HbA<sub>1c</sub> level of <7% (<53 mmol/mol) or individualised as agreed.

In summary, if lifestyle modification is not effective, metformin is the first line medicine unless contraindicated or not tolerated. Second and third line agents where necessary (added to existing metformin), should be chosen using an individualised approach, noting that agents work in different ways and are chosen to work synergistically. While sulfonylureas are considered the standard second line option, all other classes of type 2 diabetes medicines are considered alternative choices.

**Figure 2.1. [Algorithm for lowering glucose in type 2 diabetes – RACGP and Diabetes Australia 2014.](#)**<sup>26</sup>

### **2.7.3 International Guidelines**

The section focuses on international guidelines used in countries with similar health systems to Australia, with specific consideration of reimbursement practices. A review is provided of guidelines from Canada, England and Wales, New Zealand and the USA.

#### **2.7.3.1 Canada**

The Canadian Agency for Drugs and Technologies in Health (CADTH) pharmacotherapy recommendations were published in 2013, based on a systematic literature review and meta-analyses of type 2 diabetes medicines when used as second line and third line therapy.<sup>41</sup> The clinical outcomes considered were HbA<sub>1c</sub>, body weight and hypoglycaemia, as the evidence was considered insufficient for other clinical outcomes. CADTH considered the cost-effectiveness of the different medicines to determine the clinical treatment algorithm.

CADTH recommends metformin for first line treatment, followed by the addition of a sulfonylurea for most adults as second line therapy, and the addition of insulin NPH to Metformin + sulfonylurea as third line therapy. The reasons for these recommendations were:

- All of the medicine classes demonstrated similar improvements in HbA<sub>1c</sub> in both the second and third line network meta-analyses (with the exception of alpha-

glucosidase inhibitors and meglitinides in third line therapy).

- Sulfonylureas and insulin NPH were the most cost-effective treatment options.
- There are considerably more long term safety data for sulfonylureas and insulin NHP compared to medicines from the newer classes.

Based on cost-effectiveness, CADTH recommends that if insulin is not a suitable third line option, DPP-4 inhibitors may be added to metformin + sulfonylurea therapy. Cost-effectiveness considerations in the Canadian system may not be transferable to the Australian system due to differences in medicine costs, treatment practices and costs associated with macrovascular and microvascular events.

### **2.7.3.2 England and Wales**

The National Institute for Health and Care Excellence (NICE) published a guideline on the treatment of type 2 diabetes in 2009.<sup>42</sup> The guideline specifically considered the use of newer agents including DPP-4 inhibitors, TZDs, exenatide and injectable long-acting insulin analogues (insulin detemir and insulin glargine). The guideline is based on clinical and cost-effectiveness outcomes. The treatment targets for HbA<sub>1c</sub> are 6.5% (48 mmol/mol) for people on one glucose-lowering medicine and 7.5% (53 mmol/mol) for people on two or more medicines.

Metformin is the preferred first line treatment, with sulfonylurea as an alternative if metformin is contraindicated or not tolerated, the patient is not overweight, or a rapid therapeutic response is required due to hyperglycaemic symptoms. The preferred second line therapy is to add a sulfonylurea. Alternative therapies are DPP-4 inhibitors and TZDs if a sulfonylurea is contraindicated, not tolerated, or there is a significant risk of hypoglycaemia or hypoglycaemic consequences.

The preferred third line therapy is addition of insulin. Alternative treatments include triple therapy with metformin + sulfonylurea + DPP-4 inhibitor, TZD or GLP-1 receptor agonist. Again, cost-effectiveness considerations may not be transferable to the Australian system.

### **2.7.3.3 New Zealand**

The New Zealand 'Guidance on the management of type 2 diabetes' was published in 2011, and has since been incorporated into the 'New Zealand Primary Care Handbook 2012'.<sup>43</sup> The guideline draws on the SIGN guideline,<sup>40</sup> which was assessed as being of appropriate quality and relevance to New Zealand. The guideline recommends that treatment targets should be appropriate for the individual patient, with a HbA<sub>1c</sub> target of 50 - 55 mmol/mol or as individually agreed. Blood pressure and lipid targets are also provided.

The guideline emphasises the value of using medicines with clinical data on long term safety and effectiveness, including macrovascular and microvascular outcomes, such as metformin, sulfonylureas and insulin. First line pharmacotherapy is metformin, or a

sulfonylurea if metformin is contraindicated or not tolerated. Second line therapy involves the addition of a sulfonylurea, and third line therapy, the addition of insulin. DPP-4 inhibitors may be used as an alternative second or third line therapy, and GLP-1 receptor agonists may be used as an alternative third line treatment, but neither of these are funded by the New Zealand Pharmaceutical Management Agency (PHARMAC).

#### **2.7.3.4 USA**

##### ***American College of Physicians – 2012***

The American College of Physicians' guideline recommends metformin monotherapy as first line pharmacotherapy when lifestyle modifications are not effective in improving hyperglycaemia.<sup>44</sup> The guideline does not recommend a preferred second line therapy to add to metformin, due to a lack of strong evidence to support one therapy over another. Generic sulfonylureas are considered the cheapest second line therapy; however, the guideline states that adverse effects are generally worse with combination therapies that include a sulfonylurea. This guideline considers only oral agents.

##### ***American Diabetes Association – 2014***

The American Diabetes Association's guideline recommends a target HbA<sub>1c</sub> of <7% (53 mmol/mol) for most patients, with more stringent goals (such as <6.5%, 48 mmol/mol) for selected patients.<sup>45</sup> The guideline indicates that less stringent goals (e.g. <8%, 64 mmol/mol) may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, or other complications. A patient-centred approach is recommended to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycaemia risk, and patient preferences.

Figure 2.3 presents the treatment algorithm developed by the American Diabetes Association. Metformin, if not contraindicated and tolerated, is the preferred initial pharmacological agent. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA<sub>1c</sub>, insulin, with or without additional agents, should be considered as initial therapy. The guideline suggests that due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients.

**Figure 2.3. [Antihyperglycaemic therapy in type 2 diabetes – American Diabetes Association 2014](#).**<sup>45</sup>

## 2.8 PBS Restrictions

This section summarises the current PBS restrictions on type 2 diabetes medicines (refer to [Table 1.1](#) for a list of the medicines in scope of this Review). Items listed on the PBS may have one of the following restrictions:

- *Unrestricted*: No restrictions on therapeutic uses for the purpose of subsidy and may be prescribed at the prescriber's discretion.
- *Restricted*: Can only be prescribed if a patient's condition meets the stated restrictions, i.e. for a specific indication.
- *Authority Required*: Can only be prescribed if prior approval is obtained from the Department of Human Services (DHS) or the Department of Veterans' Affairs (DVA) as appropriate, usually by phone call or online.
- *Authority Required (STREAMLINED)*: Can only be prescribed for specific conditions, but do not need prior approval from the DHS or DVA. Instead the process is streamlined by the prescriber including a four digit streamlined authority code on the prescription.

Metformin, sulfonylureas and acarbose are unrestricted on the PBS and may be used in mono, dual or triple therapy and in combination with insulin. The PBS restrictions for the newer diabetes medicines include detailed criteria regarding initiation rules, switching rules and permitted co-administered therapies. In general, initiation of newer diabetes medicines requires the patient to have, or have had, an HbA<sub>1c</sub> >7% (53 mmol/mol), usually despite treatment with either metformin and/or a sulfonylurea. Appropriate blood glucose levels are provided as an alternative assessment in patients where HbA<sub>1c</sub> measurements are inappropriate. Most restrictions also contain a note on the specific combinations that are not PBS-subsidised.

As at 1 July 2014, TZDs, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists may be used in dual combination therapy with metformin or a sulfonylurea in type 2 diabetes patients meeting certain criteria. Only pioglitazone and exenatide are PBS-listed for use in triple combination therapy, and only pioglitazone is PBS-listed for use in combination with insulin. Pioglitazone has the widest PBS-listing and can be used in dual therapy, triple therapy and in combination with insulin.

Table 2.1 summarises the possible PBS-subsidised combinations of diabetes medicines, where all medicines are subsidised by the PBS. [Figure 2.4](#) provides a flow chart of pharmacotherapy options for type 2 diabetes based on the PBS restrictions.

**Table 2.1. Possible PBS-subsidised combinations of diabetes medicines (at 1 July 2014).**

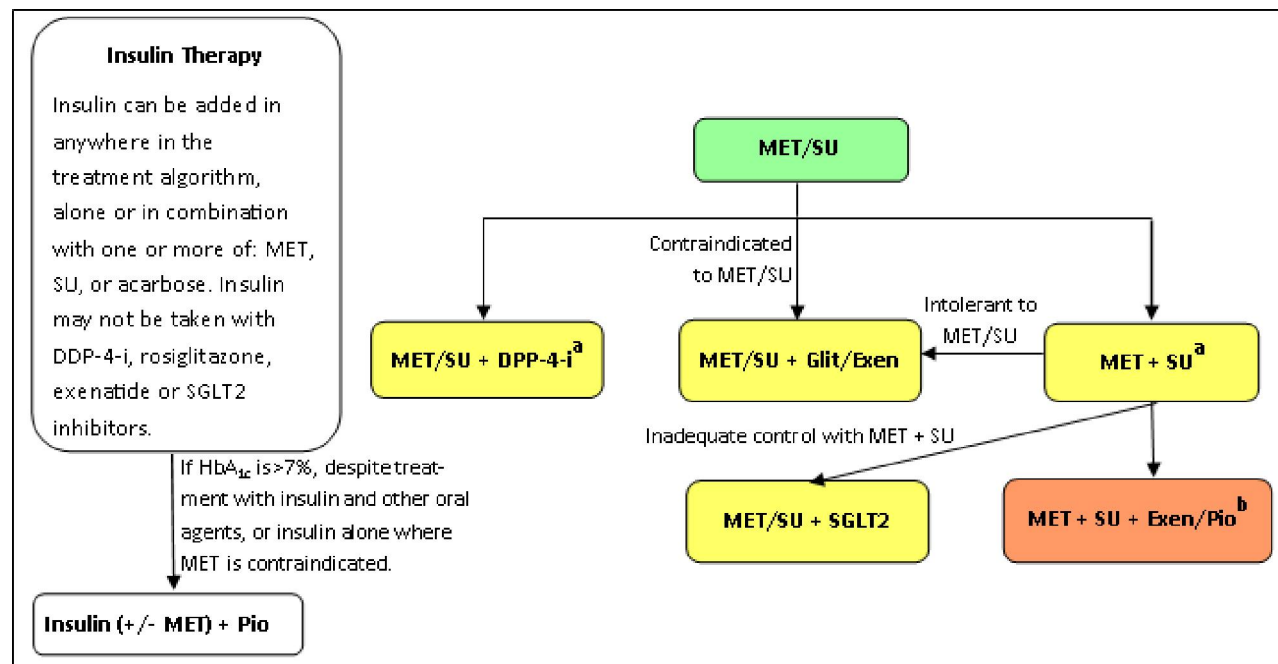
Use	Oral only	Injections ± oral
Monotherapy	Metformin SU Acarbose	Insulin
Dual combination therapy	Metformin + SU Metformin + acarbose SU + acarbose <b>DPP-4</b> + metformin <b>TZD</b> + metformin <b>SGLT2</b> + metformin <b>DPP-4</b> + SU <b>TZD</b> + SU <b>SGLT2</b> + SU	Metformin + insulin SU + insulin Acarbose + insulin <b>Pioglitazone</b> + insulin <b>Exenatide</b> + metformin <b>Exenatide</b> + SU
Triple combination therapy	Metformin + acarbose + SU <b>Pioglitazone</b> + metformin + SU	Metformin + SU + insulin Metformin + acarbose + insulin SU + acarbose + insulin <b>Exenatide</b> + metformin + SU <b>Pioglitazone</b> + metformin + insulin <b>Pioglitazone</b> + SU + insulin <b>Pioglitazone</b> + acarbose + insulin
Other combinations	-	Metformin + acarbose + SU + insulin <b>Pioglitazone</b> + metformin + SU + insulin <b>Pioglitazone</b> + metformin + acarbose + insulin <b>Pioglitazone</b> + SU + acarbose + insulin <b>Pioglitazone</b> + metformin + SU + acarbose + insulin

Abbreviations: DPP-4 = DPP-4 inhibitor; SGLT2 = SGLT2 inhibitor; and SU = sulfonylurea.

Notes: **Bolded** medications represent the newer agents with restrictions. TZDs include pioglitazone and rosiglitazone. DPP-4 inhibitors include linagliptin, saxagliptin, sitagliptin, vildagliptin and alogliptin. SGLT2 inhibitors include canagliflozin and dapagliflozin.

It is assumed that unrestricted PBS medications can be used in possible combinations which reflect clinical practice/individual physician therapeutic decisions; the PBS neither explicitly restricts nor mandates such combination use. Some of these possible combinations may not reflect best practice or likely combinations seen in practice.

**Figure 2.4. Flow chart of pharmacotherapy treatment options for type 2 diabetes based on PBS restrictions (at 1 July 2014).**



**Notes:**

Acarbose has an unrestricted listing and can be used in any combination with MET, SU and Insulin.

Green = monotherapy; yellow = dual therapy; red = triple therapy; white = mono or combination therapy.

<sup>a</sup> Switching allowed between MET + SU and MET/SU + DPP-4-i.

<sup>b</sup> Switching allowed between MET + SU + Exen and MET + SU + Pio.

**Abbreviations:** DPP-4-I = DPP-4 inhibitor (gliptin); Exen = exenatide; Glit = glitazone; MET = metformin; Pio = pioglitazone; SGLT2 = SGLT2 inhibitor (gliflozin); SU = sulfonylurea.

## 2.9 Australian Government Management Programmes and Publications

This section provides information on a number of Australian Government programmes that support diabetes management, with further programmes provided at [Appendix C](#).

### 2.9.1 NPS MedicineWise Programmes

NPS MedicineWise is an independent organisation funded by the Australian Government to provide evidence-based information to support quality use of medicines and improve the way medicines and medical tests are prescribed and used. NPS MedicineWise has developed and implemented four educational (academic detailing) programmes for health professionals focusing on type 2 diabetes since its conception in 1998. The most recent programme, *Type 2 Diabetes: Priorities and targets (2012)*, resulted in the engagement of a total of 17,448 unique health professionals, including 11,362 general practitioners (GPs).

Key messages of the programme were:

- Address blood pressure (BP) and lipids as a priority.
- Treat according to cardiovascular risk.
- Controlling BP and lipids appears more effective in reducing cardiovascular disease than tightening blood glucose levels.
- Individualise blood glucose targets based on patient factors and duration of disease.
- Lowering blood glucose levels reduces microvascular complications.
- Use the ADS position statement to individualise HbA<sub>1c</sub> targets.

Key messages of previous programmes were:

- Encourage intensive lifestyle change to slow progression to diabetes and prevent complications, and encourage continuing lifestyle interventions to decrease disease progression.
- Initiate insulin early by adding night-time basal insulin to oral diabetes medicines.
- Ensure metformin is part of ongoing therapy. Metformin is the preferred initial drug therapy unless contraindicated.
- Review use of TZDs in heart failure and ischaemic heart disease.
- Individualise lifestyle interventions, targets, monitoring and drug therapy.

The 2005 and 2008 diabetes management programmes reached 12,464 GPs (51% of all GPs) and participation was associated with a relative increase in the prescribing of metformin. The 2008 programme also resulted in increased rates of insulin prescription and relative decreases in the rates of TZD prescriptions.<sup>46</sup>

### **2.9.2 NPS MedicineWise Articles on Pharmacological Management**

NPS MedicineWise also provides online training in the management of type 2 diabetes for a variety of health professionals, including Pharmacy Practice Reviews,<sup>47</sup> Curriculum modules for students,<sup>48; 49</sup> case studies,<sup>50</sup> and Clinical e-Audits for GPs.<sup>51</sup> The key messages in the online articles on pharmacological management of type 2 diabetes are:

- Manage BP and cholesterol to reduce cardiovascular outcomes, using targets as guides.
- Individualise glycaemic targets. Tight glycaemic control is desirable for people recently diagnosed (HbA<sub>1c</sub> ≤ 48 mmol/mol, or 6.5%). Lower targets can be set for those using lifestyle interventions or metformin. For those with longer standing disease, cardiovascular disease or other comorbidities, the benefits of tight glycaemic control do not outweigh the risks of severe hypoglycaemia and a HbA<sub>1c</sub> target of ≤ 53 mmol/mol or 7% is generally appropriate.
- Metformin is the first medicine of choice.
- Adding a sulfonylurea is the preferred second-line treatment option unless there are contraindications, or for use first-line if metformin is contraindicated.

Sulfonylureas are as effective in reducing HbA<sub>1c</sub> as newer medicines and have been shown to reduce microvascular complications.

- Insulin is the preferred medicine for people with inadequate glycaemic control despite taking maximally tolerated doses of metformin and a sulfonylurea, as it reduces microvascular outcomes and is highly effective at reducing HbA<sub>1c</sub>.
- Newer medicines improve glycaemic control, but none have been shown to reduce microvascular or macrovascular complications. No combination is superior in lowering HbA<sub>1c</sub> or safety.<sup>52; 53</sup>

### **2.9.3 Diabetes Care Project**

The Diabetes Care Project is a three and a half year pilot (2011-12 to 2014-15) testing new models of health care delivery in the primary health care sector, designed to improve care for adults with either type 1 or type 2 diabetes. The pilot was implemented in three states (Queensland, South Australia and Victoria) across a mix of urban, regional and rural areas. The Australian Government is providing \$31.4 million (GST exclusive) over the three years for the Project. The Victorian Government contributed an additional \$2 million, bringing the total investment to \$33.4 million (GST exclusive).

The evaluation of the pilot will compare results between two intervention groups and a control group of general practices:

- Group 1 will pilot an IT system and an education and training programme.
- Group 2 will pilot an IT system, an education and training programme, a flexible funding model and a care facilitator role.

The evaluation of the pilot will also examine the project's impact on patients' health outcomes and other indicators such as patient well-being and experience. Results will be used to inform future policy development regarding arrangements chronic disease management. The final report on the evaluation will be provided to the Department in September 2014, and the results will then be considered by the Government. It is expected the results from the pilot will be used to inform future policy development regarding arrangements for the management of chronic disease, and may also inform elements of the new National Diabetes Strategy, expected to be developed by mid-2015.

### **2.9.4 Quality Assurance for the Aboriginal and Torres Strait Islander Medical Services (QAAMS) Pathology Programme**

The Australian Government has funded the Quality Assurance for Aboriginal and Torres Strait Islander Medical Services (QAAMS) pathology programme since 1999 to support the provision of culturally appropriate and clinically effective diabetes management in Aboriginal and Torres Strait Islander communities. The programme supports better management of diabetes by enabling participating Aboriginal Medical Services (AMS) and Aboriginal Community Controlled Health Services (ACCHS) to provide accurate diabetes-related pathology testing on site through 'point of care testing' (PoCT) for

HbA<sub>1c</sub> and ACR (urine albumin:creatinine ratio) at Indigenous health services enrolled in the programme.

The QAAMS programme is administered on behalf of the Department by the Flinders University Rural Clinical School and the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs Pty Ltd. The Australian Government is providing more than \$4 million (GST exclusive) over four years to expand the number of sites enrolled in the QAAMS programme from 120 sites to 200 sites by June 2016. As at 30 June 2014, there were 188 enrolments in the QAAMS programme (exceeding the target of 180 sites).

## PART 3 – STAKEHOLDER CONSULTATION

### 3.1 Public Consultation Processes

***Disclaimer:** Only information provided in submissions and at the Stakeholder Forum has been included in the following summaries. No attempt was made to reach consensus and the views and opinions should not be considered as medical advice.*

#### 3.1.1 Submissions addressing the ToR

Submissions addressing the ToR for the Medicines Review were invited from interested organisations and individuals. For further information on the process refer to [Part 1.3.1](#). Where permission was provided, the submissions were published on the Medicines Review Public Consultation website.

Key viewpoints expressed through the submissions include:

- Patient-centred, individualised treatment is important to quality care, optimal patient outcomes and adherence to prescribed medicines. HbA<sub>1c</sub> targets and choice of medicine should be determined for an individual taking account of factors such as: time since diagnosis, symptoms, cardiovascular profile, weight, risk of hypoglycaemia, side effects, comorbidities and features that may facilitate patient compliance.
- The NHMRC-endorsed guidelines should be regularly reviewed and updated.
- PBS restrictions are increasingly inconsistent with best practice and clinical need.
- Concern over Review processes, including transparency and appropriate consultation.

The following points were expressed by one or a small number of submissions:

#### **Industry organisations**

- Type 2 diabetes medicines differ on tolerability and ease of use to a greater extent than they differ on glucose-lowering efficacy.
- Extensive clinical experience, long term randomised controlled trial data and clinical guidelines all strongly support sulfonylureas as the second line treatment of choice.
- National and international guidelines emphasise weight control and minimisation of hypoglycaemia as cornerstones of diabetes care. Sulfonylureas have a higher risk of hypoglycaemia and weight gain than newer medicines.
- DPP-4 inhibitors do not increase the risks of hypoglycaemia, weight gain, cardiovascular events or fractures. The evidence demonstrating the effectiveness of

DPP-4 inhibitors in triple oral therapy and in combination with insulin should be assessed.

- Insulin treatment is often delayed, with many patients having significant periods of poorly managed diabetes before commencement. There is a need for more insulin self-management education and ongoing support.
- Caution should be used when prescribing TZDs due to increased risk of congestive heart failure, skeletal fracture, weight gain and fluid retention.
- Patient-centred outcomes are inadequately valued by PBAC processes.
- PBS restrictions should be simplified to align with TGA indications.
- The DUSC analysis may have overestimated use outside of the PBS restrictions for newer type 2 diabetes medicines. The analysis may have missed some people who trialled a sulfonylurea, as only five years prior prescribing history was considered.
- The prescribing of therapies outside of PBS restrictions may be unintentional, due to a misunderstanding of PBS restrictions, or deliberate, based on clinical judgment and consideration of the health outcomes most valued by the physician and patient.
- Comparing the price of newer medicines to older off-patent medicines creates a disincentive to companies to bring new medicines to the Australian market.

### ***Health professionals and related peak bodies***

- HbA<sub>1c</sub> targets should be individualised, considering the balance of risks and benefits of intensive blood glucose control. Targets below 7% may be appropriate for those with newly diagnosed and uncomplicated disease, while for older patients and those with long standing disease the risks of hypoglycaemia and adverse events may outweigh the benefits of a low HbA<sub>1c</sub> target.
- Management of concomitant hypertension and dyslipidaemia is important, as the greatest contributors to disease burden for people with type 2 diabetes are cardiovascular disease and microvascular complications.
- The effect of newer medicines on long term cardiovascular outcomes remains undetermined.
- The cost-effectiveness of diabetes medicines needs to be considered in terms of long term health outcomes and overall costs.
- There should be a system of incremental value-based pricing for the PBS subsidisation of new type 2 diabetes medicines, similar to the PBAC decision on the subsidisation of statins, especially when there is uncertainty about the long term clinical benefit of many of these medicines.
- A treatment stop clause should be introduced for when medicines do not sufficiently improve glycaemic control.

- Hypoglycaemia has a considerable impact on patients and may lead to increased hospitalisations and reduction in medication adherence. DPP-4 inhibitors and GLP-1 receptor agonists may help address the issues of weight gain and hypoglycaemia.
- The use of metformin with insulin and a DPP-4 inhibitor may be cost-effective.
- The current availability of multiple clinical guidelines may be causing prescriber confusion.
- Prescribing guidelines should be enforced, or there should be incentives for prescribers and patients to use lower cost medicines.
- Where PBS listings differ from guidelines, the rationale should be explained.
- A patient registry for people with type 2 diabetes, linking hospital, PBS and Medical Benefits Schedule (MBS) data could be used to monitor outcomes, side-effects and compliance with guidelines.
- Professional education programmes should form part of a comprehensive strategy to improve the management of diabetes.
- Pharmacists should be better used to support improved prescribing practices through incentives to encourage interaction with prescribers. Dose Administration Aid services should be subsidised for at-risk groups. Community pharmacies could provide a pre-diabetes screening programme based on the Pharmacy Diabetes Care Programme.

### ***Consumers and consumer groups***

- Triple oral therapy is a widely used and effective treatment for improving diabetes management. PBS subsidised triple oral therapy with metformin, sulfonylurea and a DPP-4 inhibitor would benefit quality care in Australia.
- The Review should consider long term outcomes and cost-effectiveness, and effects on patient quality of life.

### **3.1.2 Stakeholder Forum**

The Stakeholder Forum, held on 12 September 2013, provided an opportunity for a broad spectrum of stakeholders to inform the Medicines Review. For further information on the process refer to [Part 1.3.2](#). This section provides a brief summary of the views expressed by stakeholders. A more detailed Forum Summary was published on the Review website on 9 May 2014.

The aims of the Forum were to discuss:

- appropriate treatment pathways for type 2 diabetes

- clinical benefit and safety profiles associated with type 2 diabetes medicines
- the appropriateness and ease of use of the guidelines and PBS restrictions.

The key discussion points raised by stakeholders were:

- There should be a patient-centred, individualised approach to treatment. Choice of therapy should be based on the patient, including consideration of age, stage of disease at consultation, health literacy, the availability of education and support, weight, comorbidities and lifestyle. This needs to be considered in the context of the current evidence, and the side effect profiles and mode of action of the medicines.
- Most third line agents are comparable to sulfonylureas in terms of HbA<sub>1c</sub> lowering. However, diabetes outcomes should not be measured by HbA<sub>1c</sub> levels alone. Other important outcomes include avoidance of hypoglycaemia, weight, side effects, hospitalisations, long term health outcomes, and development of microvascular and macrovascular complications.
- It is important to try to minimise hypoglycaemic events due to their multi-dimensional effect on patients, including quality of life, productivity, risk of falls in the elderly, and for severe hypoglycaemia, limiting expensive hospital admissions.
- Patients should be involved in treatment choice and provided with information by their clinician to assist in this decision. Some patients may prefer a treatment strategy that involves earlier intervention and lower HbA<sub>1c</sub> targets.
- Current treatment guidelines create confusion because they reflect the PBS reimbursement criteria and not the most current clinical evidence. The treatment guidelines should be updated and consolidated into a single set of guidelines. This will require collaboration between peak bodies and the NHMRC.
- The treatment algorithm should be evidence-based, patient-centred, easy to implement in clinical practice, and should make clear the PBS requirements and criteria for subsidy. Microvascular and macrovascular risks, blood pressure and lipid levels need to be incorporated.
- Treatment pathways need to consider prevention, education and lifestyle factors. Community and school based education programs for children and parents are important to motivate people to address lifestyle factors.
- Stakeholders noted that the Australian Diabetes Society and the RACGP were developing updated guidelines.

### 3.2 Internal Working Group

The Internal Working Group provided input to the Medicines Review, including:

- Information on Australian Government type 2 diabetes prevention programmes, including programmes targeted at Aboriginal and Torres Strait Islander populations.
- Information on type 2 diabetes management programmes, including the Diabetes Care Project.

### 3.3 Reference Group

The Reference Group provided input to the Medicines Review, including:

- Highlighting that variance in pharmacotherapy algorithms for type 2 diabetes in different countries is likely to be due to cost-effectiveness concerns in these countries.
- Raising that MSAC had supported public funding of a new MBS item for quantitation of HbA<sub>1c</sub> for the diagnosis of diabetes in Australia.
- Providing guidance on the approach to the systematic literature review, including that the review:
  - focus on long term and patient-relevant outcomes, rather than surrogate measures, e.g. HbA<sub>1c</sub>
  - highlight literature not previously seen by the PBAC, particularly comparisons for dual therapies not previously considered by the PBAC
  - focus on triple therapy, particularly clinical effectiveness
  - need not provide a meta-analysis of monotherapy and dual therapy trials as the PBAC had already assessed the literature and made decisions on these
  - exclusion criteria of 250 participants per arm should be reduced for the triple therapy trials to 100 per arm as only a limited number of studies would be available otherwise
  - only undertake a meta-analysis of trials that studied medicines added to existing medications if outcomes were comparable, and that only safety should be considered in this group.
- Reviewing the trials identified in the systematic literature review to ensure that all relevant studies were included.
- Identifying that some groups may be discouraging the use of sulfonylureas, against evidence-based practice and guidelines, and that additional prescriber education on the role of sulfonylureas may be needed.
- Requesting that the cost of the medicines be included in the Report and any prescriber education resulting from the Review.

## PART 4 – UTILISATION ANALYSIS (TOR 1 & 2)

**ToR 1:** Describe the utilisation and patterns of treatment of PBS listed drugs for type 2 diabetes, and compare these with PBS restrictions.

**ToR 2:** Consider if the utilisation of PBS listed drugs in current clinical practice represents expected cost-effective use.

### 4.1 Key findings

- Overall Government expenditure on type 2 diabetes medicines increased from around \$130 million in 2000 to \$501 million in 2013. In 2013, the highest expenditure was on insulins.
- Metformin and sulfonylureas were the most commonly prescribed oral type 2 diabetes medicines between January 2000 and April 2014. The use of metformin, FDC products, and DPP-4 inhibitors increased over this time period. The use of TZDs increased rapidly from listing in 2003 to 2007, but then declined, most likely as a result of safety concerns with rosiglitazone.
- In patients initiating diabetes pharmacotherapy between 2003–04 and 2009–10, metformin was the most common first line medicine, in line with clinical guidelines.
- In the first 3.5 years after starting therapy, more than 60% of patients with type 2 diabetes did not add or switch medicines and fewer than 5% of patients added or switched medicines outside the PBS restrictions.
- For patients initiating a third line agent (a DPP-4 inhibitor, TZD or exenatide) between July and December 2011, 47.7% had not received a supply of both metformin and a sulfonylurea in the 2 years prior. The PBS restrictions at the time required prior use of metformin and a sulfonylurea, except where contraindicated.
- Use outside the restrictions in patients initiating a third line agent, was highest for those initiating a DPP-4 inhibitor + metformin FDC (55%), a DPP-4 inhibitor (49%), or rosiglitazone + metformin FDC (46%), and lowest for those initiating exenatide (20%). The DUSC considered that the availability of FDCs may be contributing to use outside of the PBS restrictions.
- Of patients prescribed a third line agent between February 2011 and May 2012, 27.9% were co-prescribed a regimen of medicines that did not comply with PBS subsidy criteria.
- Of the third line agents, pioglitazone had the least use beyond the PBS restrictions for co-prescribed therapies (13% of pioglitazone users).

- The use of a DPP-4 inhibitor with both metformin + sulfonylurea (triple oral therapy) contributed the most to use outside PBS restrictions in terms of co-prescribed therapies involving a third line agent. Some use of DPP-4 inhibitor monotherapy was also evident. This use of DPP-4 inhibitors had not been accepted as cost-effective by the PBAC.
- Of patients prescribed exenatide, 29.6% were prescribed the medicine in a regimen of co-prescribed therapies that did not comply with PBS subsidy criteria, primarily use in combination with insulin (16.1% of patients). This use had not been accepted as cost-effective by the PBAC.
- The DUSC considered that the overall rate of use beyond the PBS restrictions in relation to third line agents is at least 30%, and that this is a conservative estimate of non-cost-effective use.

## 4.2 Introduction

This part of the report summarises an analysis of the utilisation of type 2 diabetes medicines undertaken for the DUSC. The DUSC requested the analysis as there had been a number of changes to type 2 diabetes products listed on the PBS and safety concerns had arisen for some medicines. DUSC also noted that the PBS restrictions had become complex over time.

The specific objectives of the analysis were to:

- describe the utilisation and patterns of treatment of medicines for type 2 diabetes, including the sequence of therapies and agents administered concomitantly; and
- compare this use with current PBS restrictions.

Within that framework, this report covers four aspects of utilisation:

1. Overall utilisation of PBS listed medicines for diabetes, including the number of prescriptions and expenditure.
2. Patterns of use when patients initiate pharmacotherapy for type 2 diabetes.
3. Medicines used prior to initiating third line agents (DPP-4 inhibitors, TZDs and exenatide) and compliance with PBS restrictions.
4. Co-administration of medicines to treat type 2 diabetes and compliance with PBS restrictions for third line agents (DPP-4 inhibitors, TZDs and exenatide).

The scope of the analysis included all medicines listed on the PBS that are used to treat diabetes (Anatomical Therapeutic Chemical (ATC) classification A10). Note that both exenatide and basal insulin were subject to special pricing arrangements during the

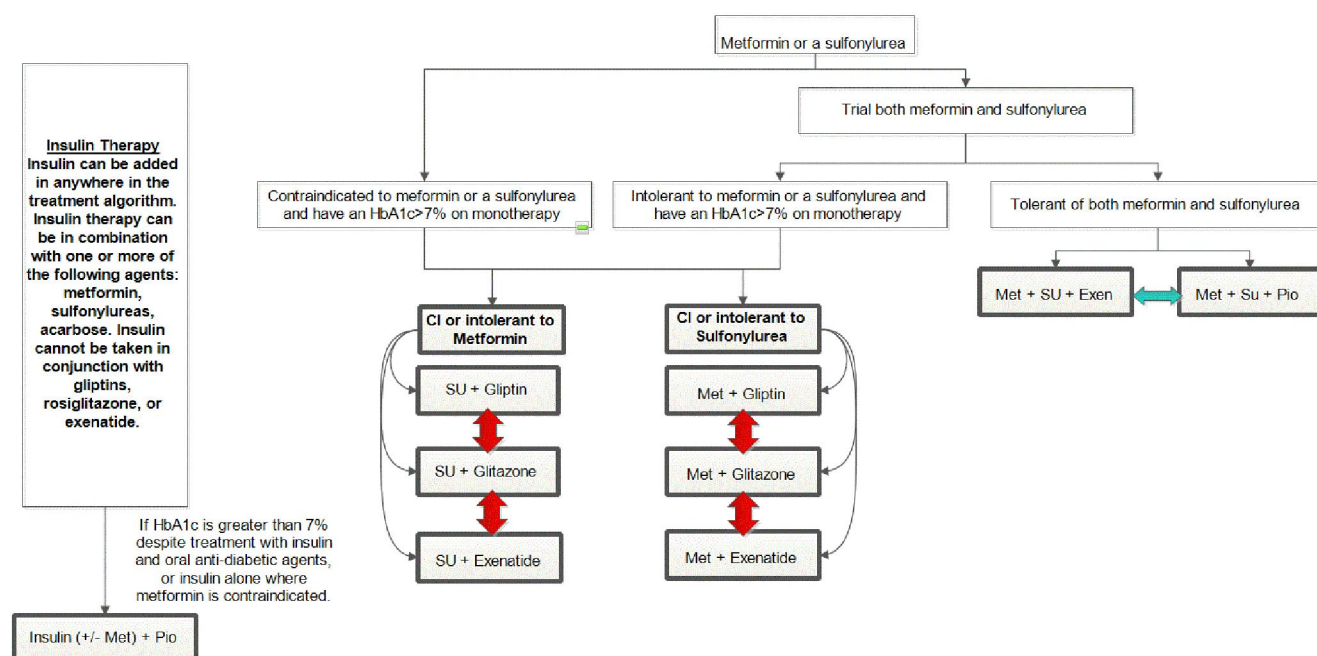
period of the analysis. The Glossary contains an explanation of the terms used in this analysis and [Appendix D](#) contains a list of medicine abbreviations.

Analyses 1 and 2 on overall utilisation of diabetes medicines and initiating medicines were considered by the DUSC in October 2012. Analyses 3 and 4, on compliance with PBS restrictions regarding prior therapies and co-prescribed medicines, were considered in February 2013. This Report contains an updated version of analysis 1.

#### 4.2.1 Restrictions

At October 2012, metformin, sulfonylureas, acarbose and all insulins except for insulin detemir were unrestricted benefits on the PBS. Insulin detemir was a restricted benefit for type 1 diabetes. Rosiglitazone and rosiglitazone + metformin FDC were authority required listings due to safety concerns. Exenatide, pioglitazone and DPP-4 inhibitors (as single agents and FDC products) were authority required (streamlined) listings and could be prescribed through the PBS only for the treatment of type 2 diabetes in specific circumstances. The PBS restrictions are presented as a flow chart in Figure 4.1. In practice, metformin was usually considered first line therapy, with a sulfonylurea added on to metformin as a second line agent. [Appendix E](#) contains further detail on the PBS restrictions and TGA-approved indications for type 2 diabetes medicines at the time of the analysis.

**Figure 4.1. PBS restrictions for type 2 diabetes medicines (at October 2012).**



**Notes:** HbA1c = glycosylated haemoglobin.

The red and blue arrows indicate where switching between medicines is permitted without having to requalify with respect to HbA<sub>1c</sub> levels. Acarbose has an unrestricted listing and can be used at any point in therapy.

## **4.3 Methods**

### **4.3.1 Overall utilisation of diabetes medicines**

The number of prescriptions and expenditure for all medicines used in the treatment of diabetes were extracted from the DUSC database for the period January 2000 to April 2014. The DUSC database combines data for PBS prescriptions submitted to the Department of Human Services (DHS) for payment of a PBS/RPBS subsidy by the Government, with an estimate of under-copayment and private prescriptions based on dispensing data from a sample of pharmacies. From April 2012, the survey estimate of under-copayment data is replaced by actual under-copayment data collected by DHS. Private prescription data was removed from this analysis, as data collection for private prescriptions ceased in September 2012. The prescription data presented in this analysis are based on the date of supply to the patient.

Government expenditure data are available for prescriptions where a PBS subsidy is paid. Government expenditure for subsidised PBS/RPBS prescriptions presented in this Report is based on the prices published in the PBS Schedule minus the patient copayment. Where special pricing arrangements apply, final Government expenditure may differ from that shown.

### **4.3.2 Initiating medicines for patients with type 2 diabetes**

This part of the analysis examined patterns of medicine use when patients initiated pharmacotherapy for type 2 diabetes.

De-identified pharmacy claim data for PBS-subsidised prescriptions for all diabetes medicines was extracted from the DHS (Medicare) database for the period July 2002 to December 2011. From this extract, four cohorts of concessional patients initiating treatment for type 2 diabetes were defined to allow comparison of utilisation over time. The selected cohorts established for the years 2003/04, 2005/06, 2007/08 and 2009/10 were chosen to align with changes in availability of drugs on the PBS. A follow-up period of 3.5 years was defined for the 2003/04, 2005/06 and 2007/08 cohorts. For the 2009/10 cohort a follow-up period of only 18-30 months was possible.

Concession only cohorts were used because some medicines used to treat diabetes are priced below the general patient copayment, and the supply of under-copayment medicines is not captured for general patients in the dataset. The DUSC considered that patterns of use in general and concessional patients were likely to be sufficiently similar to allow extrapolation of the concessional cohort findings to the total population with diabetes. It is also worth noting that the majority of patients with diabetes were concession patients.

Patients were assumed to be initiating on therapy if they did not have a prescription for a type 2 diabetes medicine supplied in the previous 12 months. The following patients were assumed to have type 1 diabetes and were excluded from the analysis:

- Patients who started treatment with insulin alone and who were  $\leq 20$  years of age.
- Patients aged  $> 20$  years at initiation who received insulin detemir and no other product over their prescription history.

Treatment pathways post-initiation were determined for individual de-identified patients from their prescription supply history. The analysis of prescription pathways included an assessment of whether new therapy was introduced as a replacement for an existing drug (switch) or as an additional form of therapy (add). All analyses were based on the date of supply of the medicines.

#### **4.3.3 Therapies used before third line agents**

This analysis examined an incident cohort of patients initiating therapy with a third line agent (DPP-4 inhibitor, TZD or exenatide), to determine patterns of prior prescribing and compliance with the PBS restrictions.

De-identified PBS/RPBS pharmacy claim data for all diabetes medicines supplied between July 2009 and July 2012 (inclusive) were extracted from the DHS (Medicare) database. From this extract, a cohort including all concession patients who received a first supply of a DPP-4 inhibitor, TZD or exenatide between July and December 2011 (inclusive) was extracted. A first supply was defined as no prescription dispensed in at least the previous two years. For this cohort, prescription histories were analysed to determine whether metformin and/or a sulfonylurea had been dispensed in the two years prior to initiation of the DPP-4 inhibitor, TZD or exenatide; a subsequent analysis looked at whether metformin and/or a sulfonylurea had been dispensed in the previous five years.

The DPP-4 inhibitors were considered as a group as they all had the same PBS restrictions at the time of the analysis. Rosiglitazone and pioglitazone were considered separately as pioglitazone had more subsidised indications than rosiglitazone and the medicines had different safety profiles.

Patients who initiated a third line agent were classified into the following groups based on prescriptions supplied in the two years prior to the patient's initiation date:

1. Metformin only.
2. Sulfonylurea only.
3. Neither metformin nor sulfonylurea.
4. Metformin and sulfonylurea supplied and deemed to be co-administered for more than five consecutive weeks.
5. Metformin and sulfonylurea supplied and deemed to be co-administered from 1-5 consecutive weeks.

6. Metformin and sulfonylurea supplied but not deemed to be co-administered at any time.

Group 5 above was included to distinguish patients who added metformin or sulfonylurea but did not persist with treatment. This group may represent patients who trialled, but were found to be intolerant to, one of the drugs in the combination.

To classify patients into the above groups, the analysis estimated medicine treatment regimens from prescription supply.

While sample packs of sulfonylureas could lead to an overestimation of non-compliance with PBS restrictions. The DUSC noted that anecdotally, there were few sample packs of sulfonylureas being provided. The committee did not consider that this would greatly affect the conclusions regarding the extent of usage beyond the PBS restriction.

#### **4.3.4 Co-administration**

This part of the analysis examined a prevalent cohort of patients, to determine patterns of co-administered diabetes medicines and compliance with PBS restrictions for third line agents.

De-identified PBS/RPBS pharmacy claim data for all diabetes medicines supplied between July 2010 and July 2012 (inclusive) were extracted from the DHS (Medicare) database. From these data, a cohort including all concession patients was selected, and the medicine regimens were determined for individual de-identified patients for the period between February 2011 and May 2012. The data extract was longer than the analysis period to correctly establish the medication regimen.

Regimens that included a third line agent were assessed for compliance with the PBS restrictions regarding co-administered medicines. While it was possible for regimens to be non-compliant with PBS restrictions in more than one way, for the purposes of this analysis, these regimens were only counted once.

Where therapies overlapped for five weeks or less, a switch was deemed to have occurred. Overlaps of greater than five weeks were considered co-administration of therapy. The DUSC considered this overlap period to be appropriate, as the pack sizes for the third line agents provide approximately one month of therapy. The five week overlap window may misclassify some patients who co-administered therapy for less than one month as switching therapy, but the DUSC considered this a reasonable balance between sensitivity and specificity.

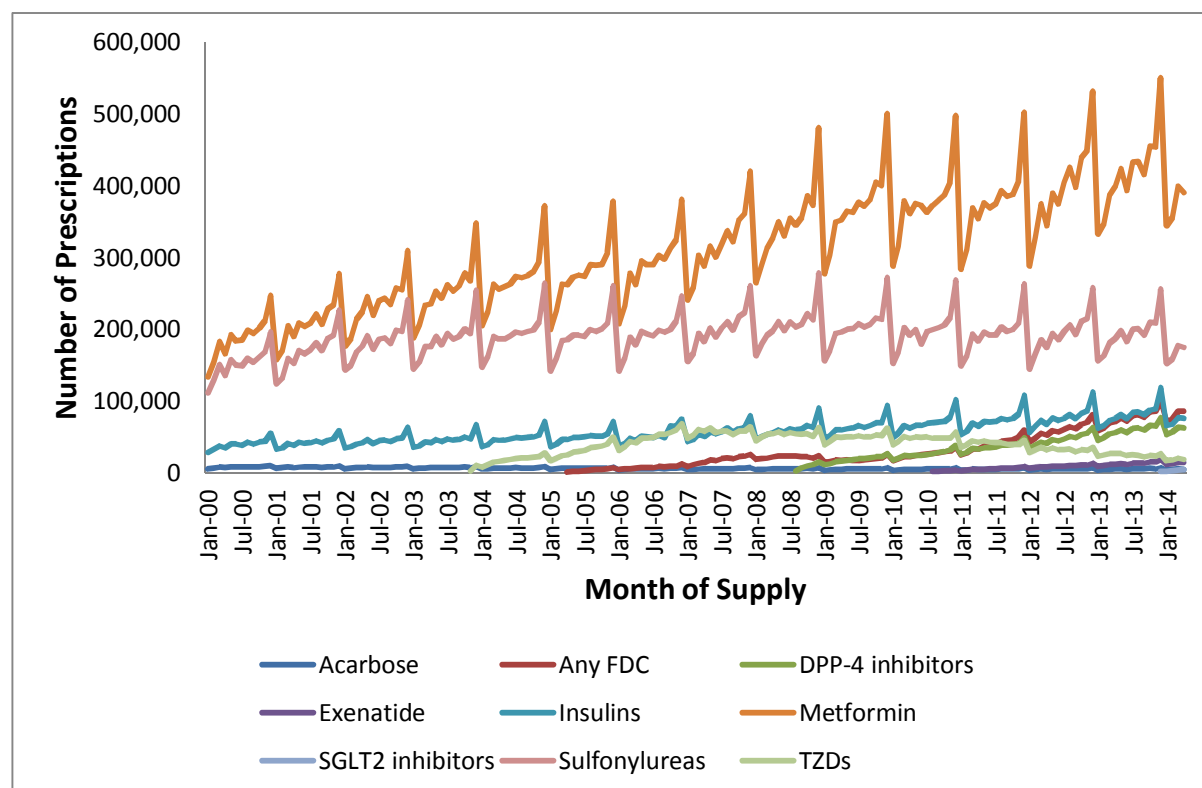
## **4.4 Results and discussion**

### **4.4.1 Overall utilisation of diabetes medicines**

Metformin and sulfonylureas were the most commonly prescribed diabetes medicines between 2000 and 2013 (Figure 4.2). During this time, the use of metformin increased

from 2.3 million to 5.0 million prescriptions per year, while the use of sulfonylureas has remained relatively stable at around 2.3 million prescriptions per year since 2004. The utilisation of acarbose was reasonably stable and low throughout the period, at around 55,000 prescriptions per year since 2006 (data not shown). In Figure 4.2, the increase in prescriptions seen in December and subsequent decline in January each year is due to seasonal fluctuations associated with the PBS Safety Net.

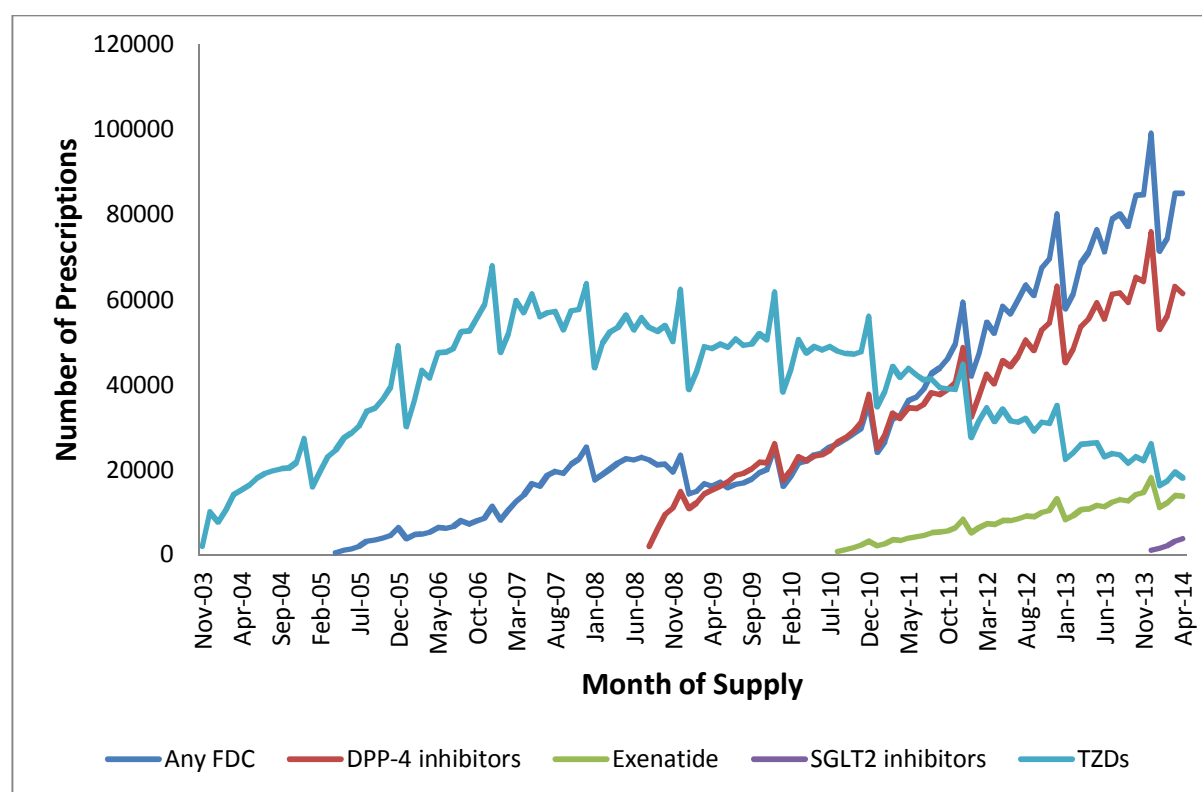
**Figure 4.2. Diabetes medicines prescriptions supplied, January 2002–April 2014.**



Notes: 'Any FDC' includes sitagliptin, linagliptin, vildagliptin, alogliptin, saxagliptin, glibenclamide and rosiglitazone FDCs with metformin. 'DPP-4 inhibitors' includes sitagliptin + simvastatin FDC.

Figure 4.3 shows the number of prescriptions dispensed for third line agents (DPP-4 inhibitors, TZDs and exenatide) and FDCs, between January 2000 and April 2014. The DPP-4 inhibitors show rapid uptake following the PBS listing of the first DPP-4 inhibitor (sitagliptin) in 2008, to total over 700,000 single agent prescriptions supplied in 2013. There was also rapid uptake of FDC products, particularly following the listings of DPP-4 inhibitor FDCs, which commenced in 2009. The majority of FDC products are metformin + DPP-4 inhibitors. The utilisation of TZDs rose quickly from entry in 2003 to 2007, then declined, most likely as a result of safety concerns with rosiglitazone and subsequent changes to the PBS restrictions.

**Figure 4.3. Third line agent prescriptions supplied, January 2002–April 2014.**



Notes: 'Any FDC' includes sitagliptin, linagliptin, vildagliptin, alogliptin, saxagliptin, glibenclamide and rosiglitazone FDCs with metformin. 'DPP-4 inhibitors' includes sitagliptin + simvastatin FDC.

### ***Overall Australian Government expenditure***

Table 4.1 provides the overall annual cost to Government of diabetes medicines and percentage annual growth in costs. The higher rates of growth in 2004 and 2007 coincided with the first twelve months after listing of the TZDs and insulin glargine, respectively.

Average annual growth in PBS/RPBS costs between 2000 and 2013 was 11%, while average annual growth in prescriptions supplied was only 6%. This indicates an increase in prescribing of more expensive diabetes medicines.

**Table 4.1. Annual PBS/RPBS prescriptions supplied and cost to Government of diabetes medicines, 2000–2013.**

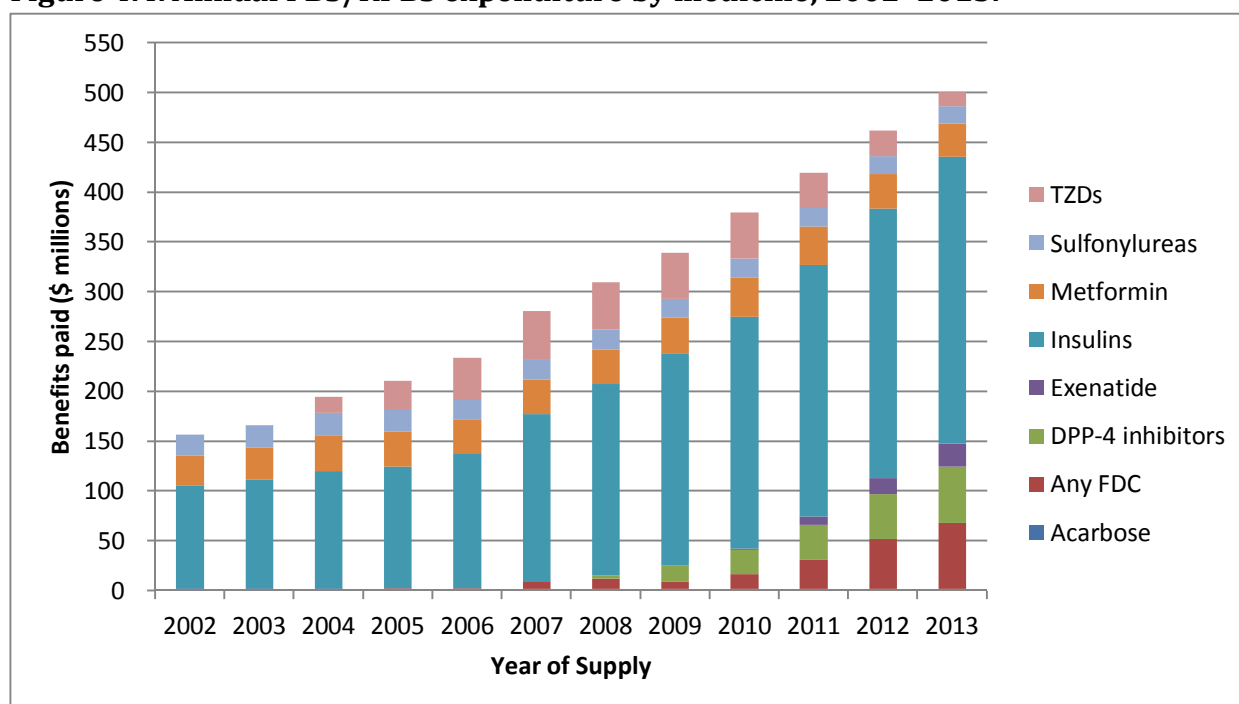
Year	Prescriptions supplied	Annual growth in prescriptions	Government expenditure	Annual growth in expenditure
2000	3,898,933	NA	\$128,681,781	NA
2001	4,356,569	11%	\$143,646,722	12%
2002	4,830,299	10%	\$157,055,941	9%
2003	5,092,080	5%	\$166,373,731	6%
2004	5,505,649	8%	\$194,826,167	17%

Year	Prescriptions supplied	Annual growth in prescriptions	Government expenditure	Annual growth in expenditure
2005	5,695,728	3%	\$210,458,609	8%
2006	6,011,862	5%	\$233,935,455	11%
2007	6,437,522	7%	\$280,959,589	20%
2008	6,773,040	5%	\$309,788,244	10%
2009	7,104,840	5%	\$339,287,977	10%
2010	7,406,082	4%	\$379,614,336	12%
2011	7,672,208	3%	\$419,438,924	10%
2012	8,039,091	5%	\$462,115,848	10%
2013	8,387,797	4%	\$500,764,881	8%

Notes: Includes PBS/RPBS prescription data only.

Figure 4.4 shows annual Government expenditure by medicine group between 2002 and 2013. The highest expenditure in 2013 was on insulins (\$288 million), followed by FDCs (\$66 million), DPP-4 inhibitors (\$57 million), metformin (\$33 million), exenatide (\$23 million), sulfonylureas (\$17 million), TZDs (\$14 million) and acarbose (\$2 million). [Appendix F](#) shows PBS/RPBS prescriptions dispensed and expenditure over the twelve months to April 2014, by medicine.

**Figure 4.4. Annual PBS/RPBS expenditure by medicine, 2002–2013.**



Notes: 'Any FDC' includes sitagliptin, linagliptin, vildagliptin, alogliptin, saxagliptin, glibenclamide and rosiglitazone FDCs with metformin. 'DPP-4 inhibitors' includes sitagliptin + simvastatin FDC. SGLT2 inhibitors excluded.

Special pricing arrangements exist for some insulins and exenatide. Final Government expenditure on these medicines may differ from that presented.

#### 4.4.2. Initiating medicines for patients with type 2 diabetes

The analysis of initiating therapies shows a marked increase over time in the proportion of people initiating metformin as their first type 2 diabetes medicine from 61.8% in 2003/04 to 79.4% in 2009/10, with a corresponding decrease in patients initiating a sulfonylurea from 27.6% in 2003/04 to 9.7% in 2009/08. Table 4.2 summarises initiating therapy for each of the four cohorts.

**Table 4.2. Initiating therapy by cohort.**

Initiating therapy	Cohort 1 2003/04	Cohort 2 2005/06	Cohort 3 2007/08	Cohort 4 2009/10
Metformin	61.8%	69.1%	75.4%	79.4%
Sulfonylurea	27.6%	19.8%	13.1%	9.7%
Metformin + sulfonylurea	4.3%	3.5%	3.4%	3.4%
TZDs	0.2%	7%	9%	7%
Acarbose	0.1%	0.4%	0.5%	0.4%
Mixed insulin	2.4%	0.1%	0.2%	0.1%
Short acting insulin	1.5%	2.1%	1.6%	1.1%
Basal + short acting insulin	0.6%	0.5%	1.9%	1.4%
Basal insulin	1%	1%	0.8%	0.7%

Table 4.3 shows the proportion of people who had additional therapy or switched therapy within 3.5 years of initiation for the first three cohorts (data for cohort 4 is not shown due to insufficient follow up time). Around 65% of patients in these cohorts did not add or switch medicines within 3.5 years of initiation. The majority of patients who added or switched medicines, did so within the PBS restrictions. Less than 5% of patients added or switched beyond the PBS restrictions. This usually involved the addition of a third line agent (DPP-4 inhibitor, TZD or exenatide) without trialling both metformin and a sulfonylurea first (data not shown).

**Table 4.3. Addition and switching during first 3.5 years of therapy.**

Addition or switch	Cohort 1 2003/04	Cohort 2 2005/06	Cohort 3 2007/08
No addition or switch	62.9%	65.4%	62.8%
Add within PBS restrictions	27.0%	23.6%	21.0%
Add beyond PBS restrictions	0.8%	1.7%	3.0%
Switch within PBS restrictions	3.8%	4.3%	4.2%
Switch beyond PBS restrictions	0.0%	0.0%	0.5%

#### 4.4.3. Therapies used before third line agents

This analysis used an incident cohort of patients who commenced a third line agent between July–December 2011 and examined the previous treatment regimens of these patients. Table 4.4 shows the proportion of patients that initiated on each third line agent between July and December 2011. DPP-4 inhibitors were the most common third line agents used making up 85% of the initiating patients, and rosiglitazone was the least common third line agent used at less than 1% of initiating patients.

**Table 4.4. Number and percentage of concession patients initiating on each third line therapy between July and December 2011.**

Third line agent	No. of patients	% of patients
DPP-4 inhibitor	7,686	45%
DPP-4 inhibitor + metformin FDC	6,940	40%
Pioglitazone	1,481	9%
Exenatide	1,015	6%
Rosiglitazone + metformin FDC	66	<1%
Rosiglitazone	59	<1%

Table 4.5 provides a summary of the regimen histories for patients who initiated a third line agent between December and July 2011. Overall, 47.7% of patients initiating a DPP-4 inhibitor, TZD or exenatide had not received a supply of both metformin and a sulfonylurea in the previous two years. When the prior history period was extended to five years, 44.6% of patients had not received metformin and a sulfonylurea (data not shown).

**Table 4.5. Regimen histories for concession patients who initiated a third line agent between July and December 2011.**

Pre-initiation treatment regimen summary	Patients (no.)	% Patients
Regimen histories <b>not containing</b> both metformin and a sulfonylurea	8,233	47.7%
• Metformin only supplied	6,230	36.1%
• Sulfonylurea only supplied	1,158	6.7%
• Neither metformin nor sulfonylurea supplied	845	4.9%
Regimen histories <b>containing</b> both metformin and a sulfonylurea	9,014	52.3%
• Metformin and sulfonylurea deemed to be co-administered for more than 5 consecutive weeks	7,515	43.6%
• Metformin and sulfonylurea deemed to be co-administered from 1–5 consecutive weeks	352	2.0%
• Metformin and sulfonylurea supplied but not deemed to be co-administered at any time	1,147	6.7%

Pre-initiation treatment regimen summary	Patients (no.)	% Patients
Total	17,247	100.0%

Notes: Analysis is based on drugs supplied in the 24 months prior to initiation of a third line agent. The analysis of the pre-initiation regimen considered both single agent and FDC products.

Table 4.6 shows the percentage of patients who initiated a third line therapy who had previously been supplied metformin and/or a sulfonylurea. This analysis suggests that the degree of compliance with PBS restrictions on use of therapies before initiation of third line agents, varies according to the third line agent used. About half the patients who initiated a DPP-4 inhibitor, or a FDC containing metformin and a DPP-4 inhibitor, did so without being supplied both metformin and a sulfonylurea in the previous two years. The majority of these patients were only supplied metformin, and around 5% of patients were supplied neither metformin nor a sulfonylurea.

**Table 4.6. Regimen histories for concession patients who initiated a third line agent between July and December 2011, by third line agent as a percentage of patients initiating third line therapy.**

Third line agent	Glip	Glip + met FDC	Pio	Exen	Rosi + met FDC	Rosi
Total histories <b>not containing</b> both metformin and a sulfonylurea	49%	55%	27%	20%	46%	39%
• Metformin only supplied	34%	47%	11%	17%	33%	22%
• Sulfonylurea only supplied	11%	3%	7%	2%	2%	12%
• Neither metformin nor sulfonylurea supplied	4%	6%	9%	1%	11%	5%
Total histories <b>containing</b> both metformin and a sulfonylurea	51%	45%	73%	80%	54%	61%
• Metformin and sulfonylurea co-administered for >5 consecutive weeks	42%	38%	64%	62%	50%	46%
• Metformin and sulfonylurea co-administered from 1 to 5 consecutive weeks	2%	2%	2%	3%	0%	5%
• Metformin and sulfonylurea supplied but not co-administered at any time	7%	5%	7%	15%	4%	10%

#### 4.4.4. Co-administration

This analysis aimed to describe the medicine regimens of concessional patients who were supplied any diabetes medicine between February 2011 and May 2012.

Throughout this period, the number of concessional patients on a DPP-4 inhibitor + metformin FDC more than tripled, from around 5,000 patients to over 16,000 patients. In the week beginning 24 May 2012 (the last week of the study period), 84% of diabetes patients were using a regimen that did not contain a third line agent, and 61% of patients were using only metformin, a sulfonylurea, or both. Almost 2% of patients were using triple oral therapy involving metformin with a sulfonylurea and a DPP-4 inhibitor, a regimen that does not comply with the PBS restrictions for DPP-4 inhibitors (data not shown).

Regimens containing a DPP-4 inhibitor, TZD or exenatide were then further assessed to determine compliance with PBS restrictions. Table 4.7 shows the ten most common diabetes medicine regimens for concessional patients using a third line agent, with regimens non-compliant with the PBS restrictions highlighted. The total rate of compliance with PBS restrictions for medicine regimens that contain a DPP-4 inhibitor, TZD or exenatide is presented in Table 4.8.

**Table 4.7. Ten most common diabetes medicine regimens for concessional patients using a third line agent.**

Regimen	% of patients
Metformin + DPP-4 inhibitor	36%
Metformin + Sulfonylurea + DPP-4 inhibitor	12%
Metformin + Sulfonylurea + Pioglitazone	12%
Sulfonylurea + DPP-4 inhibitor	8%
DPP-4 inhibitor	4%
Metformin + Pioglitazone	4%
Sulfonylurea + Pioglitazone	3%
Metformin + DPP-4 inhibitor + Insulin	3%
Metformin + Sulfonylurea + Exenatide	2%
Pioglitazone	2%
Other regimens	14%

Notes: Data from week beginning 24 May 2012. FDCs considered by their constituent medicines. Regimens non-compliant with PBS restrictions highlighted.

**Table 4.8. Patients on regimens containing a third line agent and the proportion that comply or do not comply with PBS restrictions for co-administered medicines (including a breakdown of non-compliant regimens).**

PBS restriction compliance status	No. of patients	% of patient regimens
Compliant (total)	57,317	72.1%
Non-compliant (total)	22,229	27.9%
• Use of a DPP-4 inhibitor or rosiglitazone with metformin + sulfonylurea	10,882	13.7%
• Use of insulin with a DPP-4 inhibitor, rosiglitazone or exenatide	4,606	5.8%
• Use of a DPP-4 inhibitor, rosiglitazone or exenatide without metformin or a sulfonylurea	3,779	4.8%
• Use of two or more of: DPP-4 inhibitors, TZDs and/or exenatide	1,584	2.0%
• Use of pioglitazone without metformin, a sulfonylurea or insulin	1,378	1.7%

Note: Data from week beginning 24 May 2012.

Compliance of patient regimens was then examined by third line agent. Table 4.9 shows that the non-compliance rate was highest for regimens containing rosiglitazone at 48.4%, and lowest for regimens containing pioglitazone at 12.9%. For the DPP-4 inhibitors and rosiglitazone, use with metformin and a sulfonylurea was the most common non-compliant regimen. For exenatide, use with insulin was the most non-compliant regimen.

This part of the analysis only considered agents co-administered in the current regimen and did not assess whether the pathway to treatment with the third line agent complied with PBS restrictions. Some regimens classified here as compliant with PBS restrictions, would not have complied with requirements to try metformin and a sulfonylurea unless contraindicated before initiating a third line agent.

**Table 4.9. Patient regimens containing a third line agent and percentage compliance with PBS restrictions for co-prescribed medicines, by medicine or class (including a breakdown of non-compliant regimens).**

Compliance status	DPP-4 inhibitor	Pioglitazone	Rosiglitazone	Exenatide
Compliant (total)	65.4%	87.0%	51.7%	70.4%
Non-compliant (total)	34.6%	13.0%	48.3%	29.6%
• Use with metformin and a sulfonylurea	18.5%	Compliant	33.3%	Compliant
• Use of insulin with a third line agent	7.1%	Compliant	4.9%	16.1%
• Use without metformin or a sulfonylurea	6.3%	Compliant	5.6%	5.9%
• Use without metformin, a sulfonylurea or insulin	Compliant	6.7%	Compliant	Compliant
• Use of two or more third line agents	2.7%	6.2%	4.6%	7.7%

Notes: Data for the week beginning 24 May 2012. DPP-4 inhibitors and rosiglitazone includes the single component products and the FDCs.

## 4.5 Conclusion and DUSC Commentary

The DUSC suggested that a flow chart of PBS restrictions for type 2 diabetes medicines, similar to Figure 4.1, could be included in the PBS Schedule to reduce confusion regarding the current complex wording. This approach would be similar to the ‘general statement for lipid lowering drugs prescribed as pharmaceutical benefits’.

In the first 3.5 years of pharmacological treatment for type 2 diabetes, the vast majority of patients initiating treatment were treated in accordance with the PBS restrictions and clinical guidelines. Most patients initiate pharmacotherapy for type 2 diabetes with metformin (around 80% in 2009/10), which is consistent with clinical guidelines, and most (60–65%) do not add or switch therapy in the first 3.5 years. Of those who switched or added, less than 5% did so outside the PBS restrictions. However, the DUSC was concerned that the proportion of use outside of the PBS restrictions had grown over time and was likely to be more extensive in patients who had been treated for diabetes for longer than 3.5 years. The DUSC requested analyses to assess the proportion of use of third line agents that is in accordance with PBS restrictions, for both prior therapies and co-prescribed medicines (analyses 3 and 4).

For concessional patients who initiated a DPP-4 inhibitor, TZD or exenatide between July and December 2011, 47.7% had not received a supply of both metformin and a sulfonylurea in the preceding two years. The PBS restrictions for these medicines during the study period required a prior trial of metformin and a sulfonylurea, except

where contraindicated. When the prior history period was extended to five years, 44.6% of patients had not received metformin and a sulfonylurea (data not shown).

The DUSC considered that the proportion of people who did not take metformin before initiating a third line agent (6.7%) appeared reasonable based on reported rates of metformin contraindication in patients with type 2 diabetes.<sup>54</sup> However, the high percentage of patients (41%) who started third line agents without a trial of a sulfonylurea appeared to represent substantial use outside of the anticipated listing and expected cost-effective use. This pattern of prescribing was most extensive with DPP-4 inhibitor + metformin FDCs (53%), rosiglitazone + metformin FDC (44%), and DPP-4 inhibitor single agents (38%).

The DUSC considered that the prevalence of true contraindication to a sulfonylurea (primarily severe hepatic dysfunction and severe renal impairment according to the Product Information) is low. In addition, a trial of the medicine is required to demonstrate intolerance to a sulfonylurea. The proportion of patients co-administered metformin with a sulfonylurea for a short period of time, which would be consistent with a trial of treatment, was very low at 2%. The DUSC concluded that 'intolerant' to a sulfonylurea appears to be interpreted more liberally in clinical practice than was anticipated.

The DUSC considered that the use of third line agents in lieu of a sulfonylurea has not been established as cost-effective and would almost certainly not represent cost-effective use. These medicines are much more expensive than sulfonylureas and were not PBS listed as an alternative to those medicines at the time of the analysis, unless there was a contraindication or intolerance.

A proportion of patients classified in this analysis as meeting the PBS restriction for a DPP-4 inhibitor due to previous history of co-administered metformin and a sulfonylurea for more than 5 weeks, may have switched to a DPP-4 inhibitor for reasons other than genuine intolerance. The extent of this use beyond PBS criteria could not be captured with prescription data. Therefore, the rate of non-compliant prescribing based on PBS subsidy criteria is likely to be a conservative estimate.

The DUSC noted that use beyond the PBS restrictions appears to be greater with FDC products, than when concomitant agents are supplied and that the availability of FDC products may be contributing to patterns of use. Only one FDC of metformin with a sulphonylurea (glibenclamide) is available on the PBS, and glibenclamide is not the sulphonylurea of choice for many patients as it has a higher reported rate of hypoglycaemia than glimepiride or gliclazide. Pioglitazone is not available in a FDC. There were two DPP-4 inhibitor with metformin FDCs available during the study period, and since that time an additional three have been included on the PBS.

In an analysis of a prevalent cohort of concessional patients prescribed a third line agent between February 2011 and May 2012, at least 27.9% of patients were prescribed the third line agent in a regimen of co-prescribed therapies that did not comply with

PBS subsidy criteria. The DUSC noted that 27.9% was the lower estimate of use outside the PBS restrictions, as the pathway to third line therapy was not assessed in this analysis, and a proportion of regimens would be reached via a pathway inconsistent with PBS criteria.

Of the third line agents, pioglitazone had the least use beyond the PBS restrictions with only 13.0% of patient regimens non-compliant, and the greatest alignment between PBS restrictions and clinical guidelines. The highest rate of use outside of the restrictions was with rosiglitazone (48.4%); however, total utilisation of rosiglitazone was very low and declining. Use outside of the restriction may have reflected patients who remained on a regimen that no longer met the current PBS restriction, refractory patients, or prescriber confusion due to multiple changes to the restrictions for rosiglitazone.

The use of triple oral therapy with a DPP-4 inhibitor, metformin and a sulfonylurea contributed most to use outside the restrictions. Use of DPP-4 inhibitor monotherapy was also evident (6.3% of all patient using a DPP-4 inhibitor). DPP-4 inhibitors were being used in a number of ways that either had not been considered, or had not been accepted to be cost-effective, by PBAC. The DUSC also considered that the long term safety of this relatively new class of agents had not been established. DPP-4 inhibitors were of high cost compared to some of the therapies they were substituting in practice (such as sulfonylureas and pioglitazone). The PBAC rejected an application for PBS listing of a DPP-4 inhibitor and metformin FDC for use in triple oral therapy with a sulfonylurea in July 2013, on the basis that no appropriate evidence was presented to inform efficacy/safety in triple therapy.

For exenatide, some use beyond PBS restrictions was apparent, most of which was combination use with insulin (16.1% of patients using exenatide), or use with other third line agents (7.7% of patients supplied exenatide). The cost-effectiveness of this use has not been assessed by the PBAC.

Of patients using third line agents, 27.9% are being prescribed a combination of medicines not indicated in the PBS restriction, and 47.7% have not been treated with both a metformin and a sulphonylurea (a small proportion of whom would have a genuine contraindication). Taking this into consideration, the DUSC concluded that the overall rate of use beyond the PBS restrictions in relation to third line agents is at least 30%. The committee suggested that this is a conservative estimate of non-cost-effective use.

## PART 5 – PBS LISTING OF TYPE 2 DIABETES MEDICINES (ToR 3)

*ToR 3: Consolidate the clinical trial evidence used to support PBS listings of diabetes medicines listed since 2002.*

### 5.1 Key Findings

- TGA-approved indications not subsidised by the PBS include use of newer type 2 diabetes medicines as: monotherapy; TZD + DPP-4 inhibitor/SGLT2 inhibitor combinations; triple therapy with metformin + sulfonylurea + DPP-4 inhibitor/SGLT2 inhibitor; insulin + DPP-4 inhibitor/SGLT2 inhibitor/GLP-1 receptor agonist combinations; and initial use of DPP-4 inhibitor/SGLT2 inhibitor with metformin.
- A total of 177 clinical studies/systematic reviews assessing the newer type 2 diabetes medicines or the nominated comparators, were identified from 47 submissions to the PBAC.
- Only 17 submissions provided direct head-to-head evidence against the main comparator.
- The newer diabetes medicines have been positioned after the use of metformin and/or a sulfonylurea based on a series of non-inferiority comparisons originating from insulin.
- Superiority claims were made in 14 submissions. No submission received a positive recommendation on the basis of a clinical claim of superiority.
- The PBAC has acknowledged marginal differences in change in HbA<sub>1c</sub> between medicines, but has never accepted a claim of superiority due to the difficulty in translating these differences to clinical outcomes. When presented, the nominated HbA<sub>1c</sub> non-inferiority margin was generally 0.3–0.4% (3–4 mmol/mol).
- The PBAC has acknowledged that there may be differences between treatments in weight management and hypoglycaemia outcomes, but the magnitude and clinical importance of these differences has not been adequately demonstrated.
- None of the newer diabetes medicine submissions has presented microvascular/macrovascular events as a key outcome.
- The PBAC has noted the lack of long term safety data for many of these medicines, particularly given the safety issues that arose after the listing of rosiglitazone. The PBAC has considered additional cardiovascular safety data for two DPP-4 inhibitors.

## 5.2 Introduction and Scope

This section summarises the report developed by the University of Newcastle to address ToR 3 of the Review.

This report considered submissions for PBS listing for type 2 diabetes medicines for which prescribing restrictions apply (restricted listings), dating from 2002 to 2013. Pioglitazone and rosiglitazone submissions considered prior to 2002 are also included, as both of these agents have been used as comparators for subsequent diabetes medicine submissions. The submissions for insulins were not considered, as insulin is beyond the scope of the Review.

The included type 2 diabetes medicines, referred to as the newer diabetes medicines in this section of the Report, are:

- *Thiazolidinediones (glitazones)* – rosiglitazone, pioglitazone, and the related FDC product metformin + rosiglitazone.
- *DPP-4 inhibitors (gliptins)* – sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin and the related FDC products metformin + sitagliptin, metformin + vildagliptin, simvastatin + sitagliptin, linagliptin + metformin, metformin + saxagliptin, alogliptin + metformin, metformin XR + sitagliptin and metformin XR + saxagliptin.
- *SGLT2 inhibitors (gliflozins)* – dapagliflozin and canagliflozin.
- *GLP-1 analogues* – exenatide, exenatide long-acting (LA) and liraglutide.

The review collated and consolidated data based on the following issues:

- Types of PBS restrictions applied for individual medicines and classes of medicines.
- Differences between TGA approved indications and PBS listings for individual agents.
- Comparators used in the applications for listing.
- The clinical evidence used by the submissions to support the applications for listing.
- Reasons for rejection by the PBAC relating to the clinical evidence presented.

Agents considered that are not currently PBS-listed (as of 1 January 2014) are liraglutide, exenatide LA and the combinations of alogliptin + metformin, linagliptin + metformin, metformin + saxagliptin, metformin XR + saxagliptin and metformin XR + sitagliptin.

## 5.3 Methods

A manual search was undertaken to identify all of the newer diabetes medicines submissions reviewed by the PBAC from 2002 to 2013, and earlier submissions of the TZDs. The data sources include the 2012 DUSC Review ([Part 4](#)), published PBS

Schedules, PBAC meeting minutes, Pharmaceutical Evaluation Section (PES) commentaries, Public Summary Documents and the TGA eBusiness Services website (to access Product Information documents. The documents informing this review were those that were available up to January 2014.

These data were supplemented by additional searches to reconcile trial identifiers with subsequently published studies. This included literature searches using trial identifiers and information on trial interventions as search terms. The PubMed database and the ClinicalTrials.gov registry were searched for records of the clinical trials. A Google search was also undertaken to identify trials not indexed in the nominated databases.

All of the identified documents were reviewed to extract the relevant data. The key information extracted and examined regarding the PBAC submissions were: meeting date, requested listing, comparator, clinical evidence presented, clinical claim(s), type of economic evaluation (cost-minimisation or cost-effectiveness analysis) and PBAC recommendation.

Clinical trial evidence was classified into three classes: direct randomised trials providing direct comparisons, indirect comparisons and supplementary data. For the purposes of this review, direct randomised trials were defined as head-to-head comparisons of active treatments (with differences often assessed using a pre-specified non-inferiority margin) or comparisons of active treatments where the outcome was demonstration of superiority of one treatment arm over the other. For FDC products, bioequivalence studies were also presented.

## 5.4 Results and Discussion

### 5.4.1 PBS Restrictions and TGA Indications

#### ***PBS Restrictions***

*Note: This section of the report was updated to reflect PBS restrictions as of 1 July 2014.*

*For further information on PBS restrictions for type 2 diabetes medicines refer to [Part 2.8](#).*

The wording of the current PBS restrictions for the newer diabetes medicines includes detailed criteria regarding initiation rules, switching rules and permitted co-administered therapies. All of the identified newer PBS-listed diabetes medicines (TZDs, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 analogues) may be used in dual combination therapy with metformin or a sulfonylurea in type 2 diabetes patients. As of July 2014, there were three dual therapy restrictions for combination therapy with metformin or a sulfonylurea:

- *TZDs and GLP-1 analogues*: Dual therapy with metformin or a sulfonylurea, where HbA<sub>1c</sub> is >7% despite treatment with metformin or a sulfonylurea, and

where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

- *SGLT2 inhibitors*: Dual therapy with metformin or a sulfonylurea, where HbA<sub>1c</sub> is >7% despite treatment with metformin or a sulfonylurea, and the condition is unable to be adequately controlled by treatment with metformin and a sulfonylurea. (During the July 2013 meeting, the PBAC recommended the restriction for SGLT2 inhibitors be modified to better reflect current clinical practice in which patients whose diabetes cannot be successfully managed with a combination of metformin and a sulfonylurea, irrespective of reason, are moved to dual therapy).
- *DPP-4 inhibitors*: Dual therapy with metformin or a sulfonylurea, where where HbA<sub>1c</sub> is >7% despite treatment with metformin or a sulfonylurea. (During the July 2013 meeting, the PBAC recommended this restriction for alogliptin. As of April 2014, the restriction for the remaining DPP-4 inhibitors was altered to remove the requirement for patients to have contraindications to, or be intolerant of, a combination of metformin + sulfonylurea).

Few medications are PBS-listed for use in triple combination therapy with metformin + sulfonylurea (pioglitazone and exenatide only) and only pioglitazone is currently PBS-listed for use in combination with insulin.

### ***Comparison between PBS Restrictions and TGA Indications***

Table 5.1 (older medicines) and Table 5.2 (newer medicines) highlight the differences between the TGA-approved indications and PBS listings for type 2 diabetes medicines (cells shaded in grey).

**Table 5.1. Older diabetes medicines - TGA-approved indications versus PBS listings (as at 1 January 2014).**

		Mono-therapy	Dual therapy [+MET/SU]	Dual therapy [+TZD]	Triple therapy [+MET+SU]	Insulin combination
<b>Biguanides</b>						
Metformin/ Metformin XR	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
<b>Sulfonylureas</b>						
Glibenclamide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Gliclazide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glimepiride	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glipizide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
<b>Alpha glucosidase inhibitors</b>						
Acarbose	TGA	✓	✓	✓ <sup>a</sup>	✓	✓
	PBS	✓	✓	x	✓	✓

Source: Schedule of Pharmaceutical Benefits (January 2014) and Product Information documents.  
Abbreviations: MET, metformin; PBS, Pharmaceutical Benefits Scheme; SU, sulfonylurea; TGA, Therapeutic Goods Administration

Note: The references to mono-, dual and triple therapy are in relation to the active ingredient(s), not products. The (✓) indicates that the drug has been TGA-approved or PBS listed (as appropriate) for this indication. Cells in grey highlight differences between TGA/PBS indications

<sup>a</sup> Acarbose is TGA-approved as adjunct therapy. However, the TZDs are not TGA-approved or PBS-listed for use with acarbose.

**Table 5.2. Newer diabetes medicines - TGA-approved indications versus PBS listings (at 1 January 2014).**

		Mono-therapy	Dual therapy [+MET/SU]	Dual therapy [+TZD]	Triple therapy [+MET+SU]	Insulin combination
<b>TZDs (Glitazones)</b>						
Rosiglitazone	TGA	✓	✓	N/A	✗	✗
	PBS	✗	✓	N/A	✗	✗
Pioglitazone	TGA	✓	✓	N/A	✓	✓ <sup>a</sup>
	PBS	✗	✓	N/A	✓	✓ <sup>a</sup>
<b>DPP-4 inhibitors (Gliptins)</b>						
Sitagliptin	TGA	✓ <sup>f</sup>	✓	✓ <sup>b</sup>	✓	✓
	PBS	✗	✓	✗	✗	✗
Saxagliptin	TGA	✗	✓ <sup>d</sup>	✓ <sup>b</sup>	✓	✓
	PBS	✗	✓ <sup>d</sup>	✗	✗	✗
Vildagliptin	TGA	✗	✓	✓ <sup>b,c</sup>	✓	✓
	PBS	✗	✓	✗	✗	✗
Linagliptin	TGA	✓ <sup>f</sup>	✓	✗	✓	✓
	PBS	✗	✓	✗	✗	✗
Alogliptin	TGA	✗	✓	✓ <sup>b</sup>	✓	✓
	PBS	✗	✓	✗	✗	✗
<b>SGLT2 inhibitors (gliflozins)</b>						
Dapagliflozin	TGA	✓ <sup>f</sup>	✓	✗	✗	✓
	PBS	✗	✓	✗	✗	✗
Canagliflozin	TGA	✓ <sup>f</sup>	✓	✓	✓	✓
	PBS	✗	✓	✗	✗	✗
<b>GLP-1 receptor agonists</b>						
Exenatide	TGA	✗	✓	✗	✓	✓
	PBS	✗	✓	✗	✓	✗
Exenatide LA	TGA	✗	✓	✗	✓	✗
	PBS	✗	✗ <sup>e</sup>	✗	✗ <sup>e</sup>	✗
Liraglutide	TGA	✗	✓	✗	✓	✗
	PBS	✗	✗ <sup>e</sup>	✗	✗ <sup>e</sup>	✗
<b>Others</b>						
Repaglinide	TGA	✗	✓ <sup>g</sup>	✗	✗	✓ <sup>h</sup>
	PBS	✗	✗	✗	✗	✗
<b>Fixed dose combinations</b>						
Glibenclamide+ metformin	TGA	N/A	✓	N/A	N/A	✓
	PBS	N/A	✓	N/A	N/A	✓
Metformin+ rosiglitazone	TGA	N/A	✓	✓	✗	✗
	PBS	N/A	✓ <sup>g</sup>	✓ <sup>g</sup>	✗	✗
Metformin+	TGA	N/A	✓	N/A	✓	✓

		Mono-therapy	Dual therapy [+MET/SU]	Dual therapy [+TZD]	Triple therapy [+MET+SU]	Insulin combination
sitagliptin	PBS		✓ <sup>g</sup>		✗	✗
Metformin+ vildagliptin	TGA PBS	N/A	✓ ✓ <sup>g</sup>	N/A	✓ ✗	✓ ✗
Simvastatin+ sitagliptin	TGA PBS	N/A	✓ ✓	✓ ✗	✗ ✗	✗ ✗
Metformin+ saxagliptin	TGA PBS	N/A	✓ ✗ <sup>e</sup>	N/A	✓ ✗	✓ ✗
Linagliptin+ metformin	TGA PBS	N/A	✓ ✗ <sup>e</sup>	N/A	✓ ✗	✗ ✗
Alogliptin+ metformin	TGA PBS	N/A	✓ ✗ <sup>e</sup>	N/A	✓ ✗	✓ ✗
Metformin XR+ saxagliptin	TGA PBS	N/A	✓ ✗ <sup>e</sup>	N/A	✓ ✗	✓ ✗
Metformin XR+ sitagliptin	TGA PBS	N/A	✓ ✗ <sup>e</sup>	N/A	✓ ✗	✓ ✗

Source: Schedule of Pharmaceutical Benefits (January 2014) and Product Information documents.

Abbreviations: LA = long acting; MET = metformin; N/A = not applicable; and SU = sulfonylurea.

Note: The references to mono-, dual and triple therapy are in relation to the active ingredient(s), not products. The (✓) indicates that the drug has been TGA-approved or PBS listed (as appropriate) for this indication. Cells in grey highlight differences between the TGA-approved and PBS listed indications.

<sup>a</sup> TGA-approved for dual therapy in combination with insulin. However, the PBS-listing does not specify the diabetes medicines to be used in combination with insulin and appears broader.

<sup>b</sup> TGA-approved for dual therapy in combination with TZDs. However, TZDs are not TGA-approved for use with DPP-4 inhibitors.

<sup>c</sup> Pioglitazone only.

<sup>d</sup> The TGA-approved indication is wider, as includes use as initial combination therapy when dual metformin and saxagliptin therapy is appropriate

<sup>e</sup> Recommended for listing only. PBS listing not available at January 2014.

<sup>f</sup> If metformin is not suitable (the exception is linagliptin, where both metformin and sulfonylureas are specified).

<sup>g</sup> Only dual therapy with metformin allowed.

<sup>h</sup> Not satisfactorily controlled on sulfonylureas or repaglinide alone.

There are a number of differences between TGA-approved indications for use and PBS listings for the newer diabetes medicines. The PBS listings are influenced by the requested listings and evidence presented to the PBAC by the sponsor, including evidence on cost-effectiveness. Where clinical practice guidelines are consistent with TGA-approved indications, there is the potential for PBS restrictions to limit access to medicines recommended in clinical guidelines.

Some of the TGA-approved indications for use of the newer diabetes medicines have been considered and rejected by the PBAC, whereas others have yet to be submitted to the PBAC. These include the lack of PBS subsidy for the TGA indications of:

- monotherapy with the newer diabetes medicines
- TZD + DPP-4 inhibitor combinations
- TZD + SGLT2 inhibitor combinations
- triple therapy with metformin + sulfonylurea + DPP-4 inhibitor/SGLT2 inhibitor

- insulin + DPP-4 inhibitor/SGLT2 inhibitor/GLP-1 receptor agonist combinations
- initial use of metformin + DPP-4 inhibitor/SGLT2 inhibitor.

While the PBS listings are generally more restrictive, the PBS listing for pioglitazone appears broader than the TGA indication. The current PBS listing allows use in any combination with insulin, while the TGA indication specifies dual therapy with pioglitazone and insulin only. The TGA-indication for acarbose does not specify concurrent diabetes medicines and TZDs are neither TGA-approved nor PBS-listed for use in combination with acarbose. There have been no submissions to the PBAC for the explicit concomitant use of acarbose with TZDs.

#### **5.4.2 Included submissions and comparators**

The clinical trial evidence was consolidated from a total of 47 submissions for newer diabetes medicines considered by the PBAC. Some of the submissions requested multiple listings, nominated more than one comparator and/or presented various comparisons. Twenty-six (55%) of the included submissions received positive recommendations, 17 (36%) submissions were rejected and four (9%) submissions were deferred by the PBAC.

Superiority claims in terms of comparative efficacy were made in 14 submissions. No submission has received a positive recommendation on the basis of a clinical claim of superiority. Non-inferiority or equivalence claims were made in 24 submissions (some submissions made both superiority and non-inferiority/equivalence claims) and there were 12 FDC submissions with bioequivalence data.

The newer diabetes medicines have been positioned after the use of metformin and/or a sulfonylurea based on a series of non-inferiority comparisons originating from insulin:

- TZDs were listed for dual therapy, triple therapy and combination with insulin based on comparisons against insulin (or comparisons against another TZD already listed for the indication).
- The first DPP-4 inhibitor was listed for dual therapy based on comparisons against the TZDs. Subsequent DPP-4 inhibitors were listed based on comparisons with the first DPP-4 inhibitor. DPP-4 inhibitors have failed to demonstrate non-inferiority to TZDs for the triple therapy and combination with insulin listings.
- SGLT2 inhibitors were listed for dual therapy based on comparisons against the first DPP-4 inhibitor. There has been no submission for use in triple therapy. SGLT2 inhibitors have failed to demonstrate non-inferiority to the TZDs for use in combination with insulin.
- The first GLP-1 analogue was listed for dual therapy and triple therapy based on comparisons with insulin glargine/TZDs. The subsequent GLP-1 analogues were recommended for listing based on comparisons with the first GLP-1 analogue. There has been no submission for use in combination with insulin.

### 5.4.3 Clinical trial evidence

A total of 177 clinical studies/systematic reviews assessing the newer type 2 diabetes medicines or the nominated comparators, were identified from the 47 submissions. Seventeen submissions (36%) presented some direct head-to-head evidence against the main comparator. Other submissions relied on either formal indirect comparisons (14 submissions; 30%) or informal indirect comparison of treatments (3 submissions; 6%). Twelve submissions (26%) for FDCs presented bioequivalence and some clinical data. One submission (2%) did not present clinical data versus the comparator.

Given the large volume of clinical evidence, this review organised the clinical trial evidence presented in the submissions based on the categories of:

- monotherapy
- dual combination therapy with metformin or a sulfonylurea
- triple combination therapy with metformin and a sulfonylurea
- combination with insulin
- FDCs.

#### ***Monotherapy***

None of the newer diabetes medicines has been recommended for use as monotherapy. The PBAC considered a request to list rosiglitazone for use as monotherapy in November 2007. Sulfonylureas were nominated as the comparator and a direct comparison of rosiglitazone and a sulfonylurea was presented. The PBAC rejected the submission on the basis of considerable concerns about safety, uncertain clinical benefit and uncertain cost-effectiveness.

#### ***Dual therapy with metformin or a sulfonylurea***

A history of the submissions for dual therapy with either metformin or a sulfonylurea that have been recommended by the PBAC are shown in Table 5.3.

The sponsors for two of the newer diabetes medicines (rosiglitazone, sitagliptin) have provided cost-effectiveness analyses for second-line treatment as an alternative to sulfonylureas. However, both submissions failed to demonstrate superiority compared to sulfonylureas.

### ***Triple therapy with metformin and a sulfonylurea***

Pioglitazone and exenatide are the only newer diabetes medicines currently listed for triple therapy with metformin + sulfonylurea, while exenatide LA and liraglutide have been recommended, but are not yet listed on the PBS. A history of the submissions for triple therapy with metformin + sulfonylurea that have been recommended by the PBAC are shown in Table 5.4.

Linagliptin was considered for triple therapy in July 2012. Pioglitazone was accepted as the appropriate comparator, as it was the only product listed at the time for triple oral therapy. The submission was based on an indirect comparison. The PBAC rejected the submission on the basis of uncertain comparative clinical effectiveness and considerable economic uncertainty.

Vildagliptin was considered for triple therapy at the July 2013 meeting. The PBAC rejected the submission due to the inappropriate comparator. The PBAC considered that an appropriate comparator would need to be a mixed comparator of sulfonylurea, acarbose, insulin and exenatide. In addition, the PBAC considered that the evidence did not support the submission's claim for equivalence in efficacy and safety to pioglitazone, linagliptin and exenatide.

**Table 5.3. History of PBAC recommended submissions for dual therapy use of newer diabetes medicines with metformin or a sulfonylurea.**

Medicine	Meeting	Comparator (Secondary)	CMA/CEA	Notes
<b>Rosiglitazone</b>	March 2001	Insulin	CMA	<ul style="list-style-type: none"> <li>A subsequent submission (Nov 2007) to remove the need for patients to be contraindicated or intolerant to sulfonylureas was rejected on the basis of considerable safety concerns, uncertain clinical benefit and uncertain cost-effectiveness.</li> </ul>
<b>Pioglitazone</b>	Sept 2001	Rosiglitazone	CMA	
<b>Sitagliptin</b>	March 2008	Rosiglitazone	CMA	<ul style="list-style-type: none"> <li>PBAC noted that the data available suggest that sitagliptin may be associated with less weight gain; however, there are no longer term data to confirm persistence of these effects. The data on changes in systolic blood pressure are limited and it was unclear that these changes represent clinically meaningful differences.</li> <li>A subsequent submission (March 2008) to remove the need for patients to be contraindicated or intolerant to sulfonylureas was rejected on the basis of uncertain evidence of benefit over the comparator and highly uncertain cost-effectiveness.</li> </ul>
<b>Exenatide</b>	Nov 2008	Insulin glargine	CMA	<ul style="list-style-type: none"> <li>PBAC recommended listing on a cost-minimisation basis with insulin glargine, taking into account the higher costs associated with the initiation and titration of dose with insulin glargine.</li> <li>The PBAC considered that the long term benefits and durability of the claim of superior weight management had not been adequately established.</li> <li>The price of exenatide is based on insulin glargine and rosiglitazone.</li> <li>There were two previous rejected submissions (July 2007 and March 2008).</li> </ul>
<b>Saxagliptin</b>	March 2010	Sitagliptin	CMA	
<b>Vildagliptin</b>	March 2010	Sitagliptin (Pioglitazone, Rosiglitazone)	CMA	

<b>Linagliptin</b>	Nov 2011	Sitagliptin	CMA	
<b>Liraglutide</b>	March 2013	Exenatide	CMA	<ul style="list-style-type: none"> <li>Three previous submissions were rejected (Nov 2010, July 2011 and Nov 2011). Rejected submissions claimed superior efficacy and equivalent safety to exenatide. PBAC accepted the difference in HbA<sub>1c</sub> of -0.33% to be marginally clinically meaningful; however noted that the mean difference could be as low as -0.18%. PBAC considered there is clinical uncertainty about the relationship between intensive glycaemic control and diabetes related complications, including the use of HbA<sub>1c</sub> as a surrogate for cardiovascular outcomes. The PBAC noted that the long term safety of liraglutide is unknown.</li> </ul>
<b>Alogliptin</b>	July 2013	Sitagliptin	CMA	<ul style="list-style-type: none"> <li>Recommended without the requirement for patients to have contraindications to, or be intolerant of a combination of metformin and a sulfonylurea and that listing should be at a reduced price that takes into account the likely proportion of use in patients who have not trialled a sulfonylurea and where cost-effectiveness has not been established. This restriction and revised prices were subsequently extended to the other DPP-4 inhibitors.</li> </ul>
<b>Dapagliflozin</b>	July 2013	Sitagliptin	CMA	<ul style="list-style-type: none"> <li>PBAC recommended that cost-offsets be applied to account for an increased rate of adverse events such as genital mycotic infections and urinary tract infections.</li> <li>PBAC considered that an Authority Required (not streamlined) listing would be appropriate for this new class.</li> <li>PBAC considered that the risk of use outside the restriction (patients whose diabetes cannot be successfully managed with a combination of metformin and a sulfonylurea, irrespective of reason ) could be managed through a risk share agreement.</li> </ul>
<b>Canagliflozin</b>	July 2013	Sitagliptin (Dapagliflozin)	CMA	
<b>Exenatide LA</b>	Nov 2013	Exenatide (Liraglutide)	CEA	<ul style="list-style-type: none"> <li>Considered at least non-inferior and recommended on a cost-minimisation basis to exenatide. PBAC agreed that the price should be adjusted for reduced needle use.</li> <li>There were two previous submissions rejected (July 2011 and July 2013). The July 2011 submission claimed superior efficacy and equivalent safety. The PBAC considered the 0.53% difference in HbA<sub>1c</sub> from pooling the results of two trials comparing exenatide LA to exenatide, statistically significant and clinically meaningful. However, there was uncertainty about the pooled result, with large differences in the HbA<sub>1c</sub> reduction between the exenatide twice daily arms of the studies. The PBAC considered that the long term safety of exenatide LA is unknown.</li> </ul>

CMA = Cost-minimisation analysis; CEA = Cost-effectiveness analysis.

**Table 5.4. History of PBAC recommended submissions for triple therapy use of newer diabetes medicines with metformin + sulfonylurea.**

<b>Medicine</b>	<b>Meeting</b>	<b>Comparator (Secondary)</b>	<b>CMA/CEA</b>	<b>Notes</b>
<b>Rosiglitazone</b>	Nov 2004	Insulin	CMA	<ul style="list-style-type: none"> <li>Listing removed in February 2009, due to safety concerns.</li> </ul>
<b>Pioglitazone</b>	Nov 2007	Rosiglitazone	CMA	
<b>Exenatide</b>	Nov 2008	Insulin glargine	CMA	<ul style="list-style-type: none"> <li>Refer to Table 5.3.</li> </ul>
<b>Liraglutide</b>	March 2013	Exenatide	CMA	<ul style="list-style-type: none"> <li>Refer to Table 5.3.</li> </ul>
<b>Exenatide LA</b>	Nov 2013	Exenatide (Liraglutide)	CEA	<ul style="list-style-type: none"> <li>Refer to Table 5.3.</li> </ul>

CMA = Cost-minimisation analysis; CEA = Cost-effectiveness analysis.

### ***Combination therapy with insulin***

Pioglitazone is the only newer diabetes medicine currently listed for combination therapy with insulin (recommended for listing in September 2001). The PBS listing of rosiglitazone in triple therapy was removed in October 2008 following safety concerns.

The PBAC rejected submissions to list dapagliflozin and saxagliptin in triple therapy with insulin in March 2012 and July 2012, respectively. In both submissions, pioglitazone was nominated as the comparator. The PBAC considered that insulin should also be considered a comparator, as some use of these agents would be for patients with the objective of reducing the dose of concomitant insulin, reducing hypoglycaemia and/or improving diabetes control.

Both submissions excluded PNFP-014, the pivotal trial in the September 2001 pioglitazone submission.<sup>55</sup> The PBAC did not accept the claim of non-inferior efficacy, as the non-inferiority criterion was not met in either submission when PNFP-014 was included. The PBAC accepted the claim of equivalent safety for saxagliptin, but did not accept the claim of non-inferior safety in the dapagliflozin submission, due to concerns about the long term safety with dapagliflozin and increased risk of urinary and genital tract infections.

### ***FDCs***

All the FDCs include metformin or metformin XR (with the exception of the simvastatin + sitagliptin combination which is no longer listed). The PBAC has generally recommended listing of the metformin + DPP-4 inhibitor FDCs on a cost-minimisation basis with the components (noting the reduced DPP-4 inhibitor prices introduced to account for use where cost-effectiveness has not been demonstrated).

## **5.4.4 Outcomes**

All of the submissions for the newer diabetes medicines reviewed by PBAC have presented data on mean change in HbA<sub>1c</sub> from baseline. Other outcomes reported include: proportions of HbA<sub>1c</sub> responders, changes in fasting plasma glucose, hypoglycaemia, weight management, lipid profiles, insulin resistance/sensitivity, reduction in insulin requirement and time to treatment failure.

### ***HbA<sub>1c</sub>***

The majority of submissions presented data on glycosylated haemoglobin (HbA<sub>1c</sub>) outcomes (e.g. change from baseline, responder analyses using various thresholds) and many of the submissions attempt to establish non-inferiority in terms of glycaemic control. The PBAC has never accepted a claim of superiority based on HbA<sub>1c</sub> outcomes (due to difficulty in translating differences in HbA<sub>1c</sub> to clinical outcomes), but has previously acknowledged marginal differences in change in HbA<sub>1c</sub>. When presented, the

nominated non-inferiority margin for change in HbA<sub>1c</sub> from baseline generally ranged from 0.3% to 0.4%.

The European Medicines Agency (EMA) guidance suggests that a non-inferiority margin of 0.3% is generally acceptable,<sup>56</sup> and the draft Food and Drug Administration (FDA) guidance suggests that a non-inferiority margin of 0.3% or 0.4% is typically accepted.<sup>57</sup> The Stage 1 Blood Glucose Test Strips Review and the Stage 2 Insulin Pumps Review, generally considered a 0.5% reduction in HbA<sub>1c</sub> to be of clinical significance,<sup>58; 59</sup> noting that there is no consensus on this issue and smaller reductions may be considered important from a public health perspective if achieved on a wide scale.<sup>60</sup>

No clear independent effect of glycaemic control on macrovascular complications has been demonstrated and the effect on premature mortality remains uncertain.<sup>6</sup> A Cochrane review investigating intensive glycaemic control versus conventional glycaemic control found that there is insufficient evidence to demonstrate an effect on all-cause or cardiovascular mortality. Intensive glycaemic control may reduce the occurrence of non-fatal myocardial infarction (MI), lower extremity amputation and microvascular disease; but these measured effects in studies are of uncertain reliability and may be due to the risks of bias and random errors.<sup>61</sup>

### ***Macrovascular and microvascular***

None of the newer diabetes medicine submissions has presented microvascular/macrovascular events as a key outcome. However, the PBAC has considered additional data on cardiovascular safety for two DPP-4 inhibitors.<sup>4; 5</sup> The PBAC noted that saxagliptin did not increase or decrease the rate of ischaemic events, though the rate of hospitalisation for heart failure was increased. The PBAC also noted that rates of major adverse cardiovascular events were not increased with alogliptin as compared with placebo.

The PBAC also noted other limitations of the clinical evidence, including the lack of long term safety data (particularly given the safety issues that arose after the listing of rosiglitazone) and uncertain applicability of the clinical evidence (e.g. duration of treatment, background therapies, treatment details).

### ***Other outcomes***

Some submissions have made additional claims based on other outcomes such as weight management and hypoglycaemia. The PBAC has previously acknowledged that there may be differences between treatments in regards to these outcomes, but the magnitude and clinical importance of these differences has not been adequately demonstrated. The lack of long term clinical outcome and safety data has been identified as an area of concern.

#### 5.4.5 PBAC's reasons for rejecting requests for PBS listings

The PBAC's reasons for rejection were analysed for key themes, which are summarised below.

Comparator issues:

- Comparator's pharmacological mechanism of action meant it was not the most appropriate choice.
- Different mode of administration.
- Consideration of multiple or alternate comparators, where the appropriate comparator(s) is uncertain or unlikely to account for all substitutions.
- Consideration of insulin as a comparator, given that the use of concomitant diabetes medicines with insulin may facilitate reduction in the dose of insulin.
- Comparator no longer appropriate, due to changing place in clinical practice and safety concerns.

Clinical data issues:

- Inadequate data to support the therapeutic claim.
- Small magnitude of benefit.
- Inconsistency.
- Clinical uncertainty about the relationship between intensive glycaemic control and diabetes related complications, including the use of HbA<sub>1c</sub> as a surrogate for cardiovascular outcomes.
- Clinical claims based on other surrogate measures (e.g. weight management).
- Lack of long term clinical outcome data.
- Lack of head-to-head comparisons. Differences in the common comparator arms for indirect comparisons further contributed to the uncertainty.
- Quality of the data supporting the clinical claim. For example, the use of observational data and subjective outcomes from open-label studies.
- Inadequate basis for the selective inclusion/exclusion of trials.
- Safety concerns, including the unknown long term safety profile.
- Applicability of the trials in clinical practice, e.g. dosing and intensification of therapy.
- Clinical and safety data presented were not up to date.
- Applicability of the trial population to the proposed PBS population (HbA<sub>1c</sub> and age).

## Part 6 – New Clinical Trial Evidence (ToR 4)

**ToR 4:** Collate and evaluate any additional clinical studies or meta-analyses for drugs currently PBS listed for type 2 diabetes that the PBAC has not seen and that would inform their consideration.

### 6.1 Key Findings

- The systematic literature review on the safety and efficacy of type 2 diabetes medicines identified 87 publications covering 72 RCTs, including 43 trials not seen by the PBAC previously.
- No long term macrovascular or microvascular outcome data for acarbose, insulin, SGLT2 inhibitors and GLP-1 receptor agonists was identified. Limited trial data are available with a duration of over six months and many trials were underpowered to detect differences in adverse events.
- One dual therapy trial considered a combination not yet seen by the PBAC. Compared to TZD monotherapy, TZD + DPP-4 inhibitor reduced HbA<sub>1c</sub> (-0.9%; 95% CI: -1.1, -0.7) and increased weight (1.1 kg; p-value not reported).<sup>1</sup> The results may not be applicable to Australian practice as the patients were treatment naïve.
- Twenty-one triple therapy RCTs were identified and assessed for risk of bias: high – 4 trials, unclear – 12 trials, and low – 5 trials. HbA<sub>1c</sub>, body mass index (BMI) and age at baseline were similar in the analysed trials.
- All triple therapy combinations of medicines provided a significantly better reduction in HbA<sub>1c</sub> at six months compared to metformin + sulfonylurea dual therapy, in the range of 0.7–1.1%, except for metformin + TZD + DPP-4 inhibitor. This improvement was clinically relevant when GLP-1 receptor agonists or insulin were added to metformin + sulfonylurea (upper CI >0.3%).
- None of the triple therapy combinations demonstrated clinically relevant differences in HbA<sub>1c</sub> at six months compared with other triple therapies. However, metformin + sulfonylurea + GLP-1 receptor agonist was significantly better at reducing HbA<sub>1c</sub> than metformin + TZD + DPP-4 inhibitor.
- Most triple therapy regimens resulted in weight gain after six months of treatment compared to metformin + sulfonylurea, with SGLT2 inhibitors + metformin + sulfonylurea and GLP-1 receptor agonist + metformin + sulfonylurea showing a significant reduction (SGLT2 inhibitors: MD: -2.4 kg; 95% CI: -4.1, -0.6; and GLP-1 receptor agonists: MD: -1.5 kg; 95% CI: -2.4, -0.6). All other combinations caused similar or more weight gain than metformin + sulfonylurea (-0.3 to 3.5 kg).
- In terms of body weight change, when used in combination with metformin + sulfonylurea: SGLTs inhibitors were superior to DPP-4 inhibitors, insulin and TZDs;

GLP-1 receptor agonists were superior to DPP-4 inhibitors, insulin and TZDs; and DPP-inhibitors and insulin were superior to TZDs.

- Four trials were identified that examined long term outcomes when a sulfonylurea, TZD or DPP-4 inhibitor was added to existing therapy. All provided a statistically significant reduction in HbA<sub>1c</sub> and increased the risk of hypoglycaemia (in trials of greater than two years duration) compared to existing medication. Trial populations and outcome definitions varied between trials precluding meta-analysis.
- The addition of sulfonylurea to existing medication reduced major microvascular events (HR: 0.86; 95% CI: 0.77, 0.97).
- Addition of TZDs to existing medication reduced major macrovascular events (HR: 0.84; 95% CI: 0.72, 0.98), while DPP-4 inhibitors had no effect on this outcome. TZDs increased the risk of heart failure, and TZDs and DPP-4 inhibitors increased the risk of hospitalisation due to heart failure.

## 6.2 Introduction and Scope

This section summarises the report developed by Griffith University to address ToR 4 of the Review. Medicines considered in the literature review were those listed on the PBS, or considered for listing, for the treatment of type 2 diabetes to November 2013 (see Table 1.1). PBS-listed insulins that were also considered include: aspart, lispro mix 75/25, glulisine, neutral, detemir, glargine and isophane.

After an initial literature review and consultation with the expert Reference Group, the following approach was recommended for the systematic literature review on the comparative efficacy and safety of type 2 diabetes medicines:

1. Monotherapy: Listing of trials comparing monotherapy treatments.
2. Dual therapy:
  - a. Listing of trials which include dual therapy comparisons previously seen by the PBAC.
  - b. Full data extraction and analyses of efficacy and safety of dual therapy trials that include a combination not currently listed on the PBS.
3. Triple therapy: Full assessment of the comparative efficacy and safety (including meta-analyses and network analyses) for trials which include triple therapy.
4. Treatment added to existing medication: Full assessment of the comparative efficacy and safety for trials which include type 2 diabetes medicines added to existing medication.

## 6.3 Methods

The systematic literature review was performed in four steps:

1. Identify the most relevant systematic reviews.
2. Update the literature search for identified systematic reviews from step 1.
3. Identify the relevant randomised controlled trials (RCTs) from steps 1 and 2.
4. Update the literature search to include additional trials for triple therapy.

Ovid MEDLINE and The Cochrane Library Database were searched on 5 March 2014, using search terms for diabetes mellitus type 2 and the medicines in scope or derivatives of these. Systematic reviews were identified for each medicine category or for multiple medicine categories based on inclusion criteria and were assessed to identify the most relevant reviews. In all, 494 references were identified in the searches and three systematic reviews were considered most relevant to this review and were included in the final analysis ([Table 6.1](#)).

**Table 6.1. Included systematic reviews identified in a search of treatments for type 2 diabetes on 5 March 2014.**

Publication (Author, year)	Treatments included in the systematic review
Bennet, 2011 <sup>62</sup>	MET, SU, TZD, GLP-1 receptor agonists, acarbose (insulin included in the searches from 2002)
Berhan, 2013 <sup>63</sup>	SGLT2 inhibitors
Monami, 2010 <sup>64</sup>	DPP-4 inhibitors

Abbreviations: MET = metformin; SU = sulfonylurea.

The clinical trials from the systematic literature reviews were extracted for further consideration. Systematic literature searches were carried out to update the three identified systematic reviews. Ovid MEDLINE and The Cochrane Library Database were searched on 11 March 2014. The key inclusion criteria were that the duration of the trial needed to be at least 24 weeks and that at least 250 patients were included in each treatment arm. Trials published between January 2003 and March 2014 were included.

Greater emphasis was placed on identifying efficacy for triple medicine combinations. Therefore, the inclusion criteria were modified for the triple therapy trials to reflect this interest and trials with more than 100 participants were included.

### ***Data extraction and analysis***

Risk of bias assessment was performed for each included RCT and was assessed using the Cochrane Collaboration's 'Risk of bias' tool (Version 5.1.0).<sup>65</sup> Data for the following clinical outcomes was extracted from the trials:

- HbA<sub>1c</sub>

- change in body weight
- adverse events
- hypoglycaemia (all, serious and nocturnal)
- serious adverse events
- mortality
- cardiovascular events
- microvascular events
- urinary tract infections
- pancreatitis.

The PBAC has previously considered a difference of 0.3–0.4% in HbA<sub>1c</sub> to be clinically important.<sup>66</sup> Therefore, a difference of 0.3% is considered the minimum clinically important difference (MCID) in HbA<sub>1c</sub> for the purpose of this report. For the other outcomes (e.g. body weight, adverse events, hypoglycaemia, serious adverse events, cardiac events), no MCID has been established.

Data from the RCTs were extracted into Microsoft Excel including all outcome measures and measures of variability; standard deviations, standard errors and 95% confidence intervals were imputed where necessary. The data was then imported into STATA for meta-analysis and network meta-analysis. Where multiple trials were available, head-to-head meta-analyses were performed using a random effects model.

A multiple-treatments network analysis was undertaken to summarise the results of triple therapy for each of the outcomes where a network existed (HbA<sub>1c</sub>, body weight, serious adverse events, hypoglycaemia and serious hypoglycaemia) using the trial data in the clinical evidence base. The network analysis assumes that more than one treatment arm can come from an individual trial. The estimated overall treatment effects were calculated using the “network meta” and “mvmeta” commands in STATA using a random effects model. Possible covariates (HbA<sub>1c</sub>, age and BMI) were examined prior to carrying out the network analysis to ensure similarities in baseline characteristics. The measurements of treatment effect calculated were mean differences (and their 95% confidence intervals) for continuous data, and odds ratios (and their 95% confidence intervals) for dichotomous outcomes.

No meta-analyses or network analyses were performed for the trials with monotherapy, dual therapy or existing medication. The reason for not performing these analyses was that no further analyses were required by the Reference Group for monotherapy and dual therapy. For existing medication, the included patients, trial design, background therapies and reported outcomes were heterogeneous precluding further meta-analyses.

## 6.4 Results and Discussion

In all, 2,720 publications were identified in the database searches. When filtered by the inclusion criteria, 87 publications covering 72 RCTs were identified as relevant for the review:

- Monotherapy: 13 trials, including 11 not considered by the PBAC previously.
- Dual therapy: 28 trials, including 14 not considered by the PBAC previously.
- Monotherapy and dual therapy: 2 trials, neither have been considered by the PBAC previously.
- Triple therapy: 21 trials, including 14 not considered by the PBAC previously.
- Treatment added to existing medication: 8 trials, including 2 not considered by the PBAC previously.

The systematic literature review did not identify long term macrovascular or microvascular outcome data for acarbose, insulin, SGLT2 inhibitors and GLP-1 receptor agonists.

### 6.4.1 Monotherapy

Details of the identified monotherapy trials are provided in [Appendix G](#), Table 1. This systematic review identified that of the newer type 2 diabetes medicines, recent monotherapy trials meeting the inclusion criteria are only available for DPP-4 inhibitors and TZDs. There were no direct head-to-head trials comparing metformin to TZDs, but there are four trials comparing metformin to DPP-4 inhibitors (two not yet seen by the PBAC). On the advice of the Reference Group, no further assessment of the trials was performed.

### 6.4.2 Dual Therapy

For the majority of the dual therapy trials, that included comparisons previously considered by the PBAC, no further assessment of efficacy and safety was performed. Details of the identified dual therapy trials are provided in [Appendix G](#), Table 2.

The Reference Group considered that the data for Yoon 2011<sup>1</sup> that compared TZD vs. TZD + DPP-4 inhibitor (pioglitazone + sitagliptin) added important further information, as this combination has not previously been considered by the PBAC. Participants in this trial were recruited between 2006 and 2008. Participants were multi-national and included adult patients that were medicine naïve with elevated HbA<sub>1c</sub> of ≥8.0% and ≤12.0%. There were no significant differences at baseline between the two treatment arms.

On the basis of direct comparison evidence it could be argued that compared to TZD monotherapy, TZD + DPP-4 inhibitors resulted in:

- superior efficacy (HbA<sub>1c</sub> only; -0.9%; 95% CI: -1.1 to -0.7)
- increased weight gain (1.1 kg; p-value not reported)
- similar safety.

The trial had some limitations, including a short duration of 24 weeks and a low number of specific adverse events. Assessed risk of bias was unclear. Further, as the patients were treatment naïve, the results may not be applicable to Australian practice where both dual therapy and these medicines are unlikely to be used as first line therapy.

### 6.4.3 Triple Therapy

#### 6.4.3.1 Identified trials

The literature search identified 22 publications covering 21 trials with type 2 diabetes patients receiving triple therapy. The majority of trials were of 24–26 weeks duration (13/21 trials), with only 2 trials<sup>67; 68</sup> with a duration longer than one year. Figure 6.1 presents the network of trials in the triple therapy comparisons, and Table 6.2 provides details of the comparisons included in the triple therapy trials.

Trials that only compared the same treatment groups were excluded from the network analyses (comparisons 4 and 10 in Table 6.2). Additionally, one trial did not link to the network, as none of the treatment arms were included in any of the other trials (comparison 11 in Table 6.2). No evidence was identified for triple therapy that included acarbose.

#### *Trial quality*

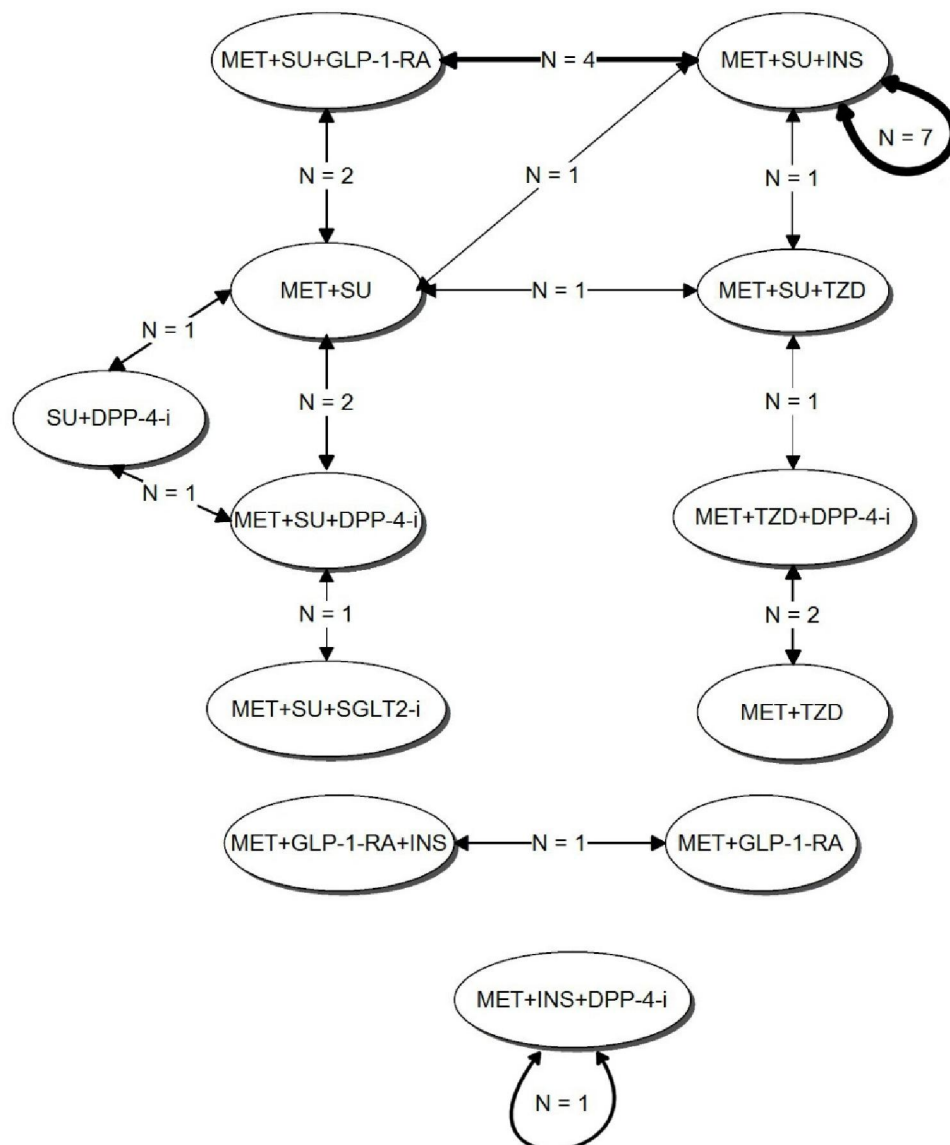
The triple therapy trials were assessed for bias. Overall, four trials were identified as having a high risk of bias, twelve trials were identified as having an unclear risk of bias, and five trials as having a low risk of bias.

All trials were stated as RCTs; however, nine trials did not provide information on how randomisation occurred, resulting in an unclear risk of selection bias. Nine trials were double-blind in which participants and personnel were blinded to treatment allocation, resulting in a low risk of performance and detection bias, while the twelve open-label trials had a high risk of performance and detection bias. In the majority of the trials, incomplete outcome data was handled using the last observation carried forward. A number of trials had differing levels of attrition between the treatment arms, increasing the risk of attrition bias. As seven trials did not provide a trial register number, these have an unclear risk of reporting bias. The paper by Al-Shaikh 2006 provided no information on trial design and could be subject to other biases.<sup>69</sup> The majority of the trials were supported by pharmaceutical companies, making the risk of additional bias unclear.

The primary outcome of interest for each trial was mean difference in HbA<sub>1c</sub> from the control group and most trials were powered to assess this outcome, except Rosenstock

2006 and Al-Shaikh 2006 which did not provide power calculations.<sup>69; 70</sup> The publications did not report whether the trials were adequately powered for the secondary outcomes.

**Figure 6.1. Network of trial evidence available for triple therapy at six months.**



Abbreviations: DPP-4-i = DPP-4 inhibitor; GLP-1-RA = GLP-1 receptor agonist; INS = insulin; MET = metformin; SGLT2-i = Sodium glucose co-transporter 2 inhibitor; and SU = sulfonylurea. Note that the network is different for each identified outcome, as not all trials reported all outcomes

**Table 6.2. Comparisons included in the triple therapy trials.**

Comparison	Intervention 1	Intervention 2	No. of trials	Trials	N	Duration (weeks)	Risk of Bias	Primary outcome	Other outcomes	Seen by PBAC? <sup>a</sup>
1	MET + SU + DPP-4	MET + SU	2	Hermansen 2007 <sup>71</sup>	441	24	Low	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G	No
				Owens 2011 <sup>72</sup>	1,055	24	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G, UTI	Yes
2	MET + SU + TZD	MET + SU	1	Dailey 2004 <sup>73</sup>	365	24	Unclear	HbA <sub>1c</sub>	BW, AE, Hypo-G	Yes
3	MET + SU + GLP-1	MET + SU	2	Kendall 2005 <sup>74</sup>	733	30	High	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G	Yes
				Russell-Jones 2009 <sup>75 b</sup>	581	26	Low	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G, Pan	Yes
4	MET + SU + INS	MET + SU + INS	7	Al-Shaikh 2006 <sup>69</sup>	221	26	High	HbA <sub>1c</sub>	BW	No
				Bergenstal 2009 <sup>76 c</sup>	372	24	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G,	No
				Esposito 2008 <sup>77</sup>	116	36	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G,	No
				Holman 2007 <sup>78</sup>	708	1 year	Unclear	HbA <sub>1c</sub>	BW, AE, Hypo-G,	No
				Janka 2005 <sup>79</sup>	371	24	Unclear	HbA <sub>1c</sub>	BW, AE, Hypo-G,	No
				Strojek 2009 <sup>80</sup>	469	26	Unclear	HbA <sub>1c</sub>	BW, AE, Hypo-G,	No
				Yang 2013 <sup>81</sup>	521	24	High	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G,	No
5	MET + SU + GLP-1	MET + SU + INS	4	Russell-Jones 2009 <sup>75 b</sup>	581	26	Low	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G, Pan	Yes
				Bergenstal 2009 <sup>76 c</sup>	372	24	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G	No
				Heine 2005 <sup>82</sup>	549	26	Unclear	HbA <sub>1c</sub>	BW, SAE, Hypo-G	Yes
				Nauck 2007 <sup>83</sup>	501	1 year	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G	No
6	MET + SU + TZD	MET + SU + INS	1	Rosenstock 2006 <sup>70</sup>	216	24	High	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G	Yes
7	MET + SU + DPP-4	MET + SU + SGLT2	1	Scherthaner 2013 <sup>84</sup>	755	52	Low	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G, UTI	Yes
8	MET + TZD + DPP-4	MET + TZD	2	Bosi 2011 <sup>85</sup>	803	1 year	Low	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G, UTI	No
				DeFronzo 2012 <sup>86</sup>	1,554	26	Unclear	HbA <sub>1c</sub>	AE, SAE, Hypo-G, UTI	No
9	MET + TZD + DPP-4	MET + SU + TZD	1	Derosa 2013 <sup>67</sup>	453	3 years	Low	HbA <sub>1c</sub>	BW	No
10	MET + INS + DPP-4	MET + INS + DPP-4	1	Zinman 2012 <sup>68</sup> & Rodbard 2013 <sup>87</sup>	1,030	1 & 2 years	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G,	No
11	MET + GLP-1 + INS	MET + GLP-1	1	DeVries 2012 <sup>88</sup>	323	26	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Pan	No

Abbreviations: DPP-4 = DPP-4 inhibitor; GLP-1 = GLP-1 receptor agonist; MET = metformin; SU = sulfonylurea; INS = insulin; yr = year; BW = body weight; AE = adverse event; SAE = serious adverse event; SGLT2 = sodium glucose co-transporter 2 inhibitor; and Hypo-G = hypoglycaemia.

<sup>a</sup> Trials included in submissions from 2002 to November 2013.

<sup>b</sup> Trial included three treatment arms (MET + SU + GLP-1-RA, MET + SU and MET + SU + INS) and provided information for comparison 3 and 5.

<sup>c</sup> Trial included three treatment arms (MET + SU + INS, MET + SU + INS and MET + SU + GLP-1-RA) and provided information for comparisons 4 and 5.

### Baseline characteristics

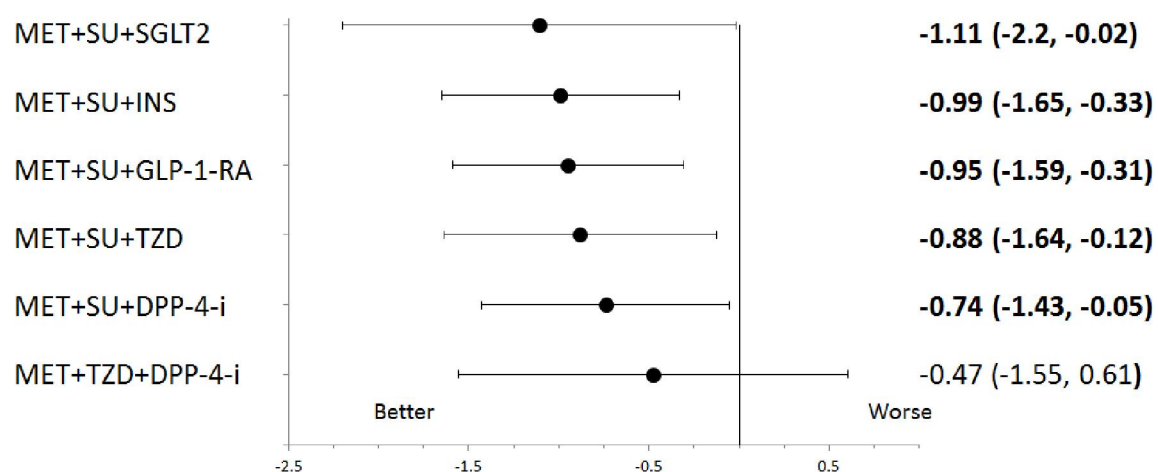
Baseline characteristics across the triple therapy trials varied and were expected to result in some heterogeneity when the network analyses were performed. There were differences in race, gender and baseline body weight between the different trials. The key features of the triple therapy trials were that patients were adult type 2 diabetes patients with HbA<sub>1c</sub> of 7% (53 mmol/mol) or higher, this would be similar to the Australian population using these medicines. However, some applicability problems may arise for the trials where triple therapy was used in patients that were treatment naïve,<sup>67; 70</sup> as Australian patients on triple therapy will generally have received monotherapy and dual therapy for a period of time before receiving triple therapy. HbA<sub>1c</sub>, BMI and age at baseline were similar in each of the trials that were included in the meta-analyses and network analyses, increasing the reliability of the outcomes from these analyses.

#### 6.4.3.2 Efficacy

##### HbA<sub>1c</sub>

Thirteen RCTs were identified for inclusion in the network analysis for HbA<sub>1c</sub> at six months.<sup>67; 70; 71; 72; 73; 74; 75; 76; 82; 83; 84; 85; 86</sup> Figure 6.2 and 6.3 present forest plots for the HbA<sub>1c</sub> results for triple therapy showing the mean difference between the treatment comparisons.

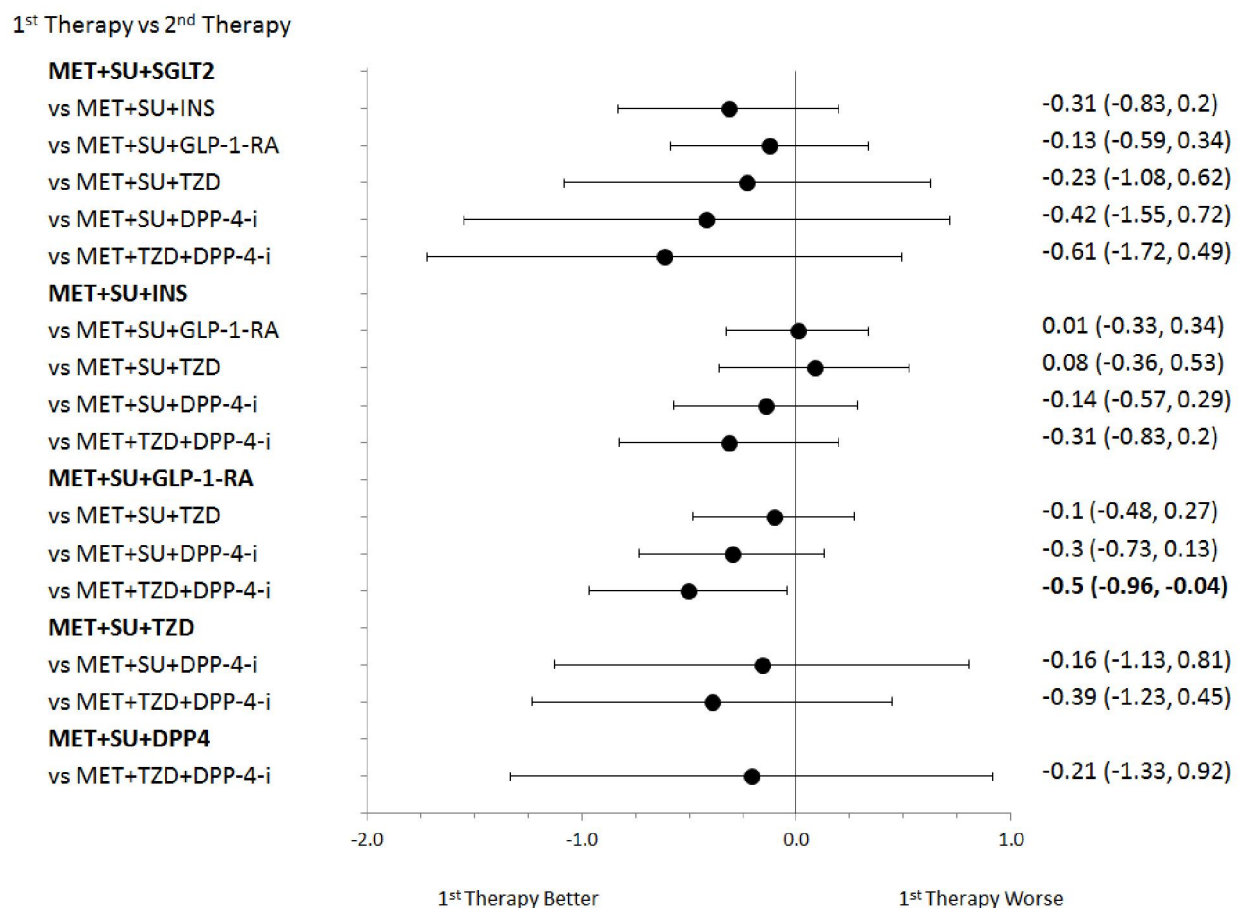
**Figure 6.2. Forest plot of mean difference in HbA<sub>1c</sub> (%) (95% CI) at six months for triple therapy combinations compared to metformin + sulfonylurea dual therapy – network analysis.**



Statistically significant difference are marked in **bold**.

Abbreviations: CI = confidence interval; DPP-4-i = DPP4 inhibitor; GLP-1-RA = GLP-1 receptor agonist; INS = insulin; MET = metformin; SGLT2 = SGLT2 inhibitor; and SU = sulfonylurea.

**Figure 6.3. Forest plot of mean difference in HbA<sub>1c</sub> (%) (95% CI) at six months for triple therapy combinations compared to each other – network analysis.**



Statistically significant difference are marked in **bold**.

Abbreviations: CI = confidence interval; DPP-4-i = DPP4 inhibitor; GLP1 = GLP-1 receptor agonist; INS = insulin; MET = metformin; SGLT2 = SGLT2 inhibitor; and SU = sulfonylurea.

All triple therapy combinations of medicines in the network analysis provided a significantly better reduction in HbA<sub>1c</sub> compared to metformin + sulfonylurea dual therapy, in the range of 0.7–1.1% (8–12 mmol/mol), except for metformin + TZD + DPP-4 inhibitor (-0.47%; 95% CI: -1.55, 0.61). This improvement was clinically relevant when GLP-1 receptor agonists or insulin were added to metformin + sulfonylurea (upper CI greater than the MCID of 0.30%). Metformin + sulfonylurea + SGLT2 inhibitor produced the largest reduction in HbA<sub>1c</sub> compared to metformin + sulfonylurea dual therapy.

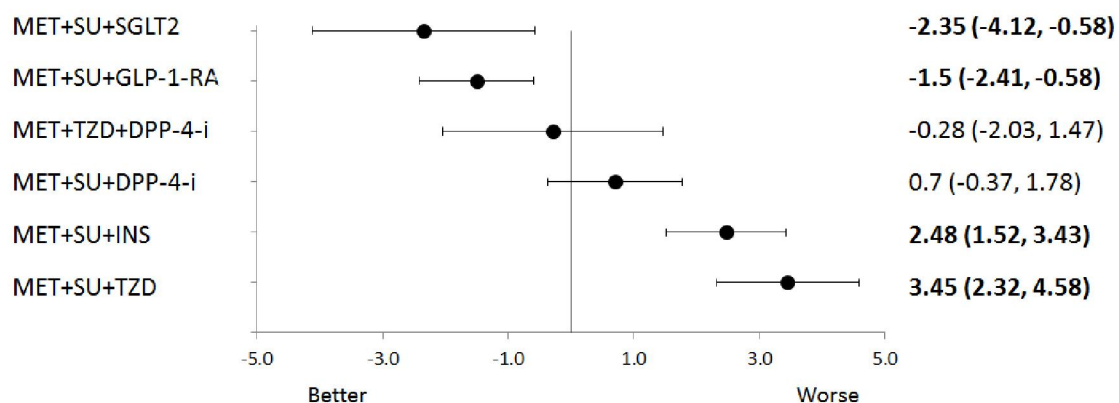
None of the triple therapy combinations demonstrated clinically relevant differences compared with other triple therapies. However, metformin + sulfonylurea + GLP-1 receptor agonist was significantly better at reducing HbA<sub>1c</sub> than metformin + TZD + DPP-4 inhibitor.

The addition of insulin to metformin + GLP-1 receptor agonist (not shown in the figures above) provided a significant and clinically important reduction of HbA<sub>1c</sub> compared to metformin + GLP-1 receptor agonist dual therapy (mean difference -0.52%; 95% CI: -0.68, -0.36).

### **Body weight**

Twelve RCTs were identified for inclusion in the network analysis for body weight change.<sup>67; 70; 71; 72; 73; 74; 75; 76; 82; 83; 84; 86</sup> Figure 6.4 and 6.5 present forest plots for the network analysis of body weight for triple therapy showing the mean difference between the treatment comparisons.

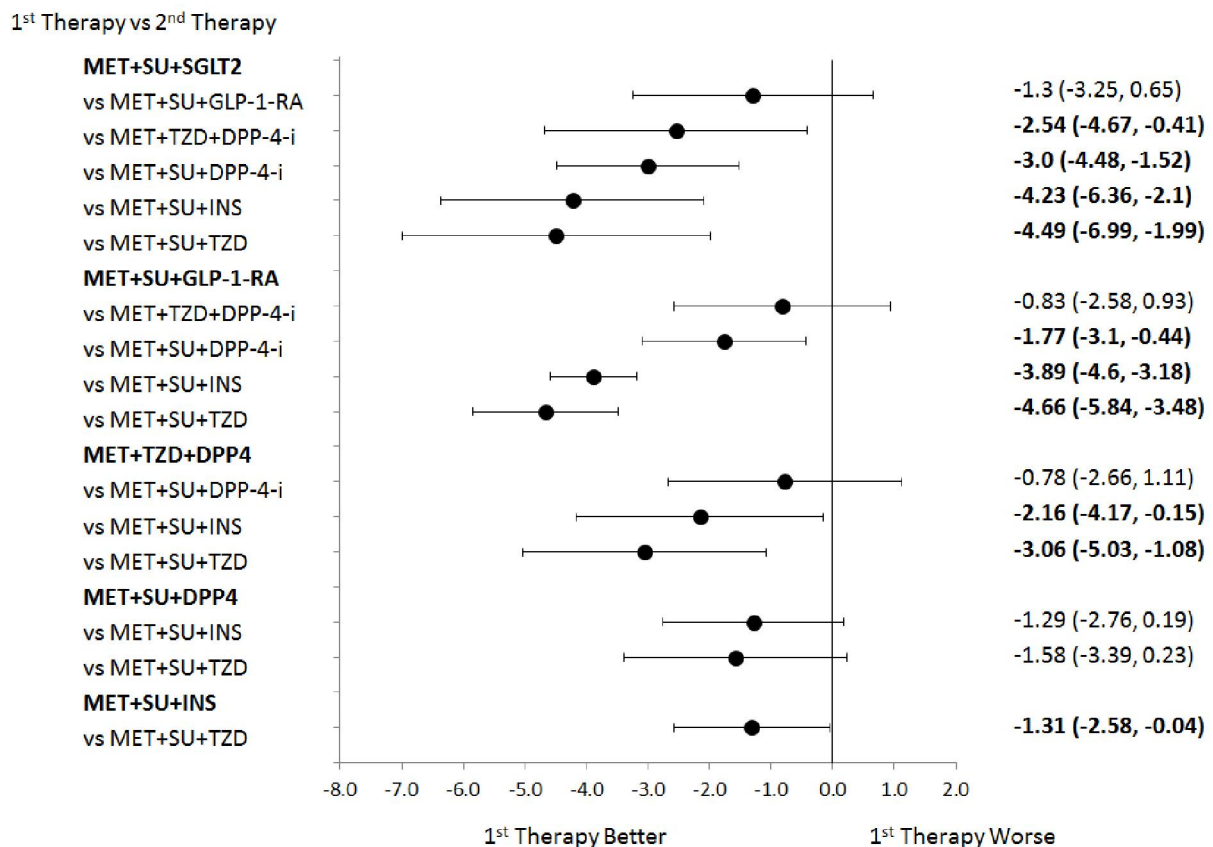
**Figure 6.4. Forest plot of mean difference in change in body weight (kg) (95% CI) at six months for different triple therapy combinations compared to metformin + sulfonylurea dual therapy – network analysis.**



Statistically significant difference are marked in **bold**.

Abbreviations: CI = confidence interval; DPP-4-i = DPP4 inhibitor; GLP-1-RA = GLP-1 receptor agonist; INS = insulin; MET = metformin; SGLT2 = SGLT2 inhibitor; and SU = sulfonylurea.

**Figure 1.5. Forest plot of mean difference in body weight change (95% CI) at six months for different triple therapy combinations compared to each other – network analysis.**



Statistically significant difference are marked in **bold**.

Abbreviations: CI = confidence interval; DPP-4-i = DPP4 inhibitor; GLP-1-RA = GLP-1 receptor agonist; INS = insulin; MET = metformin; SGLT2 = SGLT2 inhibitor; and SU = sulfonylurea.

Both the metformin + sulfonylurea + SGLT2 inhibitor/GLP-1 receptor agonist combinations showed a significant reduction in body weight compared to metformin + sulfonylurea (SGLT2 inhibitor: MD: -2.4 kg; 95% CI: -4.1, -0.6; GLP-1 receptor agonist: MD: -1.5 kg; 95% CI: -2.4, -0.6). All other combinations caused similar or more weight gain than metformin + sulfonylurea (-0.3 to 3.5 kg).

In combination with metformin + sulfonylurea, SGLT2 inhibitors were superior in terms of body weight change to TZDs (-4.5 kg; 95% CI: -7.0, -2.0), insulin (-4.2 kg; 95% CI: -6.4, -2.1), and DPP-4 inhibitors (-3 kg; 95% CI: -4.5, -1.5).

In combination with metformin + sulfonylurea, GLP-1 receptor agonists were superior in terms of body weight change to TZDs (-4.7 kg; 95% CI: -5.8, -3.5), insulin (-3.9 kg; 95% CI: -4.6, -3.2), and DPP-4 inhibitors (-1.8 kg; 95% CI: -3.2, -0.5).

In combination with metformin + sulfonylurea, DPP-4 inhibitors were not different in terms of body weight change when compared to insulins (-1.3 kg, 95% CI: -2.8, 0.2) and

TZDs (-1.6 kg; 95% CI: -3.4, 0.2), and when combined with metformin + TZD (0.78 kg; 95% CI: -1.1, 2.7). In combination with metformin + TZD, DPP-4 inhibitors were superior to sulfonylureas (-3.1 kg; 95% CI: -5.0, -1.1).

The common triple therapy combination of metformin + sulfonylurea + insulin was superior in weight change to metformin + sulfonylurea + TZD (-1.3 kg; 95% CI: -2.5 to -0.0 kg), and was inferior to metformin + TZD + DPP-4 inhibitor (2.2 kg; 95% CI: 0.2 to 4.2 kg).

Not shown in the figures above due to a lack of common arms with the network, the addition of insulin to metformin + GLP-1 receptor agonist had significantly reduced effect on body weight change compared to metformin + GLP-1 receptor agonist dual therapy (0.79 kg; 95% CI: 0.08, 1.49), however it provided a mild reduction in overall weight of 0.16 kg.

### 6.4.3.3 Safety

#### Adverse events

No network existed for analysis of adverse events. While adverse events were presented in most trials, the total number of participants that experienced an adverse event was only presented in six trials that compared different treatment groups. Adverse events were difficult to compare as the trials were generally of short duration (four trials of six months,<sup>71; 72; 86; 88</sup> and three trials of one year<sup>83; 84; 85</sup>) and the event rates were too low to provide meaningful analysis. Table 6.3 summarises the odds ratio of adverse events between different triple therapy combinations from direct trials.

Two other trials (three publications) presented adverse event data for trials of a duration of one year or more, but these trials compared medicines of the same triple therapy treatment groups.<sup>68; 78; 87</sup>

**Table 6.3. Comparison of adverse events between different triple therapy combinations.**

Intervention	Comparator	Trials	Duration	OR (95% CI)	Heterogeneity
<b>Triple therapy vs dual therapy</b>					
MET + SU + DPP-4	MET + SU	Owens 2011 <sup>72</sup> Hermansen 2007 <sup>71</sup>	24 weeks	1.12 (0.92, 1.37)*	I <sup>2</sup> = 0%
MET + TZD + DPP-4	MET + TZD	Bosi 2011 <sup>85</sup>	1 year	1.13 (0.97, 1.32)	N/A
		DeFronzo 2012 <sup>86</sup>	26 weeks	0.92 (0.81, 1.05)	N/A
MET + GLP-1 + INS	MET + GLP-1	DeVries 2012 <sup>88</sup>	26 weeks	<b>1.50 (1.19, 1.90)</b>	N/A
<b>Triple therapy vs triple therapy</b>					
MET + SU + GLP-1	MET + SU + INS	Nauck 2007 <sup>83</sup>	1 year	<b>2.46 (1.70, 3.55)</b>	N/A
MET + SU + SGLT2	MET + SU + DPP-4	Scherthaner 2013 <sup>84</sup>	1 year	0.99 (0.70, 1.39)	N/A

Statistically significant difference are marked in **bold**.

Abbreviations: CI = confidence interval; DPP-4 = DPP-4 inhibitors; GLP-1-RA= GLP-1 receptor agonist; INS = insulin; MET = metformin; OR = odds ratio; SGLT2 = SGLT2 inhibitor; SU = sulfonylurea; and N/A = not applicable.

Notes: \* Based on meta-analysis of two trials.

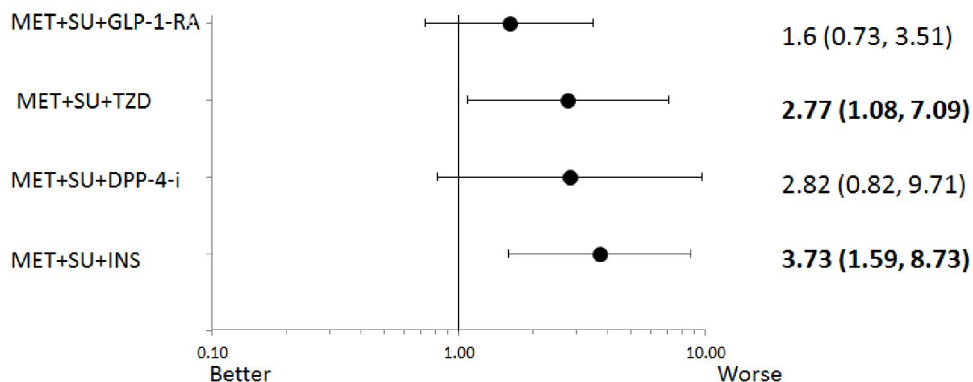
Only two comparisons showed significant differences in adverse events:

- Metformin + sulfonylurea + GLP-1 receptor agonist had significantly higher adverse events than metformin + sulfonylurea + insulin.
- Insulin + metformin + GLP-1 receptor agonist treatment resulted in significantly higher adverse events compared to metformin + GLP-1 receptor agonist dual therapy.

### **Hypoglycaemia**

Seven RCTs were identified for inclusion in the network analysis for hypoglycaemia at six months.<sup>70; 71; 72; 73; 74; 75; 76</sup> Figure 6.6 and 6.7 present forest plots for the network analysis of hypoglycaemia for triple therapy showing the mean difference between the treatment comparisons.

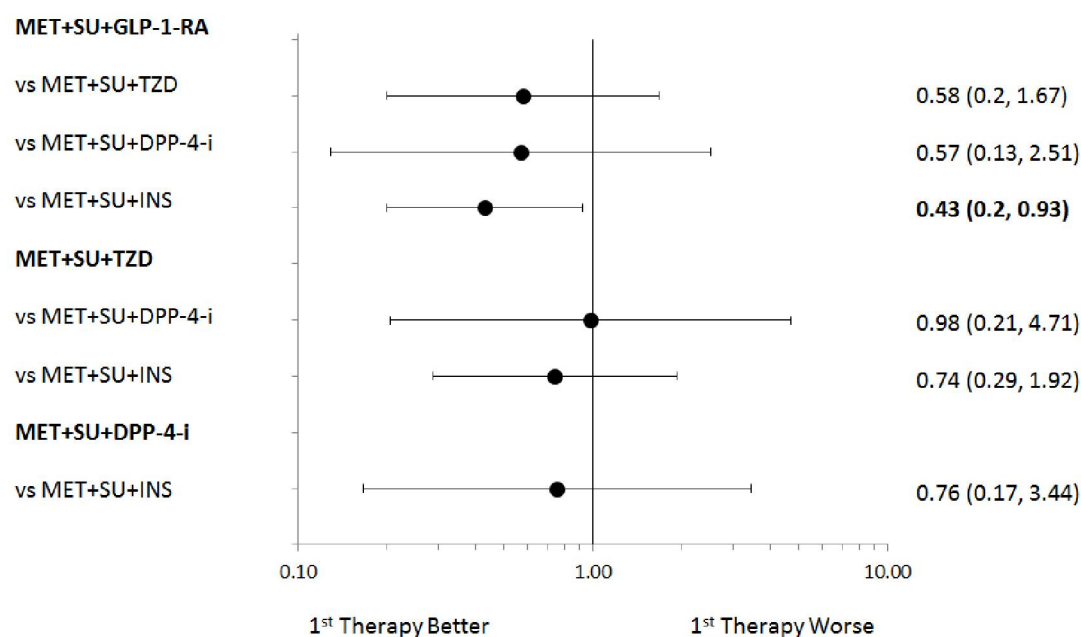
**Figure 6.6. Forest plot of hypoglycaemic events (OR; 95% CI) for different triple therapy combinations compared to metformin + sulfonylurea – network analysis.**



Statistically significant difference are marked in **bold**.

Abbreviations: OR = odds ratio; CI = confidence interval; DPP-4-i = DPP-4 inhibitor; GLP-1 = GLP-1 receptor agonist; INS = insulin; MET = metformin; and SU = sulfonylurea.

**Figure 6.7. Forest plot of hypoglycaemic events (OR; 95%CI) at six months for different triple therapy combinations compared to each other – network analysis.**



Statistically significant difference are marked in **bold**.

Abbreviations: OR = odds ratio; CI = confidence interval; DPP-4-i = DPP-4 inhibitor; GLP-1 = GLP-1 receptor agonist; INS = insulin; MET = metformin; and SU = sulfonylurea.

TZD and insulin in combination with metformin + sulfonylurea increased the odds of hypoglycaemia when compared to metformin + sulfonylurea alone. Metformin + sulfonylurea + GLP-1 receptor agonist reduced the odds of hypoglycaemia compared to metformin + sulfonylurea + insulin.

#### **6.4.3.4 Other outcome measures**

Reporting of mortality, cardiovascular and microvascular disease, severe hypoglycaemia, urinary tract infections and pancreatitis varied throughout the trials and it was often not possible to ascertain if the outcome did not occur or was not reported. Definitions for hypoglycaemia, serious hypoglycaemia and serious adverse events were also different between trials. For those trials that did report these outcomes, event rates were too low to provide meaningful analyses. There were no statistically significant differences in severe hypoglycaemia, mortality, cardiovascular events, urinary tract infections or pancreatitis in any of the trials that reported these outcomes. It is not possible to draw definitive conclusions about other outcomes based on these analyses as the majority of trials were of short duration and involved a low number of participants.

#### 6.4.3.5 Discussion

The key findings for efficacy in triple therapy demonstrated that all combinations of medicines (except for metformin + TZD + DPP-4 inhibitor) in the network analysis provided a significantly better reduction in HbA<sub>1c</sub> when compared to metformin + sulfonylurea dual therapy, in the range of 0.7–1.1% (8–12 mmol/mol). This improvement was clinically relevant when GLP-1 agonist or insulin was added to metformin + sulfonylurea (upper CI greater than the MCID of 0.30%).

None of the triple therapy combinations demonstrated clinically relevant differences in HbA<sub>1c</sub> when compared with other triple therapies. However, metformin + sulfonylurea + GLP-1 receptor agonist was significantly better at reducing HbA<sub>1c</sub> than metformin + TZD + DPP-4 inhibitor.

Only the triple therapy combinations of metformin + sulfonylurea + SGLT2 inhibitor/GLP-1 receptor agonist showed significant reductions in body weight compared to metformin + sulfonylurea dual therapy.

In terms of body weight change, when used in combination with:

- metformin + sulfonylurea:
  - SGLT2 inhibitors and GLP-1 receptor agonists were superior to DPP-4 inhibitors, insulin and TZDs.
  - Insulin was superior to TZDs.
  - DPP-4 inhibitors were not significantly different from insulin or TZDs.
- metformin + TZD:
  - DPP-4 inhibitors were superior to sulfonylureas.

When used in combination with metformin + sulfonylurea, insulin had lower adverse events and higher hypoglycaemia events than GLP-1 receptor agonists. Due to the short duration of most trials, low number of participants, limited reporting of adverse events, and the low number of events, meaningful analysis of adverse events including hypoglycaemia, was difficult. The trials were not powered to assess adverse events and it was not always clear whether outcomes were not reported, or did not occur.

The main limitations regarding this review of the comparative efficacy and safety of type 2 diabetes medicines when used as triple therapy are:

- Limited trial data are available with a duration of over six months.
- Many of the trials were underpowered to detect differences in adverse events.
- There is heterogeneity between the trials with differences in patient characteristics, inclusion/exclusion criteria and duration.
- There were differences between the trials for definitions in certain outcomes, including serious adverse events, hypoglycaemia, and severe hypoglycaemia.
- Performing a network analysis, which uses indirect comparison analyses, may introduce statistical uncertainty.

#### 6.4.4 Medicines Added to Existing Therapy

The literature search identified 12 publications covering 8 RCTs comparing diabetes medicines added to existing therapy. Table 6.4 provides details of these trials.

[Appendix G](#), Table 3 provides a summary of the non-cardiovascular results for the four trials with duration greater than one year; and [Appendix G](#), Table 4 provides the results for the four trials with duration less than one year.

The existing medication trials varied in terms of their key features, including countries included (although most were large, worldwide studies), design, risk of bias and the patient population characteristics. The two trials examining DPP-4 inhibitors added to existing medication, may be comparable as both trials were large, recruited patients over a similar time period, and are worldwide, double-blind and placebo-controlled.<sup>4; 5</sup> Although the inclusion and exclusion criteria for the existing medication trials have components that are similar, high levels of heterogeneity would be expected due to patient differences, especially surrounding current medications, age and concomitant disease.

##### ***Trial quality***

All of the eight trials were RCTs; half were open-label and half were double-blind. The risk of performance and detection bias in the open-label trials is high as treatment allocation was known to participants and personnel. In general, the risk of attrition bias was low across all trials, with intention to treat populations being used in most analyses. Last observation carried forward, which may not be the most appropriate method, was used in most cases to account for missing data. Attrition rates across treatment arms were similar in all trials except Ji 2013, which had a high risk of bias due to large differences in follow-up rates between treatment arms.<sup>89</sup> Buse 2013 had similar levels of attrition across treatment arms; however, the reasons for attrition were not balanced resulting in the risk of attrition bias being unclear.<sup>90</sup> All trials provided trial register numbers, and the outcomes reported in the papers matched those in the register. All trials were supported by pharmaceutical companies resulting in an unclear risk of additional bias.

##### ***HbA<sub>1c</sub>***

The addition of a sulfonylurea, TZD or DPP-4 inhibitor to existing therapy led to a reduction in HbA<sub>1c</sub> compared to the control group of between 0.3% to 0.75% at the end of the long-term trials (18 months to 5 years duration).<sup>2; 3; 4; 5</sup> The addition of DPP-4 inhibitors to existing medication (insulin +/- metformin) showed a clinically meaningful effect on the change in HbA<sub>1c</sub> over 24 weeks with a mean difference of -0.6% compared to existing medication (95% CI: -0.7, -0.4%).<sup>91</sup> Two trials reported different GLP-1 receptor agonist regimens with existing medication, with both trials finding no difference between the therapies.<sup>89; 90</sup> One trial compared two different insulin therapies which were also shown to be equivalent.<sup>92</sup>

**Table 6.4. Comparisons included for the eight trials identified examining medicines added to existing therapy.**

Intervention 1	Intervention 2	Publications	N	Design/ Duration	Disease characteristics	RoB	Primary outcome	Other outcomes	Seen by PBAC? <sup>a</sup>
EM + SU	EM	ADVANCE 2008 <sup>2</sup> Zoungas 2010 <sup>93</sup>	11,140	R, OL 5 years	Macro- or micro-vascular disease or ≥1 other risk factor of vascular disease.	Unclear	Composite of major macrovascular events <sup>b</sup> and major microvascular events <sup>c</sup> , assessed both jointly and separately.	HbA <sub>1c</sub> , BW, Hypo-G, CV events	No
EM + TZD	EM	Dormandy 2005 <sup>3</sup> Doehner 2012 <sup>94</sup> Erdmann 2010 <sup>95</sup>	5,238	R, DB 34.5 mths	Macrovascular disease.	Low	Composite of all-cause mortality, non-fatal MI, stroke, ACS, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle.	HbA <sub>1c</sub> , BW, SAE, CV events	Yes
EM + DPP-4	EM	Scirica 2013 <sup>4</sup>	16,492	R, DB, PC 2.1 years	CVD or multiple risk factors for vascular disease.	Low	Composite of CV death, MI or ischaemic stroke.	HbA <sub>1c</sub> , Hypo-G, Pan, CV events	Yes
		White 2013 <sup>5</sup>	5,380	R, DB, PC 18 mths	Recent ACS	Low	Composite of death from CVD, non-fatal MI or non-fatal stroke.	HbA <sub>1c</sub> , BW, SAE, Pan, CV events	Yes
EM + GLP-1	EM + GLP-1	Ji 2013 <sup>89</sup>	681	R, OL 26 weeks	Type 2 diabetes	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G	Yes
EM + GLP-1	EM + GLP-1	Buse 2013 <sup>90</sup>	911	R, OL 26 weeks	Type 2 diabetes	Unclear	HbA <sub>1c</sub>	BW, AE, Hypo-G	Yes
EM + INS	EM + INS	Buse 2009 <sup>92</sup> Herman 2011 <sup>96</sup>	2,091	R, OL 24 weeks	Type 2 diabetes, insulin naïve	Unclear	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G	Yes
EM + INS + DPP-4	EM + INS	Vilsboll 2010 <sup>91</sup>	641	R, DB, PC 24 weeks	Type 2 diabetes	Low	HbA <sub>1c</sub>	BW, AE, SAE, Hypo-G, UTI	No

Abbreviations: EM = existing medication; DPP-4 = DPP-4 inhibitor; GLP-1 = GLP-1 receptor agonist; SU = sulfonylurea; INS = insulin; SGLT2 = SGLT2 inhibitor; mths = months; BW = body weight; AE = adverse event; SAE = serious adverse event; Hypo-G = hypoglycaemia; Pan = pancreatitis; RoB = risk of bias; ACS = acute coronary syndrome; CV = cardiovascular; CVD = cardiovascular disease; R = Randomised; OL = Open label; DB = Double blind, PC = Placebo controlled; and MI = myocardial infarction.

Notes: <sup>a</sup> Trials in submissions from 2002–2013; <sup>b</sup> Death from CV causes, non-fatal MI or non-fatal stroke; <sup>c</sup> New or worsening nephropathy or retinopathy.

### ***Body weight***

The addition of a sulfonylurea or a GLP-1 receptor agonist to existing medication produced weight reduction from baseline;<sup>2; 89</sup> however, in the sulfonylurea trial existing medication was associated with even greater weight reduction.<sup>89</sup> The addition of TZDs and insulin showed weight gain from baseline of around 3.6 kg.<sup>3; 92</sup>

### ***Adverse events***

For the trials that reported all adverse events (n=4) and serious adverse events (n=6), none demonstrated a difference in events across the treatment arms. The addition of sulfonylureas (OR: 1.4; 95% CI: 1.31, 1.49),<sup>2</sup> TZDs (OR: 1.39; 95% CI: 1.23, 1.57)<sup>3</sup> and DPP-4 inhibitors (OR: 1.17; 95% CI: 1.07, 1.28)<sup>4</sup> to existing therapy increased the occurrence of hypoglycaemia at two years, while the addition of DPP-4 inhibitors to existing therapy showed no difference in hypoglycaemic events at 18 months (OR: 1.04; 95% CI: 0.84, 1.29).<sup>5</sup>

Only one trial reported on urinary tract infections. There was no difference between the rate of urinary tract infection at 24 weeks when DPP-4 inhibitors were added to existing medication, compared to existing medication (OR: 1.49, 95% CI: 0.52, 4.22).<sup>91</sup> There was also no difference between the rates of pancreatitis when DPP-4 inhibitors were added to existing medication, compared to existing medication at 18 months or 2.1 years.<sup>4; 5</sup>

### ***Cardiovascular outcomes***

There were four trials greater than one year duration that were specifically aimed at examining cardiovascular disease and mortality in patients at high risk of heart failure. Table 6.5 summarises the cardiovascular outcomes between different therapy combinations from the direct trials. The definition/grouping of cardiovascular disease outcomes was reported differently in these trials. There were also differences in included patients, trial design, and background medication.

While in all trials the added medication provided a reduction in HbA<sub>1c</sub>, only sulfonylureas reduced the level of combined major microvascular and macrovascular outcomes (HR: 0.90; 95% CI: 0.82, 0.98). Major microvascular events were reduced (HR: 0.86; 95% CI: 0.77, 0.97), particularly there was a reduction in nephropathy as measured by macroalbuminuria (2.9% vs. 4.1%; HR: 0.70; 95% CI: 0.57, 0.85), with a trend toward a reduction in the need for renal replacement therapy. No statistically significant reductions were observed for major macrovascular events (HR: 0.94; 95% CI: 0.84, 1.06) or for death from any cause (HR: 0.93; 95% CI: 0.83, 1.06). More patients with sulfonylurea added to existing medication were hospitalised for any cause (44.9% vs. 42.8%; HR: 1.07; 95% CI: 1.01, 1.13), which may be partly explained by additional hospitalisations for severe hypoglycaemia.<sup>2</sup>

The addition of TZDs to existing medication reduced major macrovascular outcomes (death from any cause, non-fatal MI excluding silent MI, or stroke) (HR: 0.84; 95% CI: 0.72, 0.98). However, the risk of heart failure (OR: 1.49; 95% CI: 1.23, 1.8) and

hospitalisation due to heart failure (OR: 1.42; 95% CI: 1.1, 1.83) was increased, but there was no difference in fatal heart failure.<sup>3</sup>

Two trials examining the addition of DPP-4 inhibitors to existing medication did not show a difference in primary endpoints between the DPP-4 inhibitor group and placebo.<sup>4; 5</sup> However, DPP-4 inhibitors added to existing medication did increase the risk of hospitalisation due to heart failure compared to existing medication (HR: 1.27; 95% CI: 1.07, 1.51).<sup>4</sup>

**Table 6.5. Primary and key secondary cardiovascular outcome results from the medicines added to existing therapy trials with a duration of >1 year.**

Comparison	EM vs. EM + SU	EM vs. EM + TZD	EM vs. EM + DPP-4 inhibitors	
Trial publication	Advance 2008 <sup>2</sup>	Dormandy 2005 <sup>3</sup>	Scirica 2013 <sup>4</sup>	White 2013 <sup>5</sup>
Trial duration	5 years (median)	34.5 months	2.1 years	18 months
N	EM + SU: 5,571 EM: 5,569	EM + TZD: 2,605 EM: 2,633	EM + DPP-4: 8,280 EM + PBO: 8,212	EM + DPP-4: 2,701 EM + PBO: 2,679
Death from any cause	0.93 (0.83, 1.06) <sup>a</sup>	0.96 (0.78, 1.18) <sup>a</sup>	NR	NR
Heart failure	5 (-14 to 21) <sup>d</sup>	<b>1.49 (1.23, 1.8)<sup>b</sup></b>	NR	NR
Hospitalisation due to heart failure	NR	<b>1.42 (1.1, 1.83)<sup>b</sup></b>	<b>1.27 (1.07, 1.51)<sup>a</sup></b>	NR
Major microvascular events: new or worsening nephropathy or retinopathy	<b>0.86 (0.77, 0.97)<sup>a</sup></b>	NR	NR	NR
Major macrovascular events: CV death, non-fatal MI and non-fatal stroke.	0.94 (0.84, 1.06) <sup>a</sup>	<b>0.84 (0.72, 0.98)<sup>a</sup></b>	1.00 (0.89, 1.12) <sup>a</sup>	0.96 ( $\leq$ 1.16) <sup>c</sup>
Death from any cause, non-fatal MI, stroke, acute coronary syndrome, leg amputation/revascularisation and coronary revascularisation	NR	0.90 (0.80, 1.02) <sup>a</sup>	NR	NR
Combined major macrovascular and microvascular events	<b>0.90 (0.82, 0.98)<sup>a</sup></b>	NR	NR	NR
CV death, MI, stroke, hospitalisation for unstable angina, HF, or coronary revascularisation: secondary efficacy end point	NR	NR	1.02 (0.94, 1.11) <sup>a</sup>	NR
CV death, MI, stroke or urgent revascularization due to unstable angina: secondary efficacy end point	NR	NR	NR	0.95 ( $\leq$ 1.14) <sup>c</sup>

Statistically significant difference are marked in **bold**.

Abbreviations: CV = cardiovascular, MI = myocardial infarction; EM = Existing medication; DPP-4 = DPP-4 inhibitor; NR = Not reported; and SU = sulfonylurea.

Notes: <sup>a</sup> Hazard ratio (95% confidence interval); <sup>b</sup> Odds ratio (95% CI); <sup>c</sup> Hazard ratio (the upper boundary of the one-sided repeated CI, at an alpha level of 0.01); <sup>d</sup> Relative risk reduction (95% CI).

## ***Discussion***

Four trials were identified that examined long term effects for “real life” situations where an additional drug was added to patients at risk of heart disease on concurrent existing diabetes medicines. These trials demonstrated that the addition of an extra drug (sulfonylurea, TZD or DPP-4 inhibitor) provided a statistically significant reduction in HbA<sub>1c</sub> compared to being on existing medication alone, with no difference in magnitude between the three therapeutic groups. Only sulfonylurea addition provided weight reduction, with TZD and DPP-4 inhibitors demonstrating weight gain compared to baseline. When added to existing medication, sulfonylurea, TZD and DPP-4 inhibitors had increased odds ratios of hypoglycaemia compared to existing medication in trials of greater than two years duration.

There are very limited data on the long term effectiveness and safety of combined therapies. The addition of sulfonylurea to existing medication provided some reduction in the level of combined microvascular and macrovascular outcomes compared to existing medication alone, particularly major microvascular events. The other therapies that compared the addition of a drug to existing medication showed an increased risk of heart failure (TZD) and hospitalisation due to heart failure (TZD and DPP-4 inhibitors). Addition of TZDs to existing medication was associated with a reduction in major macrovascular events, while DPP-4 inhibitors had no effect on this outcome. It is important to note that the trials may not be comparable due to differences in included patients, trial design, background medication, outcome definitions and improvement in glycaemic control.

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## GLOSSARY

Authority required benefits	Restricted benefits that require prior approval from the DHS or the Department of Veterans' Affairs
Authority required (streamlined) benefits	Restricted benefits that do not require prior approval from the DHS or the Department of Veterans' Affairs but require the recording of a streamlined authority code on the prescription
Co-administration	Assumed use (determined from prescriptions supplied) of two or more medicines at the same time
Compliant treatment regimen	Drug regimens meeting requirements for PBS subsidy
Copayment	A payment made by the user at the time of service as part of the total payment for that service and any associated product
Dual therapy	In this report, dual therapy means use of either metformin or a sulfonylurea in combination with another anti-diabetic therapy for the management of type 2 diabetes
Gliptin	Dipeptidyl peptidase 4 (DPP-4) inhibitor – products included in this report were linagliptin, saxagliptin, sitagliptin, vildagliptin and alogliptin
Glitazone	Thiazolidinedione – products included in this report were pioglitazone and rosiglitazone
GLP-1 analogue	Glucagon-like peptide-1 analogue – products included in this report include exenatide
Government expenditure	Expenditure by the Australian Government, excluding out of pocket costs, including copayments, and private prescriptions
Initiating or starting treatment	<p>In part II of this report, refers to a patient with no prescription supplied for any anti-diabetic medicine in at least the previous 12 months. These patients are assumed to be starting drug treatment for their diabetes for the first time</p> <p>In part III and IV of this report, refers to a patient being supplied with a prescription for a certain drug for the first time. The patient may have been on other diabetes medicines in the past</p>
Monotherapy	In this report, refers to use of a single drug at any given time to manage type 2 diabetes

Non-compliant treatment regimen	Drug regimens not meeting requirements for PBS subsidy
Published price	The price of the drug as published in the Pharmaceutical Benefits Schedule
Regimen	A drug or combination of drugs deemed to be taken at the same time by a patient at a point in time
Restricted benefit	A restriction that means the relevant drug can be prescribed through the PBS only for specific therapeutic uses
Special pricing arrangement	A commercial-in-confidence arrangement between the Commonwealth and a pharmaceutical company that affects the actual price paid by the Commonwealth for supplied medicines
Switch	Changing from one subsidised therapy to another
Third line therapy or agent	In this report, refers to DPP-4 inhibitors, TZDs and exenatide
Triple therapy	In this report triple therapy refers to use of metformin or a sulfonylurea in combination with two other anti-diabetic therapies to manage type 2 diabetes
Under-copayment	A PBS medicine that costs less than the general patient copayment

## APPENDICES

### Appendix A: Context for the Diabetes Post-market Review

#### *The National Medicines Policy (NMP)*

The NMP is a broad framework that aims to improve health outcomes for all Australians through improving both access to, and appropriate use of, medicines.

The four central objectives of the policy are:

- timely and affordable access to medicines for all Australians;
- appropriate standards of quality, safety, and efficacy of medicines;
- quality use of medicines; and
- maintenance of a responsible and viable medicines industry in Australia.

Post-market reviews contribute to the quality use of medicines objective of the NMP.

Quality use of medicines is defined as:

- selecting management options wisely;
- choosing suitable medicines if a medicine is considered necessary; and
- using medicines safely and effectively.

The definition of quality use of medicines applies equally to decisions about medicine use by individuals and decisions that affect the health of the population.

#### *The Pharmaceutical Benefits Scheme (PBS)*

The PBS provides reliable, timely, and affordable access to a wide range of medicines for all Australians. Under the PBS, the Australian Government subsidises medicine costs to help people afford prescription medicines for most medical conditions. The PBS is part of the Australian Government's broader NMP.

#### *The Pharmaceutical Benefits Advisory Committee (PBAC)*

The PBAC is an independent expert body appointed by the Australian Government, comprised of medical practitioners, other health professionals, health economists and consumer representatives. The PBAC meets three times a year, usually in March, July and November. Additional special meetings may be held as required.

The PBAC is responsible for evaluating the clinical and cost-effectiveness of medicines in order to make recommendations relating to listing on the PBS. Recommendations for new listings are informed by evidence of a medicine's clinical effectiveness, safety, and cost-effectiveness ('value for money') compared with other treatments.

The PBAC has a broad statutory function under the *National Health Act 1953*, to advise the Minister on any matters concerning the operation of the PBS. This includes making

further recommendations regarding the safety, effectiveness and cost-effectiveness of medicines after they have been listed. Therefore, the PBAC considers the need for, and provides recommendations on, post-market reviews.

The PBAC has two sub-committees to assist with analysis and advice: the Drug Utilisation Sub-Committee (DUSC) and the Economics Sub-Committee (ESC). Information relating to the PBS, and the PBAC, DUSC and ESC meeting dates, agendas and outcomes are available on the [PBS website](#).

### ***Post-market Review Programme***

Post-market reviews are a systematic and formal approach to monitoring the use of medicines listed on the PBS. The Post-market Review Programme was established to support quality use of medicines and the ongoing evidence-based cost and clinically effective use of PBS listed medicines.

Applications to list a medicine on the PBS are considered by the PBAC on a case-by-case basis at the time a submission for listing is made. This means that a medicine is only considered in the context of treatments and evidence available at that time. Over time, new medicines are listed on the PBS, more data on medicine safety and efficacy becomes available, and treatment guidelines change. As a result, the actual use or health outcomes of a medicine may be different to what was considered by the PBAC at the time of listing. The post-market review process provides a mechanism for medicines to be considered in the full and current treatment context, including actual utilisation, comparative efficacy, treatment guidelines and health outcomes.

The Post-market Review Programme aims to achieve four main goals:

- improved patient safety through better understanding of adverse events and medicine-related harms
- ensuring the ongoing viability of the PBS through better targeting of medicines use and avoiding preventable wastage or inappropriate prescribing
- developing a better understanding of medicines use, to validate intended clinical benefit and inform medicines evaluation processes
- strengthened medicines pricing management, including through better management of clinical and economic uncertainty.

Post-market reviews are initiated due to concerns related to safety, cost-effectiveness, clinical effectiveness, higher than predicted use and/or international differences in use, of a medicine or a group of medicines. A full post-market review will only proceed following PBAC recommendation and Ministerial approval. Post-market reviews follow a standard process detailed on the [Post-Market Review website](#).

## **Appendix B: List of organisations invited to the Stakeholder Forum**

As the Medicines Review Stakeholder Forum was held on the same day as the Forum for Stage 2 of the Diabetes Review on insulin pumps, the following list includes organisations and manufacturers relevant to both reviews.

### ***Sponsors and Manufacturers***

Alphapharm Pty Ltd	Janssen-Cilag Australia Pty Ltd
Apotex Pty Ltd	Managing Diabetes Pty Ltd
Ascent Pharma Pty Ltd	Medical Specialists Australia Pty Ltd
Aspen Group of Companies	Medtronic Australasia Pty Ltd
AstraZeneca	Merck Sharp and Dohme (Australia) Pty Ltd
Aurobindo Pharma Pty Ltd	Novartis Pharmaceuticals Australia Pty Ltd
Australasian Medical and Scientific Ltd	Novo Nordisk Pharmaceuticals Pty Ltd
Bayer	Pharmacor Pty Ltd
Boehringer Ingelheim Pty Ltd	Ranbaxy Australia Pty Ltd
Bristol-Myers Squibb Australia	Roche Diagnositcs Australia Pty Ltd
Eli Lilly Australia Pty Ltd	Sandoz Pty Ltd
Generic Health Pty Ltd	Sanofi Aventis Australia
GlaxoSmithKline Australia Pty Ltd	Servier Laboratories (Australia) Pty Ltd

### ***Non-Government Organisations***

Australasian Paediatric Endocrine Group  
Australian Society of Clinical and Experimental Pharmacologists and Toxicologists  
Australian College of Nurse Practitioners  
Australian College of Nursing  
Australian College of Rural and Remote Medicine  
Australian Diabetes Council  
Australian Diabetes Educators Association  
Australian Medical Association  
Australian Paediatric Society  
Baker IDI Heart and Diabetes Institute  
Consumers Health Forum of Australia

Diabetes Australia  
Diabetes WA  
Dietitians Association of Australia  
General Medicines Industry Association  
Juvenile Diabetes Research Foundation  
Medical Technology Industry Association  
Medicines Australia  
National Association of People With HIV  
National Aboriginal Community Controlled Health Organisation  
Pharmaceutical Society of Australia  
Royal Australasia College of Physicians  
Royal Australian College of General Practitioners  
Rural Doctors Association of Australia  
The Australian Centre for Behavioural Research in Diabetes  
The Pharmacy Guild of Australia  
National Association of Diabetes Centres  
Quality Assurance for Aboriginal and Torres Strait Islander Medical Services Program

***Government Organisations***

Australian Institute of Health and Welfare  
National Health and Medical Research Institute  
NPS MedicineWise

## **Appendix C: Australian Government Diabetes Initiatives**

### ***Overweight and Obesity Initiatives***

The Australian Government funds a number of activities that promote physical activity and healthy eating, including:

Get Up & Grow: healthy eating and physical activity guidelines and resources for early childhood settings. Also adapted for Aboriginal and Torres Strait Islander educators and families with children attending early childhood settings (\$5.8 million over eight years from 2007-08).

Stephanie Alexander Kitchen Garden program: teaches primary school students in Years 3 – 6 how to grow, harvest, prepare and share fresh food in the belief that this approach will provide a better chance of positively influencing children's food choices (\$18.2 million from 2008-09).

2013 Clinical Practice Guidelines: for the Management of Overweight and Obesity in Adults, Adolescents and Children in Australia, and development of a Healthy Weight Guide for consumers (\$2.7 million over six years from 2009-10).

2013 Australian Dietary Guidelines: suite of documents including the Australian Guide to Healthy Eating for consumers (\$2.0 million over five years from 2007-08).

Physical activity guidelines for children, young people, adults and older Australians: are available online. New guidelines, Australia's Physical Activity and Sedentary Behaviour Guidelines for children, young people and adults were released in February 2014.

National Healthy School Canteen (NHSC) project: nationally consistent tools and training for canteen managers to assess the nutritional value of foods and beverages and make healthier menu selections for school canteens (\$2 million from 2006-07 over four years).

Healthy Kids Checks: for all three and a half year olds to improve childhood health – claimable under Medicare.

Get Set 4 Life: Habits for Healthy Kids Guide for parents of children receiving the Healthy Kids Check.

Walk Safely to School Day (WSTSD): \$200,000 in 2013-14. WSTSD is a national community awareness raising event targeting primary school aged children. The objective of the event is to raise awareness of the health benefits of physical activity, in particular walking and other forms of active transport, and to encourage participation in activities at a local school level. WSTSD is conducted by the Pedestrian Council of Australia (PCA).

Sporting Schools Initiative : (\$100.3 million over 3 years from 2014-15 to 2016-17). This initiative will encourage school aged children to participate in sport-based physical activity before, during and after school.

Healthy Spaces and Places: \$780,000 was provided between 2008-09 and 2011-12 to the Planning Institute of Australia (PIA), the Heart Foundation and the Australian Local Government Association partnership to produce a national web-based planning guide to assist planners to incorporate active living principles into the built environment.

Funding the Collaboration of Community-based Obesity Prevention Sites (CO-OPS): based at Deakin University to work with obesity prevention sites to assist with planning, implementing and evaluating interventions (\$4.99 million from 2007-08 to 2014-15).

SALSA (Students as Lifestyle Activists) Program: (\$350,000 over 3 years 2012-13; 2013-14; 2014-15) – for a peer educational program that provides high school students with the necessary knowledge and skills to maintain a balanced and healthy lifestyle.

National Nutrition Policy: A national nutrition policy is expected to be developed that will identify, prioritise, drive and monitor nutrition initiatives in Australia. (Funding of \$1.1 million is available for the development of the nutrition policy).

Voluntary Food Reformulation: The Australian Government encourages food reformulation in processed foods to enable consumers to have healthier food choices. The Government's voluntary food reformulation initiative aims to reduce high risk nutrients such as salt, saturated fat and sugar in commonly consumed processed foods. Under the initiative, leading manufacturers and retailers have agreed to sodium and saturated fat reduction targets across a variety of foods. Current approved funding for the initiative is \$200,000 over two years to June 2015.

### ***Significant Australian Government Initiatives in Diabetes***

Medicare Benefits Schedule (MBS): Rebated diabetes-specific items. Diabetes is also managed under generic GP items, but these cannot be tracked (between 1996-97 and 2012-13, almost \$457 million was expended on more than 23.4 million diabetes-specific services).

Pharmaceutical Benefits Scheme (PBS): Subsidised prescription pharmaceuticals for the treatment of diabetes (between 1996-97 and 2012-13, almost \$4.3 billion was expended for this purpose).

National Diabetes Services Scheme (NDSS): Subsidised diabetes equipment and products (between 2002-03 and 2012-13, more than \$1.4 billion was spent).

NHMRC research grants: More than \$547 million was provided for 4,133 research studies into diabetes between 2000-01 and 2012-13.

The Medical Research Future Fund (MRFF): To be introduced on 1 January 2015, with initial funding of \$1 billion (projected to grow to \$20 billion by 2020), the MRFF will facilitate Australia maintaining a world class medical research sector, with access to cutting edge innovation and clinical breakthroughs in our hospitals.

The Government also made an election commitment to provide \$35 million towards the Australian Type 1 Diabetes Clinical Research Network supporting clinical research activity. Funding for this commitment, which is additional to a \$5 million Government contribution to establish the Network in 2010, is managed by the Australian Research Council (in the Education Portfolio).

The Practice Incentives Program (PIP) Diabetes Incentive: Supports general practice to provide earlier diagnosis and effective management of diabetes (\$184.7 million over twelve years, 2001-02 to 2012-13).

The Diabetes Care Project: Testing new models of health care delivery, designed to include care for adults with either type 1 or type 2 diabetes (\$33.4 million over three and a half years, 2011-12 and 2014-15, comprising \$31.4 million from the Australian Government and and \$2 million from the Victorian Government). It is thought to be the largest randomised controlled trial ever undertaken on an integrated care intervention and is currently in the evaluation phase.

The Type 1 Diabetes Insulin Pump Programme: Means-tested subsidy to provide insulin pumps to Australians, aged under 18 years, with type 1 diabetes (around \$7 million provided over four years from 2012-13).

Australian National Diabetes Audit (ANDA): Involves the collection, collation, analysis, audit and reporting of clinical diabetes and patient education and self-care data in specialist diabetes centres across all states and territories (\$193,117 over three years 2012-13 to 2014-15). This activity was previously managed via the ANDIAB project.

Australian National Diabetes Information Audit and Benchmarking (ANDIAB) Project: Involves the collection, collation, analysis, audit and reporting of clinical diabetes servicing in specialist diabetes centres (\$528,000 over eight years, 2005-06 to 2012-13). This activity is now managed by the Australian National Diabetes Audit (ANDA).

Australian Islet Transplantation Program (ITP): Treatment option for a small number of Australians with a severe diabetic condition (\$30 million was provided to the JDRF for the ITP between 2005-06 and 2009-10).

National Centre for Monitoring Vascular Diseases (NCMVD): Administered by the Australian Institute of Health and Welfare for developing, collating and interpreting data relevant to chronic disease – diabetes, CVD and chronic kidney disease – prevention, detection, management and care (\$6.7 million over three years until 30 June 2016).

National (insulin-treated) Diabetes Register (NDR): Administered by the Australian Institute of Health and Welfare. Contains records of people in Australia who commenced using insulin to treat their diabetes after 1 January 1999 (\$5.5 million from 2005-06 through 2014-15).

National Gestational Diabetes Register (NGDR): (\$126,000 provided to establish the Register in 2010-11).

Connecting Diabetes: Online diabetes counselling (\$1.1 million over three years from 2012-13).

TEAM T1 (Teens Empowered and Actively Managing Type 1) Program: Structured diabetes self-management program for adolescents with type 1 diabetes (\$1.9 million over three years from 2012-13).

Quality Assurance for the Aboriginal and Torres Strait Islander Medical Services (QAAMS) Pathology Programme: supports the provision of culturally appropriate and clinically effective diabetes management in Aboriginal and Torres Strait Islander communities (\$4.24 million over three years 2013-14 to 2015-16).

## Appendix D: Utilisation analysis – Medicine name abbreviations

Exen	Exenatide
FDC	Fixed dose combination
Glip	Gliptin (also known as dipeptidyl peptidase-4 inhibitors)
Glit	Glitazone (also known as thiazolidinedione)
Met	Metformin
GLP-1	Glucagon-like peptide-1
Insulin - basal	Insulin glargine and insulin detemir
Insulin - fast	Short acting/ultra short acting insulin: insulin neutral, insulin glulisine, insulin lispro, insulin aspart
Insulin - intermediate or Insulin - mixed	Insulin isophane, insulin isophane and insulin neutral, insulin lispro and lispro protamine, insulin aspart and aspart protamine
Pio	Pioglitazone
Rosi	Rosiglitazone
SCD	Standard coverage days
Sul	Sulfonylurea (glimepiride, gliclazide, glibenclamide, glipizide)

## Appendix E: Utilisation analysis – TGA listings and PBS restrictions

The indications approved by the Therapeutic Goods Administration (TGA) and the PBS listings current at the time of the utilisation analysis are provided in this appendix. The alignment between PBS listings and TGA-approved indications are shown for type 2 diabetes medicines that became available through the PBS prior to 2002 (Table 1) and at various time points between 2003 and 2012 (Table 2). Cells shaded in grey indicate differences between TGA-approved indications and PBS listings.

**Table 1. Medicines for diabetes PBS listed before 2002: TGA-approved indications versus PBS listings.**

		Mono-therapy	Dual therapy [+met or sul]	Dual therapy [+TZD]	Triple therapy [+met+sul]	With insulin
Metformin	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glibenclamide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Gliclazide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glimepiride	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Glipizide	TGA	✓	✓	✓	✓	✓
	PBS	✓	✓	✓	✓	✓
Acarbose	TGA	✓	✓	✓ <sup>a</sup>	✓	✓
	PBS	✓	✓	✗	✓	✓

**Source:** Schedule of Pharmaceutical Benefits and Product Information (October 2012)

**Notes:** The references to mono-, dual and triple therapy are in relation to the active ingredient(s), not products. The (✓) indicates that the drug can be part of the regimen by virtue of not being specifically excluded. The (✗) indicates that the drug can't be part of the regimen. Cells in grey highlight differences between TGA/PBS indications.

<sup>a</sup> Acarbose is TGA-approved as adjunct therapy. However, the TZDs are not TGA-approved for use with acarbose

Acarbose, metformin, sulfonylureas (glibenclamide, gliclazide, glipizide and glimepiride) and combinations such as metformin + glibenclamide are all unrestricted benefits in the General Schedule of the PBS, and there are no restrictions for prescribers in using these agents for monotherapy, dual or triple therapy or in combination with insulin for the management of type 2 diabetes.

**Table 2. Medicines for diabetes listed between 2003 and 2012: TGA-approved indications versus PBS listings.**

Medicine		Mono-therapy	Dual therapy [+met or sulf]	Dual therapy [+glip or TZD]	Triple therapy [+met+sulf]	With insulin
Rosiglitazone	TGA	✓	✓	✗	✗	✗
	PBS	✗	✓	✗	✗	✗
Pioglitazone	TGA	✓	✓	✗	✓	✓ <sup>a</sup>
	PBS	✗	✓	✗	✓	✓ <sup>a</sup>
Sitagliptin	TGA	✗	✓	✓ <sup>b</sup>	✗	✗
	PBS	✗	✓	✗	✗	✗
Saxagliptin	TGA	✗	✓ <sup>e</sup>	✓ <sup>b</sup>	✗	✓
	PBS	✗	✓ <sup>e</sup>	✗	✗	✗
Vildagliptin	TGA	✗	✓	✓ <sup>b,c</sup>	✗	✗
	PBS	✗	✓	✗	✗	✗
Linagliptin	TGA	✗	✓	✗	✓	✗
	PBS	✗	✓	✗	✗	✗
Exenatide BD	TGA	✗	✓	✗	✓	✓
	PBS	✗	✓	✗	✓	✗
Metformin+ glibenclamide	TGA	✗	✓	✗	✓	✓
	PBS	✗	✓	✗	✓	✓
Rosiglitazone+ metformin	TGA	✗	✓	✓	✗	✗
	PBS	✗	✓ <sup>d</sup>	✓	✗	✗
Vildagliptin+ metformin	TGA	✗	✓	✗	✗	✗
	PBS	✗	✓ <sup>d</sup>	✗	✗	✗
Sitagliptin+ metformin	TGA	✗	✓	✗	✗	✗
	PBS	✗	✓ <sup>d</sup>	✗	✗	✗

Source: Schedule of Pharmaceutical Benefits and Product Information (October 2012)

Abbreviations: met = metformin; sulf = sulfonylurea; glip = DPP-4 inhibitor; and glit = TZD.

Notes: The references to mono-, dual and triple therapy are in relation to the active ingredient(s), not products. The (✓) indicates that the drug can be part of the regimen by virtue of not being specifically excluded. The (✗) indicates that the drug can't be part of the regimen. Cells in grey highlight differences between TGA/PBS indications

<sup>a</sup> TGA-approved for dual therapy in combination with insulin. However, the PBS listing does not specify the diabetes medicines to be used in combination with insulin and appears broader

<sup>b</sup> TGA-approved for dual therapy in combination with TZDs. However, TZDs are not TGA-approved for use with DPP-4 inhibitors

<sup>c</sup> Pioglitazone only

<sup>d</sup> Only dual therapy with metformin allowed

<sup>e</sup> The TGA-approved indication is wider, and includes use as initial combination therapy when dual saxagliptin and metformin therapy is appropriate.

**Table 3. Full PBS restriction wording by restriction and medicine.**

Restriction	Medicine
Unrestricted	<p>Metformin</p> <p>Glibenclamide</p> <p>Gliclazide</p> <p>Glimepiride</p> <p>Glipizide</p> <p>Acarbose</p> <p>Insulin aspart</p> <p>Insulin aspart and protamine suspension</p> <p>Insulin detemir</p> <p>Insulin glargine</p> <p>Insulin glulisine</p> <p>Insulin lispro</p> <p>Insulin lispro and protamine suspension</p> <p>Insulin neutral</p> <p>Insulin neutral and insulin isophane (biphasic isophane)</p> <p>Metformin and glibenclamide FDC</p>
<p>Authority required (streamlined)</p> <p>Dual oral combination therapy with metformin or a sulfonylurea</p> <p>Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c<sup>a</sup> is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.</p>	<p>Rosiglitazone (telephone Authority required)</p> <p>Pioglitazone</p> <p>Sitagliptin</p> <p>Saxagliptin</p> <p>Vildagliptin</p> <p>Linagliptin</p> <p>Exenatide</p>
<p>Authority required</p> <p>Type 2 diabetes in a patient whose HbA1c<sup>a</sup> is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with metformin and where a sulfonylurea is contraindicated or not tolerated.</p>	<p>Rosiglitazone and metformin</p>
Authority required (streamlined)	Pioglitazone

Restriction	Medicine
Combination therapy with insulin Type 2 diabetes, in combination with insulin, in a patient whose HbA1c <sup>a</sup> is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with insulin and oral anti-diabetic agents, or insulin alone where metformin is contraindicated.	
Authority required (streamlined) Triple oral combination therapy with metformin and a sulfonylurea Type 2 diabetes, in combination with metformin and a sulfonylurea, in a patient whose HbA1c <sup>a</sup> is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.	Pioglitazone Exenatide
Authority required (streamlined) 3543 Type 2 diabetes in a patient whose HbA1c <sup>a</sup> is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with metformin and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.	Metformin and sitagliptin FDC Metformin and vildagliptin FDC
Authority required (streamlined) 3149; 3686 Continuation of therapy in type 2 diabetes mellitus in a patient who has previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and sitagliptin / metformin and vildagliptin.	Metformin and sitagliptin FDC Metformin and vildagliptin FDC

<sup>a</sup> The date and level of the qualifying HbA1c must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:

- (a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or
- (b) red cell transfusion within the previous 3 months.

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per litre in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records.

**Table 4. Date of PBS listing of medicines used to treat diabetes.**

Medicine	Date	Summarised restriction
Glimepiride	Nov 2000	Unrestricted benefit
Rosiglitazone	Nov 2003	Dual oral – with either metformin or a sulfonylurea*
	Aug 2005	Combination therapy with insulin – PBS subsidisation ceased late 2008

Medicine	Date	Summarised restriction
	Aug 2006	Triple therapy with metformin and sulfonylurea- PBS subsidisation ceased Feb 2009
Rosiglitazone with metformin FDC	Dec 2006	Dual therapy when sulfonylurea is contraindicated or not tolerated
Pioglitazone	Nov 2003	Dual oral – with either metformin or a sulfonylurea*
	Nov 2003	Combination therapy with insulin
	Feb 2008	Triple therapy – with metformin and a sulfonylurea
Insulin detemir	Oct 2006	Restricted benefit – type one diabetes
Insulin glargine	Oct 2006	Unrestricted benefit
Insulin glulisine	Jul 2007	Unrestricted benefit
Sitagliptin	Aug 2008	Dual oral – with either metformin or a sulfonylurea*
Sitagliptin with metformin FDC	Aug 2009	Dual therapy when sulfonylurea is contraindicated or not tolerated
Exenatide	Aug 2010	Dual oral – with either metformin or a sulfonylurea*
	Aug 2010	Triple therapy – with metformin and a sulfonylurea
Vildagliptin	Aug 2010	Dual oral – with either metformin or a sulfonylurea*
Vildagliptin with metformin FDC	Apr 2011	Dual therapy when sulfonylurea is contraindicated or not tolerated
Saxagliptin	Jun 2011	Dual oral – with either metformin or a sulfonylurea*
Linagliptin	Mar 2012	Dual oral – with either metformin or a sulfonylurea*

Notes: \* Where one of metformin or a sulfonylurea is contraindicated or not tolerated.

Metformin and insulin neutral were listed on the PBS in 1963. All other drugs covered by this analysis, except those in Table 4 above, were listed between 1992 and 2002.

Rosiglitazone was delisted for combination therapy with insulin in late 2008 and delisted for triple therapy with metformin and a sulfonylurea in February 2009.

In March 2010, the PBAC recommended that restrictions on all currently PBS-subsidised DPP-4 inhibitors and TZDs be modified to allow patients to switch between agents in these two classes without having to requalify with respect to glycosylated haemoglobin levels (HbA<sub>1c</sub>). Although the evidence to support switches from a DPP-4 inhibitor to a TZD and vice versa is limited, PBAC considered it unreasonable to require a loss of diabetic control prior to switching. This same recommendation to allow switching was subsequently applied to exenatide.

## Appendix F: PBS/RPBS Prescriptions and Expenditure by Medicine

Details of PBS/RPBS prescriptions dispensed during the twelve months ending April 2014 for newer type 2 diabetes medicines. Items included and prices based on the 1 August 2014 PBS Schedule.

Drug Name	Form & Strength	Item No.	MQ packs/ MQ units/ No. of Rpts.	DPMQ (Price)	No. of Scripts	Cost to Govt	Abbreviated restriction
TZDs							
Pioglitazone	15 mg tablet	8694N	1/28/5	\$32.13	45,121	\$1,421,399	Authority Required (STREAMLINED)
	30 mg tablet	8695P	1/28/5	\$45.19	117,722	\$5,476,143	In combination with Met or Su, and contraindicated/intolerant to Met + Su.
	45 mg tablet	8696Q	1/28/5	\$55.39	84,447	\$5,062,349	In combination with insulin. In combination with Met + Su. HbA <sub>1c</sub> >7%.
Rosiglitazone	4 mg tablet	8689H	1/28/5	\$61.49	6,572	\$374,785	Authority Required
	8 mg tablet	8690J	1/28/5	\$90.94	7,257	\$586,155	In combination with Met or Su, and contraindicated/intolerant to Met + Su. HbA <sub>1c</sub> >7%.
TZD + metformin combinations							
Rosiglitazone + metformin	2 mg + 500 mg tablet	9059T	1/56/5	\$63.58	1,628	\$92,197	Authority Required
	2 mg + 1 g tablet	9060W	1/56/5	\$65.54	4,474	\$243,032	Contraindicated/intolerant to Su.
	4 mg + 500 mg tablet	9061X	1/56/5	\$93.04	1,455	\$119,374	HbA <sub>1c</sub> >7%.
	4 mg + 1 g tablet	9062Y	1/56/5	\$95.00	8,236	\$679,977	
DPP-4 inhibitors							
Alogliptin <sup>a</sup>	6.25 mg tablet	2944Y	1/28/5	\$59.20	264	\$12,069	Authority Required (STREAMLINED)
	12.5 mg tablet	2933J	1/28/5	\$59.20	529	\$23,991	In combination with Met or Su.
	25 mg tablet	2986E	1/28/5	\$59.20	1,490	\$62,392	HbA <sub>1c</sub> >7%.
Linagliptin	5 mg tablet	3387G	1/30/5	\$62.95	180,797	\$14,811,371	

Drug Name	Form & Strength	Item No.	MQ packs/ MQ units/ No. of Rpts.	DPMQ (Price)	No. of Scripts	Cost to Govt	Abbreviated restriction
Saxagliptin	2.5 mg tablet	10128C	1/28/5	\$59.20	–	–	
	5 mg tablet	8983T	1/28/5	\$59.20	104,351	\$7,829,503	
Sitagliptin	25 mg tablet	9180E	1/28/5	\$59.20	28,339	\$2,272,930	
	50 mg tablet	9181F	1/28/5	\$59.20	80,558	\$6,413,969	
	100 mg tablet	9182G	1/28/5	\$59.20	282,045	\$21,386,177	
Vildagliptin	50 mg tablet	3415R	1/60/5	\$62.95	57,752	\$4,750,890	
DPP-4 inhibitor + metformin combinations							
Alogliptin + metformin <sup>b</sup>	12.5 mg + 500 mg tablet	10033C	1/56/5	\$61.30	157	\$6,932	Authority Required (STREAMLINED) HbA <sub>1c</sub> >7% despite treatment with metformin. Continuing: Patient stabilised on metformin + the relevant DPP-4 inhibitor.
	12.5 mg + 850 mg tablet	10032B	1/56/5	\$62.70	107	\$5,402	
	12.5 mg + 1 g tablet	10035E	1/56/5	\$63.26	500	\$22,819	
Linagliptin + metformin <sup>c</sup>	2.5 mg + 500 mg tablet	10038H	1/60/5	\$65.20	256	\$12,878	
	2.5 mg + 850 mg tablet	10045Q	1/60/5	\$66.69	102	\$4943	
	2.5 mg + 1 g tablet	10044P	1/60/5	\$67.29	635	\$31,936	
Saxagliptin + metformin <sup>c</sup>	2.5 mg + 1 g tablet: MR	10048W	1/56/5	\$63.26	893	\$40,575	
	5 mg + 500 mg tablet: MR	10055F	1/28/5	\$60.25	245	\$11,022	
	5 mg + 1 g tablet: MR	10051B	1/28/5	\$61.30	859	\$38,110	
Sitagliptin + metformin	50 mg + 500 mg tablet	9449H	1/56/5	\$61.30	107,632	\$8,248,078	
	50 mg + 850 mg tablet	9450J	1/56/5	\$62.70	66,912	\$5,169,337	
	50 mg + 1 g tablet	9451K	1/56/5	\$63.26	439,983	\$33,775,009	
	50 mg + 1 g tablet: MR	10090C	1/56/5	\$63.26	–	–	
	100 mg + 1 g tablet: MR	10089B	1/28/5	\$61.30	–	–	
Vildagliptin + metformin	50 mg + 500 mg tablet	5474D	1/60/5	\$62.12	40,226	\$3,210,966	
	50 mg + 850 mg tablet	5475E	1/60/5	\$63.61	28,617	\$2,290,197	
	50 mg + 1 g tablet	5476F	1/60/5	\$64.21	164,880	\$13,178,960	

Drug Name	Form & Strength	Item No.	MQ packs/ MQ units/ No. of Rpts.	DPMQ (Price)	No. of Scripts	Cost to Govt	Abbreviated restriction
SGLT2 inhibitors							
Canagliflozin <sup>a</sup>	100 mg tablet	2873F	1/30/5	\$96.61	554	\$47,376	Authority Required
	300 mg tablet	2987F	1/30/5	\$96.61	843	\$66,453	In combination with Met or Su, and not able to be adequately controlled by Met + Su. HbA <sub>1c</sub> >7%.
Dapagliflozin <sup>a</sup>	10 mg tablet	10011X	1/28/5	\$90.40	10,553	\$762,323	
GLP-1 receptor agonists							
Exenatide <sup>d</sup>	5 µg/0.02 mL injection, 60 unit doses	3423E	1/1/5	\$122.79	41,781	\$5,817,477	Authority Required (STREAMLINED)
	10 µg/0.04 mL injection, 60 unit doses	3424F	1/1/5	\$131.65	117,339	\$16,539,129	In combination with Met or Su, and contraindicated/intolerant to Met + Su. In combination with Met + Su. HbA <sub>1c</sub> >7%.

**Abbreviations:** DPMQ = Dispensed price for maximum quantity, MQ = Maximum quantity, MR = Modified release; Met = Metformin; and Su = Sulfonylurea.

**Notes:** Dashes indicate medicines listed after 1 April 2014.

<sup>a</sup> Alogliptin, canagliflozin and dapagliflozin were listed on 1 December 2013.

<sup>b</sup> Alogliptin + metformin FDC was listed on 1 February 2014.

<sup>c</sup> Linagliptin + metformin and saxagliptin + metformin listed 1 March 2014.

<sup>d</sup> Special pricing arrangements exist for exenatide. Therefore, the final cost to Government may differ from that shown.

## Appendix G: Literature Review – Supplementary Tables

**Table 1. Included monotherapy trials, treatment comparisons and outcomes.**

Monotherapy			Treatment arm				Outcomes										Seen by PBAC? <sup>a</sup>
Author, Year	Trial duration	N	1	2	3	4	HbA <sub>1c</sub>	BW	AE	SAE	Hypo-G	Mor	CVD	MVD	UTI	Pan	
PBO vs.																	
TZDs																	
Chou, 2012 <sup>97</sup>	26 weeks	1,912	RIVO	RIVO	PIO	PBO	x	x	x	x	x	x	x		x		No
DPP-4 inhibitors																	
Pan, 2012 <sup>98</sup>	24 weeks	568	SAX	PBO			x	x	x	x	x	x	x		x	x	No
MET vs.																	
SU																	
Kahn, 2006 <sup>99 b</sup>	4 years	4,360	MET	GLIB	ROS		x	x	x	x	x	x	x				Yes
Wright, 2006 <sup>100</sup>	6 years	5,102	MET	SU	Diet alone						x						No
TZDs																	
Kahn, 2006 <sup>99 b</sup>	4 years	4,360	MET	ROS	GLIB		x	x	x	x	x	x	x				Yes
Schernthaner, 2004 <sup>101</sup>	52 weeks	1,199	MET	PIO			x	x	x			x	x				No
DPP-4 inhibitors																	
Aschner, 2010 <sup>102</sup>	24 weeks	1,050	MET	SIT			x	x	x	x	x	x			x		Yes
Bosi, 2009 <sup>103 b</sup>	24 weeks	1,179	MET	VIL	MET + VIL		x	x	x	x	x	x	x				Yes
Jadzinsky, 2009 <sup>104</sup> Pfutzner, 2011 <sup>105</sup>	24 weeks 76 weeks	1,306	MET + SAX	MET + SAX	MET + PBO	SAX + PBO	x x	x x	x x	x x	x x	x x	- x		- x		No
Schweizer, 2007 <sup>106</sup>	52 weeks	780	MET	VIL			x	x	x	x	x						No
SU vs.																	
TZDs																	
Jain, 2006 <sup>107</sup>	56 weeks	502	GLIB	PIO			x	x	x	x	x	x	x				No
Kahn, 2006 <sup>99 b</sup>	4 years	4,360	GLIB	ROS	MET		x	x	x	x	x	x	x				Yes
Tolman, 2009 <sup>108</sup>	3 years	2,097	GLIB	PIO			x		x	x	x	x	x				No
DPP-4 inhibitors																	
Foley, 2009 <sup>109</sup>	104 weeks	1,092	GLZ	VIL			x	x	x		x						No

Monotherapy			Treatment arm				Outcomes										Seen by PBAC? <sup>a</sup>
Author, Year	Trial duration	N	1	2	3	4	HbA <sub>1c</sub>	BW	AE	SAE	Hypo-G	Mor	CVD	MVD	UTI	Pan	
Alpha-glucosidase inhibitors vs.																	
DPP-4 inhibitors																	
Pan, 2008 <sup>110</sup>	24 weeks	661	ACA	VIL			x	x	x	x	x	x					No
TZDs vs.																	
TZDs																	
Goldberg, 2005 <sup>111</sup>	24 weeks	802	PIO	ROS			x	x	x		x						Yes
DPP-4 inhibitors																	
Rosenstock, 2007 <sup>112</sup> Rosenstock, 2009 <sup>113</sup>	24 weeks 2 years	786	ROS	VIL			x x	x x	x x	x x	x x	x x					No
DPP-4 inhibitors vs.																	
DPP-4 inhibitors																	
Bosi, 2009 <sup>103</sup> *	24 weeks	1,179	VIL	VIL + MET	MET		x	x	x	x	x	x	x				Yes

**Abbreviations:** ACA = acarbose; AE = adverse event; BW = body weight; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; GLIB = glibenclamide; GLZ = gliclazide; HbA<sub>1c</sub> = glycated haemoglobin; Hypo-G = hypoglycaemia; MET = metformin; Mor = mortality; MVD = microvascular disease; Pan = pancreatitis; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; PIO = pioglitazone; RIVO = rivoglitazone; ROS = rosiglitazone; SAE = serious adverse event; SAX = saxagliptin; SIT = sitagliptin; SU = sulfonylurea; UTI = urinary tract infection; VIL = vildagliptin

**Notes:** <sup>a</sup> \* Trials included in submissions from 2002 to November 2013; <sup>b</sup> Trial used for more than one comparison.

**Table 2. Included dual therapy trials, treatment comparisons and outcomes.**

Dual therapy			Treatment arm				Outcomes										Seen by PBAC? <sup>a</sup>	
Author, Year	Trial duration	N	1	2	3	4	HbA <sub>1c</sub>	BW	AE	SAE	Hypo-G	Mor	CVD	MVD	UTI	Pan		
MET vs.																		
MET + TZDs																		
Bailey, 2005 <sup>114</sup>	24 weeks	568	MET	MET + ROS			x	x	x	x	x	x	x				Yes	
Borges, 2011 <sup>115</sup>	80 weeks	688	MET	MET/ROS			x	x	x	x	x	x	x				No	
Stewart, 2006 <sup>116</sup>	32 weeks	526	MET	MET + ROS			x	x	x	x	x		x				No	
Weissman, 2005 <sup>117</sup>	24 weeks	766	MET	MET + ROS			x	x	x		x	x	x				Yes	
MET + DPP-4 inhibitors																		
Bosi, 2009 <sup>103</sup> b	24 weeks	1,179	MET	VIL	MET + VIL		x	x	x	x	x	x	x				Yes	

Dual therapy			Treatment arm				Outcomes										Seen by PBAC? <sup>a</sup>
Author, Year	Trial duration	N	1	2	3	4	HbA <sub>1c</sub>	BW	AE	SAE	Hypo-G	Mor	CVD	MVD	UTI	Pan	
Charbonnel, 2006 <sup>118</sup>	24 weeks	701	MET + SIT	MET + PBO			x	x	x	x	x				x		Yes
Filozof, 2010 <sup>119</sup>	24 weeks	914	MET	MET + VIL			x	x	x	x	x				x		Yes
Goldstein, 2007 <sup>120</sup>	24 weeks	1,091	MET	MET + SIT	MET + SIT		x	x	x	x	x	x					Yes
Jadzinsky, 2009 <sup>104 b</sup> Pfutzner, 2011 <sup>105 b</sup>	24 weeks 76 weeks	1,306	MET + SAX	MET + SAX	MET + PBO	SAX + MET	x x	x x	x x	x x	x x	x x			- x		No
Olansky, 2011 <sup>121</sup>	44 weeks	1,250	MET	MET/SIT			x	x	x	x	x	x					No
Yang, 2011 <sup>122</sup>	24 weeks	570	MET + PBO	MET + SAX			x	x	x	x	x	x			x	x	No
<b>DPP-4 inhibitors vs.</b>																	
<i>DPP-4 inhibitors + MET</i>																	
Bosi, 2009 <sup>103 b</sup>	24 weeks	1,179	MET	VIL	MET + VIL		x	x	x	x	x	x	x				Yes
<b>TZDs vs.</b>																	
<i>TZDs + DPP-4 inhibitors</i>																	
Yoon, 2011 <sup>1</sup>	24 weeks	520	PIO + SAX	PIO + PBO			x	x	x	x	x	x					No
<i>DPP-4 inhibitors + MET</i>																	
Wainstein, 2012 <sup>123</sup>	32 weeks	521	PIO	SIT/MET			x	x	x	x	x	x					No
<b>MET + SU vs.</b>																	
<i>SU + TZDs</i>																	
Hanefeld, 2004 <sup>124</sup> Seufert, 2008 <sup>125</sup>	52 weeks 2 years	639	MET + SU	PIO + SU			x x	x x	x x	x x	x x	x -					No
<i>MET + TZDs</i>																	
Hamann, 2008 <sup>126</sup>	52 weeks	596	MET + GLZ or GLIB	MET + ROS			x	x	x	x	x	x	x				No
Matthews, 2005 <sup>127</sup> Seufert, 2008 <sup>125</sup>	52 weeks 2 years	630	MET + SU	MET + PIO			x x	x x	x x	x x	x x	x -					Yes
Home, 2009 <sup>128</sup> Komajda, 2010 <sup>129</sup> Mahaffey, 2013 <sup>130</sup>	5.5 years	4,447	MET + SU	MET or SU + ROS			x x x	x x x	x x x	x x x	x x x	x x x					No
<i>MET + SGLT2 inhibitors</i>																	
Nauck, 2011 <sup>131</sup>	52 weeks	814	MET + GLIP	MET + DAP			x	x	x	x	x	x			x		Yes
<i>MET + DPP-4 inhibitors</i>																	
Arechavaleta, 2011 <sup>132</sup>	30 weeks	936	MET + GMP	MET + SIT			x	x	x	x	x	x					Yes

Dual therapy			Treatment arm				Outcomes										Seen by PBAC? <sup>a</sup>
Author, Year	Trial duration	N	1	2	3	4	HbA <sub>1c</sub>	BW	AE	SAE	Hypo-G	Mor	CVD	MVD	UTI	Pan	
Ferrannini, 2009 <sup>133</sup>	52 weeks	2,789	MET + GMP	MET + VIL			x	x	x	x	x	x					Yes
Filozof, 2010 <sup>134</sup>	52 weeks	1,007	MET + GLZ	MET + VIL			x	x	x	x	x				x		Yes
Gallwitz, 2012 <sup>135</sup>	2 years	1,552	MET + GMP	MET + LIN			x	x	x	x	x	x	x		x	x	Yes
Nauck, 2007 <sup>83</sup>	52 weeks	1,172	MET + GLIP	MET + SIT			x	x	x	x	x	x			x		Yes
Krobot, 2012 <sup>136</sup>	52 weeks						-	-	-	-	x	-			-		
Seck, 2010 <sup>137</sup>	2 years						x	x	x	x	x	x			x		
Goke, 2010 <sup>138</sup>	52 weeks	858	MET + GLIP	MET + SAX			x	x	x	x	x	x				x	No
Goke, 2013 <sup>139</sup>	104 weeks						x	x	x	x	x	x				x	
Matthews, 2010 <sup>140</sup>	2 years	3,118	MET + GMP	MET + VIL			x	x	x	x	x	x					No
MET + GLP-1 receptor agonists																	
Gallwitz, 2012 <sup>141</sup>	2-3 years	1,029	MET + GMP	MET + EXN			x	x	x	x	x	x			x	x	Yes
MET + SGLT 2 inhibitors																	
Cefalu, 2013 <sup>142</sup>	52 weeks	1,450	MET + GMP	MET + CAN	MET + CAN		x	x	x	x	x	x			x		Yes
MET + TZDs vs.																	
MET + TZDs																	
Perez, 2009 <sup>143</sup>	24 weeks	600	MET + PIO	MET/PIO			x	x	x	x	x	x			x		No
MET + DPP-4 inhibitors																	
Bolli, 2007 <sup>144</sup>	24 weeks	576	MET + PIO	MET + VIL			x	x	x	x	x	x	some				No
Bolli, 2009 <sup>145</sup>	52 weeks						x	x	x	x	x						
MET + INS vs.																	
MET + DPP-4 inhibitors																	
Aschner, 2012 <sup>146</sup>	24 weeks	515	MET + GLA	MET + SIT			x	x	x	x	x		x				No

**Abbreviations:** AE = adverse event; BW = body weight; CAN = canagliflozin; CVD = cardiovascular disease; DAP = dapagliflozin; EXN = exenatide; GLA = glargine; GLIB = glibenclamide; GLIP = glipizide; GLP-1 = GLP-1 receptor agonist; GLZ = gliclazide; GMP = glimepiride; Hypo-G = hypoglycaemia; INS = insulin; MET = metformin; Mor = mortality; MVD = microvascular disease; Pan = pancreatitis; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; PIO = pioglitazone; ROS = rosiglitazone; SAE = serious adverse event; SAX = saxagliptin; SGLT 2 = sodium glucose co-transporter 2; SIT = sitagliptin; SU = sulfonylurea; UTI = urinary tract infection; VIL = vildagliptin; and LIN = linagliptin.

**Notes:** Row highlighted in grey was identified as a trial of interest for the PBAC.

<sup>a</sup> Trials included in submissions from 2002 to November 2013; <sup>b</sup> Trial is also included for monotherapy comparisons.

**Table 3. Results of trials with duration >1 year – therapies added to existing medication.**

	EM vs. EM + SU		EM vs. EM + TZD		EM vs. EM + DPP-4 inhibitors			
	Advance 2008 <sup>2</sup>		Dormandy 2005 <sup>3</sup>		Scirica 2013 <sup>4</sup>		White 2013 <sup>5</sup>	
	EM + GLZ	EM	EM + PIO	EM + PBO	EM + SAX	EM + PBO	EM + ALO	EM + PBO
Trial duration	5 years (median)		34.5 months		2.1 year		18 months	
N	5,571	5,569	2,605	2,633	8,280	8,212	2,701	2,679
HbA <sub>1c</sub> ; % (IQR) mean change from baseline	<b>-0.99</b>	<b>-0.24</b>	<b>-0.8</b> <b>(-1.6, -0.1)</b>	<b>-0.3</b> <b>(-1.1, 0.4)</b>	-	-	<b>-0.33</b>	<b>-0.03</b>
BW; kg mean change from baseline	<b>-0.1</b>	<b>-1.0</b>	<b>3.6</b>	<b>-0.4</b>	-	-	1.09	1.04
Any AE; %	-	-	-	-	-	-	80.0%	78.8%
SAE; %	-	-	46.2%	48.4%	-	-	33.6%	35.5%
Hypo-G; %	<b>53.0%</b>	<b>38.0%</b>	<b>27.9%</b>	<b>20.1%</b>	<b>15.3%</b>	<b>13.4%</b>	6.7%	6.5%
Severe hypo-G; %	<b>2.7%</b>	<b>1.5%</b>	0.7%	0.4%	<b>2.1%</b>	<b>1.7%</b>	0.7%	0.6%
UTI; %	-	-	-	-	-	-	-	-
Pancreatitis; %	-	-	-	-	0.3%	0.3%	0.6%	0.4%
Mortality; %	8.9%	9.6%	6.8%	7.1%	5.1%	4.6%	5.7%	6.5%

Statistically significant difference are marked in **bold**.

Abbreviations: AE = adverse event; ALO = alogliptin; BW = body weight; IQR = inter-quartile range; EM = existing medication; GLZ = gliclazide; Hypo-G = hypoglycaemia; PBO = placebo; PIO = pioglitazone; SAE = serious adverse event; SAX = saxagliptin; SU = sulfonylurea; and UTI = urinary tract infection.

**Table 4. Results of the short-term trials – therapies added to existing medication.**

	EM vs. EM + GLP-1-RA				EM vs. EM + INS		EM vs. MET + INS + DPP-4-i	
	Ji 2013 <sup>89</sup>		Buse 2013 <sup>90</sup>		Buse 2009 <sup>92</sup>		Vilsboll 2010 <sup>91</sup>	
	EM + EXN weekly	EM + EXN bid	EM + EXN	EM + LIR	EM + INS Lis	EM + INS Gla	SIT + INS ± MET	PBO + INS ± MET
Trial duration	26 weeks		26 weeks		24 weeks		24 weeks	
n	340	338	461	450	1,045	1,046	322	319
HbA <sub>1c</sub> *, % (SD)	-1.43 (0.07)	-1.12 (0.07)	-1.28 (0.05)	-1.48 (0.05)	-1.8 (1.3)	-1.7 (1.3)	-0.6 (0.1)	0 (0.1)
BW*; kg (95% CI or SD)	-1.63 (0.16)	-2.45 (0.16)	-2.68 (0.18)	-3.57 (0.18)	3.6 (4.0)	2.5 (4.0)	0.1 (-0.2, 0.4)	0.1 (-0.3, 0.4)

Any AE; %	67.4%	74.0%	61.4%	68.2%	-	-	52.2%	42.9%
SAE; %	3.8%	2.7%	2.8%	1.6%	6.2%	4.3%	6.2%	3.4%
Hypo-G; %	19.7%	26.3%	8.7%	11.3%	-	-	-	-
Severe hypo-G; %	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.6%	0.3%
UTI; %	-	-	-	-	-	-	2.8%	1.9%
CVD; %	-	-	-	-	29.0%	26.0%	-	-
Mortality; %	0.0%	0.0%	0.4%	0.4%	0.5%	0.2%	0.0%	0.0%

**Abbreviations:** AE = adverse event; bid = twice daily; BW = body weight; CI = confidence interval; CVD = cardiovascular disease; DPP-4-i = DPP-4 inhibitor; EM = existing medication; EXN = exenatide; Gla = glargine; GLP-1-RA = GLP-1 receptor agonist; Hypo-G = hypoglycaemia; INS = insulin; LIR = liraglutide; Lis = lispro mix 75/25; MET = metformin; PBO = placebo; SAE = serious adverse event; SD = standard deviation; SIT = sitagliptin; UTI = urinary tract infection

**Notes:** \* mean change from baseline.