9.01 Clinical and cost utility analysis of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for the treatment of type 2 diabetes mellitus in the Australian setting

1 Purpose of item

That PBAC:

1.1 **Note** the 'Clinical and cost utility analysis of GLP-1 RAs for the treatment of type 2 diabetes mellitus (T2DM) in the Australian setting' report (the GLP-1 RA report).

1.2 **Note** the Economic Sub-Committee (ESC) Advice, and sponsor Pre-Subcommittee Responses (PSCRs) and pre-PBAC responses for this item.

1.3 **Advise** if the GLP-1 RA report supports the request from a stakeholder for a broader Pharmaceutical Benefits Scheme (PBS) restriction for GLP-1 RAs.

1.4 **Advise** the Department if the PBAC recommends that any further work be undertaken on the utilisation, cost-effectiveness, or restrictions for T2DM medicines.

2 Background

Stakeholder correspondence/engagement

2.1 In September 2019, a stakeholder sent a letter to the PBAC requesting broader listings for GLP-1 RAs and sodium-glucose cotransporter 2 (SGLT2) inhibitors on the PBS. The stakeholder considered that PBS reimbursement should support the use of these medicines in people with T2DM who have cardiovascular disease (CVD), or multiple CV risk factors, and HbA1c >6.5%, based on the results of several CV outcome trials.

2.2 In October 2019, the PBAC responded to the request, noting that it is required to consider the clinical effectiveness, safety and cost-effectiveness of the medicine compared with other treatments, when considering amendments to PBS listings.

2.3 The sponsors of PBS-listed GLP-1 RAs (AstraZeneca Pty Ltd, Novo Nordisk Pty Ltd and Eli Lilly Pty Ltd) were consulted on the GLP-1 RA report prior to the June 2022 ESC meeting and were provided with a copy of the ESC Advice. Sponsors were consulted prior to the July 2022 PBAC meeting.

DUSC Review of Medicines for the treatment of diabetes – 2017

2.4 The most recent DUSC review of the utilisation of T2DM medicines was the review of 'Medicines for the treatment of diabetes' in February 2017.[1]

2.5 This review found that the top five most common regimens for the treatment of diabetes were (starting with the most common): metformin monotherapy, insulin

[1] Department of Health, February 2017, DUSC review, *Medicines for the treatment of diabetes*.

monotherapy, dipeptidyl peptidase-4 (DPP4) inhibitor + metformin, metformin + sulfonylurea (SU), and insulin + metformin.

2.6 At the time of the DUSC review, exenatide was the only GLP-1 RA listed on the PBS, with the once weekly dosing formulation listed in 2016. Dulaglutide was PBS-listed in 2018 and semaglutide in 2020.

2.7 The DUSC review highlighted several issues with use outside the restrictions for T2DM medicines, including use of SGLT2 inhibitors, DPP4 inhibitors and exenatide in monotherapy.

Cost-effectiveness review of T2DM medicines

2.8 At the PBAC Executive meeting on 19 September 2019, the PBAC noted that while there is a growing body of evidence suggestive of additional CV benefits associated with SGLT2 inhibitors and GLP-1 RAs, the cost-effectiveness of any additional benefit remains unknown in the Australian context.

2.9 The PBAC requested that the Department address the question of the cost-effectiveness of SGLT2 inhibitors and GLP-1 RAs as add-on therapy to metformin in the treatment of T2DM, for patients with established CVD or at high CV risk, without the requirement to have a specific unmet glycaemic target. The Department contracted a project on the cost-effectiveness of T2DM medicines in stages.

Cost-effectiveness review of T2DM medicines – Stage 1

2.10 The Stage 1 report presented a systematic review of the published estimates of cost-effectiveness of T2DM medicines (excluding insulin). The review focused on:

1) Monotherapy vs monotherapy for patients who have a contraindication or intolerance to metformin. No studies were identified.
2) Dual therapy vs dual therapy, where metformin was one of the components of the dual therapy.

2.11 The review found most studies to be of moderate to high quality, but noted the following issues with respect to converting incremental cost-effectiveness ratios (ICERs) from studies in other countries to a value in the Australian setting:

- Substantial variation in the rates of complications across different regions of the world.
- Long-term declining trends in rates of complications and death due to diabetes.
- Unit costs for different healthcare resource utilisation categories being substantially different across countries, which impacts on the calculations of incremental costs.

Cost-effectiveness review of SGLT2 inhibitors for T2DM – Stage 2

2.12 Stage 2 focussed on modelling the comparison of SGLT2 inhibitors versus SUs for the treatment of T2DM as add-on therapy to metformin, using the United Kingdom Prospective Diabetes Study Outcomes Model Version 2 (UKPDS OM2) calibrated to the Australian setting by using Australian-specific mortality, cost and patient data.

2.13 The report for the 'Cost-effectiveness review of SGLT2 inhibitors for the treatment of T2DM' (the SGLT2 inhibitor report) concluded that:

- SGLT2 inhibitors decreased the risk of all-cause and CV-related mortality when compared to SUs. Reductions in systolic blood pressure and weight, but not HbA1c, were also seen when comparing SGLT2 inhibitors to SUs in the treatment of T2DM as add-on therapy to metformin.
- SGLT2 inhibitors were likely to improve life expectancy and quality-adjusted life expectancy (quality-adjusted life years, or QALYs) versus SUs, but were likely to lead to an overall increase in lifetime costs per patient.

2.14 The SGLT2 inhibitor report forecast ICERs of $29,939 per QALY gained for men and $27,316 per QALY gained for women, based on a lifetime treatment effect duration. These ICERs apply to Australians with T2DM who are treated with SGLT2 inhibitors as dual therapy with metformin.

2.15 The ESC considered the SGLT2 inhibitor report at the October 2021 meeting and advised the PBAC that the methods, inputs, and assumptions used in the clinical and economic evaluation were generally reasonable and well described.

2.16 The PBAC considered the SGLT2 inhibitor report at the November 2021 and March 2022 meetings and recommended the listing of dapagliflozin and empagliflozin for the treatment of T2DM, as add-on therapy to metformin, in patients with established CVD or at high CV risk, without the requirement to have a specific unmet glycaemic target. This recommendation was contingent upon expenditure over the five years (2022-2026) on SGLT2 inhibitors for the current T2DM market and the proposed T2DM population with CVD/high CV risk being limited to $1.5 billion. The PBAC noted that based on the estimates provided by the Department, this would equate to a price reduction in the order of 15% for T2DM indications.

3 Key findings of the GLP-1 RA report

Utilisation

3.1 The PBAC noted that the listing of the once weekly dosing formulations of GLP-1 RAs appear to have grown the market with R/PBS prescriptions dispensed for GLP-1 RAs increasing from around 263,000 in 2016 when the first once weekly formulations were listed, to around 1.2 million in 2021 (an increase of 460%) (Figure 1). The proportion of expenditure on GLP-1 RAs compared to total expenditure on T2DM medicines (excluding insulins) doubled over the five years from 2016-17 to 2020-21 from 10% ($25.7 million) to 21% ($101.3 million) based on published prices (Table 1).

3.2 The utilisation of exenatide has declined since 2018, with the once weekly formulation of exenatide delisted in February 2022. Dulaglutide and semaglutide are now the most prescribed GLP-1 RAs on the PBS.

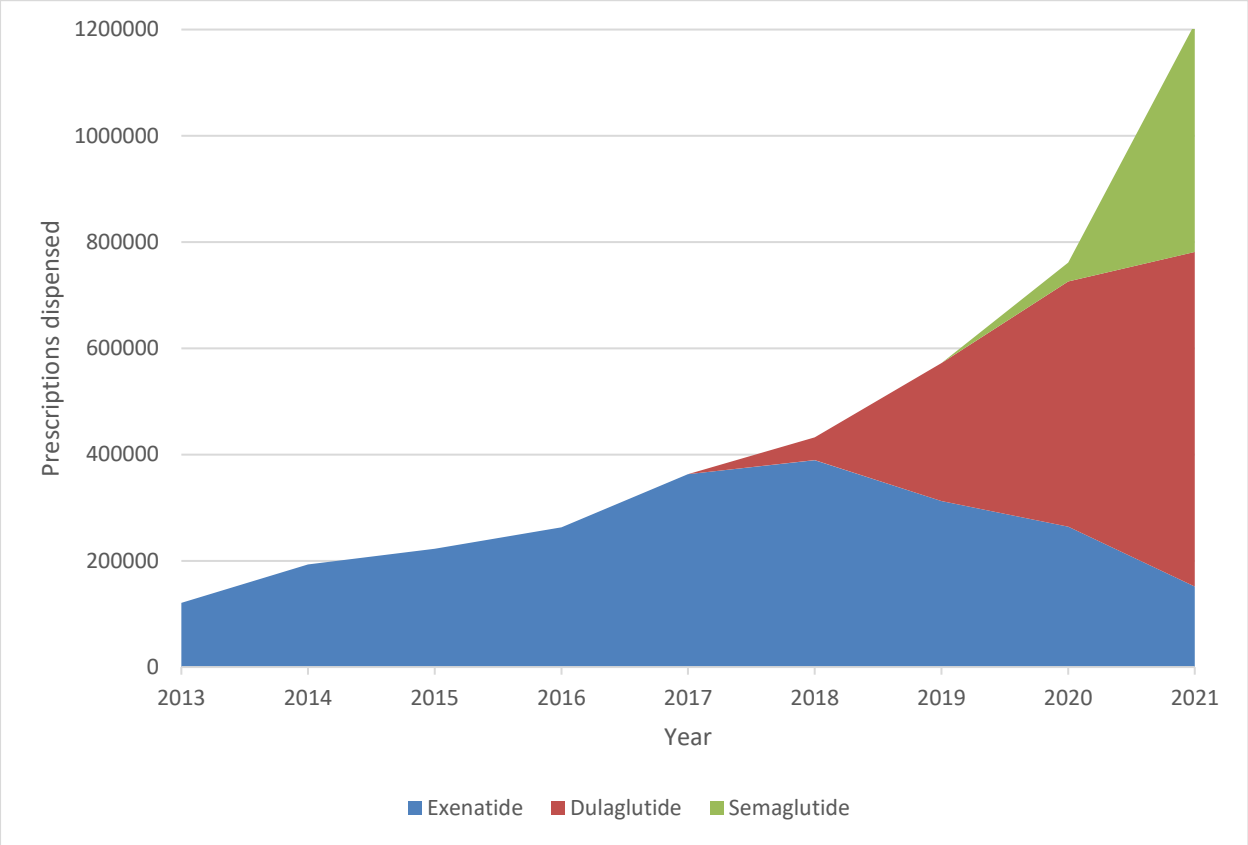

Figure 1: Stacked area graph of R/PBS prescriptions dispensed for GLP-1 RAs, 2013 to 2021
Source: Services Australia PBS Item Reports accessed 12/04/22.

Table 1: Total R/PBS benefits paid for all PBS-listed T2DM medicines (excluding insulins) and GLP-1 RAs (based on published prices), for financial years 2016-17 to 2020-21

Year	2016-17	2017-18	2018-19	2019-20	2020-21
All T2DM medicines	$247,993,296	$297,774,723	$347,469,544	$395,900,534	$476,881,273
GLP-1 RAs	$25,681,158	$36,397,938	$50,251,518	$68,230,400	$101,335,034
GLP-1 RAs % of all T2DM	10%	12%	14%	17%	21%

Source: DoH PBS Data, extracted 6/8/21; Services Australia PBS Item Reports, accessed 12/04/22.

PBS restrictions for GLP-1 RAs

3.3 The PBAC noted that GLP-1 RAs are currently PBS subsidised for T2DM patients as:

- dual therapy with metformin, where metformin + SU is contraindicated/not tolerated
- dual therapy with SU, where metformin + SU is contraindicated/not tolerated (semaglutide and exenatide only)
- dual therapy with insulin, where metformin is contraindicated/not tolerated
- triple therapy with metformin + SU/insulin.

3.4 To qualify for initial treatment with a GLP-1 RA, the patient must have, or have had, a HbA1c greater than 7% (or blood glucose levels greater than 10 mmol/L in more than 20% of tests over a 2-week period) despite prior treatment.

3.5 GLP-1 RAs are not PBS-subsidised for use as monotherapy, or in combination with a DPP4 inhibitor, a thiazolidinedione (glitazone), or an SGLT2 inhibitor.

3.6 PBAC noted that the Therapeutic Goods Administration (TGA) registered indications for GLP-1 RAs are broader than the PBS restrictions and allow use in monotherapy (sometimes requiring contraindication/intolerance to metformin), and in combination with a broad range of other T2DM medicines.

3.7 The PBS restrictions for GLP-1 RAs differ from the restrictions for SGLT2 inhibitors and DPP4 inhibitors in that dual therapy with metformin/SU requires contraindication/intolerance to metformin + SU. The PBS restrictions for SGLT2 inhibitors and DPP4 inhibitors also previously required contraindication/intolerance to a combination of metformin + SU. However, in 2013, as a result of the 2012/13 DUSC 'Analysis of drugs for type 2 diabetes',[2] the PBAC recommended that the restrictions for DPP4 inhibitors be amended to remove the requirement for contraindication/intolerance to a SU, contingent on a price reduction to account for the likely amount of non-cost-effective use, and that approximately 40% of use should be cost-minimised to the price of the average daily dose of a SU. In 2014, the PBAC recommended alignment of the restrictions and prices for SGLT2 inhibitors with DPP4 inhibitors.

3.8 Table 2 contains a summary of the PBS restrictions for T2DM medicines.

Table 2: Abridged PBS restrictions for T2DM medicines (excluding insulins) at December 2021

a. Unrestricted medicines

Class	Drug
Biguanide	Metformin
Sulfonylurea	Glibenclamide
Sulfonylurea	Gliclazide
Sulfonylurea	Glimepiride
Sulfonylurea	Glipizide
Alpha glucosidase inhibitor	Acarbose

[2] Department of Health, October 2012 & February 2013, DUSC review, Type 2 Diabetes.

b. Authority Required (STREAMLINED) medicines

Class	Drug	Dual oral with Met/SU	Triple therapy with Met + SU	With insulin (+/- Met)[3]	Triple therapy with Met +
DPP4i	Alogliptin[2]	✓	X	X	X
DPP4i	Linagliptin[2,5]	✓	✓	✓	SGLT2i
DPP4i	Saxagliptin[2,5]	✓	✓	X	SGLT2i
DPP4i	Sitagliptin[2,5]	✓	✓	✓	SGLT2i
DPP4i	Vildagliptin[2]	✓	✓	✓	X
SGLT2i	Dapagliflozin[2,4]	✓	✓	✓	DPP4i
SGLT2i	Empagliflozin[2,4]	✓	✓	✓	DPP4i
SGLT2i	Ertugliflozin[2,4]	✓	X	X	DPP4i
TZD	Pioglitazone	✓[1]	✓	✓	X
GLP-1 RA	Exenatide	✓[1]	✓	✓	X
GLP-1 RA	Dulaglutide	✓[1,6]	✓	✓	X
GLP-1 RA	Semaglutide	✓[1]	✓	✓	X

Abbreviations: DPP4i – dipeptidyl peptidase 4 inhibitors, GLP-1 RA – glucagon-like peptide-1 receptor agonist, Met – metformin, SGLT2i – sodium-glucose cotransporter 2 inhibitors, SU – sulfonylurea, TZD – thiazolidinediones.

Notes:

1. Only if the patient is contraindicated or intolerant to metformin and a sulfonylurea.
2. Fixed dose combination products with metformin are also available for these medicines and listed for the same indications. FDCs are not subsidised for initial therapy.
3. Despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.
4. FDC with DPP-4 inhibitor available.
5. FDC with SGLT2 inhibitor available.
6. Restricted to use in combination with metformin, not sulfonylurea.

Clinical management algorithm and place of GLP-1 RAs in therapy

3.9 A brief review of Australian and international clinical management algorithms and treatment guidelines for T2DM indicates that there is some variation regarding the place of GLP-1 RAs in therapy.

3.10 Most clinical guidelines recommend GLP-1 RAs for adults with T2DM who are unable to achieve optimal blood glucose levels as a second-line therapy following metformin for either all patients, or for patients with established or at high risk of CVD, and/or CKD. A notable exception is the UK National Institute for Health and Care Excellence (NICE) guideline,[3] which considers cost-effectiveness, in which GLP-1 RAs are only recommended for triple therapy, and only under certain circumstances.

3.11 The PBAC noted that apart from the NICE Guidelines, international diabetes, cardiology, and renal societies generally recommend GLP-1 RAs and SGLT2 inhibitors

[3] NICE. Type 2 diabetes in adults: management, NICE guideline [NG28], Updated 31 March 2022, Type 2 diabetes in adults: treatment options if further interventions are needed. Cited: 19 April 2022.

as add-on therapy to metformin (unless contraindicated/intolerant) for T2DM patients with established CVD or high CV risk regardless of HbA1c levels.

3.12 The PBAC noted that the 'Australian Evidence-Based Clinical Guidelines for Diabetes v1.3',[4] which are endorsed by the Australian Diabetes Society (ADS) and National Health and Medical Research Council (NHMRC), recommend the addition of a GLP-1 RA to other glucose lowering medication(s) in adults with T2DM who have CVD, multiple CV risk factors and/or kidney disease; are contraindicated/intolerant to SGLT2 inhibitors; and are unable to achieve optimal blood glucose levels on their baseline therapy.

Clinical evaluation

3.13 The University of Melbourne was contracted to prepare a clinical and cost utility evaluation report using the adaptation and calibration of a reference model (UKPDS OM2) to assess the cost-effectiveness of GLP-1 RAs compared to SUs as dual therapy with metformin for the treatment of T2DM, without the requirement for a specific unmet glycaemic target. Like the SGLT2 inhibitor report, this involved using Australian-specific mortality, cost and patient data to calibrate the original UKPDS OM2 to allow cost utility analysis in a contemporary Australian setting.

3.14 The comparator for the analysis was SUs. SUs are listed on the PBS as unrestricted benefits, allowing use in patients with T2DM irrespective of HbA1c. Based on the 2017 DUSC analysis of diabetes medicines, SUs are also one of the most common oral medications used in combination with metformin in Australia. DPP4 inhibitors are more commonly used but the PBS listings for DPP4 inhibitors require patients to have a HbA1c >7% prior to initiation.

3.15 A literature review was undertaken to source clinically relevant outcomes from published meta-analyses which compared GLP-1 RAs to SUs, as add-on therapy to metformin. The methods used were based on the Cochrane Handbook for Systematic Reviews of Interventions. Evidence from six recent meta-analyses (Table 3) informed the key clinical findings in the GLP-1 RA report.

3.16 Three additional studies, previously included in the SGLT2 inhibitor report, were used to provide clinical data on the effectiveness of SUs (Table 3). The PBAC considered the additional studies on the effectiveness of SUs should be considered supportive only.

[4] Living Evidence for Diabetes Consortium, Australian Evidence-Based Clinical Guidelines for Diabetes, v1.3. Cited: 8 July 2022.

Table 3: Included meta-analyses

a. Studies identified through the literature review

First Author & Year	Publication title	Publication citation
Alexander 2021	The Longer-Term Benefits and Harms of Glucagon-LikePeptide-1 Receptor Agonists: A Systematic Review and Meta-Analysis	Alexander JT, Staab EM, Wan W, et al. Journal of General Internal Medicine. 2021 Sep 10:1-24.
Mannucci 2021	Efficacy and safety of glucose-lowering agents in patients with type 2 diabetes: A network meta-analysis of randomized, active comparator-controlled trials	Mannucci E, Naletto L, Vaccaro G, et al. Nutrition, Metabolism and Cardiovascular Diseases. 2021 Apr 9;31(4):1027-34.[2]
Tsapas 2021	GLP-1 receptor agonists for cardiovascular outcomes with and without metformin. A systematic review and meta-analysis of cardiovascular outcomes trials	Tsapas A, Karagiannis T, Avgerinos I, et al. Diabetes Research and Clinical Practice. 2021 Jun 15.
Taheri 2019	Efficacy and Safety of Dulaglutide Compared to Liraglutide: A Systematic Review and Meta-analysis in Patients with Type 2 Diabetes Mellitus	Taheri S, Saffaei A, Amani B, et al. Iranian journal of pharmaceutical research: IJPR. 2019;18(4):2180.
Grenet 2018	GLUcose COntrol Safety & Efficacy in type 2 DIabetes, a systematic review and NETwork meta-analysis	Grenet G, Ribault S, Nguyen GB, et al. PloS one. 2019 Jun 25;14(6):e0217701.
Waldrop 2018	Incretin-based therapy in type 2 diabetes: An evidence based systematic review and meta-analysis	Waldrop G, Zhong J, Peters M, et al. Journal of Diabetes and its Complications. 2018 Jan 1;32(1):113-22.

b. Studies included to provide additional evidence on effectiveness of SUs

First Author & Year	Publication title	Publication citation
Qian 2018	Comparison of oral antidiabetic drugs as add-on treatments in patients with type 2 diabetes uncontrolled on metformin: a network meta-analysis.	Qian D, Zhang T, Zheng P, et al. Diabetes Therapy. 2018;9:1945-1958.
Chen 2019	Sodium-glucose co-transporter 2 inhibitors compared with sulfonylureas in patients with type 2 diabetes inadequately controlled on metformin: a meta-analysis of randomized controlled trials.	Chen Z and Li G. Clinical drug investigation. 2019;1-11.
Rados 2016	The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials.	Rados DV, Pinto LC, Remonti LR, et al. PLoS medicine. 2016;13:e1001992.

Source: Table 2.3 and page 18, GLP-1 RA report, Section 2 & 3.

3.17 The clinical evaluation concluded that GLP-1 RAs decreased weight, systolic blood pressure (SBP) and hypoglycaemic events when compared to SUs but increased gastrointestinal events. No statistically significant benefit for GLP-1 RAs when compared to SUs was shown on all-cause mortality, or fatal or non-fatal CV events.

3.18 The PBAC noted some limitations with the clinical evidence. Out of the 15 included trials, only one trial included gliclazide, the most used SU in Australia, and SU type was not reported in 8 studies. The PBAC noted that there was marked heterogeneity between the trials related to participant age (52 to 66 years), HbA1c at baseline (7.4% to 8.7%), and trial duration (14 to 271 weeks). Overall, the analysis of clinical effectiveness relied upon small short-term studies, indirect naïve comparisons, and included GLP-1 RAs not listed on the PBS, such as lixisenatide, albiglutide and

liraglutide.

3.19 The PBAC noted that the report had accepted the meta-analyses' risk of trial bias assessments as these used the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, rather than undertaking separate assessments. However, the PBAC noted that 3 of the 6 included meta-analyses were deemed to be of low quality using the Amstar 2 tool.

3.20 Noting that there is a paucity of trial data to support an analysis of the comparative clinical effectiveness of dulaglutide and semaglutide with gliclazide, the PBAC considered the clinical claims related to mortality, HbA1c, blood pressure and weight in the report to be uncertain resulting in low confidence in the results of the cost utility analysis.

3.21 The PBAC noted the systematic review and network meta-analysis by Tsapas et al, 2020,[5] found that in patients at increased CV risk receiving metformin therapy, dual therapy with specific GLP-1 RAs had a favourable effect on certain CV outcomes compared to placebo. When compared to SUs (which were assessed as a drug class) as add-on therapy to metformin in patients at increased CV risk, subcutaneous semaglutide and dulaglutide showed significantly reduced odds of stroke, but no significant benefits in all-cause mortality, CV death, myocardial infarction, hospitalisation for heart failure, or amputation.

3.22 Although not directly applicable to this GLP-1 RA clinical and cost-utility analysis, the PBAC noted a published systematic review and network meta-analysis by Palmer et al, 2021,[6] which compared the CV outcomes of SGLT2 inhibitors and GLP-1 RAs. Palmer et al concluded that GLP-1 RAs and SGLT2 inhibitors had similar effects on all-cause mortality, CV mortality and non-fatal myocardial infarction, but GLP-1 RAs reduced non-fatal stroke more than SGLT2 inhibitors, while SGLT2 inhibitors reduced hospital admissions for heart failure more than GLP-1 RAs.

3.23 The PBAC also advised that the clinical evidence did not currently support a drug class effect for all GLP-1 RAs, noting a review by Nauck and Meier, 2019,[7] which highlighted varying effects on major adverse cardiovascular events (MACE) and all-cause death across individual GPL-1 RAs. The PBAC noted that lixisenatide, which was included in the review but is not PBS-listed, did not show benefits in MACE, all-cause death, or hospitalisation for heart failure in the ELIXA trial.

Economic evaluation

3.24 The PBAC noted the economic evaluation was presented as a cost utility evaluation using the adaptation and calibration of the UKPDS OM2. This involved using Australian-specific mortality, cost and patient data to calibrate the original UKPDS

[5] Tsapas A et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes, Ann Intern Med. 2020;173:278-286.

[6] Palmer SC et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *BMJ*, 2021;372:m4573.

[7] Nauck MA and Meier JJ. Management of Endocrine Diseases: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? *European Journal of Endocrinology*, 2019;181(6):R211-234.

OM2 to allow cost utility analysis in a contemporary Australian setting. The key components of the economic model are shown in Table 4.

Table 4: Key components of the economic model

Component	Description
Type of analysis	Cost Utility Analysis presented with a Cost-effectiveness Analysis
Outcomes	Cost, quality-adjusted life years (QALYs) and incremental cost per life year (LY) gained and per QALY gained of GLP-1 RAs compared to SUs
Time horizon	Model base case is measured over lifetime. Treatment effects were assumed for patients remaining lifetime.
Method(s) used to generate results	The UK Prospective Diabetes Study Outcomes Model Version 2 (UKPDS OM2). This is a patient-level simulation model using probabilistic discrete-time computer simulation based on parametric proportional hazards risk equations.
Health states	Health states are considered in relation to complication events including amputation, myocardial infarction, stroke, ischemic heart disease, congestive heart failure, blindness, renal failure, foot ulcer, body mass index changes, gastrointestinal adverse events and hypoglycaemic events.
Utility values	Health state utility values for diabetes complication health states specifically for Australia are not currently available. The utility values were taken mainly from the UKPDS study, supplemented by values from other studies.
Cycle length	The UKPDS OM2 used annual cycles
Transition probabilities	Equations which predict transition probabilities for events and deaths were recalibrated from the UKPDS OM2 to predict rates of mortality with those reported for a large cohort of Australians with Type 2 diabetes.[8] In the absence of data on annual rates of the complications for the Australian population of patients with T2DM, the rates of fatal and non-fatal cardiovascular (CV) events and other-cause mortality were modified so that the standardized mortality rate ratios (SMRs) of the modelled population compared to the Australian general population matched the SMRs of the patients with T2DM compared to the Australian general population in the period 2004-2010.[1] The treatment effects of GLP-1 RAs compared to SUs were based on recent meta-analyses of relevant clinical trials.
Software	The UKPDS OM2 implemented in STATA that has been adapted to reflect both contemporary risk of death in people with T2DM in Australia and capture the known treatments effects of GLP-1 RAs compared to SUs.

Source: Table 3A.1, GLP-1 RA report, Section 2 & 3.

3.25 The economic evaluation modelled two scenarios:

- The base case analysis considered differences in the effects of GLP-1 RAs and SUs primarily on: weight/body mass index (BMI), SBP, hypoglycaemic events and gastrointestinal events.
- The scenario that favoured GLP-1 RAs used a more favourable HbA1c reduction for GLP-1 RAs, and included reductions in CV events, CV-related mortality, and all-cause mortality based on the non-statistically significant point estimates in the included studies, which favoured GLP1-RAs.

[8] Harding JL, Shaw JE, Peeters A, et al. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997–2010. *Diabetes care.* 2014;37:2579-2586.

3.26 The model also incorporated additional effects on quality of life (QoL) in both the base case and favourable scenarios for change in BMI, and occurrence of hypoglycaemic events and gastrointestinal events.

3.27 ICER estimates for GLP-1 RAs compared to SUs in the lifetime treatment effect scenarios are shown in Table 5.

3.28 PBAC noted that in the modelling scenario favouring GLP-1 RAs and incorporating additional QoL effects the ICERs remained high at $75,000 to $95,000 per QALY for men and women.

Table 5: ICER estimates for GLP-1 RAs compared to SUs for treatment of T2DM as add-on therapy to metformin for men and women, at current prices and with 5% discount rate to costs and outcomes.

Scenario	ICER per QALY (lifetime treatments effects)
Base case – No additional QoL effects	$855,000 to <$955,000
GLP-1 RA Favourable – No additional QoL effects	$95,000 to <$115,000
Base case – Additional QoL effects	$115,000 to <$255,000
GLP-1 RA Favourable - Additional QoL effects	$75,000 to <$95,000

Source: Table 3A.12, GLP-1 RA report, Section 2 & 3
Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years

3.29 The PBAC considered that the base case analysis may have underestimated the comparativeness effectiveness of GLP-1 RAs compared to SUs on BMI, HbA1c and CV outcomes as the clinical evaluation included trial evidence for older GLP-1 RAs that are not PBS-listed. Overall, the small difference in life years and QALYs gained between GLP-1 RAs and SUs, and the higher medication costs for GLP-1 RAs were driving the high estimated ICERs in the economic model.

3.30 The PBAC noted sensitivity analyses exploring the impact of price reductions to GLP-1 RAs and change in discount rate were intended to offset some of the uncertainties related to the incremental benefit of GLP-1 RAs and other model inputs. The ICER remained very sensitive to the assumptions about the treatment effect of GLP-1 RAs and utilities.

3.31 The PBAC noted that the ICERs in the report are higher than in many studies on the comparativeness cost-effectiveness of GLP-1 RAs compared to SUs, which typically reported ICERs between $40,000 to $50,000 per QALY. However, in the report this difference is explained by the use of a modified version of the UKPDS OM2 that has been calibrated to the lower risk of mortality in Australia. Such differences underlie the need to calibrate diabetes models to account for the mortality risk of the contemporary Australian diabetes population when conducting economic evaluations.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Main issues identified

4.1 The main issues raised by the cost-effectiveness reviews of SGLT2 inhibitors and GLP-1 RAs are:

- High overall R/PBS expenditure and growth in the market for SGLT2 inhibitors and GLP-1 RAs.

- Potential for use outside the restrictions for SGLT2 inhibitors and GLP-1 RAs due to weight loss and reduced hypoglycaemia benefits associated with these medicines compared to SUs. This may include use in monotherapy, and for GLP-1 RAs, use in patients not contraindicated/intolerant to metformin + SU. The PBS restrictions for T2DM medicines do not always align with treatment algorithms in clinical guidelines and there are within-class inconsistencies in restrictions. These issues may be contributing to prescribing outside the restrictions.
- There are limited PBS-subsided monotherapy treatment options for patients contraindicated/intolerant to metformin and who do not wish to use a SU, acarbose or insulin. The review of cost-effectiveness studies did not identify any studies comparing monotherapy options for patients with T2DM who are contraindicated/intolerant to metformin.

5 Sponsor comments

5.1 PBAC noted the PSCRs and pre-PBAC responses provided by sponsors of GLP-1 RAs and acknowledged the concerns raised in relation to the comparative clinical evidence.

6 PBAC Outcome

6.1 The PBAC did not recommend expansion of the PBS listings for GLP-1 RAs to include patients with T2DM with CVD/high CV risk, as add-on therapy to metformin without a glycaemic requirement. The PBAC recommended leaving the current PBS restrictions for GLP1-RAs unchanged.

6.2 The PBAC noted that there is some variation regarding the place of GLP-1 RAs in the clinical treatment algorithm for T2DM but most treatment guidelines for T2DM recommend GLP-1 RAs as add-on therapy to metformin for patients with CVD or at high CV risk, without a specific glycaemic requirement. The PBAC noted that the 'Australian Evidence-Based Clinical Guidelines for Diabetes v1.3',[9] recommend use of GLP-1 RAs only in patients contraindicated or intolerant to SGLT2 inhibitors.

6.3 Overall, PBAC considered that the clinical trial data included in the GLP-1 RA report was not robust and the comparative effectiveness of GLP-1 RAs and SUs remained uncertain. The PBAC noted that there were a paucity of trials directly comparing PBS-listed GLP-1 RAs with gliclazide, and that the most common comparator in GLP-1 RAs trials was placebo. The PBAC considered that a wider review of the clinical evidence may be informative, such as considering evidence comparing GLP-1 RAs to other therapies for T2DM such as SGLT2 inhibitors and DPP4 inhibitors.

6.4 The PBAC considered that the clinical evidence did not currently support a drug class effect for GLP-1 RAs, noting the review by Nauck and Meier, 2019,[10] which highlighted varying effects for GLP-1 RAs upon major adverse cardiovascular events (MACE) and

[9] Living Evidence for Diabetes Consortium, Australian Evidence-Based Clinical Guidelines for Diabetes, v1.3. Cited: 8 July 2022.

[10] Nauck MA and Meier JJ. Management of Endocrine Diseases: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? *European Journal of Endocrinology*, 2019;181(6):R211-234.

all-cause death.

6.5 The PBAC noted the cost-utility evaluation used the UKPDS OM2 adapted and calibrated with contemporary risk of mortality for T2DM patients in Australia. The PBAC considered that due to the paucity of comparative clinical evidence used to inform the model, the resulting ICERs were not reliable for decision making. Noting the potentially high and uncertain estimates of cost-effectiveness, the PBAC did not recommend broadening the current PBS restrictions for GLP-1 RAs.

6.6 The PBAC remained concerned over the price difference between GLP-1 RAs and SGLT2 inhibitors, noting that this difference was based on the requirement for patients initiating a GLP-1 RA to have a contraindication or intolerance to a combination of metformin and a SU. The PBAC noted that clinicians may have a broader interpretation of contraindication to SU in clinical practice than in the clinical trials and estimates of use that supported the PBS listing.

6.7 The PBAC recommended an updated review of the utilisation of T2DM medicines, considering the current treatment pathways and extent of use outside the PBS restrictions for DPP4 inhibitors, SGLT2 inhibitors and GLP-1 RAs. The analysis should include an estimation of the extent of use of GLP-1 RAs outside of the PBS restrictions, such as use in monotherapy, and in dual therapy in patients not contraindicated or intolerant to a combination of metformin and a SU.

Outcome:

Not recommended

7 Context for Decision

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