9.02 Cost-effectiveness review (CER) of sodium-glucose cotransporter 2 (SGLT2) inhibitors for type 2 diabetes mellitus (T2DM)

1 Purpose of Item

That the Pharmaceutical Benefits Advisory Committee (PBAC):

1.1 **CONSIDER** the Cost-effectiveness review (CER) of sodium-glucose cotransporter 2 (SGLT2) inhibitors for type 2 diabetes mellitus (T2DM) (the SGLT2 inhibitor report).

1.2 **ADVISE** on the suitability of the proposed options for expanding the PBS restrictions to allow earlier subsidised access to SGLT2 inhibitors as add-on therapy to metformin in T2DM patients with established or at high risk of cardiovascular disease (CVD), without the requirement to have a specific unmet glycaemic target. Specifically, advice is sought on:

- Proposed restriction wording and the appropriate criteria, thresholds or guideline/s that should be used to define cardiovascular (CV) risk factors and the target population.
- Whether T2DM patients with kidney disease should be included in the proposed restriction, noting the PBAC's separate consideration of dapagliflozin for people with chronic kidney disease (CKD) in patients with or without T2DM.
- Therapy combinations included in the proposal, that is, whether the inclusion of sulfonylurea (SU) + SGLT2 inhibitor dual therapy combination is appropriate.
- Therapy combinations not currently included in the proposal (See Table 2: Streamlined codes where advice is required).

2 Background

2.1 In September 2019, a stakeholder sent a letter to the PBAC requesting broader listings for glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors on the Pharmaceutical Benefits Scheme (PBS). The request indicated that PBS reimbursement for these medicines did not include all populations for whom benefit is shown in clinical trials. The stakeholder considered that PBS reimbursement should support the use of these medicines in people with T2DM with CVD, or with multiple CV risk factors, and glycated haemoglobin (HbA1c) >6.5%, based on the results of several CV outcome trials.

2.2 In October 2019, the PBAC responded to the stakeholder noting the request to amend the PBS listings for GLP-1 RAs and SGLT2 inhibitors in a broader patient population. The PBAC noted 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. The PBAC noted that amendments to PBS listing are generally initiated by the pharmaceutical sponsor of the medicine and advised it would accept submissions from sponsors to extend the PBS listings of GLP-1 RAs and SGLT2 inhibitors at any time.

2.3 The Department subsequently contracted a project on the cost-effectiveness of T2DM medicines focussing in the first instance on the cost-effectiveness of SGLT2 inhibitors compared to sulfonylureas (SU) as add on therapy to metformin. This comparison was chosen because of the increasing body of evidence supporting patient relevant outcomes in patients with T2DM and the request from clinicians for broader subsidised access.

3 Cost-effectiveness Review (CER) of SGLT2 inhibitors for T2DM

Clinical and economic evaluation

3.1 The Department engaged a contractor to prepare a clinical and cost-utility evaluation report using an adaptation and calibration of a reference model (UK Prospective Diabetes Study Outcomes Model 2 [UKPDS OM2]) to assess the cost-effectiveness of SGLT2 inhibitors compared to SUs as dual therapy with metformin for the treatment of T2DM. This involved using Australian-specific mortality, cost and patient data to calibrate the original UKPDS Outcomes Model to allow a cost-effectiveness analysis in a contemporary Australian setting.

3.2 The clinical evaluation concluded that SGLT2 inhibitors decreased the risk of all-cause and CV-related mortality when compared to SUs. Improvements were seen in blood pressure outcomes, weight reductions and myocardial infarctions when comparing SGLT2 inhibitors to SUs in the treatment of T2DM.

3.3 The economic evaluation found that 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.

3.4 The SGLT2 inhibitor report forecast incremental costs per life year gained of $19,706 per life year ($29,939 per QALY gained) for men and $18,395 per life year gained ($27,316 per QALY gained) for women. The incremental cost-effectiveness ratios (ICERs) for SGLT2 inhibitors compared with SUs were less than $50,000 per QALY for a wide range of assumptions regarding the duration of treatment effects and costs associated with managing diabetes-related complications.

Context and proposal to amend PBS restrictions for SGLT2 inhibitors

3.5 Section 1 of the SGLT2 inhibitor report presented the context and proposed options to expand PBS restrictions to allow earlier subsidised access to SGLT2 inhibitors in T2DM patients with established CVD or at high risk of CVD, as add-on therapy to metformin without the requirement to have a specific unmet glycaemic target.

3.6 Current PBS restrictions for second-line T2DM medicines (including SGLT2 inhibitors) refer to a general HbA1c target of 7% and patients may be eligible for add-on therapies if this target is not met despite use of prior therapies. The proposed PBS restrictions were based on the clinical evidence in the SGLT2 inhibitor report that SGLT2 inhibitors reduce the risk of all-cause and CV-related mortality and took into consideration current guidelines of the Royal Australian College of General Practitioners (RACGP)[1],

[1] The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP, 2020.

the Australian Diabetes Society (ADS)[2] and the National Vascular Disease Prevention Alliance (NVDPA), now part of the Australian Chronic Disease Prevention Alliance (ACDPA).

3.7 The intent of the PBS restriction proposal was that any restriction criteria expanding access to patients with T2DM with or at high risk of CVD, would be added as an *additional* means for patients to access SGLT2 inhibitors as dual therapy. Therefore, restrictions relating to existing access would not be removed, as to not unintentionally restrict access. While it is expected that a large proportion of people with T2DM also have CVD or CV risk factors, there may be some T2DM patients who do not.

4 Budget impact

4.1 The net cost of the proposed restriction changes to allow earlier access to SGLT2 inhibitor medicines in the T2DM population with CVD or CV risk factors was estimated to be $108 million in 2022, increasing to $200 million in 2026, estimated using current PBS-listed prices (Table 1). These estimates were based on Scenario 1 (base case) which assumed a 50% uptake in the eligible population in 2022, increasing by 10% every year up to 90% in 2026.

Table 1: Net cost to PBS (Scenario 1 - base case)

Year	Cost to PBS
2022	$108,170,098
2023	$130,708,501
2024	$153,548,365
2025	$176,689,690
2026	$200,132,476
Total	**$769,249,128**

Source: Table 4.13, SGLT2 inhibitor report.

4.2 Two other scenarios which assumed either higher (Scenario 2) or lower (Scenario 3) uptake rates are presented in the SGLT2 inhibitor report and had a large impact on the estimated cost to the PBS.

4.3 Estimates of the eligible population, that is, those who initiate an SGLT2 inhibitor earlier in the treatment algorithm, were based on the PBS population currently receiving metformin monotherapy or dual therapy with metformin and a SU. The proportion of this population who have either CVD or two or more CV risk factors is unknown. The SGLT2 inhibitor report assumed that the total metformin monotherapy or dual therapy metformin + SU population may be eligible and provided three uptake scenarios to show the impact of this assumption on the net cost to the PBS.

4.4 The eligible population will be larger if the PBAC recommends earlier access to SGLT2 inhibitors for patients currently treated with SU monotherapy and insulin monotherapy.

[2] Australian Diabetes Society (2 July 2021) Australian Blood Glucose Treatment Algorithm for T2DM - Australian Blood Glucose Treatment Algorithm for type 2 diabetes.

5 Requested advice and proposed PBS restrictions

5.1 The PBAC was asked to consider whether PBS restrictions for SGLT2 inhibitor medicines should be expanded to allow earlier subsidised access to SGLT2 inhibitors as add-on therapy to metformin in T2DM patients with established or at high risk of CVD, without the requirement to have a specific unmet glycaemic target.

5.2 Three options for proposed restriction wording were presented for the PBAC's consideration, and advice on the inclusion of various SGLT2 inhibitor therapy combinations was sought.

Restriction Option 1

5.3 Proposed restriction changes for Option 1:

Clinical Criteria

- Criterion: Patient must have cardiovascular disease (CVD); OR
- Criterion: Patient must have at least two cardiovascular risk factors in addition to diabetes mellitus type 2; OR
- Criterion: Patient must have kidney disease

Prescriber instructions

- Multiple CV risk factors are defined as men 55 years of age and older or women 60 years of age or older with T2DM with one or more traditional risk factors (including hypertension, dyslipidaemia, or smoking). People with kidney disease include those with an eGFR of 30mL/min/173m2 of body-surface area.

Restriction Option 2

5.4 Proposed restriction changes for Option 2:

Clinical Criteria

- Criterion: Patient must have established cardiovascular disease (CVD); OR
- Criterion: Patient must have a level of absolute risk of a cardiovascular event greater than 15% over 5 years as calculated using the Australian Absolute Cardiovascular Disease Risk Calculator (National Vascular Disease Prevention Alliance).

Administrative advice

- The Australian Absolute Cardiovascular Disease Risk Calculator is available at www.cvdcheck.org.au

Restriction Option 3

5.5 Proposed restriction changes for Option 3:

Clinical Criteria

- Criterion: Patient must have established cardiovascular disease (CVD); OR
- Criterion: Patient must have a level of absolute risk of a cardiovascular event greater than 15% over 5 years as calculated using the Australian Absolute Cardiovascular Disease Risk Calculator; OR

- Criterion: Patient must have known clinically determined high risk of CVD not requiring the use of the absolute cardiovascular risk assessment according to the National Vascular Disease Prevention Alliance guidelines.

Administrative advice

- The Australian Absolute Cardiovascular Disease Risk Calculator is available at www.cvdcheck.org.au.
- The National Vascular Disease Prevention Alliance guidelines for the management of Absolute Cardiovascular Disease Risk 2012 specifies a range of conditions already known to be at clinically determined high risk of CVD and do not require absolute CV risk assessment. These include:
  - diabetes and age >60 years
  - diabetes with microalbuminuria (>20 mcg/min or urine albumin-to-creatine ratio [UACR] >2.5 mg/mmol for men and >3.5 mg/mmol for women)
  - moderate or severe chronic kidney disease [CKD] (persistent proteinuria or estimated glomerular filtration rate [eGFR] <45 ml/min1.73 m^2)
  - a previous diagnosis of familial hypercholesterolaemia
  - systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
  - serum total cholesterol >7.5 mmol/L.

Therapy combinations included in proposal

5.6 Consistent with the comparisons and findings in the SGLT2 inhibitor report, the proposal was targeted at allowing earlier access to an SGLT2 inhibitor as add-on therapy to metformin (i.e. dual therapy metformin + SGLT2 inhibitor). Authority Required (Streamlined) codes proposed for inclusion are shown in Table 2.

5.7 The PBS Authority Required (Streamlined) code 7506 currently allows an SGLT2 inhibitor to be used as dual therapy in combination with either metformin or a SU, within the same restriction. Although this CER compared the cost-effectiveness of SGLT2 inhibitors to SUs as dual therapy with metformin for the treatment of T2DM, it is proposed that streamlined code 7506 be included in the proposed restriction changes on the assumption that metformin + SGLT2 inhibitor combination represents the most use under this streamlined code (compared with SU + SGLT2 inhibitor use).

5.8 Advice was sought on whether this is an acceptable assumption, or whether SU + SGLT2 inhibitor use should be removed from this proposal (i.e. the existing streamlined code and restriction would need to be amended to create two separate codes to separate combination use as either: metformin + SGLT2 inhibitor, or SU + SGLT2 inhibitor).

5.9 Advice from the PBAC was also sought on the list of treatment combinations in Table 3. These include dual therapy with an SGLT2 inhibitor + insulin, or triple therapy combinations where all components other than the SGLT2 inhibitor are Unrestricted Benefits that do not require patients to have an unmet glycaemic target in order to initiate treatment.

Table 2: Authority Required (Streamlined) codes included in proposal

Streamlined code	Therapy combination	Changes proposed
7506	SGLT2 inhibitor: Dual therapy - SGLT2 inhibitor + MET/SU	Yes
5631	SGLT2 inhibitor + MET FDC: Dual therapy - SGLT2 inhibitor + MET	Yes
5953	SGLT2 inhibitor + MET FDC: Dual therapy - Empagliflozin + MET	Yes

Source: Table 1.5, SGLT2 inhibitor report. Abbreviations: FDC – fixed dose combination; MET – metformin; SU – sulfonylurea.

Table 3: Authority Required (Streamlined) codes where PBAC advice is required

Streamlined code	Therapy combination	Changes proposed
4991	SGLT2 inhibitor: Dual therapy - SGLT2 inhibitor + insulin	Advice required
5629	SGLT2 inhibitor: Triple therapy - SGLT2 inhibitor + MET + SU	Advice required
5798	SGLT2 inhibitor + MET FDC: Triple therapy - SGLT2 + MET + SU	Advice required
5657	SGLT2 inhibitor + MET FDC: Triple therapy - SGLT2 + MET + insulin	Advice required

Source: Table 1.6, SGLT2 inhibitor report. Abbreviations: FDC – fixed dose combination; MET – metformin; SU – sulfonylurea.

5.10 The remaining SGLT2 inhibitor streamlined codes/treatment combinations were excluded from the PBS restriction change proposal on the basis that they were either:

- For continuing treatment, and patients can access these items provided they have qualified under the relevant 'initial treatment' restriction.
- A triple therapy combination, where one of the medicines in the combination (other than the SGLT2 inhibitor) specifies a glycaemic requirement for PBS subsidy. Changing this restriction may unintentionally allow patients to bypass the current glycaemic requirements associated with other second-line medicines for T2DM.

6 PBAC Outcome

6.1 The PBAC deferred making a decision to recommend expansion of PBS restrictions to allow earlier subsidised access to SGLT2 inhibitors in T2DM patients as add-on therapy to metformin if they have established or are at high risk of CVD, without the requirement to have a specific unmet glycaemic target. The PBAC requested further analyses due to the very high and uncertain net cost to the PBS over the first five years of listing and PBAC concerns about the acceptability of the estimated cost-effectiveness for the proposed expanded listings at current SGLT2 inhibitor prices.

6.2 The PBAC considered sponsor comments, the ESC and DUSC October 2021 advice, and the SGLT2 inhibitor report.

6.3 The PBAC noted the SGLT2 inhibitor report presented a cost-utility evaluation using an adaptation and calibration of a reference model [UKPDS OM2] to assess the cost-effectiveness of SGLT2 inhibitors compared to SUs as dual therapy with metformin for the treatment of T2DM. The PBAC noted the model appropriately used Australian-specific mortality, cost and patient data to calibrate the original UKPDS OM to reflect a contemporary Australian setting. The PBAC noted the ICERs for the base case were $29,939/QALY for men and $27,316/QALY for women, and that the ICERs for SGLT2 inhibitors compared with SUs remained below $50,000 per QALY for a wide range of assumptions regarding the duration of treatment effects and costs associated with diabetes-related complications. The evidence presented in the report also suggested

that SGLT2 inhibitors are likely to be clinically effective compared to SU in the second-line setting for T2DM. However, the PBAC recalled it has previously considered preventative therapies, particularly those with a high and uncertain net cost to the PBS, to need a lower ICER to demonstrate cost-effectiveness, than the base case ICER presented in the report. The PBAC considered that a price reduction for SGLT2 inhibitors would be required to bring the ICER for the expanded listing into an acceptable range. The PBAC requested the Department present revised scenarios and modelled estimates of cost to the PBS to further inform the range of acceptable ICERs for subsidised access to SGLT2 inhibitors for the proposed population.

6.4 The PBAC acknowledged the clinical rationale for expanding the PBS listings for SGLT2 inhibitors to a broader population but noted DUSC advice that the expansion of these listings in the proposed population will have a substantial financial impact and associated opportunity cost. The (Scenario 1 base case) net cost to the PBS of the proposed restrictions allowing earlier access to SGLT2 inhibitor medicines in the T2DM population was estimated to be $108 million in 2022, increasing to $200 million in 2026 based on current prices.

6.5 The PBAC noted DUSC concerns that while the eligible population and uptake rates presented in the base case estimates appear reasonable based on the information available, uncertainty remains about whether the population and estimated cost to the Government could be higher given the strong clinical and consumer interest in expanded access to SGLT2 inhibitors, supported by current clinical guidance and sponsor promotion. The PBAC noted that according to Australian Institute of Health and Welfare (AIHW) data in 2011-12, the number of Australians with diabetes with a HbA1c less than 7% was approximately 500,000 persons but the proportion of these patients who have CVD or two or more CVD risk factors is not known. This was consistent with the proposed eligible T2DM population identified in the PBS dataset on which the CER estimates were based.

6.6 The PBAC considered the total net cost of $769 million over the first five years of listing to be high and uncertain, and with some concerns that this may represent a conservative estimate of the financial impact to the PBS. The PBAC noted prescribing practices have and will continue to change with SGLT2 inhibitors being used for their CV and renal benefits, rather than just for their glycaemic effects and the potential for use outside the restrictions into pre-diabetes and other conditions. The PBAC considered that the eligible population and projected budget impact may also be affected by recent submissions for SGLT2 inhibitors for other clinical indications.

6.7 The PBAC recalled that at its July 2021 meeting, it deferred its decision to recommend both submissions for dapagliflozin for CKD and HFrEF. At the time, PBAC was concerned about the risk of use outside the proposed PBS restriction and the extent of overlap between the three indications. The submissions had estimated the overall net impact of the HFrEF and CKD listings but had not provided estimates with respect to the existing T2DM indication. The PBAC considered "that these estimates were necessary to inform its advice to the Australian Government about an appropriate risk share agreement (RSA) to ensure that the subsidy of dapagliflozin is restricted to the populations in whom PBAC has considered it cost effective." (see paragraph 7.1, Dapagliflozin (heart failure) Public Summary Document, July 2021 PBAC meeting).

6.8 The PBAC recalled that it obtained this additional information from the sponsor at its September 2021 intracycle meeting. The PBAC recommended extending the existing listing of dapagliflozin to include a General Schedule Authority Required (Streamlined) listing for the treatment of patients with HFrEF. The PBAC considered that the estimates for HFrEF formed a reliable basis for an RSA for this indication. At this meeting, the PBAC did not recommend extending the existing listing of dapagliflozin to include a General Schedule Authority Required (Streamlined) listing for the treatment of patients with CKD. The PBAC remained of the view that the financial estimates for CKD remained high and substantially overestimated and did not form a reliable basis for an RSA.

6.9 Consistent with its July 2021 and September 2021 deliberations, the PBAC remained concerned with the likely significant overlap and potential movement of patients between the proposed expanded listings for SGLT2 inhibitors for use in T2DM patients with CVD/high CV risk, those recommended for HFrEF, and what PBAC may consider for the population with CKD. The PBAC noted this may weaken the robustness of an indication-specific RSA.

6.10 The PBAC considered the clinical evaluation findings that concluded SGLT2 inhibitors decreased the risk of all-cause and CV-related mortality, CV events and hospitalisation when compared to SUs. However, the PBAC noted that the review did not include any CV outcome trials suggesting that ertugliflozin has comparable CV benefits to dapagliflozin and empagliflozin. Therefore, the PBAC advised that ertugliflozin should be excluded from any potential expansion of this class of medicines until more evidence becomes available.

6.11 The PBAC noted ESC advice that considered further work was required on the proposed restrictions. The ESC advice also suggested that the PBS restrictions for ezetimibe provide a detailed example for defining a population with CVD or high CV risk and could potentially be used as a basis for the proposed SGLT2 inhibitor restrictions. The PBAC was cognisant that adding detailed clinical criteria and administrative advice to the PBS restrictions for SGLT2 inhibitors would add to the complexity of the SGLT2 inhibitor restrictions but noted that where possible it would be appropriate to maintain consistency where precedents for defining CV risk in PBS restrictions already exist.

6.12 The PBAC considered the clinical criterion “Patient must identify as Aboriginal or Torres Strait Islander” should be included as one of the eligibility options, recognising the higher risk of CVD in this population.

6.13 The PBAC considered the clinical criterion “Patient must have kidney disease” should be excluded from the proposed PBS restrictions noting its separate consideration of submissions for dapagliflozin for CKD and potential for use outside the PBS restriction and overlap across CKD and T2DM indications. The PBAC also noted that the presence of microalbuminuria (>20 mcg/min or urine albumin-to-creatine ratio [UACR] >2.5 mg/mmol for men and >3.5 mg/mmol for women) is an independent risk factor for CVD.

6.14 The PBAC requested that the Department seek further information on outstanding issues relating to the cost-effectiveness of SGLT2 inhibitors in the expanded T2DM

population, the patient numbers across all PBS indications for SGLT2 inhibitor medicines and the overall budget impact for consideration at a subsequent meeting.

7 Outcome

Deferred.

8 Context for Decision

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