

9.04 Cost-effectiveness review of SGLT2 inhibitor medicines for type 2 diabetes mellitus

1 Purpose of Item

That the Pharmaceutical Benefits Advisory Committee (PBAC):

- 1.1 **Note** the Addendum to the cost-effectiveness review (CER) of sodium-glucose cotransporter 2 (SGLT2) inhibitor medicines for type 2 diabetes mellitus (T2DM), which provides revised incremental cost-effectiveness ratios (ICERs) and estimates of the financial impact to the Pharmaceutical Benefits Scheme (PBS) of listing SGLT2 inhibitors as add-on therapy to metformin for people with T2DM and established cardiovascular disease (CVD) or high cardiovascular (CV) risk without the requirement to have a specific unmet glycaemic target, based on 15%, 25% and 50% price reductions. Financial estimates for modelled price reductions to the current SGLT2 inhibitor market for T2DM are also provided.
- 1.2 **Recommend** any changes to the price, PBS restrictions, or risk-sharing arrangements for SGLT2 inhibitors.
- 1.3 **Advise** the department if the PBAC would like any further work undertaken on the cost-effectiveness of T2DM medicines.

2 Background

Cost-effectiveness Review of T2DM medicines

- 2.1 In September 2019, a stakeholder wrote to the PBAC requesting broader listings for glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors on the PBS. 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 HbA1c >6.5%, based on the results of several CV outcome trials.
- 2.2 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 sulfonylureas (SUs) as dual therapy with metformin for the treatment of T2DM (the SGLT2 inhibitor report). 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. This comparison was of interest to the PBAC given emerging evidence of CV benefits and weight loss associated with SGLT2 inhibitors.

- 2.3 The SGLT2 inhibitor report concluded that:
- SGLT2 inhibitors decreased the risk of all-cause and CV-related mortality when compared to SUs. Compared to SUs, SGLT2 inhibitors saw greater reductions in systolic blood pressure and weight, but no significant difference in HbA1c reductions.
 - 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.
- 2.4 The CER 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 the Australians with T2DM who are treated with SGLT2 inhibitors as dual therapy with metformin and include the currently eligible population as well as those with CVD or high CV risk. The ICERs were sensitive to shorter treatment effect durations; \$72,425 per QALY gained for men and \$82,331 per QALY gained for women, based on a three-year treatment effect to match the duration of the clinical trials. Varying the cost associated with complications also had an impact on the ICER.

PBAC Consideration – November 2021

- 2.5 At its November 2021 meeting, the PBAC considered the SGLT2 inhibitor report, ESC and DUSC October 2021 advice, and sponsor pre-sub-committee and pre-PBAC responses. The PBAC were asked to advise on the suitability of the proposed PBS restrictions that would allow earlier subsidised access to SGLT2 inhibitors for patients with T2DM as add-on therapy to metformin if they have established CVD or are at high CV risk, without the requirement to have a specific unmet glycaemic target. The net cost of the proposed restriction changes was estimated to be \$108 million in 2022, increasing to \$200 million in 2026, based on current PBS-listed prices. The base case estimates assumed a 50% uptake in the eligible population in 2022, increasing by 10% every year up to 90% uptake in 2026.
- 2.6 The PBAC deferred a decision to recommend expanding the listings of SGLT2 inhibitors due to several concerns, including:
- the net cost to the PBS over the first five years of listing was very high and uncertain
 - the cost-effectiveness of the proposed listings was uncertain given the ICER for the base case and sensitivity analyses were higher than PBAC would normally accept for preventative treatments
 - effectively targeting the eligible population, specifically patients with T2DM with high CV risk in the proposed PBS restrictions.
- 2.7 The PBAC acknowledged the clinical rationale for expanding the PBS listings for SGLT2 inhibitors to the population with T2DM and CVD or high CV risk and HbA1c <7%.

However, noting DUSC concerns that while the eligible population and treatment uptake rates presented in the base case estimates appeared reasonable, uncertainty remained about whether the estimated cost to the Government could be even 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 the potential for use of SGLT2 inhibitors outside the restrictions, in pre-diabetes and other conditions.

- 2.8 The PBAC considered that a price reduction for SGLT2 inhibitor medicines would be required to bring the ICER for the expanded listing into an acceptable range and to reduce the uncertainty in the overall cost to the PBS. The PBAC requested that the Department provide modelled ICERs and financial estimates where the current price of SGLT2 inhibitors was reduced by 15%, 25% and 50%.
- 2.9 The PBAC recalled that it had recommended extending the existing listing of dapagliflozin to include a General Schedule Authority Required (Streamlined) listing for the treatment of patients with heart failure with reduced ejection fraction (HFrEF) at the September 2021 intracycle meeting. The PBAC considered that the estimates for HFrEF formed a reliable basis for a risk-sharing arrangement (RSA), [REDACTED]. 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 chronic kidney disease (CKD). The PBAC considered that the financial estimates for CKD were high and substantially overestimated.
- 2.10 The PBAC was 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.
- 2.11 The PBAC considered the clinical evaluation findings and noted that the review did not include any CV outcome trials suggesting that ertugliflozin has comparable CV benefits to dapagliflozin and empagliflozin. The PBAC advised that ertugliflozin should be excluded from any potential expansion of this class of medicines until more evidence becomes available.
- 2.12 The PBAC noted the ESC advice on the proposed restrictions, which suggested either simplification of the proposed restriction to enable prescribers to assess CV risk on a case-by-case basis, instead of using a prescribed tool or risk calculator, or consideration of a broader list of risk factors, potentially using the clinical criteria for ezetimibe as an example. The ESC advice noted that the CVD Risk Calculator introduces a dimension of complexity for prescribers and does not consider a wide range of risk factors such as family history, Aboriginal and Torres Strait Islander status, socioeconomic status, waist circumference and physical activity levels.

- 2.13 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.
- 2.14 The PBAC considered the clinical criterion “Patient must have kidney disease” should be excluded from the proposed PBS restrictions noting its separate consideration of a submission 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-creatinine ratio [UACR] >2.5 mg/mmol for men and >3.5 mg/mmol for women) is an independent risk factor for CVD.
- 2.15 The PBAC requested that a CER of GLP-1 RAs compared with SUs as add-on therapy to metformin also be conducted using the same UKPDS OM2 modified to the Australian setting.

3 Budget Impact

- 3.1 As requested by PBAC, an Addendum to the SGLT2 inhibitor report provides the modelled ICERs for SGLT2 inhibitors versus SUs as add-on therapy to metformin assuming 15%, 25% and 50% price reductions (Table 1). These ICERs apply to both the currently eligible PBS population and the proposed additional population with CVD or high CV risk and HbA1c <7%.
- 3.2 Drug treatment costs constitute a relatively small proportion of the health care costs related to T2DM and therefore the ICER was not particularly sensitive to changes in the cost of SGLT2 inhibitor medicines. The ICER was sensitive to shorter treatment effect durations and varying the cost associated with complications.

Table 1. Incremental costs per QALY gained associated with SGLT2 inhibitors compared to sulfonylureas in the lifetime treatment effect scenarios where the price of SGLT2 inhibitors is reduced by 0%, 15%, 25% and 50%.

	Current prices	15% price reduction	25% price reduction	50% price reduction
Men	\$29,939	\$28,287	\$27,185	\$24,432
Women	\$27,316	\$25,553	\$24,377	\$21,439

Source: Attachment D – Addendum to the CER of SGLT2 inhibitors for T2DM, Table 4.

- 3.3 Table 2 shows the estimated budget impact to the PBS of expanding the listing for SGLT2 inhibitors to include people with CVD or high CV risk and HbA1c <7%, and the effect of 15%, 25% and 50% price reductions.

Public Summary Document – March 2022 PBAC Meeting

Table 2. Estimated net cost to the PBS for the additional population with CVD or high CV risk and HbA1c <7%, when the price of SGLT2 inhibitors is reduced by 0%, 15%, 25% and 50%.

Year	Current prices Net cost (\$)	15% price reduction Net cost (\$)	25% price reduction Net cost (\$)	50% price reduction Net cost (\$)
2022	108,170,098	85,187,745	69,866,176	42,202,755
2023	130,708,501	102,937,527	84,423,545	50,996,153
2024	153,548,365	120,924,721	99,175,625	59,907,167
2025	176,689,690	139,149,326	114,122,417	68,935,796
2026	200,132,476	157,611,342	129,263,919	78,082,040
PBS Total net cost (\$)	769,249,128	605,810,661	496,851,682	300,123,910

Source: Attachment D – Addendum to the CER of SGLT2 inhibitors for T2DM, Table 7.

3.4 The Department also modelled the estimated R/PBS cost of applying the 15%, 25% and 50% price reductions to the current SGLT2 inhibitor market for T2DM, projected for five years (2022-2026) (Table 3).

Table 3. Estimated net cost to the PBS for 5 years (2022 to 2026) when 15%, 25% and 50% price reductions are applied to the projected current SGLT2 inhibitor market for T2DM and proposed SGLT2 inhibitor market (CVD/high CV risk and HbA1c <7%).

Price reduction (%)	Projected current T2DM market (\$)	Proposed CV market (base case) (\$)	Projected current market and proposed market (\$)
0	1,087,850,068	769,249,128	1,857,099,196
15	869,522,386	605,810,661	1,475,333,047
25	723,970,598	496,851,682	1,220,822,280
50	444,674,825	300,123,910	744,798,736

Source: Attachment D – Addendum to the CER of SGLT2 inhibitors for T2DM, Tables 8-10.

4 PBAC Outcome

- 4.1 The PBAC 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.
- 4.2 In making this recommendation, the PBAC noted the Addendum to the cost-effectiveness review report on SGLT2 inhibitors for T2DM which provided revised estimates of the net cost to the PBS and ICERs resulting from modelled price reductions to SGLT2 inhibitors, the October 2021 DUSC and ESC advice, and sponsor pre-PBAC responses.
- 4.3 The PBAC is satisfied that dapagliflozin and empagliflozin provide, for some patients, a significant improvement in efficacy over SUs, when used as add-on therapy to metformin in T2DM. The PBAC noted the results of the clinical and economic analyses

in the SGLT2 inhibitor report which indicate that SGLT2 inhibitors compared to SUs decreased the risk of all-cause and CV-related mortality and were likely to improve life expectancy and quality-adjusted life expectancy. However, SGLT2 inhibitors were likely to lead to an increase in lifetime costs per patient compared to SUs.

- 4.4 The PBAC noted that the current PBS restrictions for SGLT2 inhibitors were no longer in line with T2DM clinical treatment guidelines, which may recommend individualisation of glycaemic targets and that second-line medicine selection should be influenced by the presence of other risk factors, e.g., SGLT2 inhibitors may be recommended for patients at high CV risk.
- 4.5 The PBAC noted the study by the George Institute for Global Health on the wider health-related cost savings and societal benefits of SGLT2 inhibitors¹, referenced by one sponsor.
- 4.6 The PBAC affirmed its previous recommendation that ertugliflozin should be excluded from any potential restriction expansion until CV outcome trials demonstrate that ertugliflozin has comparable CV benefits to dapagliflozin and empagliflozin.
- 4.7 The PBAC Overview presented two options for revised restrictions for SGLT2 inhibitors. The PBAC considered that the simple restriction with minor amendments was most appropriate, as this substantially allowed the high CV risk population to be identified and would be more easily utilised by GPs. The PBAC agreed restriction for the recommended listing is at Section 5.
- 4.8 The PBAC noted sponsor comments that it was inappropriate to exclude patients with CKD from the proposed listings based on the separate consideration of PBS listing dapagliflozin for the treatment of CKD. The PBAC agreed that patients with CKD should be included within the population of high CV risk defined in the restrictions, as the exclusion of these patients would be confusing to prescribers and it may be difficult to define appropriate clinical criteria.
- 4.9 The PBAC considered that a separate clinical criterion of 'Patient identifies as Aboriginal or Torres Strait Islander' should be added to the restriction, and that the note regarding use of the maximally tolerated dose of metformin or a SU should be removed.
- 4.10 The PBAC agreed that the restriction should include a prescriber note with a definition of high CV risk and a reference to the Australian Absolute Cardiovascular Disease Risk Calculator.
- 4.11 The PBAC noted a comment from one sponsor that the restriction should include a requirement for patients to have a HbA1c >6.5%, in addition to CVD or high CV risk, to

¹ The George Institute for Global Health, [The wider benefits of SGLT2 inhibitors](#), March 2021.

Public Summary Document – March 2022 PBAC Meeting

initiate a SGLT2 inhibitor. The PBAC considered that this was unnecessary as a glycaemic requirement was not included in the inclusion/exclusion criteria for the CER.

- 4.12 The PBAC recommended that SGLT2 inhibitors be listed as add-on therapy to metformin for the treatment of T2DM patients with CVD, or high CV risk, if expenditure over the five years (2022-2026) for the current T2DM market and the proposed CVD/high CV risk population was limited to \$1.5 billion. The PBAC noted that based on the estimates in the report Addendum this would equate to a price reduction in the order of 15% for T2DM indications.
- 4.13 The PBAC noted a sponsor comment that the CER should have been undertaken as part of a post-market review (PMR) but considered that there was precedence for changing restrictions and prices based on specific background research, and that a PMR had been conducted on diabetes medicines previously.
- 4.14 The PBAC noted that there may be implications for the pricing of GLP-1 RAs and dipeptidyl peptidase-4 (DPP4) inhibitors if SGLT2 inhibitor prices are lowered. The PBAC noted that DPP4 inhibitors have a similar PBS price to SGLT2 inhibitors but have no evidence of specific CV benefits and similar effects on HbA1c to SGLT2 inhibitors.
- 4.15 The PBAC noted an error in the totals in Table 8, Attachment D – Addendum to the CER, which was repeated in Table 4.27, Attachment F – Section 4 – Financial. The total estimated cost to the PBS from 2022-2026 for the current SGLT2 inhibitor market for T2DM is \$1,087,850,068. The PBAC also noted an error in Table 11, Attachment D – Addendum to the CER, which was repeated in Table 4.30, Attachment F – Section 4 – Financial. The total estimated cost to the PBS from 2022-2026 for the current SGLT2 inhibitor market for T2DM at a 50% price reduction is \$444,674,825.

Outcome:

Recommended

5 Recommended listings

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DAPAGLIFLOZIN dapagliflozin 10 mg tablet, 28	New	1	28	5	Forxiga
EMPAGLIFLOZIN empagliflozin 10 mg tablet, 30	New	1	30	5	Jardiance
EMPAGLIFLOZIN empagliflozin 25 mg tablet, 30	New	1	30	5	Jardiance

Restriction Summary New / Treatment of Concept: New

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Type <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
New AA1	Administrative Advice: Patients should receive appropriate lifestyle modification education and support. 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 specify a range of conditions known to be at clinically determined high risk of CVD.
new	Administrative Advice: SGLT2 inhibitors are not PBS subsidised for monotherapy and should be taken with metformin, unless contraindicated or intolerant.
new	Administrative Advice: This drug is not PBS-subsidised for use in combination with a thiazolidinedione (glitazone), or a glucagon-like peptide-1.
	Condition: Diabetes mellitus type 2
8995	Indication: Diabetes mellitus type 2
9855	Clinical criteria:
	The treatment must be in combination with metformin;
	AND
New CC1	Clinical criteria:
CC1, Para A	Patient must have cardiovascular disease;
	OR
CC1, Para B	Patient must be at high risk of a cardiovascular event;
	OR
CC1, Para C	Patient must identify as Aboriginal or Torres Strait Islander.

Public Summary Document – March 2022 PBAC Meeting

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DAPAGLIFLOZIN + METFORMIN dapagliflozin 10 mg + metformin hydrochloride 1 g modified release tablet, 28	New	1	28	5	Xigduo XR 10/1000
DAPAGLIFLOZIN + METFORMIN dapagliflozin 5 mg + metformin hydrochloride 1 g modified release tablet, 56	New	1	56	5	Xigduo XR 5/1000
DAPAGLIFLOZIN + METFORMIN dapagliflozin 10 mg + metformin hydrochloride 500 mg modified release tablet, 28	New	1	28	5	Xigduo XR 10/500
EMPAGLIFLOZIN + METFORMIN empagliflozin 12.5 mg + metformin hydrochloride 1 g tablet, 60	New	1	60	5	Jardiamet 12.5 mg/1000 mg
EMPAGLIFLOZIN + METFORMIN empagliflozin 5 mg + metformin hydrochloride 1 g tablet, 60	New	1	60	5	Jardiamet 5 mg/1000 mg
EMPAGLIFLOZIN + METFORMIN empagliflozin 12.5 mg + metformin hydrochloride 500 mg tablet, 60	New	1	60	5	Jardiamet 12.5 mg/500 mg
EMPAGLIFLOZIN + METFORMIN empagliflozin 5 mg + metformin hydrochloride 500 mg tablet, 60	New	1	60	5	Jardiamet 5 mg/500 mg

Public Summary Document – March 2022 PBAC Meeting

Restriction Summary New / Treatment of Concept: New

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Type <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
New AA1	Administrative Advice: Patients should receive appropriate lifestyle modification education and support. 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 specify a range of conditions known to be at clinically determined high risk of CVD.
21881	Administrative Advice: This fixed dose combination is not PBS-subsidised for initiating dual oral combination treatment or in combination with a thiazolidinedione (glitazone), glucagon-like peptide-1 analogue, or another SGLT2 inhibitor.
	Condition: Diabetes mellitus type 2
8995	Indication: Diabetes mellitus type 2
New CC1	Clinical criteria:
CC1, Para A	Patient must have cardiovascular disease;
	OR
CC2, Para B	Patient must be at high risk of a cardiovascular event;
	OR
CC3, Para C	Patient must identify as Aboriginal or Torres Strait Islander.

These restrictions may be subject to further review. Should there be any changes made to the restrictions the sponsors will be informed.

6 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.