

6.01 DAPAGLIFLOZIN, Tablet 10 mg (as propanediol monohydrate), Forxiga[®], AstraZeneca Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested an Authority Required (STREAMLINED) listing for dapagliflozin for the treatment of type 2 diabetes, in combination with metformin and any dipeptidyl peptidase-4 (DPP4) inhibitor, in patients with inadequate glycaemic control on dual therapy of metformin and any DPP4 inhibitor.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Adults with type 2 diabetes with inadequate glycaemic control on dual therapy with metformin and a DPP4 inhibitor
Intervention	Dapagliflozin 10 mg in triple oral therapy as add on to metformin and a DPP4 inhibitor
Comparator	Long-acting insulin (individualised dose) in combination with metformin and a DPP4 inhibitor, and sulfonylurea in combination with metformin and DPP4 inhibitor
Outcomes	Reduction in HbA1c %
Clinical claim	Dapagliflozin is non-inferior in terms of efficacy and similar in terms of safety compared with long-acting insulin as add-on therapy to metformin and a DPP4 inhibitor. There was no clinical claim in terms of efficacy or safety for dapagliflozin versus sulfonylurea

Source: Constructed during evaluation

Abbreviations: DPP4, dipeptidyl peptidase 4; HbA1c, glycosylated haemoglobin

- 1.2 There were a number of issues associated with the rationale for listing including the clinical management (fixed sequence of treatment with metformin and DPP4 inhibitor and then adding dapagliflozin), comparator (need to address less costly comparators, inappropriate weighting of price across comparators) and clinical claim (whether the clinical evidence adequately supports stated claims).

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Max. Qty	Price for	Proprietary Name and Manufacturer
DAPAGLIFLOZIN Tablets 10 mg	28	5	\$57.74		Forxiga [®] AstraZeneca

Public Summary Document – July 2017 PBAC Meeting

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be in combination with metformin,</p> <p>AND</p> <p>The treatment must be in combination with a dipeptidyl peptidase 4 inhibitor (DPP4) inhibitor (<i>gliptin</i>)</p> <p>AND</p> <p><i>Patient must have previously been stabilised on dual oral therapy which includes a dipeptidyl peptidase 4 inhibitor (gliptin)</i></p> <p>OR</p> <p><i>Patient must have previously been stabilised on dual oral therapy which includes a sodium-glucose co-transporter 2 (SGLT2) inhibitor,</i></p> <p>AND</p> <p>A-patient must have, or have had, an HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a dipeptidyl peptidase 4 inhibitor (gliptin) and a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with the maximally tolerated metformin and a dipeptidyl peptidase 4 (DPP4) inhibitor,</p> <p>OR</p> <p>A-patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation of triple oral therapy with a gliptin, and with a dipeptidyl peptidase 4 inhibitor (gliptin), a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, despite treatment with the maximally tolerated of metformin and a DPP4.</p>

<p>Prescriber Instructions</p>	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment <i>triple oral therapy with a gliptin and an SGLT2 inhibitor</i> is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with an SGLT2 inhibitor <i>triple oral therapy with a gliptin and a SGLT2 inhibitor</i> was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <ul style="list-style-type: none"> a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or b) Had red cell transfusion within the previous 3 months <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with an SGLT2 inhibitor <i>triple oral therapy with a gliptin and an SGLT2 inhibitor</i>, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin or <i>and a gliptin or an SGLT2 inhibitor</i> does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.</p>
<p>Administrative Advice (not included in LI)</p>	<p><i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i></p> <p>PBS subsidised dual oral therapy does not include concomitant use of a combination of: <i>a gliptin, a glitazone or an SGLT2 inhibitor.</i></p>

- 2.2 The restriction was requested on the basis of cost-minimisation against the nominated comparators, insulin glargine in combination with metformin and sulfonylurea in triple therapy.
- 2.3 Dapagliflozin is administered as one 10 mg tablet, once daily, with treatment ongoing.
- 2.4 The requested restriction is narrower than the TGA indication, and only allows for the use of dapagliflozin as a sequential add-on therapy for patients already receiving dual therapy with metformin and a DPP4 inhibitor.
- 2.5 The Pre-Sub-Committee Response (PSCR, pg 1) argued that the restriction is appropriate because it is consistent with treatment guidelines and clinical practice as both DPP4 and sodium-glucose co-transporter-2 (SGLT2) inhibitors are second- and third-line treatments. The ESC considered that although the proposed restriction was within clinical treatment guidelines, it inappropriately limits the use of dapagliflozin in triple therapy to a fixed treatment sequence of dapagliflozin as add-on therapy in patients previously on metformin and a DPP4 inhibitor.

- 2.6 Current PBS restrictions do not allow concomitant use of SGLT2 inhibitors and DPP4 inhibitors. However, the DUSC Review of Diabetes Medicines (February 2017) indicates a growing number of patients receiving regimens containing both SGLT2 inhibitors and DPP4 inhibitors, including quadruple therapy which is outside PBS restrictions. Based on utilisation data, this usage (outside PBS restrictions) is likely to shift to the requested restriction that would subsidise concomitant use of these agents. The ESC also noted that the restriction does not preclude use with additional agents for quadruple therapy.
- 2.7 The requested PBS restriction would allow for subsidisation of off-label use of DPP4 inhibitors except for saxagliptin. Sitagliptin, linagliptin and vildagliptin have TGA indications for triple therapy with metformin and sulfonylurea and alogliptin is TGA approved for triple therapy with metformin and thiazolidinedione only. The ESC noted that dapagliflozin is TGA registered for treatment of patients with type 2 diabetes to improve glycaemic control in combination with other anti-hyperglycaemic agents. However, saxagliptin is the only DPP4 inhibitor that has a TGA indication for add-on therapy with a SGLT2 inhibitor and metformin. Further, this approach assumes that all DPP4 inhibitors are interchangeable. The submission noted that the PBAC previously recommended that the DPP4 inhibitors be considered interchangeable on an individual patient basis for the purposes of section 101(3BA) of the National Health Act 1953 (Alogliptin PSD July 2013).
- 2.8 The pre-PBAC response (p1) acknowledged the changes proposed by Secretariat and also supported the proposal for a General Statement for PBS-listed type 2 diabetes medicines to be developed. The PBAC noted that a draft general statement for the use of PBS-listed medicines for type 2 diabetes was provided in the pre-PBAC response (p4), but considered that any general statement would need additional development and consultation.

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

3 Background

- 3.1 TGA status at the time of PBAC consideration: Dapagliflozin was TGA registered on 26 October 2016 for use in patients with type 2 diabetes in combination with saxagliptin as add-on combination therapy with other glucose-lowering medicines including insulin. Dapagliflozin was first registered on the ARTG in 2012.
- 3.2 Dapagliflozin is currently listed on the PBS for dual therapy in combination with metformin or sulfonylurea, as triple therapy with metformin and sulfonylurea and as dual therapy to insulin.
- 3.3 Dapagliflozin is not currently listed on the PBS for use as monotherapy or in combination therapy with a DPP4 inhibitor, with or without metformin, and this

combination has not previously been considered by the PBAC. The PBAC previously considered and rejected a submission for empagliflozin/linagliptin FDC at the March 2017 meeting.

- 3.4 Three concurrent submissions for dapagliflozin in type 2 diabetes were presented for consideration at the July 2017 PBAC meeting:
- Dapagliflozin add-on to metformin and a DPP4 inhibitor (this submission);
 - Dapagliflozin with saxagliptin FDC (major submission; item 5.13 refers); and
 - Dapagliflozin with metformin XR FDC (minor submission; item 6.08 refers).

4 Population and disease

- 4.1 The submission positioned dapagliflozin as an alternative add-on therapy in combination with metformin and a DPP4 inhibitor for adult patients with type 2 diabetes and inadequate glycaemic control despite treatment with metformin and a DPP4 inhibitor.
- 4.2 The PBAC noted that the proposed clinical place in therapy inappropriately restricts the initiation of triple therapy to a fixed sequence of dapagliflozin add-on to metformin and a DPP4 inhibitor, this is narrower than published guidelines and clinical practice which recommend multiple options for add-on therapy across a range of glucose-lowering drugs at each line of therapy.

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

5 Comparator

- 5.1 The submission nominated a mixed comparator of long-acting insulin in combination with metformin and a DPP4 inhibitor, and sulfonylureas in combination with metformin and a DPP4 inhibitor.
- 5.2 The submissions claim that the therapy most likely to be replaced was primarily insulin, and to a lesser extent, sulfonylureas, was based on utilisation data from a 10% Medicare sample analysis and a previous version of the DUSC Diabetes Medicines Review (2016). An updated version of the review (February 2017) that was provided to the sponsor was not used in the submission.
- 5.3 The 10% Medicare sample analysis relied on the percentage reductions in insulin and sulfonylureas after metformin with DPP4 inhibitor between 2012 and 2016. The

PBAC considered that this methodology was not reliable due to a number of issues: the analysis did not consider the broader population initiating triple therapy after treatment switching or through other sequences of treatment addition (e.g. metformin and SGLT2 inhibitor first, then a DPP4 inhibitor); the analysis presented relative changes in triple therapy regimen utilisation that may not reflect absolute market growth; and the methods used to determine persistence with non-insulin drug therapy may overestimate co-administration and underestimate treatment-switching.

- 5.4 The analysis presented in the submission was inconsistent with the DUSC review, which suggested that the most commonly used agent with metformin and a DPP4 inhibitor in triple therapy is a sulfonylurea, followed by insulin (Figure 3, p15 of DUSC Diabetes Medicines Review February 2017). The DUSC review also notes sharp increases in triple therapy regimens of insulin and sulfonylurea with SGLT2 inhibitors since PBS-listings of dapagliflozin, and a growing number of patients on regimens containing both an SGLT2 inhibitor and a DPP4 inhibitor which is not subsidised under current restrictions. The PBAC also noted the advice from DUSC that multiple pathways can lead to this triple therapy regimen in clinical practice.
- 5.5 The PBAC noted that the submission did not consider other less costly triple therapy regimens that could have a component replaced by dapagliflozin as alternative comparators. In triple therapy, any of the sulfonylureas (e.g. glibenclamide, gliclazide, glimepiride, glipizide), thiazolidinediones (e.g. pioglitazone), DPP4 inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin), GLP-1 analogues (e.g. exenatide), SGLT2 inhibitors (e.g. empagliflozin), insulins (e.g. long-acting, intermediate-acting, short-acting) and acarbose could potentially be substituted by dapagliflozin.
- 5.6 The PBAC also noted that the submission did not adequately identify distinct groups of patients in whom one therapy is appropriate but the other therapy is not. Whilst the pre-PBAC response (p2) identified that it would be inappropriate for very elderly patients to use sulfonylureas because of the increased risk of hypoglycaemia, this would not account for the 70% of the cohort the submission proposed would otherwise use insulin.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission presented an indirect comparison of dapagliflozin versus insulin detemir based on a meta-analysis of two dapagliflozin trials (Study 129 and Study 10 [stratum 2]) and an insulin detemir trial (TRANSITION) with metformin and a DPP4 inhibitor as the common reference arm. The PBAC noted that these studies were identified on the basis of a strict progression through one sequence of treatment, and therefore may have excluded relevant studies.
- 6.4 Study 10 contained two strata assessing dapagliflozin in dual therapy [Stratum 1] and triple therapy [Stratum 2; dapagliflozin + DPP4 + metformin]. The submission appropriately included Study 10 [stratum 2] only as Study 10 [stratum 1] was not applicable to patients eligible for dapagliflozin as in triple therapy.
- 6.5 The submission argued that insulin detemir is a reasonable proxy for long-acting insulin used in type 2 diabetes based on previous PBAC recommendations for insulin detemir.
- 6.6 Previously, the PBAC recommended insulin detemir for type 1 diabetes on a cost-minimisation basis compared with insulin glargine in March 2006 and for type 2 diabetes (unrestricted listing) on a cost-minimisation basis compared with insulin glargine in November 2007. In recommending insulin detemir for type 2 diabetes, the PBAC considered that the dose relativity to insulin glargine should be 1.10:1, based on the analysis of trials in the submission (November 2007 PSD). This was subsequently confirmed by the PBPA. Insulin detemir has not subsequently been PBS-listed for treatment of type 2 diabetes. The PBAC considered that it may be reasonable to use the dose relativity for insulin detemir to insulin glargine previously recommended.
- 6.7 No data were presented comparing the efficacy or safety of dapagliflozin versus sulfonylureas.
- 6.8 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Dapagliflozin add-on to metformin and DPP4 inhibitor randomised trials		
Study 129 (NCT0164632)	A multicentre, randomized, double blind, placebo controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of therapy with dapagliflozin added to saxagliptin in combination with metformin compared to therapy with placebo added to saxagliptin in combination with metformin in subjects with type 2 diabetes who have inadequate glycemic control on metformin and saxagliptin. Final clinical study report for study MB102129 (Week 24). Final short-term + long-term clinical study report for study MB102129 (Week 52).	Internal study report, December 2014. Internal study report, July 2015.
	Mathieu C, Ranetti AE, Li D, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes.	Diabetes Care 2015; 38:2009-2017.
Study 10 (NCT00984867)	A 24 week, multicentre, randomised, double blind, placebo controlled, parallel group, international phase III study with a 24 week extension period to evaluate the safety and efficacy of dapagliflozin 10 mg daily in patients with type 2 diabetes who have inadequate glycaemic control on a DPP4 inhibitor (sitagliptin) alone or in combination with metformin. Report for the 24 week short term treatment period. Report for the 24 week short term treatment period plus the 24-week long-term extension period.	Internal study report, December 2011. Internal study report, March 2012.
	Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add on therapy to sitagliptin with or without metformin: a 24 week, multicenter, randomized, double blind, placebo controlled study.	Diabetes Care 2014; 37:740-750.
Insulin detemir randomised trial		
TRANSITION (NCT00789191)	Hollander P, Raslova K, Skjoth TV, et al. Efficacy and safety of insulin detemir once daily in combination with sitagliptin and metformin: the TRANSITION randomized controlled trial.	Diabetes, obesity & metabolism 2011; 13(3):268-75.

Source: Table B.3, p34 of the submission

6.9 The key features of the randomised trials used in the indirect comparison are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome
MET + DPP4 inhibitor + dapagliflozin 10 mg vs. MET + DPP4 inhibitor					
Study 129	320	Randomised, double blind, multicentre, 24 weeks plus 28 weeks extension	Low	HbA1c 7.0-10.5% on metformin ≥1500 mg plus saxagliptin 5 mg daily	Mean change in HbA1c
Study 10 [stratum 2]	447 [n=226 for stratum 2]	Randomised, double blind, multicentre, 24 weeks plus 24 weeks extension	Low	HbA1c 7.0-10.0% on metformin ≥1500 mg plus sitagliptin 100 mg daily	Mean change in HbA1c
Meta-analysis	546	Included Study 129 and Study 10 [stratum 2]; assessed mean change in HbA1c			
MET + DPP4 inhibitor + insulin detemir vs. MET + SU + DPP4 inhibitor or MET + DPP4 inhibitor					
TRANSITION	222	Randomised, open label, multicentre, 26 weeks	High	HbA1c 7.5-10.0% on metformin ≥1000 mg per day as monotherapy or in combination with another glucose-lowering drug	Mean change in HbA1c

Source: compiled during the evaluation

Abbreviations: DPP4, dipeptidyl peptidase 4; HbA1c, glycosylated haemoglobin; MET, metformin; OS, overall survival

Comparative effectiveness

6.10 No efficacy data were presented comparing dapagliflozin versus sulfonylureas.

6.11 Table 4 is a summary of the indirect comparison of mean change in HbA1c between dapagliflozin and insulin detemir.

Table 4: Mean change in HbA1c from baseline for Study 129, Study 10 [stratum 2] and TRANSITION to Week 24 and Week 26

Trial ID	Mean change in HbA1c (SE)		Mean difference (95% CI)
Dapagliflozin with metformin and a DPP4 inhibitor vs placebo with metformin and a DPP4 inhibitor			
Study 129 (Week 24)	DAPA (+ MET + SAXA) N=160	PBO (+ MET + SAXA) N=160	
	-0.82 (0.07)	-0.10 (0.07)	
Study 10 [stratum 2] (Week 24)	DAPA (+ MET + SITA) N=113	PBO (+ MET + SITA) N=113	
	-0.43 (0.06)	-0.02 (0.06)	
Meta-analysis of Studies 129 and 10 [stratum 2] Heterogeneity: I ² = 82%; Test for overall effect: P = 0.0003			-0.56 (-0.86, -0.26)
Insulin detemir with metformin and a DPP4 inhibitor vs. metformin with sitagliptin ± a sulfonylurea			
TRANSITION (Week 26)		SITA + MET ± SU N=107	IDET (+ SITA + MET) N=110
		-0.89 (NR)	-1.44 (NR)
Indirect comparison dapagliflozin vs insulin detemir, (Week 24 and Week 26)			-0.55 (-0.77, -0.33)
			-0.01 (-0.38, 0.36)

Source: Table B.24, p86 of the submission

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; FAS, full analysis set; HbA1c, glycosylated haemoglobin; IDET, insulin detemir; MET, metformin; NR, not reported; PBO, placebo; SAXA, saxagliptin; SITA, sitagliptin; SU, sulfonylurea

- 6.12 Treatment with dapagliflozin and insulin detemir were both associated with statistically significant reductions in HbA1c when added-on to metformin and a DPP4 inhibitor.
- 6.13 Results from the insulin detemir trial (TRANSITION) should be interpreted with caution given the high risk of bias due to the trial design (open-label, complex treatment switching, comparator arm mix).
- 6.14 The indirect comparison between the meta-analysis of the dapagliflozin trials and the insulin detemir trial indicated that non-inferiority was met when a margin of 0.4% is considered.
- 6.15 The submission noted statistically significant heterogeneity between Study 129 and 10 [stratum 2]. There were differences between the trial populations in terms of baseline glycaemic control, treatment regimens in the comparator arms (different DPP4 inhibitors), and a large difference in observed treatment effect between the trials. The meta-analysis of Study 129 and Study 10 [stratum 2] may not be appropriate.
- 6.16 The PBAC considered that the indirect comparison was not appropriate given the substantial heterogeneity between Studies 129 and 10, applicability and exchangeability issues with the TRANSITION trial, and large differences in the magnitude of effect between the common reference arms. In particular, the PBAC noted that there were baseline differences in HbA1c and disease severity, as well as in the baseline metformin dose and whether patients were able to also take a sulfonylurea. The PBAC considered that the indirect comparison was not sufficiently reliable to determine non-inferior efficacy.

Comparative harms

- 6.17 No safety data were presented comparing dapagliflozin versus sulfonylureas. The pre-PBAC response (p3) presented data from a study comparing dapagliflozin with glipizide (a sulfonylurea) as add-on therapy to metformin monotherapy (Study CT-004). The submission argued that these data demonstrated superior safety due to a reduced rate of hypoglycaemic events in patients taking dapagliflozin compared to glipizide. However, the sponsor did not adequately address the applicability of these results (i.e. dual therapy vs. triple therapy in the submission). Furthermore, the PBAC previously considered that glipizide was rarely used in Australia and this sulfonylurea has been associated with higher rates of hypoglycaemia and lower efficacy than other sulfonylureas that were more commonly used in Australian clinical practice (dapagliflozin Public Summary Document, March 2012 PBAC Meeting).
- 6.18 Dapagliflozin was associated with higher incidences of urogenital infections and hypoglycaemic events compared to placebo when added-on to metformin and a DPP4 inhibitor (Study 129 and Study 10 [stratum 2]).

- 6.19 Insulin detemir with sitagliptin and metformin was associated with a higher incidence of hypoglycaemia compared to metformin and sitagliptin (with or without sulfonylureas).
- 6.20 Based on the indirect comparison of dapagliflozin and insulin detemir, there were no statistically significant differences between treatments in the occurrence of any adverse events, adverse events leading to discontinuation, serious adverse events and hypoglycaemia.
- 6.21 Results from the meta-analysis of Studies 129 and 10 [stratum 2] and indirect comparison with the TRANSITION trial should be interpreted with caution given issues with applicability of the TRANSITION trial to the PBS population, substantial heterogeneity between Studies 10 and 129 and exchangeability issues with the TRANSITION trial.
- 6.22 The PBAC considered that the indirect comparison was not sufficiently reliable to determine non-inferior safety.

Clinical claim

- 6.23 The submission described dapagliflozin as non-inferior in terms of efficacy and similar in terms of safety compared with long-acting insulin, when added-on to metformin and a DPP4 inhibitor. The PBAC considered that this claim was uncertain because:
- the submission excluded trials that did not follow a fixed sequence approach to achieve triple therapy. This is inconsistent with guidelines and clinical practice and therefore the applicability of the presented trial results was limited (i.e. metformin and DPP4 inhibitor first, then add-on dapagliflozin);
 - the clinical evidence presented for long-acting insulin may not be reasonable given it was a trial assessing the addition of insulin detemir and sitagliptin (dual agents) to metformin monotherapy, which is inconsistent with clinical practice;
 - it is difficult to draw any reliable conclusions regarding the relative efficacy and safety of dapagliflozin and long-acting insulin given the uncertainties and discrepancies in the clinical evidence (high risk of bias, issues with applicability, heterogeneity and exchangeability of included studies); and,
 - the assessment of safety was limited by a lack of comparative data versus sulfonylureas, which excludes consideration of some adverse effects, such as hypoglycaemia.
- 6.24 The PBAC considered that although the indirect comparison between trials indicated non-inferiority between dapagliflozin and insulin detemir, the significant heterogeneity between studies meant that the validity of the indirect comparison

was questionable, and therefore the claim of non-inferiority between dapagliflozin and insulin detemir was uncertain.

- 6.25 The PBAC noted that the submission did not make a claim in regards to the comparative efficacy and safety of dapagliflozin versus sulfonylureas. The PBAC acknowledged that it was reasonable to assume that the addition of dapagliflozin to metformin and a DPP4 inhibitor would have some therapeutic benefit. However, the PBAC considered that there was no evidence to suggest that the benefit of metformin + dapagliflozin + a DPP4 inhibitor would be of the same magnitude as the incremental benefit of adding either dapagliflozin or a DPP4 inhibitor to metformin. The PBAC noted a number of upcoming trials which may more informative for future PBAC consideration¹.

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

Economic analysis

- 6.26 A cost-minimisation analysis of dapagliflozin versus a mixed comparator of insulin glargine and sulfonylureas was presented. However, the sponsor proposed a price (DPMQ \$57.74) for dapagliflozin equivalent to the current PBS-listed price for other indications, which is lower than the price calculated using the cost-minimisation approach (DPMQ \$[REDACTED]). The higher price calculated for dapagliflozin for this indication through the cost-minimisation analysis, compared to the current PBS price was primarily driven by the insulin component of the cost-minimisation, due to higher drug costs and claimed cost-offsets for reduced needle use, glucose test strips and diabetes education visits.
- 6.27 The PBAC considered that although the pre-PBAC response (p3) indicated that very elderly patients would be contraindicated to sulphonylureas, this did not adequately justify the 70:30 split proposed.
- 6.28 The equi-effective doses were estimated as dapagliflozin 10 mg daily and insulin glargine 50.6 IU daily. The estimates were based on a 10% Medicare sample analysis that may not be reliable due to restrictive inclusion criteria (i.e. fixed treatment sequence) that did not consider the broader PBS population, and the complex methodology that was used to calculate a mean daily dose of insulin which may not represent the dose likely to be used in practice. The PBAC considered that the methods limited the applicability of the equi-effective dose. Furthermore, the PBAC recalled that previously recommended equi-effective doses are considerably lower than the dose proposed:
- For dapagliflozin in triple oral therapy in combination with metformin and a sulfonylurea the PBAC accepted equi-effective doses of dapagliflozin 10 mg

¹ NCT02419612, NCT02551874, NCT01730534, NCT02471404

(oral) and insulin glargine 24 international units (IU) per day (Dapagliflozin PSD, March 2015).

- For dapagliflozin in combination with insulin the PBAC accepted equi-effective doses of dapagliflozin 10 mg daily and insulin glargine 26.5 IU per day (triple therapy with metformin) or 28.2 IU per day (dual therapy) (Therapeutic Relativity Sheets, April 2017).

6.29 The PBAC considered these previously recommended equi-effective doses were likely to be more reasonable estimates.

6.30 The submission did not present equi-effective doses of dapagliflozin and sulfonylureas.

6.31 A cost analysis of dapagliflozin and insulin glargine are presented in Table 5.

Table 5: Cost analysis of dapagliflozin and insulin glargine in triple therapy

Item	Unit
Drug costs	
Dapagliflozin 10 mg	\$1.57 per day
Insulin glargine (drug costs only) ^a	\$█ per day
Insulin glargine (including non-drug costs)	\$█ per day
Non-drug costs associated with insulin glargine in triple therapy	
Glucose test strip	\$0.63, 1 per day
Needles	\$0.13, 1 per day
Diabetes education	\$0.17, 1 per day

Source: Table D.2, p132 and 'Dapa add-on to MET+DPP4_SecD&E' Excel workbook of the submission

^a Insulin glargine is subject to special pricing arrangements. The submission assumed an effective ex-manufacturer price of \$█.

- 6.32 The number of test strips, needles and diabetes education visits associated with insulin glargine in triple therapy with metformin and sulfonylurea were previously accepted by the PBAC (dapagliflozin PSD, March 2015). However, the PBAC noted that, from 1 July 2016, glucose test strips are now available through the National Diabetes Service Scheme (NDSS). The average cost of test strips available through the NDSS (\$0.39 per strip) is lower than the assumed cost of \$0.63 per strip used in submission (Post-Market Review of Products Used in the Management of Diabetes July 2013). The pre-PBAC response (p4) accepted this.
- 6.33 The PBAC also noted that the cost analysis did not include any incremental costs for monitoring and managing genital and urinary tract infections due to treatment with dapagliflozin. The PBAC previously recommended that any costs associated with these adverse events should be applied to dapagliflozin in the triple oral therapy setting (dapagliflozin PSD, March 2015).
- 6.34 The submission estimated the cost of sulfonylureas from a previous PBAC consideration that recommended the listing of alogliptin as dual therapy with metformin or sulfonylurea based on a reduced price calculated as 60% of the price of DPP4 inhibitors and 40% of the price for the average daily dose of a sulfonylurea in dual therapy (alogliptin PSD, July 2013).
- 6.35 The cost of sulfonylurea was back-calculated as \$█ per day using the ex-manufacturer price of alogliptin before the price reduction (\$█ per day) and after the price reduction (\$█ per day). The dose of sulfonylurea used in triple therapy combination may be lower than the average daily dose used in dual therapy.
- 6.36 Table 6 presents the calculated price of dapagliflozin, weighted across the mixed comparator of insulin glargine and sulfonylureas using a 70:30 (insulin: sulfonylurea) ratio and estimated cost per day of insulin glargine including non-drug costs (\$█) and the estimated daily cost of sulfonylureas (\$█).

Table 6: Calculated weighted price of dapagliflozin

Product	Pack size	AEMP/unit	AEMP	DPMQ
Dapagliflozin 10 mg	28	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table D.6, p135 of the submission

Abbreviations: AEMP, ex-manufacturer price; DPMQ, dispensed price maximum quantity

Estimates in italics were calculated during the evaluation.

- 6.37 The calculated DPMQ, weighted using the estimated costs of insulin and sulfonylureas was higher than the DPMQ for current PBS-listings of dapagliflozin (\$57.74).
- 6.38 The 70:30 (insulin:sulfonylurea) weighting was derived from the 10% Medicare sample analysis based on the relative reductions in the utilisation of triple therapy regimens including insulin or sulfonylureas (in combination with a DPP4 inhibitor) between 2012 and 2016 in patients previously on metformin and a DPP4 inhibitor. The submission assumed that a decrease in relative utilisation of triple therapy regimens containing insulin or sulfonylureas was related to an increase in the relative utilisation of triple therapy regimens containing SGLT2 and DPP4 inhibitors.
- 6.39 Notwithstanding the inappropriate approach to using a mixed comparator, the PBAC considered that the 10% Medicare sample analysis was not a reliable estimate due to concerns with applicability to the broader PBS population, the use of relative changes in utilisation that may not reflect absolute market growth, and methodology used to determine persistence in therapy which may overestimate co-administration and underestimate treatment switching. The submission also did not account for the wider pool of patients in the broader triple therapy market, with dapagliflozin potentially substituting for other glucose-lowering medications (e.g. GLP-1 analogues, thiazolidinediones) as well as insulin and sulfonylurea in triple therapy regimens not initiated in a fixed sequence or via treatment switching.
- 6.40 The PBAC noted the DUSC’s advice that there were a number of additional issues with the method used to calculate the rate of substitution between insulin and sulfonylureas:
- The values used to estimate the split were from the 10% PBS sample analysis, but could not be verified from the submission.
 - This estimate relied on the percentage reductions in insulin and sulfonylurea after metformin + DPP4 inhibitor between 2012 and 2016. DUSC considered that this may be inappropriate due to rapid changes in the market over this time and potentially incomplete under co-payment prescription data in 2012.
 - The 10% PBS sample analysis method states that frequency of combination therapy that includes a potentially under co-payment prescription (ie. includes metformin or a sulfonylurea) was estimated from the frequency of these combinations in concessional patients and then extrapolated to all patients. DUSC considered concessional patients may be older and less likely to use

sulfonylurea than general patients and so this may also have impacted on the 70:30 ratio estimate, decreasing the proportion of sulfonylurea.

- the number of patients on metformin + DPP4 inhibitor + sulfonylurea in mid-2016 was approximately triple the number of patients on metformin + DPP4 inhibitor + insulin and both groups were increasing in number (Figure 4 DUSC diabetes medicines report, February 2017).

6.41 The PBAC considered that dapagliflozin added to metformin + DPP4 inhibitor dual therapy is more likely to displace a sulfonylurea than insulin.

6.42 The PBAC referred to its earlier advice that although some benefit was expected, the evidence did not suggest that the benefit of adding a third agent would be of the same magnitude as adding the same agent in the second-line setting, and it would likely be smaller. The PBAC therefore considered that it would be inappropriate for the cost of triple therapy to be at a price that represented the sum of the component parts, but rather that it should reflect this smaller incremental gain in benefit. The PBAC acknowledged a ■■■% price reduction proposed in the pre-PBAC response (p1) to the dapagliflozin with saxagliptin major submission (item 5.13 refers), but considered that this did not represent a cost-effective price. The PBAC was of the view that it may be possible to calculate a price that could be considered cost-effective if the inputs for the method to calculate the cost of treatment were adjusted to account for a lower equi-effective insulin dose, and a more appropriate split between insulin and sulfonylurea (paragraph 6.42).

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

Drug cost/patient/year: \$752.93.

6.43 At the requested DPMQ of \$57.74 for a 28 tablet pack of dapagliflozin 10 mg, the drug cost was estimated to be \$752.93 based on 13.04 scripts per patient per year. It is difficult to estimate the comparative costs of insulin glargine and sulfonylureas as the doses are variable.

Estimated PBS usage & financial implications

6.44 This submission was considered by DUSC.

6.45 The submission used a market share approach to estimate the utilisation and financial implications of listing dapagliflozin as presented in Table 7. Costs associated with insulin glargine were based on an assumed effective price (DPMQ: \$■■■■).

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients receiving triple therapy with SGLT2, 60% annual growth	█ ^a	█	█	█	█
Estimated utilisation and total costs of dapagliflozin					
Patients on dapagliflozin triple therapy (80% uptake)	█	█	█	█	█
Total PBS prescriptions (13 scripts)	█	█	█	█	█
Total cost to PBS (DPMQ \$57.74)	\$ █	\$ █	\$ █	\$ █	\$ █
Total PBS co-payments (weighted co-payment \$17.12)	\$ █	\$ █	\$ █	\$ █	\$ █
Total cost to PBS less co-payments	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated reduction in utilisation and costs of insulin glargine and sulfonylureas					
Insulin glargine scripts replaced (70% of SGLT2 triple therapy patients; █ scripts per patient)	█	█	█	█	█
Insulin glargine costs (DPMQ less co-payment)	\$ █	\$ █	\$ █	\$ █	\$ █
Sulfonylurea scripts replaced (30% of SGLT2 triple therapy patients; █ scripts per patient)	█	█	█	█	█
Sulfonylurea costs (DPMQ less co-payment)	\$ █	\$ █	\$ █	\$ █	\$ █
Total reduction in costs (DPMQ)	\$ █	\$ █	\$ █	\$ █	\$ █
Total reduction in costs (DPMQ less co-payment)	\$ █	\$ █	\$ █	\$ █	\$ █
Net financial implications of listing dapagliflozin					
Net cost to PBS (DPMQ)	\$ █	\$ █	\$ █	\$ █	\$ █
Net patient co-payments	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS less co-payments	\$ █	\$ █	\$ █	\$ █	\$ █
Non-drug cost offsets from substitution of insulin glargine	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Total cost to government	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █

Source: Section E, p136-141 and 'Dapa add-on to MET+DPP4_SecD&E' Excel workbook of the submission

Abbreviations: DPMQ, dispensed price maximum quantity; DPP4, dipeptidyl peptidase 4; SGLT2, sodium glucose transporter 2

^a Submission assumed no growth for Year 1 that was based on 2016 estimates from the 10% Medicare sample analysis.

^b Estimated based on average daily dose of sulfonylurea in dual therapy.

6.46 The redacted table shows that at year 5, the estimated number of scripts was over 200,000.

6.47 The net cost of listing dapagliflozin on the PBS was estimated to be up to less than \$10 million in the fifth year of listing, including all drug cost offsets proposed in the submission. The estimated utilisation and financial implications were highly uncertain due to the following issues raised in the evaluation:

- The estimated number of patients receiving an SGLT2 inhibitor with metformin and a DPP4 inhibitor was based on the 10% Medicare sample analysis and may not be reliable due to concerns with applicability, use of relative proportions of utilisation that may not reflect absolute market growth and persistence criteria that may overestimate co-administration and underestimate treatment

switching.

- The assumption of no growth in the SGLT2 inhibitor triple therapy market in Year 1 is likely to underestimate utilisation for that year, and to a greater extent, total utilisation in the following years.
- The utilisation of dapagliflozin is likely to be underestimated as the submission assumed dapagliflozin would only substitute for insulin glargine or sulfonylurea and did not consider dapagliflozin substitution in other relevant markets (i.e. insulin, sulfonylurea, GLP-1 analogue and thiazolidinedione regimens) or the potential for the dapagliflozin listing to contribute to the growth of the overall triple therapy market.
- The submission did not account for dapagliflozin substitution (on the PBS) in patients already receiving SGLT2 inhibitor and DPP4 inhibitor triple therapy outside of restrictions (i.e. replacing empagliflozin and dapagliflozin leakage use).
- The submission's estimates only included patients previously receiving therapy with metformin and a DPP4 inhibitor, with subsequent addition of dapagliflozin that did not account for the substantial proportion of patients likely to receive the same combination therapy through other pathways (e.g. treatment switching).
- The cost savings were likely to be overestimates, driven by the assumption that 100% of dapagliflozin use is substituting for insulin glargine (70%) and sulfonylureas (30%) based on the 10% Medicare sample analysis showing relative reductions in proportions of utilisation that may not reflect increasing use of triple therapy regimens (overall market growth) indicated by total script numbers.
- It was unclear whether the number of insulin glargine scripts per year of [REDACTED] was reliable as it was calculated based on proposed equi-effective doses of insulin glargine and dapagliflozin that was inadequately justified in the submission.

6.48 The PBAC noted the DUSC's concern that the estimates presented in the submission were substantially underestimated. The DUSC considered the main issues to be:

- the submission only considered one pathway to metformin + DPP4 inhibitor + dapagliflozin triple therapy (ie. adding dapagliflozin to metformin + DPP4 inhibitor dual therapy). DUSC considered that this triple therapy regimen will be reached via additional pathways in clinical practice; and
- DUSC expects the proposed listing will grow the current metformin + DPP4 inhibitor + SGLT2 inhibitor market. The submission estimate for Year 1 is based on only 80% of the current off-restriction SGLT2 inhibitor added to metformin + DPP-4 inhibitor market transitioning to PBS supply and does not account for any new patients using this regimen.
- cost-offsets are overestimated as they assume dapagliflozin will substitute for insulin glargine (70%) or sulfonylureas (30%). DUSC considered that dapagliflozin will more often substitute for a less expensive alternative than insulin.

- 6.49 The PBAC acknowledged the pre-PBAC response (p2) provided revised patient estimates for total dapagliflozin new triple therapy from [REDACTED] to [REDACTED] in year five, which included initiations and switching reached via additional treatment pathways. However, the PBAC noted that these estimates were still lower than what DUSC proposed, and considered they remained an underestimate.
- 6.50 The PBAC noted that in the context of high potential market growth and uptake, a risk sharing arrangement with the sponsor may be required, but that this concern could also be potentially addressed through an appropriate price.

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

Quality Use of Medicines

- 6.51 No quality use of medicines issues were identified in the submission. However, there may be potential issues associated with concurrent prescribing of similar glucose-lowering drugs with the increasing number and different combinations of fixed-dose combinations for type 2 diabetes available (e.g. an SGLT2 inhibitor and an FDC containing an SGLT2 inhibitor).
- 6.52 DUSC considered that the submission did not consider the additional PBS costs due to safety issues with dapagliflozin (eg. treating urogenital infection).

7 PBAC Outcome

- 7.1 The PBAC deferred making a decision regarding the Authority Required (STREAMLINED) listing for dapagliflozin for the treatment of type 2 diabetes, in combination with metformin and a dipeptidyl peptidase-4 (DPP4) inhibitor, to allow further work to establish a price for the triple therapy that could be considered cost-effective.
- 7.2 The PBAC considered the claim of non-inferior effectiveness and safety between dapagliflozin and insulin glargine in combination with metformin and a DP4 inhibitor was not adequately justified. The PBAC considered that the indirect comparison had a number of issues that limited the ability to assess non-inferiority including heterogeneity, applicability and exchangeability issues, and large differences in the magnitude of effect between the common reference arms. The PBAC also noted that the search strategy used may have inappropriately excluded other sequences as the trials were selected based on a fixed treatment sequence that does not accurately represent the options in clinical practice. In addition, the PBAC noted that while there may be some plausible benefits of dapagliflozin over sulfonylureas with regard to hypoglycaemia and weight gain, the submission did not present any data relating to the comparative safety or efficacy of dapagliflozin compared to sulfonylureas.

- 7.3 The PBAC acknowledged that it was reasonable to assume that the addition of dapagliflozin to metformin and a DPP4 inhibitor would have some therapeutic benefit. However, the PBAC considered that the evidence did not suggest that the benefit of metformin + dapagliflozin + a DPP4 inhibitor would be of the same magnitude as the incremental benefit of adding either dapagliflozin or a DPP4 inhibitor to metformin.
- 7.4 The PBAC also noted that there are a number of clinical trials underway that would provide valuable direct comparative data in the proposed treatment area. The PBAC therefore advised that if an agreement on a cost-effective price cannot be reached on the basis of the parameters outlined in this recommendation, no further submissions with respect to this requested listing should be made until the new clinical data becomes available for consideration.
- 7.5 The PBAC considered that the cost-minimisation approach, based on a 70:30 split between insulin and sulfonylureas, was inappropriate. The PBAC noted the issues with the analysis of the 10% Medicare sample raised by DUSC (paragraph 6.42), which meant that the estimates were unreliable. Further, the PBAC noted that the number of patients on metformin + DPP4 inhibitor + sulfonylurea in mid-2016 was approximately triple the number of patients on metformin + DPP4 inhibitor + insulin, which indicated that dapagliflozin added to metformin + DPP4 inhibitor is more likely to displace a sulfonylurea than insulin.
- 7.6 The PBAC also considered that the nominated equi-effective doses of dapagliflozin 10 mg daily (in combination with a DPP4 and metformin) and insulin glargine 50.6 IU daily (in combination with metformin) were unreasonably high. The PBAC recalled that relevant equi-effective doses previously recommended for other triple therapies were significantly lower (between 24 and 26.5 IU), and likely to be more appropriate. The PBAC also noted that cost-offsets applied for diabetes test strips were too high.
- 7.7 The PBAC noted that the cost-minimisation approach outlined above was used to justify the proposed price, which is the same as the current PBS subsidy for dapagliflozin on the PBS. However, the PBAC was of the view that because the addition of dapagliflozin to metformin + a DPP4 inhibitor was unlikely to have the same magnitude of effect dapagliflozin or a DPP4 inhibitor added to metformin alone, it would not be cost-effective for this treatment to be at the same price as the sum of the component parts.
- 7.8 The PBAC also considered that the financial estimates provided in the submission and the revised estimates in the pre-PBAC response remained an underestimate. The PBAC noted the DUSC advice that the submission excluded patients because it did not consider all pathways that potential patients may take to this combination; the submission did not take into account the potential for this listing to grow the market; and the cost-offsets were overestimated.

- 7.9 The PBAC acknowledged that the current PBS listings for diabetes medicines were confusing and difficult to interpret. The PBAC therefore recommended that it may be appropriate to develop a General Statement for PBS listed medicines to treat type 2 diabetes.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.