5.13 DAPAGLIFLOZIN/SAXAGLIPTIN, Fixed dose combination tablet 10 mg/5 mg, Qtern®, AstraZeneca

1 Purpose of Application

1.1 Authority required (STREAMLINED) listing for dapagliflozin/saxagliptin fixed dose combination (FDC) for treatment of type 2 diabetes in patients previously treated with a PBS-subsidised regimen of oral diabetic medicines including metformin plus any dipeptidyl peptidase 4 (DPP4) inhibitor.

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

Component	Description
Population	Adults with type 2 diabetes who do not achieve glycaemic control on a dual therapy of metformin and any DPP4 inhibitor
Intervention	Dapagliflozin/saxagliptin 10 mg/5 mg fixed dose combination tablet for use in combination with metformin
Comparator	Individual components of dapagliflozin 10 mg and saxagliptin 5 mg
Outcomes	Bioequivalence based on pharmacokinetic parameters (e.g. C_{max}, AUC)
Clinical claim	Dapagliflozin/saxagliptin FDC is bioequivalent to the individual components taken concomitantly

Abbreviations: AUC, area under the curve; Cmax, maximum serum concentration; DDP4, dipeptidyl peptidase-4
Source: Compiled during the evaluation

1.2 There was an issue with the clinical management proposed in the submission (fixed sequence of treatment with metformin and DPP4 inhibitor and then adding dapagliflozin).

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.

2.2

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DAPAGLIFLOZIN / SAXAGLIPTIN				QTERN® AstraZeneca
Tablet, 10 mg / 5 mg	28	5	$[redacted]	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives

Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	The treatment must be in combination with metformin. AND Patient must have previously ~~received and~~ been stabilised on ~~a PBS subsidised regimen of oral diabetic medicines~~ *dual oral therapy* which includes ~~any~~ *a* dipeptidyl peptidase 4 inhibitor (gliptin) *OR* *Patient must have previously been stabilised on dual oral therapy which includes a sodium-glucose co-transporter 2 (SGLT2) inhibitor,* *AND* Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of *triple oral therapy with* a gliptin, ~~a thiazolidinedione (glitazone), a glucogon-like peptide-1 or~~ *and* a ~~sodium-glucose co-transporter 2~~(SGLT2~~)~~ inhibitor ~~despite treatment with optimal doses of dual oral therapy~~; OR Paitents 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, ~~a glitazone, a glucagon-like peptide-1 or~~ and an SGLT2 *inhibitor* ~~despite treatment with optimal doses of dual therapy~~.
Prescriber Instructions	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 *triple oral therapy* with a gliptin, ~~or~~ *and* an SGLT2 inhibitor is initiated. The HbA1c must be no more than 4 months old at the time ~~with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated~~ *triple oral therapy with a gliptin and a SGLT2 inhibitor was initiated*. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (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. The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of ~~treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor~~ *triple oral therapy with a gliptin and an SGLT2 inhibitor*, must be document*ed* in the patient's medical records. A patient whose diabetes was previously demonstrated unable to be controlled with metformin *and an SGLT2 or glptin* does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.

Administrative Advice	**Note:** **Continuing Therapy Only:** 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. **Note:** The fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone) or a glucogaon-like peptide-1. PBS subsidised dual oral therapy does not include concomitant use of a gliptin or an SGLT2 inhibitor with a glitazone.

2.3 Listing was requested on a cost-minimisation basis compared with corresponding doses of the individual components, dapagliflozin and saxagliptin. The requested restriction is dependent on the concurrent major submission for dapagliflozin triple therapy being recommended for listing at the July 2017 PBAC meeting (item 6.01 refers).

2.4 The proposed restriction inappropriately limits the use of dapagliflozin/saxagliptin fixed dose combination to patients previously receiving metformin and a DPP4 inhibitor dual therapy, which inappropriately limits the treatment pathways compared to currently accepted clinical guidelines and practice.

2.5 The PBAC noted that the wording of the clinical criteria is not consistent with the requested restriction in the July 2017 dapagliflozin major submission. There is potential for the requested restriction to allow use of the dapagliflozin/saxagliptin FDC after any prior use of a PBS subsidised regimen of oral diabetic medicines which includes any dipeptidyl peptidase (DPP4) 4 inhibitor, and not immediately following such a regimen. The prescriber instructions inappropriately suggest that a patient whose diabetes was previously demonstrated unable to be controlled with metformin does not need to requalify on this criterion before being eligible for PBS subsidised treatment with this fixed dose combination.

2.6 Dapagliflozin/saxagliptin FDC is administered as one 10 mg/5 mg dose oral tablet, once daily, with treatment ongoing.

2.7 The PBAC noted that the proposed restriction assumed all DPP4 inhibitors are interchangeable. The PBAC also noted that as with the wording of the proposed restriction in item 6.01, quadruple therapy may not be excluded.

2.8 The pre-PBAC response (p1) acknowledged and supported the proposed changes as suggested by the Secretariat. The sponsor also supported the proposal for a General Statement for PBS-listed type two diabetes medicines to be developed. The PBAC noted that a draft general statement for medicines used to treat type 2 diabetes was provided in the pre-PBAC response for item 6.01 (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: dapagliflozin/saxagliptin FDC was TGA registered on 25 October 2016 as an adjunct to diet and exercise, in combination with metformin, to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and dapagliflozin is appropriate.

3.2 Dapagliflozin/saxagliptin FDC has not been previously considered by the PBAC. Treatment regimens including both a SGLT2 inhibitor and a DPP4 inhibitor are not permitted under current PBS restrictions.

3.3 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;
- Dapagliflozin/saxagliptin FDC (this submission); and
- Dapagliflozin/metformin XR FDC (minor submission).

4 Population and disease

4.1 Adults with type 2 diabetes in combination with metformin who do not achieve glycaemic control on a dual therapy of metformin and any DPP4 inhibitor.

4.2 The submission positioned dapagliflozin/saxagliptin FDC as a third-line treatment option for patients whose type 2 diabetes remains uncontrolled despite treatment with metformin and a DPP4 inhibitor.

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

5 Comparator

5.1 The submission nominated corresponding doses of the individual components of dapagliflozin and saxagliptin. The PBAC considered that this was an appropriate comparator. However, the use of dapagliflozin and a DPP4 inhibitor in combination with metformin has not yet been recommended for listing on the PBS. The PBAC noted that it deferred the submission to the July 2017 meeting requesting the listing of dapagliflozin for use in triple oral therapy in combination with a DPP4 inhibitor and metformin and therefore cost-effectiveness of use in this setting has not been established (item 6.01 refers).

5.2 The submission argued that the dapagliflozin/saxagliptin FDC is unlikely to replace a metformin/DPP4 inhibitor FDC due to the complexity of transitioning a patient from

one FDC to another. However, there is a potential financial advantage for General beneficiary patients to move from an FDC containing metformin to dapagliflozin/saxagliptin FDC (individually priced above the General patient copayment).

5.3 The Pre-Sub-Committee Response (PSCR, p1) maintained the view that patients taking an existing fixed dose combination of metformin and a DPP4 inhibitor would not transition to a dapagliflozin/saxaglitpin FDC as it would involve stopping the original FDC, starting metformin monotherapy and adding the new FDC, and that this would be a complex transition which would limit its uptake.

5.4 The PBAC disagreed with the sponsor's claim, because dapagliflozin and saxagliptin are fixed doses, whereas metformin needs to be titrated. The PBAC noted ESC's advice that titrating metformin can be difficult. Further, the ESC advised that use of the dapagliflozin/saxagliptin FDC rather than the metformin FDCs would potentially allow greater flexibility in metformin titration, which is often difficult in clinical practice, and that the process of switching FDCs would be much less complicated than co-prescribing single metformin with a metformin combination product. This preference was also evident in the DUSC review where there was a comparatively high frequency of single metformin with metformin combination product co-prescription (Table 10, DUSC Diabetes Public Release Document, February 2017).

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 was based on one bioequivalence study comparing dapagliflozin/ saxagliptin 10 mg/5 mg or 5 mg/2.5 mg FDC tablets to corresponding doses of the individual components of dapagliflozin and saxagliptin (n=72). Only data from the cohort administered the 10 mg/5 mg dose strength were included in the submission because only the 10 mg/5 mg dose strength is registered for this indication. Supplementary efficacy data were presented from key dapagliflozin triple therapy trials, Study 129 and Study 10.

6.4 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
Bioequivalence studies		
Study 341 [cohort 2]	A bioequivalence study of 2.5 mg saxagliptin/5 mg dapagliflozin and 5 mg saxagliptin/10 mg dapagliflozin fixed dose combination tablets relative to administration of their respective individual components in healthy subjects and a characterization of the effect of food on the fixed dose combination tablets. NCT02060201	Internal study report, October 2014
	Vakkalagadda B, Vetter ML, Rana J, et al. Bioequivalence of saxagliptin/dapagliflozin fixed dose combination tablets compared with coadministration of the individual tablets to healthy subjects.	Pharmacology Research and Perspectives 2015; 3(6): e00201, doi: 10.1002/prp2.201.
Supplementary randomised trials		
Study 129	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. NCT01646320	Internal study report, December 2014
	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 [stratum 2]	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 DPP 4 inhibitor (sitagliptin) alone or in combination with metformin; report for the 24 week short term treatment period. NCT00984867	Internal study report, December 2011
	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.

Source: Table 2, p8 of the submission.

6.5 The key features of the randomised trials are summarised in the table below.

Table 3: Key features of the included evidence, dapagliflozin/saxagliptin FDC vs. individual components

Trial	N	Design/duration of follow-up	Risk of bias	Patient population	Outcome(s)
Study 341	72	Randomised, open label, crossover study Single dose for each treatment group	Low	Healthy adults	Bioequivalence (AUC, C_{max})
Study 129	320	Randomised, double blind, placebo controlled, parallel group, multicentre study 24 weeks plus extension	Low	Adults with type 2 diabetes w/ inadequate glycaemic control on metformin + saxagliptin	Change from baseline to week 24 in HbA1c
Study 10	447	Randomised, double blind, placebo controlled, parallel group, multicentre study 24 weeks plus extension	Low	Adults with type 2 diabetes w/ inadequate glycaemic control on metformin + sitagliptin	Change from baseline to week 24 in HbA1c

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; HbA1c, glycosylated haemoglobin.
Source: compiled during the evaluation

6.6 Of the doses included in Study 341, only the 10 mg/5 mg dose strength is TGA registered in Australia, therefore only data from this cohort (n=36) was included in the submission. Study 10 was a placebo-controlled trial consisting of two strata, assessing the efficacy and safety of dapagliflozin as add-on therapy to sitagliptin monotherapy (stratum 1) and dapagliflozin as add-on therapy to metformin and sitagliptin dual therapy (stratum 2). The submission appropriately included stratum 2 only as stratum 1 (dual therapy) was not applicable to patients eligible for dapagliflozin under the requested restriction.

6.7 The results of the bioequivalence Study 341 are presented in Table 4.

Table 4: Bioequivalence of dapagliflozin/saxagliptin 10 mg/5 mg FDC to individual components

Trial	Adjusted Geometric Mean Ratio (90% CI)		
	AUC_{INF} (ng.h/mL)	**C_{max} (ng/mL)**	**AUC_{0-T} (ng.h/mL)**
Study 341 (10 mg/5 mg FDC vs individual components, fasted state)			
Dapagliflozin	1.035 (1.008, 1.063)	0.946 (0.878, 1.019)	1.036 (1.010, 1.062)
Saxagliptin	1.003 (0.969, 1.038)	1.059 (0.993, 1.129)	1.007 (0.973, 1.042)
Study 341 (FDC fed state vs FDC fasted state)			
Dapagliflozin	0.943 (0.919, 0.968)	0.648 (0.565, 0.743)	0.931 (0.908, 0.955)
Saxagliptin	1.155 (1.118, 1.194)	0.925 (0.837, 1.022)	1.155 (1.117, 1.194)

Abbreviations: AUC, area under the curve; CI, confidence intervals; C_{max}, peak serum concentration; DAPA, dapagliflozin; FDC, fixed dose combination; SAXA, saxagliptin
Source: Table 4, pp9-10 of the submission

6.8 The fixed dose combinations in Study 341 met the pre-specified bioequivalence margins against the individual components, with 90% CIs of the geometric mean ratios for the FDC compared to the individual components contained within the criterion interval of (0.80, 1.25). The TGA delegate assessed bioequivalence and

considered that it had been demonstrated for the FDC tablets and the co-administered individual components.

6.9 Supportive efficacy data from the randomised trials, Study 129 and Study 10, were presented for the primary outcome, mean change in HbA1c from baseline to Week 24. The results are summarised in Table 5. Detailed evaluation of these randomised trial data were conducted as part of the PBAC consideration for the concurrent major submission on dapagliflozin (item 6.01 refers).

Table 5: Results of mean change in HbA1c from baseline across randomised trials

Treatment group	Baseline HbA1c, mean (SD) %	Week 24 HbA1c, mean (SD) %	Adj. change from baseline, mean (SD)	Difference in adj. change, mean (95% CI)
Study 129				
MET+SAXA+DAPA (n=160)	8.24 (0.97)	7.36 (0.94)	-0.82 (0.88)	-0.72 (-0.91, -0.53)
MET+SAXA+PBO (n=160)	8.16 (0.99)	7.91 (1.05)	-0.10 (0.88)	
Study 10 [stratum 2]				
MET+SITA+DAPA (n=113)	7.80 (0.81)	7.38 (0.73)	-0.43 (0.64)	-0.40 (-0.58, -0.23)
MET+SITA+PBO (n=113)	7.87 (0.75)	7.84 (1.05)	-0.02 (0.64)	
Pooled results (weighted mean difference) I^2=82%				-0.56 (-0.86, -0.26)

Abbreviations: adj., adjusted; CI, confidence interval; DAPA, dapagliflozin; HbA1c, glycosylated haemoglobin; MET, metformin; PBO, placebo; SAXA, saxagliptin; SD, standard deviation; SITA, sitagliptin
Source: Table 5, p11 of the submission

6.10 Dapagliflozin add-on to metformin and a DPP4 inhibitor resulted in statistically significant reductions in HbA1c compared with placebo over 24 weeks of treatment. The PBAC noted that the pooled results were significantly heterogeneous given the difference in treatment effect and baseline characteristics between the two studies, and must therefore be interpreted with caution.

6.11 The PBAC noted that the submission did not explore the additive benefit of saxagliptin added to metformin and dapagliflozin. The submission also did not consider the benefit of dapagliflozin + saxagliptin + metformin over any other triple therapy combination, as it is relying on the related submission for dapagliflozin (item 6.01 refers).

Comparative harms

6.12 The FDC tablet and the individual components administered concurrently were generally safe and well tolerated by the healthy subjects in Study 341. There were no deaths or serious adverse events during the study, and no subjects discontinued due to an adverse event. Nine subjects (25%) from the 10 mg/5 mg dose cohort reported an adverse event during the study, all of which were considered treatment-relevant. The most frequently reported adverse event was nausea (4 subjects, 11.1%). The submission stated that a full assessment of comparative harms when dapagliflozin is added on to metformin and a DPP4 inhibitor was presented in the July 2017 dapagliflozin triple therapy major submission (item 6.01 refers).

Clinical claim

6.13 The submission described dapagliflozin/saxagliptin FDC as bioequivalent to the individual components taken concomitantly. The PBAC considered that this claim was adequately supported. The TGA delegate assessed bioequivalence and considered that it had been demonstrated.

6.14 However, the PBAC noted that the individual components are not currently PBS listed for use in combination with metformin, and therefore the relevance of this clinical claim is dependent on the clinical claim in the related dapagliflozin submission (item 6.01 refers) being accepted. The PBAC noted that they considered that the clinical claim in item 6.01 was uncertain.

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

Economic analysis

6.15 A cost-minimisation analysis was presented. The equi-effective doses were estimated as dapagliflozin/saxagliptin 10 mg/5 mg FDC once daily and individual components of dapagliflozin 10mg and saxagliptin 5 mg, once daily.

6.16 The cost-effectiveness of treatment with dapagliflozin, saxagliptin and metformin was dependent on consideration the July 2017 dapagliflozin major submission. The PBAC noted that they deferred this submission on the basis that cost-effectiveness had not been established.

6.17 The PBAC noted that with respect to the concurrent dapagliflozin submission, it 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. Therefore, the PBAC was of the view that it would not be cost-effective for dapagliflozin + a DPP4 inhibitor + metformin treatment to be at the same price as the sum of the component parts. The PBAC considered that this was also the case for this submission.

6.18 The PBAC acknowledged that the pre-PBAC response (p1) offered a [redacted]% price reduction to the AEMP of dapagliflozin with saxagliptin FDC (from $85.86 per pack to $[redacted] per pack of 28 tablets). However, the PBAC did not consider that this represented a price that could be considered cost-effective.

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

Drug cost/patient/year: $[redacted].

6.19 At the requested DPMQ of $[redacted] for a 28 tablet pack of dapagliflozin/saxagliptin FDC, the drug cost per year was estimated to be $[redacted] for a single patient (assuming 13 scripts per year). The equivalent cost per patient per year for treatment with the individual components of dapagliflozin and saxagliptin is $[redacted]. Treatment is ongoing. The PBAC noted that the pre-PBAC response (p1)

offered a [redacted]% price reduction on the AEMP, which would also result in a reduction to the cost per patient.

Estimated PBS usage & financial implications

6.20 This submission was considered by DUSC. The submission used a market share approach to estimate utilisation and financial implications of listing dapagliflozin/ saxagliptin FDC, with the assumption that the other concurrent dapagliflozin submissions receive a positive recommendation for listing at the same time as dapagliflozin/saxagliptin FDC.

6.21 Table 6 presents the estimated use and financial implications calculated in the submission.

Table 6: Estimated utilisation and costs of listing dapagliflozin/saxagliptin FDC

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated utilisation and total costs of DAPA/SAXA FDC					
Patients receiving triple therapy with SGLT2, 60% annual growth	[redacted] [a]	[redacted]	[redacted]	[redacted]	[redacted]
Total estimated patients with DAPA add-on to MET+DPP4 (80% uptake)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual component share of MET+DPP4 market (32%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of DAPA/SAXA FDC from individual component MET+DPP4 (10%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total DAPA/SAXA FDC prescriptions (assuming 13/patient/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost (DPMQ) DAPA/SAXA FDC	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total patient co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost DAPA/SAXA FDC (DPMQ less co-payments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated reduction in utilisation and costs of other medicines					
DAPA scripts replaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAPA costs (DPMQ less co-pay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
SAXA scripts replaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAXA costs (DPMQ less co-pay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total reduction in costs (DPMQ)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total reduction in costs (DPMQ less co-pay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications of listing dapagliflozin/saxagliptin FDC					
DAPA/SAXA FDC (DPMQ)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
DAPA/SAXA FDC (DPMQ less co-pay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] [redacted]

Abbreviations: DAPA, dapagliflozin; DPMQ, dispensed price for maximum quantity; FDC, fixed dose combination; SAXA, saxagliptin
Source: Table 7, p14 of the submission.

6.22 The redacted table above shows the number of prescriptions and net cost of listing dapagliflozin/saxagliptin FDC on the PBS was estimated to be 10,000 – 50,000 scripts and less than $10 million in the fifth year of listing. The submission's estimates of utilisation and financial implications were uncertain and likely underestimated for the following reasons identified during the evaluation:

- The estimated number of patients receiving an SGLT2 inhibitor in combination with metformin and a DPP4 inhibitor was based on the 10% Medicare sample analysis, which was poorly documented, with no capacity to check calculations. There was limited information explaining the derivation of estimates used in the submission's calculations.
- The submission used 2016 estimates for the SGLT2 inhibitor triple therapy market and assumed no growth in Year 1. The assumption was inadequately justified and was likely to underestimate utilisation for that year, and to a greater extent, total utilisation in the following years.
- Although consistent with the requested restriction, the submission's estimates of eligible patients only included those initially receiving dual therapy metformin and a DPP4 inhibitor, with subsequent addition of dapagliflozin. This approach was likely to underestimate the use of dapagliflozin as the submission did not account for the substantial proportion of patients likely to receive the same combination therapy through other pathways (e.g. treatment switching).
- The [redacted]% annual growth of the SGLT2 inhibitor triple therapy market and [redacted]% yearly uptake of dapagliflozin were assumed in the submission;
- Uptake was limited to patients who had been previously treated with individual components (and not fixed dose combinations) of metformin and a DPP4 inhibitor, and only [redacted]% of these patients were assumed to move to dapagliflozin/saxagliptin FDC when commencing triple therapy.
- The submission did not consider the potential financial advantage for General beneficiary patients to move from an FDC containing metformin to dapagliflozin/saxagliptin FDC (individually priced above the General patient copayment). There is a potential for differential market growth in the General and Concessional patient groups.

6.23 The PBAC noted the DUSC advice that the estimates presented in the submission were underestimated. The DUSC considered that the main sources of the submission's underestimate of utilisation were;

- not accounting for the requested restriction having a broader eligible patient population than the restriction in the dapagliflozin major submission; and
- assuming that no patients on metformin/DPP4 FDC therapy would switch to the dapagliflozin/saxagliptin FDC because of the complexity of the transition. This did not take into account the patient's financial incentive to make this transition.

6.24 The PBAC noted that updated estimates were provided in the pre-PBAC response, but considered that the patient estimates and the financial implications remained underestimated.

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

Quality Use of Medicines

6.25 The PBAC noted that the sponsor proposed an education program for health professionals and patients, to ensure that prescribers are aware that the FDC consists of a SGLT2 inhibitor and a DPP4 inhibitor to avoid concurrent prescribing of these medicines; and to ensure use in the appropriate population.

6.26 The PBAC considered this is appropriate. The PBAC also noted that this option provides a combination product for two drugs that have fixed dosing, which would simplify the treatment regime and provide flexibility in metformin titration. The PBAC noted that this could potentially reduce confusion and risk of metformin overdose.

6.27 The PBAC also noted that the listing of a SGLT2 inhibitor + DPP4 inhibitor FDC may increase the use of this combination therapy as dual therapy (ie. without metformin), which is outside of PBS restrictions, either in patients likely to have been treated with other diabetes medicines or in those patients who might not otherwise have been treated.

Financial Management – Risk Sharing Arrangements

6.28 The sponsor acknowledged that a Risk Share Arrangement may be required but did not provide a proposal.

6.29 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 is concern could also be potentially addressed through an appropriate price reduction.

7 PBAC Outcome

7.1 The PBAC deferred making a decision regarding the Authority Required (STREAMLINED) listing for dapagliflozin/saxagliptin fixed dose combination (FDC) for treatment of type 2 diabetes in combination with metformin, to allow further work to establish a price for the triple therapy that could be considered cost-effective.

7.2 The PBAC considered the nominated comparators as the individual components of FDC, dapagliflozin and saxagliptin, were appropriate. However, the component parts are not currently PBS listed for triple oral therapy in combination with metformin. Therefore, the clinical claim and the comparators in this submission were dependent on the outcome for the request to list dapagliflozin in triple oral therapy with metformin and a DPP4 inhibitor (item 6.01 refers). The PBAC noted that they deferred the submission requesting this listing (item 6.01, July 2017 PBAC meeting) and therefore the cost-effectiveness of treatment in this setting had not yet been established.

7.3 In deferring its decision relating to dapagliflozin in triple therapy with metformin and a DPP4 inhibitor (item 6.01, July 2017 PBAC meeting), the PBAC considered the claim

of non-inferior effectiveness and safety between dapagliflozin and the comparators were not adequately addressed. While the PBAC acknowledged that it may be reasonable that this triple therapy would have some therapeutic benefit, 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. Therefore, the PBAC was of the view that it would not be cost-effective for dapagliflozin + a DPP4 + metformin treatment to be at the same price as the sum of the component parts. The PBAC considered that this was also the case for this submission. Although the PBAC acknowledged that the pre-PBAC response offered a [redacted]% price reduction on the dapagliflozin + saxagliptin FDC, it did not consider that this represented a cost-effective price. The PBAC therefore deferred the submission in order to establish a cost-effective price for dapagliflozin + a DPP4 + metformin in the treatment of type 2 diabetes.

7.4 The PBAC considered that although the pre-PBAC response offered a price reduction, the financial impact was still likely to be underestimated. The PBAC agreed with the DUSC's view that the estimates provided in the submission were an underestimate because it excluded patients likely to receive the same combination therapy through other pathways, as well as patients who would switch from other FDCs in order to access metformin as a single component under the co-payment.

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.