6.08 DAPAGLIFLOZIN WITH METFORMIN
Tablet containing 10 mg dapagliflozin with 1000 mg metformin XR, tablet containing 10 mg dapagliflozin with 500 mg metformin XR, tablet containing 5 mg dapagliflozin with 1000 mg metformin XR, XIGDUO® XR, AstraZeneca Pty Ltd

1 Purpose of Application

1.1 The minor submission requested an Authority Required (STREAMLINED) listing for dapagliflozin and metformin (XIGDUO® XR) fixed dose combination (FDC) for the treatment of type 2 diabetes mellitus (T2DM) in combination with any dipeptidyl peptidase 4 (DPP4) inhibitor on a cost-minimisation basis to the individual components of the FDC, dapagliflozin and metformin, taken concomitantly.

2 Requested listing

2.1 Suggestions and additions on the requested restriction are indicated in italics, and strikethrough for deletions.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
DAPAGLIFLOZIN/ METFORMIN tablet, 10 mg/1000 mg	28	5	$59.25	XIGDUO® XR	AstraZeneca
DAPAGLIFLOZIN/ METFORMIN tablet, 10 mg/500 mg	28	5	$58.49		
DAPAGLIFLOZIN/ METFORMIN tablet, 5 mg/1000 mg	28	5	$60.65		

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 ~~any~~ *a* dipeptidyl peptidase~~-~~ 4 inhibitor (gliptin), AND Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a ~~dipeptidyl peptidase 4 inhibitor~~ (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 Patients 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 treatment* 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~~, a glitazone, a glucagon-like peptide-1 or~~ *and* an SGLT2 inhibitor is initiated. The HbA1c must be no more than 4 months old at the time *triple oral therapy* with a gliptin~~, a glitazone, a glucagon-like peptide-1 or~~ *and* an 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 *triple oral therapy* ~~treatment~~ with a gliptin~~, a glitazone, a glucagon-like peptide-1 or~~ *and* an SGLT2 inhibitor, must be document in the patient's medical records. A patient whose diabetes was previously demonstrated unable to be controlled with metformin ~~or~~ *and* a gliptin *or an SGLT2 inhibitor* does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.

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 glucagon-like peptide-1. PBS subsidised dual oral therapy does not include concomitant use of a gliptin or an SGLT2 inhibitor with a glitazone.

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

3 Background

3.1 Dapagliflozin with metformin XR FDC is TGA indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both dapagliflozin and metformin is appropriate. The FDC is currently listed on PBS for dual therapy and triple therapy in combination with sulfonylurea and/or insulin.

3.2 The approved PI of dapagliflozin with metformin XR FDC was updated to include triple oral therapy in combination with a DPP4 inhibitor on 25 October 2016.

3.3 The proposed restriction was not considered by PBAC previously.

4 Population and disease

4.1 The submission proposed that triple therapy with dapagliflozin + a DPP4 inhibitor + metformin is required when treatment with metformin and a DPP4 inhibitor do not provide adequate glycaemic control for type 2 diabetes.

4.2 The proposed clinical place in therapy for the FDC is third line treatment for T2DM.

5 Comparator

5.1 The minor submission nominated the co-administered individual components of the FDC, dapagliflozin and metformin, as the main comparators.

5.2 While the PBAC considered that the comparator was appropriate, the component parts are not currently PBS listed for triple oral therapy in combination with a DPP4 inhibitor and therefore cost-effectiveness of use in this setting has not been established. The appropriateness of this comparator was dependent on the PBAC considering the use of dapagliflozin in triple oral therapy with metformin and a DPP4 inhibitor to be cost-effective. The PBAC noted that it deferred the submission requesting the listing of dapagliflozin for use in triple oral therapy in combination with a DPP4 inhibitor and metformin (6.01, Dapagliflozin July 2017 PBAC Public Summary Document (PSD) refers).

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 Study 129 and Study 10. Both trials provided 24-week efficacy data comparing dapagliflozin add-on to metformin and a DPP4 inhibitor to placebo add-on to metformin and a DPP4 inhibitor. These studies were also presented in the dapagliflozin major submission and analysed as part of the evaluation of that submission (item 6.01, July 2017 PSD refers). The PBAC previously recommended the listing of saxagliptin with metformin FDC on the basis of bioequivalence to the component parts, as assessed by the TGA (July 2014 Public Summary Document).

Economic analysis

6.4 As a minor submission, an economic comparison was not provided.

6.5 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.

Drug cost/patient/ year: $760.37 to $788.45.

6.6 This is a lifetime treatment. Assuming 13 scripts per year for a single patient, the drug costs per year were estimated (Table 1).

Table 1: Drug cost / patient / year

Strength	DPMQ	Cost per year	Sensitivity analysis
Dapagliflozin 10 mg + metformin XR 1,000 mg	$59.25	$770.25	$651.75
Dapagliflozin 10 mg + metformin XR 500 mg	$58.49	$760.37	$643.39
Dapagliflozin 5 mg + metformin XR 1,000 mg	$60.65	$788.45	$667.15

*Sensitivity analysis was completed on 11 scripts per year
Source: Table 5, page 13 of the submission

Estimated PBS usage & financial implications

6.7 The minor submission estimated a net save to the PBS of less than $10 million in Year 5 of listing, with a total net save to the PBS of less than $10 million over the first 5 years of listing as a result of a lower cost per patient of the FDC over the component parts. This is summarised in Table 2.

6.8 The submission assumed that the uptake of the drug will be low because of the complexity associated with adding the FDC into the treatment regimen.

6.9 The PBAC acknowledged that the pre-PBAC response (p2) provided revised patient numbers. However, the PBAC noted the concerns raised by the DUSC with respect to the related submissions (5.13, saxagliptin with dapagliflozin and 6.01 PSDs refer), and therefore considered that the utilisation and financial implications for this submission remained uncertain.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Total estimated DAPA add-on to MET+DPP4 patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total estimated dapagliflozin add-on to MET+DPP4 prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual component share of MET+DPP4 market, %	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
XIGDUO XR share of DAPA add-on to MET+DPP4 market, %	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
XIGDUO XR patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XIGDUO XR prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of XIGDUO XR prescriptions (less co-payments)					
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost of prescriptions to be replaced by XIGDUO XR (less co-payments)					
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications of listing XIGDUO XR					
Cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

Abbreviations: DAPA – dapagliflozin; DPP4 –dipeptidyl peptidase 4 inhibitor; FDC – fixed dose combination; MET – metformin.
Source: XIGDUO XR add-on to MET+DPP4_SecD&E.xlsx, page 15 of the submission

6.10 The redacted table above shows that at year 5 the number of prescriptions was 10,000 – 50,000 and would be a modest net save to the PBS.

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

7 PBAC Outcome

7.1 The PBAC deferred making a decision regarding the Authority Required (STREAMLINED) listing for dapagliflozin and metformin fixed dose combination (FDC) in combination with a dipeptidyl peptidase 4 (DPP4) inhibitor for the treatment of type 2 diabetes mellitus (T2DM) in patients who are uncontrolled on dual oral therapy. The PBAC considered that further work was required to establish a price for treatment with dapagliflozin + a DPP4 inhibitor + metformin that could be considered cost-effective.

7.2 The PBAC noted, similar to the concurrent submissions to the July 2017 PBAC meeting (items 5.13 and 6.01 PSDs refer), the requested restriction inappropriately restricted access to the triple therapy to patients who were already taking a DPP4 inhibitor as part of dual oral therapy (i.e. a fixed treatment sequence). This is narrower than the current clinical guidelines as both DPP4 and SGLT2 inhibitors are second line treatment for T2DM.

7.3 The PBAC considered that the nominated comparators, co-administration of the individual components dapagliflozin and metformin, were appropriate. However, the

component parts are not currently PBS listed for triple oral therapy in combination with a DPP4 inhibitor. The PBAC noted that it deferred the submission requesting PBS subsidy for dapagliflozin + a DPP4 inhibitor + metformin (item 6.01 PSDs refers), and therefore, the cost-effectiveness of the saxagliptin with metformin FDC in this setting has not been established.

7.4 The PBAC referred to their advice in the related submission (dapagliflozin, item 6.01, July 2017 PSD refers) that although it was reasonable to assume that this triple therapy would have some therapeutic benefit, 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 addition either dapagliflozin or a DPP4 inhibitor to metformin. Therefore, the PBAC was of the view that it would not be cost-effective for this treatment to be at the same price as the sum of the component parts. The PBAC was of the view that this would also apply for the saxagliptin with metformin FDC.

7.5 The PBAC recalled the DUSC advice regarding the related submissions (item 5.13 and 6.01, July 2017 PBAC refers) that the estimates of use and financial impact provided with the submissions were considerably underestimated. Although PBAC acknowledged that the uptake of the saxagliptin with metformin FDC was likely to be lower than for the dapagliflozin with saxagliptin FDC, because it didn't offer the same potential cost-saving for the patient, it considered that these estimates remained uncertain.

7.6 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.