

DAPAGLIFLOZIN AND METFORMIN XR: available as DAPAGLIFLOZIN AND METFORMIN XR, Modified released tablets, 10 mg/500 mg, 10mg/1000 mg, 5 mg/1000 mg, XIGDUO® XR, AstraZeneca Pty Ltd

1 Purpose of application

1.1 The minor submission sought for the PBS indication for dapagliflozin+metformin XR (XIGDUO® XR) fixed dose combination (FDC) to be extended to include use in the Add On to Insulin (AOI) and Triple Oral Therapy (TOT) settings. This will align the PBS listings for dapagliflozin monotherapy (FORXIGA®) and the dapagliflozin+metformin FDC.

2 Requested Listing:

2.1 The submission proposed the following listings:

Add on to insulin

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	Proprietary Name and Manufacturer	
DAPAGLIFOZIN / METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/500mg	28	5		
DAPAGLIFOZIN / METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/1000mg	28	5	Xigduo® XR	AstraZeneca
DAPAGLIFOZIN / METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 5mg/1000mg	56	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority Required (Streamlined)

<p>Clinical criteria:</p>	<p>The treatment must be in combination with insulin AND Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR 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 an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents</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 with an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a dipeptidyl peptidase 4 inhibitor (DPP4), a thiazolidinedione (glitazone), a glucagon-like peptide-1 (GLP1) or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(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> <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, must be documented in the patient's medical records.</p>

Triple oral therapy

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	Proprietary Name and Manufacturer	
DAPAGLIFOZIN / METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/500mg	28	5		
DAPAGLIFOZIN / METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/1000mg	28	5	Xigduo® XR	AstraZeneca
DAPAGLIFOZIN / METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 5mg/1000mg	56	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority required (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 sulfonylurea</p> <p>AND</p> <p>Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (DPP4), a thiazolidinedione (glitazone), a glucagon-like peptide-1 (GLP1) or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea; OR</p> <p>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 with a SGLT2 inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea.</p>

Prescriber Instructions	<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 with a SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a dipeptidyl peptidase 4 inhibitor (DPP4), a thiazolidinedione (glitazone), a glucagon-like peptide-1 (GLP1) or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <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 a SGLT2 inhibitor, must be documented in the patient's medical records.</p>
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3 Background

- 3.1 Dapagliflozin+metformin XR is TGA indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate. A submission to update the dapagliflozin+metformin XR Product Information (PI) to include triple oral therapy, consistent with the dapagliflozin PI is currently under evaluation by the TGA.
- 3.2 Dapagliflozin+metformin XR was considered by the PBAC at the July 2014 meeting for an Authority Required listing for treatment of type 2 diabetes mellitus (T2DM) in a patient whose condition is not adequately controlled by treatment with metformin and a sulfonylurea and whose HbA1c is greater than 7% prior to initiation of a gliptin, glitazone, a glucagon-like peptide-1 despite or a sodium-glucose co-transporter-2 (SGLT2) inhibitor. The submission presented a cost-minimisation analysis based on non-inferiority between dapagliflozin+metformin XR and the individual components, on grounds of bioequivalence. The PBAC acknowledged that the TGA had accepted bioequivalence of dapagliflozin+metformin XR to dapagliflozin and metformin mono-components and the submission received a positive recommendation for use in patients with an HbA1c measurement greater than 7%, despite treatment with metformin alone. Due to supply issues, of which the Department is aware, listing is not expected until 1 October 2015.
- 3.3 At the March 2015 PBAC meeting, dapagliflozin (10mg tablet) was recommended for listing for the treatment of type 2 diabetes mellitus in combination with metformin and a sulfonylurea (triple oral therapy). In that submission, the sponsor requested a listing for the dapagliflozin+metformin XR FDC for use in combination with sulfonylurea so as to align the restrictions between dapagliflozin and the FDC. However, the PBAC considered that the appropriate process for consideration of the sponsor's request, made in the pre-PBAC response, would be through a minor submission.
- 3.4 Dapagliflozin (10mg tablet) is currently listed on the PBS in combination with insulin and for dual oral therapy in combination with metformin or a sulfonylurea in patients inadequately controlled on either metformin or a sulfonylurea alone.

4 Pricing considerations

- 4.1 The proposed dispensed price for maximum quantity (DPMQ) for dapagliflozin+metformin XR for use in the AOI and TOT settings is consistent with the price recommended for dual therapy, i.e. the sum of the component prices of dapagliflozin and metformin immediate release (IR).
- 4.2 The requested price for dapagliflozin+metformin XR for use in the AOI and TOT setting is presented in Table 1.

Table 1: Requested price by dose for 28 days of treatment of dapagliflozin+metformin XR as add-on therapy to insulin with metformin and triple oral therapy in combination with a sulfonylurea

	XIGDUO XR (10 mg dapagliflozin / 500 mg metformin XR) x 28	XIGDUO XR (10 mg dapagliflozin / 1000 mg metformin XR) x 28	XIGDUO XR (5 mg dapagliflozin / 1000 mg metformin XR) x 56
Ex-manufacturer	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Price to pharmacy	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
DPMQ	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Abbreviations: DPMQ, dispensed price maximum quantity; mg, milligrams; XR, extended release
 Source: Xigduo XR Minor PBAC Submission Apr-15 - AOI & TOT.xls (excel spreadsheet as part of the submission package)

- 4.3 Consistent with the July 2014 submission, the submission estimated there would be minimal financial implications to the PBS if dapagliflozin+metformin XR FDC is listed, as it anticipated that dapagliflozin+metformin XR FDC will substitute for dapagliflozin and metformin mono-components over time.
- 4.4 The estimated use and financial implications of listing dapagliflozin+metformin XR FDC on the PBS is summarised in the table below.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Extent of use						
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of services	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost of listing dapagliflozin+metformin on the PBS/RPBS						
Cost to the PBS/RPBS	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Savings to PBS/RPBS from substitution of dapagliflozin+metformin mono-components						
Savings to the PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost of listing dapagliflozin+metformin on the PBS/RPBS						
Net cost to the PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	\$ [REDACTED]

- 4.5 The redacted table above shows that the estimated use and financial implications of dapagliflozin+metformin XR FDC for AOI and TOT is 50,000 - 100,000 patients treated and a saving to the PBS/RPBS of less than \$10 million.

5 Other relevant factors

- 5.1 At the March 2015 PBAC meeting, the PBAC noted that dapagliflozin is associated with a higher rate of urinary tract and genital infections compared with placebo.

6 PBAC Outcome

- 6.1 The PBAC recommended that the listing of dapagliflozin+metformin XR for the treatment of type 2 diabetes mellitus be extended to include use in the Add On to Insulin and Triple Oral Therapy settings, consistent with the current listings for dapagliflozin. The requested restrictions are consistent with the TGA indication and previous recommendations of the PBAC.
- 6.2 In its consideration of sitagliptin for triple oral therapy in July 2015, the PBAC agreed that the listings for DPP-4 inhibitors and SGLT2 inhibitors for triple oral therapy in type 2 diabetes mellitus should be consistent. Accordingly, the PBAC recommended the following change to the clinical criterion for dapagliflozin+metformin XR (additions in italics and deletions in strikethrough): “...despite treatment with ~~maximally tolerated doses of metformin and a sulfonylurea~~ *either metformin or a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug*”.
- 6.3 Dapagliflozin+metformin XR FDC is suitable for prescribing by nurse practitioners for continuing therapy only where a patient has been initiated by a medical practitioner.
- 6.4 The Safety Net 20 Day Rule should apply.

Outcome:

Recommended

7 Recommended listing

- 7.1 Amend recommended listing as follows:

Add on to insulin

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DAPAGLIFOZIN/METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/1000mg	28	5	Xigduo® XR	AstraZeneca
DAPAGLIFOZIN/METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/500mg	56	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority Required (Streamlined)

<p>Clinical criteria:</p>	<p>The treatment must be in combination with insulin</p> <p>AND</p> <p>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 glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR</p> <p>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 with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.</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 with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <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 a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records.</p>
<p>Administrative Advice</p>	<p>This fixed dose combination is not PBS-subsidised as initial therapy or for use in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.</p>

Triple oral therapy

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	Proprietary Name and Manufacturer
DAPAGLIFOZIN/METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/500mg	28	5	
DAPAGLIFOZIN/METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/1000mg	28	5	Xigduo® XR AstraZeneca
DAPAGLIFOZIN/METFORMIN HYDROCHLORIDE EXTENDED RELEASE Tablet, 10mg/500mg	56	5	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority Required (Streamlined)
Clinical criteria:	<p>The treatment must be in combination with a sulfonylurea</p> <p>AND</p> <p>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 glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug;</p> <p>OR</p> <p>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 with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 despite treatment with either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug.</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 with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <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 a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records</p>
<p>Administrative Advice</p>	<p>This fixed dose combination is not PBS-subsidised as initial therapy or for use in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.</p>

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.