

4.03 DAPAGLIFLOZIN

**tablet 10 mg (as propanediol monohydrate),
Foxiga[®] ;**

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;**

DAPAGLIFLOZIN WITH SAXAGLIPTIN

**fixed dose combination tablet 10 mg/ 5 mg
Qtern[®] , AstraZeneca Pty Ltd**

1 Purpose of Application

1.1 The minor submission was a resubmission to seek an Authority Required (STREAMLINED) listing for dapagliflozin in combination with a dipeptidyl peptidase 4 (DPP4) inhibitor and metformin for the treatment of Type 2 Diabetes Mellitus (T2DM). The request relates to the following products:

- dapagliflozin (FORXIGA[®]) tablets,
- dapagliflozin with metformin (XIGDUO[®] XR) fixed dose combination (FDC) tablets, and
- dapagliflozin with saxagliptin (QTERN[®]) FDC tablets.

2 Requested listing

2.1 The submission suggested no changes to the previous requested listing. The pre-PBAC response to the original submission acknowledged and supported the proposed changes as suggested by the Secretariat.

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Background

3.1 This was the first resubmission requesting the listing of these agents for triple oral therapy with dapagliflozin, saxagliptin and metformin. At the July 2017 meeting, the PBAC deferred making decision on the listing to enable a price for treatment with

dapagliflozin + a DPP4 inhibitor + metformin that could be considered cost-effective to be established.

- 3.2 The PBAC has also previously rejected an application for this treatment setting (i.e. a DPP4 inhibitor + SGLT2 inhibitor + metformin) for empagliflozin and linagliptin, and the PBAC also considered a resubmission for this at the November 2017 meeting.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

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

Clinical trials

- 4.3 No new clinical trials were presented in the re-submission.
- 4.4 The PBAC noted that in considering the submission for empagliflozin + linagliptin, it had accepted a claim of non-inferiority for empagliflozin + linagliptin and dapagliflozin + saxagliptin, both in combination with metformin.

Drug cost/patient/year: \$ [REDACTED] (a revised cost with the [REDACTED] % price reduction)

- 4.5 Based on 13 scripts per year for a single patient, the estimated costs of treatment over 12 months for the dapagliflozin + saxagliptin FDC is \$ [REDACTED] per year.
- 4.6 The PBAC noted that the sponsor offered a [REDACTED] % price reduction on the AEMP of the dapagliflozin 10 mg + saxagliptin 5 mg FDC, [REDACTED].
- 4.7 The PBAC noted that the pre-PBAC response cited a previous PBAC decision relating to the listing of a long-acting muscarinic antagonist (LAMA)/ long acting beta2-agonist (LABA) combination for chronic obstructive pulmonary disease (COPD), in which the price reduction of the FDC did not flow on its individual components to justify this position. However, the PBAC considered that this previous recommendation was for a dual therapy that would replace two single agents, and was a considerably different circumstance, such that it does not serve as a precedent for this request, where triple therapy can be achieved through different combinations of PBS listed medicines that do not involve the FDC.

Estimated PBS usage & financial implications

- 4.8 The minor resubmission accepted the Drug Utilisation Sub-Committee's estimates of utilisation as per the previous submission.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the Authority Required (STREAMLINED) listing of dapagliflozin, dapagliflozin with metformin fixed dose combination (FDC) and dapagliflozin with saxagliptin FDC, for use in triple oral therapy with a DPP4 inhibitor + SGLT2 inhibitor + metformin, in patients with type 2 Diabetes Mellitus (T2DM) on the basis of cost-minimisation to empagliflozin with linagliptin.
- 5.2 The PBAC recalled that it recommended the PBS listing of the empagliflozin with linagliptin FDC for use in triple oral therapy at the price proposed in the submission noting that the incremental benefit of adding a third oral agent was smaller in magnitude than the benefit observed when adding either agent in the dual therapy setting. However, the PBAC considered that the price reduction proposed by the sponsor accounted for this decrement of benefit in triple oral therapy as well as the uncertainty inherent in this approach. The PBAC considered that a similar approach would be appropriate for the listing of dapagliflozin and saxagliptin when used in this setting.
- 5.3 The PBAC also recommended the PBS listings of dapagliflozin with and without metformin be amended to allow these medicines to be used in triple oral therapy with a DPP4 inhibitor + SGLT2 inhibitor + metformin.
- 5.4 The PBAC recalled that the equi-effective doses previously recommended were empagliflozin 10 mg or 25 mg to dapagliflozin 10 mg, and linagliptin 5 mg to saxagliptin 5 mg, and considered that these same equi-effective doses applied in the triple oral therapy.
- 5.5 The PBAC noted that the restriction is complex, and that the restrictions for the individual components and the respective FDCs with metformin should be consistent. The PBAC also advised that these restrictions should also apply to the currently listed saxagliptin and saxagliptin with metformin FDC, and reiterated its recommendation that a general statement for type 2 diabetes may be appropriate.
- 5.6 The PBAC advised that, under subsection 101(3BA) of the National Health Act, 1953 dapagliflozin with saxagliptin should be treated as interchangeable on an individual patient basis with empagliflozin with linagliptin.
- 5.7 The PBAC considered that dapagliflozin with saxagliptin FDC, dapagliflozin, saxagliptin, and their respective FDCs with metformin are suitable for prescribing by nurse practitioners for continuing therapy only, where the therapy has been initiated by a medical practitioner, and that they should not be exempt from the Early Supply Rule, because the Early Supply Rule currently applies to the existing listings for these drugs.
- 5.8 The PBAC noted that this submission is not eligible for an Independent Review as it has received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
DAPAGLIFLOZIN Tablets 10 mg, 28	1	5	Forxiga®	AstraZeneca

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 checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with metformin, AND The treatment must be in combination with a dipeptidyl peptidase 4 inhibitor (gliptin) AND Patient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 4 inhibitor (gliptin) OR Patient must have previously been stabilised on dual or triple oral therapy which included a sodium-glucose co-transporter 2 (SGLT2) inhibitor, AND Patient must have, or have had, an HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a gliptin and a SGLT2 inhibitor, 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 initiation of triple oral therapy with a gliptin, and an SGLT2 inhibitor.

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<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 triple oral therapy with a gliptin and an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with a gliptin and a SGLT2 inhibitor 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 triple oral therapy with a gliptin and an SGLT2 inhibitor, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin 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.</p>
<p>Administrative Advice</p>	<p>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.</p> <p>This drug is not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.</p> <p>PBS subsidised dual oral therapy does not include concomitant use of a combination of: a gliptin, a glitazone or an SGLT2 inhibitor.</p>

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
DAPAGLIFLOZIN/ METFORMIN tablet, 10 mg/1000 mg, 28	1	5	XIGDUO® XR AstraZeneca
DAPAGLIFLOZIN/ METFORMIN tablet, 10 mg/500 mg, 28	1	5	
DAPAGLIFLOZIN/ METFORMIN tablet, 5 mg/1000 mg, 28	1	5	

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 checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be in combination with a dipeptidyl peptidase- 4 inhibitor (gliptin), AND Patient must have previously been stabilised on dual or triple oral therapy which included a sodium-glucose co-transporter 2 (SGLT2) inhibitor,</p> <p>OR <i>Patient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 1 inhibitor (gliptin),</i></p> <p>AND Patient must have, or have had, an HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a gliptin and an SGLT2 inhibitor,</p> <p>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 initiation of triple oral therapy with a gliptin and an SGLT2 inhibitor.</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 triple oral therapy with a gliptin and an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with a gliptin and 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> <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 triple oral therapy with a gliptin and an SGLT2 inhibitor, must be document in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin 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.</p>
<p>Administrative Advice</p>	<p>Note:</p> <p>Continuing Therapy Only:</p> <p>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.</p> <p>Further information can be found in the Explanatory Notes for Nurse Practitioners.</p> <p>Note:</p> <p>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.</p> <p>PBS subsidised dual oral therapy does not include concomitant use of a gliptin or an SGLT2 inhibitor with a glitazone.</p>

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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
DAPAGLIFLOZIN / SAXAGLIPTIN Tablet, 10 mg / 5 mg	28	5	QTERN® AstraZeneca

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 checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be in combination with metformin.</p> <p>AND</p> <p>Patient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 4 inhibitor (gliptin),</p> <p>OR</p> <p>Patient must have previously been stabilised on dual or triple oral therapy which included a sodium-glucose co-transporter 2 (SGLT2) inhibitor,</p> <p>AND</p> <p>Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a gliptin and an SGLT2 inhibitor;</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 of triple oral therapy with a gliptin and an SGLT2 inhibitor.</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 triple oral therapy with a gliptin and an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with a gliptin and an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or 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 triple oral therapy with a gliptin and an SGLT2 inhibitor, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin and an SGLT2 inhibitor or gliptin does not need to requalify on this criterion before being eligible for PBS subsidised treatment with this fixed dose combination.</p>

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Administrative Advice	<p>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.</p> <p>Note: This fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1, an insulin, another dipeptidyl peptidase 4 inhibitor (gliptin), or another SGLT2 inhibitor.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAXAGLIPTIN tablet, saxagliptin 2.5 mg, 28	1	5	Onglyza®	AstraZeneca Pty Ltd
tablet, saxagliptin 5 mg, 28	1	5		

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 checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with metformin AND The treatment must be in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor; AND Patient must have previously been stabilised on dual or triple oral therapy which included an SGLT2 inhibitor, OR Patient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 4 inhibitor (gliptin), AND Patient must have, or have had, an HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a gliptin and an SGLT2 inhibitor, 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 initiation of triple oral therapy with a gliptin, and an SGLT2 inhibitor.

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<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 triple oral therapy with a gliptin and an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with a gliptin and a SGLT2 inhibitor 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 triple oral therapy with a gliptin and an SGLT2 inhibitor, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin 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.</p>
<p>Administrative Advice</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><i>This drug is not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1 or an SGLT2 inhibitor.</i></p> <p>PBS subsidised dual oral therapy does not include concomitant use of a combination of: a gliptin, a glitazone or an SGLT2 inhibitor.</p>

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SAXAGLIPTIN WITH METFORMIN tablet, saxagliptin 2.5 mg + metformin hydrochloride 1 g, 56	1	5	Kombiglyze XR®	AstraZeneca Pty Ltd
tablet, saxagliptin 5 mg + metformin hydrochloride 500 mg, 28	1	5		
tablet, saxagliptin 5 mg + metformin hydrochloride 1 g, 28	1	5		

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 checked="" type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor AND Patient must have previously been stabilised on dual or triple oral therapy which included an SGLT2 inhibitor, OR Patient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 1 inhibitor (gliptin), AND Patient must have, or have had, an HbA1c measurement greater than 7% prior to the initiation of triple oral therapy with a gliptin and an SGLT2 inhibitor, 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 initiation of triple oral therapy with a gliptin, and an SGLT2 inhibitor.

<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 triple oral therapy with a gliptin and an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time triple oral therapy with a gliptin and 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> <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 triple oral therapy with a gliptin and an SGLT2 inhibitor, must be document in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin 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.</p>
<p>Administrative Advice</p>	<p>Note: Continuing Therapy Only:</p> <p>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.</p> <p>Note:</p> <p>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.</p> <p>PBS subsidised dual oral therapy does not include concomitant use of a gliptin or an SGLT2 inhibitor with a glitazone.</p>

7 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.

8 Sponsor's Comment

We look forward to seeing Australians have an additional treatment option to management their type 2 diabetes. We also welcome the opportunity to simplify the current the current complex restrictions.