

6.14 EMPAGLIFLOZIN

Tablet 10 mg, tablet 25 mg, Jardiance®

EMPAGLIFLOZIN WITH METFORMIN

Tablet containing 12.5 mg empagliflozin with 1 g metformin hydrochloride,

Tablet containing 12.5 mg empagliflozin with 500 mg metformin hydrochloride,

Tablet containing 5 mg empagliflozin with 1 g metformin hydrochloride,

Tablet containing 5 mg empagliflozin with 500 mg metformin hydrochloride,

Jardiamet® 12.5 mg/1000 mg, 12.5 mg/500 mg, 5 mg/ 1000 mg, and 5 mg/500 mg

LINAGLIPTIN

Tablet 5 mg, Trajenta®

LINAGLIPTIN WITH METFORMIN

Tablet containing 2.5 mg linagliptin with 1000 mg metformin hydrochloride, Tablet containing 2.5 mg linagliptin with 500 mg metformin hydrochloride,

Tablet containing 2.5 mg linagliptin with 850 mg metformin hydrochloride

Trajentamet®, Boehringer Ingelheim Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested the Authority Required (STREAMLINED) listing of empagliflozin, linagliptin and their respective fixed dose combination (FDC) products with metformin, for use in triple oral therapy (empagliflozin + linagliptin + metformin) in patients with Type 2 Diabetes Mellitus (T2DM), who are uncontrolled on dual oral therapy and who are intolerant or contraindicated to a sulfonylurea, have had an adverse event to previous treatment with a sulfonylurea, or have failed a triple oral therapy treatment which included a sulfonylurea. In its Pre-Sub-Committee Response (PSCR) for the concurrent major submission for an FDC of empagliflozin with linagliptin, the sponsor indicated it would accept the restriction wording and authority level considered most appropriate by the PBAC.

2 Requested listing

- 2.1 The Pre-PBAC response indicated that the sponsor would accept the wording and level of restriction that was considered most appropriate by the PBAC.

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

3 Background

- 3.1 Empagliflozin is TGA registered for use in T2DM as monotherapy, or “in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control”, or “in patients with T2DM and established cardiovascular disease to reduce the risk of cardiovascular death.” Empagliflozin with metformin FDC is indicated as “an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both empagliflozin and metformin is appropriate”.
- 3.2 Linagliptin and its FDC with metformin were recently approved by the TGA for use in combination therapy with an SGLT2 inhibitor and metformin.
- 3.3 The PBAC previously considered a submission for empagliflozin and linagliptin FDC at its March 2017 meeting for the requested listing. However, the PBAC has not previously considered the empagliflozin and linagliptin single component drugs, or their FDCs with metformin for this triple oral therapy.
- 3.4 The PBAC also considered a submission to the November 2017 meeting requesting the listing of dapagliflozin, in combination with any DPP4 inhibitor and metformin.

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 The minor submission is relying on the clinical evidence presented in the empagliflozin with linagliptin FDC major submission to the November 2017 meeting to support the efficacy and safety of triple oral therapy with empagliflozin + linagliptin + metformin, as well as evidence to demonstrate bioequivalence of empagliflozin with linagliptin FDC with concomitant use of its components.
- 4.4 The PBAC has previously accepted that the empagliflozin + metformin and linagliptin + metformin FDCs are bioequivalent to the corresponding individual components taken concomitantly.

Economic analysis

- 4.5 This submission relied on the empagliflozin with linagliptin FDC major submission to the November 2017 PBAC meeting to establish the cost-effectiveness of the requested listing.
- 4.6 The submission proposed the same DPMQs as the existing listings. However, the PBAC recalled that the pre-PBAC response for the empagliflozin with linagliptin FDC offered a ■■■% price reduction on the AEMP of the sum of components.
- 4.7 The PBAC noted that no reduced price was offered for the single components and the FDCs for empagliflozin or linagliptin in combination with metformin, included in this submission.
- 4.8 The PBAC noted that the pre-PBAC response cited a previous PBAC recommendation 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

- 4.9 The minor submission assumed that if the individual components are listed for the same indication as empagliflozin with linagliptin FDC, the total number of patients treated with empagliflozin with linagliptin plus metformin will be the same as that proposed in the empagliflozin + linagliptin FDC submission, but distributed between the empagliflozin with linagliptin FDC, the empagliflozin or linagliptin with metformin FDCs, and combined use of the individual components.
- 4.10 In addition, with respect to the empagliflozin + linagliptin FDC submission, the ESC “considered that the financial estimates were highly dependent on the proposed restriction, and were therefore uncertain”. Therefore, more detailed estimated have not been included and will need to be negotiated with the sponsor before implementation of the recommendation.

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 empagliflozin, empagliflozin with metformin fixed dose combinations (FDC), linagliptin, and linagliptin with metformin FDCs, for use in triple oral therapy (DPP4 + SGLT2 + metformin) in patients with type 2 Diabetes Mellitus (T2DM) on the basis of acceptable cost-effectiveness demonstrated by the concurrent major submission for the empagliflozin and linagliptin FDC.

- 5.2 The PBAC recalled that at the November 2017 meeting, it recommended the listing of empagliflozin with linagliptin FDC for use in combination with metformin in patients with T2DM. The PBAC also recalled that it has previously accepted bioequivalence between empagliflozin with linagliptin FDC and the concomitant use of empagliflozin and linagliptin individual components (empagliflozin with linagliptin PSD, March 2017 para 7.6), as well as the bioequivalence of empagliflozin, linagliptin, and metformin with their respective FDCs. The PBAC therefore considered that it would be reasonable to extend the listings of empagliflozin, linagliptin and their respective FDC products with metformin to allow their use in triple combination therapy with metformin, a DPP4, and an SGLT2 inhibitor.
- 5.3 The PBAC noted that the proposed wording for the empagliflozin with linagliptin FDC restriction has been amended through the consideration process, particularly to remove the requirement for intolerance or contraindication to sulfonylureas and that the restrictions for the drugs in this submission will also need to be consistent with the restriction for the empagliflozin with linagliptin FDC.
- 5.4 The PBAC noted that no reduced price was offered for the single components, and the FDCs for empagliflozin or linagliptin in combination with metformin, included in this submission. However, the PBAC also noted that the empagliflozin and linagliptin individual components and respective FDCs with metformin are used in a number of different combinations. The PBAC was therefore of the view that it would be difficult to determine the expected proportion of utilisation of these drugs in triple therapy comprised of an SGLT2, a DPP4 and metformin. Further, the PBAC noted previous advice from the Drug-Utilisation Sub-Committee that due to the advantages to patients in terms of both reduced copayments and flexibility in metformin dosing, uptake of the empagliflozin with linagliptin FDC over other combinations is likely to be high. The PBAC also noted the price reduction offered for the empagliflozin + linagliptin FDC and considered this was sufficient to account for any utilisation of the single component and other FDCs in this triple therapy combination.
- 5.5 The PBAC considered that empagliflozin, linagliptin and their FDCs with metformin for use in triple therapy of empagliflozin, linagliptin and metformin are suitable for inclusion in the PBS medicines for prescribing by nurse practitioners for continuing therapy only, where the therapy has been initiated by a medical practitioner.
- 5.6 The PBAC considered that empagliflozin, linagliptin and their FDCs with metformin should not be exempt from the Early Supply Rule because the Early Supply Rule currently applies to the existing listings for these drugs.
- 5.7 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	№.of Rpts	Proprietary Name and Manufacturer	
EMPAGLIFLOZIN				
Tablet, 25 mg, 30	1	5	Jardiance®	Boehringer Ingelheim Pty Ltd
Tablet, 10 mg, 30	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 metformin,</p> <p>AND</p> <p>The treatment must be in combination with a dipeptidyl peptidase 4 inhibitor inhibitor (gliptin)</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, 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,</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>

<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>

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
EMPAGLIFLOZIN WITH METFORMIN tablet, empagliflozin 12.5 mg + metformin hydrochloride 500 mg, 60	1	5	Jardiamet®	Boehringer Ingelheim Pty Ltd
tablet, empagliflozin 12.5 mg + metformin hydrochloride 1 g, 60	1	5		
tablet, empagliflozin 5 mg + metformin hydrochloride 500 mg, 60	1	5		
tablet, empagliflozin 5 mg + metformin hydrochloride 1 g, 60	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),</p> <p>AND</p> <p>Patient must have previously been stabilised on dual or triple oral therapy which included an SGLT2 inhibitor,</p> <p>OR</p> <p><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</p> <p>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,</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>

<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 <i>triple oral therapy</i> with a gliptin <i>and</i> an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time <i>triple oral therapy</i> with a gliptin <i>and</i> 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 <i>triple oral therapy</i> with a gliptin <i>and</i> 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 <i>and</i> a gliptin <i>or</i> 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>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
LINAGLIPTIN tablet, linagliptin 5 mg, 30	1	5	Trajenta® Boehringer Ingelheim Pty Ltd

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>The treatment must be in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor;</p> <p>AND</p> <p>Patient must have previously been stabilised on dual or triple oral therapy which included an SGLT2 inhibitor,</p> <p>OR</p> <p>Patient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 1 inhibitor (gliptin),</p> <p>AND</p> <p>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</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>

<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>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
LINAGLIPTIN WITH METFORMIN tablet, linagliptin 2.5 mg + metformin hydrochloride 500 mg, 60	1	5	Trajentamet®	Boehringer Ingelheim Pty Ltd
tablet, linagliptin 2.5 mg + metformin hydrochloride 1 g, 60	1	5		
tablet, linagliptin 2.5 mg + metformin hydrochloride 850 mg, 60	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 sodium-glucose co-transporter 2 (SGLT2) inhibitor,</p> <p>AND</p> <p>Patient must have previously been stabilised on dual or triple oral therapy which included an SGLT2 inhibitor,</p> <p>OR</p> <p>Patient must have previously been stabilised on dual or triple oral therapy which included a dipeptidyl peptidase 1 inhibitor (gliptin),</p> <p>AND</p> <p>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,</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>

<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

The sponsor had no comment.