

5.06 EMPAGLIFLOZIN WITH METFORMIN, ORAL TABLET, 5MG/500MG, 5MG/850MG, 5MG/1000MG, 12.5MG/500MG, 12.5MG/850MG, 12.5MG/1000MG JARDIANCETM®/JARDIAMET®, BOEHRINGER INGELHEIM

1 Purpose of Application

1.1 Authority Required (Streamlined) listing for empagliflozin/metformin immediate release fixed dose combination (FDC) for treatment of Type 2 diabetes.

2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough. The sponsor has two concurrent listings for empagliflozin in triple therapy with metformin and a sulfonylurea, and empagliflozin in combination with insulin. The sponsor requested that the wording of the restriction for the FDC be updated to include use with a sulfonylurea or insulin, in the case that the concurrent submissions are successful. The Secretariat has therefore suggested additional restriction wordings for PBAC to consider should these listings be recommended.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
EMPAGLIFLOZIN/METFORMIN Oral tablet, 5mg/500mg	60	5	\$62.76	Jardiancemet®/ Jardiamet® Boehringer Ingelheim
EMPAGLIFLOZIN/METFORMIN Oral tablet, 5mg/850mg	60	5	\$63.96	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 5mg/1000mg	60	5	\$64.45	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 12.5mg/500mg	60	5	\$62.76	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 12.5mg/850mg	60	5	\$63.96	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 12.5mg/1000mg	60	5	\$64.45	

Authority required (Streamlined):

Dual therapy for Type 2 diabetes.

1. Empagliflozin/metformin

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-

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Severity:	-
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<p>Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with metformin; 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 despite treatment with metformin.</p>
Population criteria:	-
Foreword	-
Definitions	-
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 dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (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 result 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>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.</p>
Administrative Advice	<p>The fixed dose combination is not PBS-subsidised for use in combination with a sulfonylurea (triple oral therapy)^a, as initial therapy or in combination with an insulin^b, a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.</p>
Cautions	-

^a Remove if recommended by the PBAC for use in triple therapy

^b Remove if recommended by the PBAC for use with insulin

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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
Episodicity:	-
Severity:	-
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	Patient must have previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and empagliflozin.
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
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. The fixed dose combination is not PBS-subsidised for use in combination with a sulfonylurea (triple oral therapy) ^a , as initial therapy or in combination with an insulin ^b , a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.
Cautions	-

^a Remove if empagliflozin is recommended by the PBAC for use in triple therapy

^b Remove if empagliflozin is recommended by the PBAC for use with insulin

2. Empagliflozin/metformin (triple therapy)

Category / Program	GENERAL – General Schedule (Code GE)
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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
Episodicity:	-
Severity:	-
Condition:	<i>Diabetes mellitus type 2</i>
PBS Indication:	<i>Diabetes mellitus type 2</i>
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<i>The treatment must be in combination with a sulfonylurea,</i> <i>AND</i> <i>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 optimal doses of dual oral therapy;</i> <i>OR</i> <i>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 optimal doses of dual oral therapy.</i>
Population criteria:	-
Foreword	-
Definitions	-

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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 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 result 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>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: The fixed dose combination is not PBS-subsidised for use, as initial therapy or in combination with an insulin^a, 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 two of either: a gliptin, a glitazone or an SGLT2 inhibitor.</p>
<p>Cautions</p>	<p>-</p>

^aRemove if empagliflozin is recommended by the PBAC for use with insulin

3. Empagliflozin/metformin (insulin add-on)

<p>Category / Program</p>	<p>GENERAL – General Schedule (Code GE)</p>
<p>Prescriber type:</p>	<p><input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input checked="" type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
<p>Episodicity:</p>	<p>-</p>
<p>Severity:</p>	<p>-</p>
<p>Condition:</p>	<p>Diabetes mellitus type 2</p>
<p>PBS Indication:</p>	<p>Diabetes mellitus type 2</p>
<p>Treatment phase:</p>	<p>-</p>

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<p><i>The treatment must be in combination with insulin, AND</i></p> <p><i>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</i></p> <p><i>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.</i></p>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	<p><i>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.</i></p> <p><i>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.</i></p> <p><i>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</i></p> <p><i>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</i></p> <p><i>(b) Had red cell transfusion within the previous 3 months.</i></p> <p><i>The result 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.</i></p>

<p>Administrative Advice</p>	<p>Note: Continuing Therapy Only: <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.</i> <i>Further information can be found in the Explanatory Notes for Nurse Practitioners.</i></p> <p>Note: <i>The fixed dose combination is not PBS-subsidised for use in combination with a sulfonylurea (triple oral therapy)^a, as initial therapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.</i></p>
<p>Cautions</p>	<p>-</p>

^a Remove if empagliflozin is recommended by the PBAC for use in triple therapy

- 2.1 The listing was requested on a cost-minimisation basis compared to the individual components of the FDC, empagliflozin and metformin, taken concomitantly.

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

3 Background

- 3.1 TGA status at time of PBAC consideration: empagliflozin/metformin FDC was submitted under the TGA/PBAC parallel process and approved for registration by the TGA delegate on July 17, 2015.
- 3.2 The individual components of the FDC, empagliflozin and metformin, are currently TGA registered for use as individual tablets.
- 3.3 Empagliflozin 10mg and 25mg were TGA registered on 30 April 2014 for the treatment of Type 2 diabetes to improve glycaemic control in adults as: monotherapy in patients who are intolerant to metformin; add-on combination therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- 3.4 There were two concurrent submissions for empagliflozin in type 2 diabetes: empagliflozin in triple therapy with metformin and a sulfonylurea, and empagliflozin in combination with insulin. The sponsor requested that the wording of the restriction for the FDC be updated to include use with a sulfonylurea or insulin, in the case that the concurrent submissions are successful.

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

4 Clinical place for the proposed therapy

- 4.1 Type 2 diabetes where metformin alone does not provide adequate control.
- 4.2 Empagliflozin/metformin FDC will provide a treatment alternative for patients taking concomitant empagliflozin and metformin for the treatment of Type 2 diabetes.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

5 Comparator

- 5.1 The submission nominated the co-administered individual components of the FDC (empagliflozin and metformin immediate release) as the main comparator. This was appropriate. The submission included dapagliflozin 10mg with metformin as a secondary comparator.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

6 PBAC 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 Two bioequivalence analyses were considered. The first compared the equivalence of taking empagliflozin 5mg twice daily to empagliflozin 10mg taken once daily (1276.9). The second aimed to establish bioequivalence of the six FDC tablets to their individual components taken concomitantly (1276.5, 1276.6, 1276.7, 1276.8, 1276.23, 1276.24).
- 6.4 Trial 1276.10 provided 16 week efficacy data comparing once daily (10mg, 25mg) and twice daily (5mg, 12.5mg) empagliflozin dosing regimens.
- 6.5 The submission also presented a series of indirect comparisons of empagliflozin and dapagliflozin using placebo and a sulfonylurea as the common comparator, in patients on background metformin therapy. This was an update of the evidence previously considered as part of the empagliflozin dual therapy submission at the July 2014 PBAC meeting.
- 6.6 Details of the trials presented in the submission are provided in the Table 1.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Bioequivalence trials		
Empagliflozin/metformin FDC vs individual components		
Study 1276.5	Relative bioavailability of a 12.5mg BI 10773 / 1000mg metformin fixed dose combination tablet compared with its mono-components and administered with and without food (an open-label, randomised, single	Internal study report June 2011

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	dose, three-way crossover, Phase I trial in healthy volunteers). NCT01211197	
Study 1276.6	Bioequivalence of empagliflozin with metformin (500mg) fixed dose combination tablets compared to single tablets administered together in healthy male and female volunteers under fed conditions (an open label, randomised, single-dose, four-way crossover study). NCT01844531	Internal study report May 2014
Study 1276.7	Bioequivalence of empagliflozin with metformin (850mg) fixed dose combination tablets compared to single tablets administered together in healthy male and female volunteers under fed conditions (an open label, randomised, single-dose, four-way crossover study). NCT01672788	Internal study report April 2013
Study 1276.8	Bioequivalence of empagliflozin with metformin fixed dose combination tablets compared to single tablets administered together in healthy male and female volunteers under fed and fasted conditions (an open-label, randomised, single-dose, crossover study). NCT01811953	Internal study report October 2013
Study 1276.23	Relative bioavailability of empagliflozin (12.5mg or 5mg)/metformin (850mg or 500mg) fixed dose combination tablets compared to single tablets administered together to healthy Chinese male and female volunteers in an open-label, randomised, single-dose, two-way crossover study. NCT02102932	Internal study report Not recorded (trial concluded August 2014)
Study 1276.24	Bioequivalence of empagliflozin with metformin (12.5mg/500mg) fixed dose combination tablet compared to tablets administered together in healthy male and female volunteers under fed conditions (an open-label, randomised, single-dose, two-period, two-sequence crossover study). NCT02028767	Internal study report July 2014
<i>Empagliflozin twice daily vs once daily</i>		
Study 1276.9	Relative bioavailability of 5mg BI 10773 administered twice daily compared to 10mg BI 10773 given once daily after multiple oral doses in healthy male and female volunteers (an open-label, randomised, crossover, clinical phase I study). EudraCT:2009-012524-90	Internal study report May 2010
Common reference using placebo + metformin		
<i>Empagliflozin + metformin vs placebo + metformin</i>		
Study 1245.10	A Phase II, randomized, parallel group safety, efficacy, and pharmacokinetics study of BI 10773 (1mg, 5mg, 10mg, 25mg, and 50mg) administered orally once daily over 12 weeks compared double blind to placebo with an additional open-label sitagliptin arm in Type 2 diabetic patients with insufficient glycemic control despite metformin therapy. NCT00749190	Internal study report September 2010
	Rosenstock J, Seman LJ, Jelaska A et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in Type 2 diabetes with mild hyperglycaemia.	Diabetes Obes Metab 2013; 15(12):1154-60
Study 1245.23	A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10mg, 25mg) administered orally, once daily over 24 weeks in patients with Type 2 diabetes mellitus with insufficient glycaemic control despite treatment with metformin alone or metformin in combination with a Sulphonylurea. NCT01159600	Internal study report September 2012
	Haring HU, Merker L, Seewaldt-Becker E et al. Empagliflozin as add-on to metformin in patients with Type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial.	Diabetes Care 2014b;37:1650-1659.
Study 1245.31 (extension of 1245.23)	A phase III double-blind, extension, placebo-controlled parallel group safety and efficacy trial of BI 10773 (10 and 25mg once daily) and sitagliptin (100mg once daily) given for minimum 76 weeks (including 24 weeks of preceding trial) as monotherapy or with different background therapies in patients with Type 2 diabetes mellitus	Internal study report (final) May 2014

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	previously completing trial 1245.19, 1245.20 or 1245.23. NCT01289990	
	A phase III double-blind, extension, placebo-controlled parallel group safety and efficacy trial of BI 10773 (10 and 25mg once daily) and sitagliptin (100 mg once daily) given for minimum 76 weeks (including 24 weeks of preceding trial) as monotherapy or with different background therapies in patients with Type 2 diabetes mellitus previously completing trial 1245.19, 1245.20 or 1245.23.	Internal study report (interim) December 2012
Study 1276.10	A randomised, double blind, placebo controlled, parallel group efficacy and safety study of oral administration of empagliflozin twice daily versus once daily in two different daily doses over 16 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with Type 2 diabetes mellitus and insufficient glycaemic control. NCT01649297	Internal study report April 2014
Dapagliflozin + metformin vs placebo + metformin		
Study CT-014	A phase III study of BMS-512148 (dapagliflozin) in patients with Type 2 diabetes who are not well controlled on metformin alone.	NCT00528879
	Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with Type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial.	Lancet 2010; 375: 2223-2233
	Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. [Erratum appears in BMC Med. 2013;11:193].	BMC Med. 2013; 11:43
	Basile J, Ptaszynska A, Ying L, Sugg J, Parikh S. The effects of dapagliflozin on cardiovascular risk factors in patients with Type 2 diabetes mellitus.	Circulation: Cardiovascular Quality and Outcomes 2012;5.
Study CT-012	A 24-week, multicentre, International, double blind, Randomised, parallel group, placebo controlled, phase III study with a 78-week extension period to evaluate the effect of dapagliflozin in combination with metformin on body weight in subjects with Type 2 diabetes mellitus who have inadequate glycemic control on metformin alone.	NCT00855166
	Bolinder J, Ljunggren O, Johansson L et al. Dapagliflozin produces long-term reductions in body weight, waist circumference and total fat mass in patients with Type 2 diabetes inadequately controlled on metformin.	Diabetologia 2012; 55: S308
	Bolinder J, Ljunggren O, Kullberg J et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with Type 2 diabetes mellitus with inadequate glycemic control on metformin.	Journal of Clinical Endocrinology and Metabolism 2012; 97(3): 1020-1031
	Bolinder J, Ljunggren O, Johansson L et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with Type 2 diabetes mellitus inadequately controlled on metformin.	Diabetes, Obesity and Metabolism 2014; 16(2): 159-169
	Grandy S, Langkilde AM, Ingelgard A, Sugg JE, Parikh SJ. Quality of life (EQ-5D) among Type 2 diabetes mellitus patients treated with dapagliflozin for 24 weeks.	Diabetes 2012; 261:A600.
	Grandy S, Hashemi M, Langkilde AM, Parikh S, Sjostrom CD. Changes in weight loss-related quality of life among Type 2 diabetes mellitus patients treated with dapagliflozin.	Diabetes, Obesity & Metabolism 2014a;16:645-650.
	Grandy S, Langkilde AM, Sugg JE, Parikh S, Sjostrom CD. Health-related quality of life (EQ-5D) among Type 2 diabetes mellitus patients treated with dapagliflozin over 2 years.	International Journal of Clinical Practice 2014b;68:486-494.
	Ingelgard A, Grandy S, Langkilde A, Sugg JE, Parikh SJ. Health-related quality of life (EQ-5D) among Type 2 diabetes mellitus patients	Diabetologia 2012;55:S320.

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	treated with dapagliflozin for 24 weeks.	
	Ljunggren O, Bolinder J, Johansson L et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled Type 2 diabetes mellitus on metformin	Diabetes, Obesity & Metabolism 2012a;14:990-999.
	Ljunggren O, Bolinder J, Johansson L et al. Dapagliflozin has no long-term effect on markers of bone turnover or bone mineral density in patients with inadequately controlled Type 2 diabetes on metformin.	Diabetologia 2012b;55:S306-S307.
Study CT-003	A 16-week, multicentre, randomised, double-blind, placebo-controlled phase III study to evaluate the safety and efficacy of dapagliflozin 2.5mg BID, 5mg BID and 10mg QD versus placebo in patients with Type 2 diabetes who are inadequately controlled on metformin-IR monotherapy.	NCT01217892
	Schumm-Draeger PM, Burgess L, Koranyi L, Hrubá V, Hamer-Maansson JE, de Bruin TW. Twice-daily dapagliflozin co-administered with metformin in Type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial.	Diabetes, Obesity & Metabolism 2015;17:42-51.
Yang 2014	A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin in combination with metformin in Asian subjects with Type 2 diabetes who have inadequate glycaemic control on metformin alone.	NCT01095666
	Yang W, Han P, Liu B et al. Dapagliflozin (DAPA) reduces HbA1c in Asian patients with T2DM after metformin (MET) failure. (Abstract only)	American Diabetes Association Conference Publication: 2014; 63:June.
Empagliflozin + metformin vs sulfonylurea + metformin		
Study 1245.28	A phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with Type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment. NCT01167881	Internal study report (final) February 2013
	A phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with Type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment.	Internal study report (interim) January 2013
	Ridderstrale M, Svaerd R, Zeller C et al. Rationale, design and baseline characteristics of a 4-year (208-week) phase III trial of empagliflozin, an SGLT2 inhibitor, versus glimepiride as add-on to metformin in patients with Type 2 diabetes mellitus with insufficient glycaemic control.	Cardiovascular Diabetology 2013;12:129.
	Ridderstrale M, Andersen KR, Zeller C et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with Type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial.	The Lancet Diabetes & Endocrinology 2014a;2:691-700.
Dapagliflozin + metformin vs sulfonylurea + metformin		
Study CT-004	A 52-week international, multi-centre, randomised, parallel-group, double-blind, active-controlled, phase III study with a 156-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with Type 2 diabetes who have inadequate glycaemic control on metformin therapy alone.	NCT00660907
	Nauck MA, Del PS, Meier JJ et al. Dapagliflozin versus glipizide as add-on therapy in patients with Type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial.	Diabetes Care 2011; 34:2015-22

	Nauck M, Del PS, Meier JJ et al. [Dapagliflozin versus glipizide as add-on therapy in patients with Type 2 diabetes who have inadequate glycaemic control with metformin]. [German].	Deutsche Medizinische Wochenschrift 2013;138:Suppl-15.
	Nauck MA, Del PS, Duran-Garcia S et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose Type 2 diabetes mellitus is inadequately controlled with metformin.	Diabetes, Obesity & Metabolism 2014;16:1111-1120.

Source: Table B.6 of the submission

6.7 The key features of the bioequivalence trials are summarised in Table 2.

Table 2: Key features of the included bioequivalence trials

Trial	N	Design	FDC tested (empagliflozin/metformin IR)	Risk of bias	Patient population			Outcome(s)
					BMI kg/m ²	Age (years)	Ethnicity	
Bioequivalence trials								
1276.5	16	R, OL, CO	12.5mg/1000mg	Low	18.5 - 29.9	18 – 55	Caucasian	AUC _{0-infty} , C _{max}
1276.6	24	R, OL, CO	12.5mg/500mg 5mg/500mg	Low	18.5 - 29.9	18 – 50	Caucasian	AUC _{0-infty} , C _{max}
1276.7	36	R, OL, CO	12.5mg/850mg 5mg/850mg	Low	18.5 - 29.9	18 - 50	Caucasian	AUC _{0-infty} , C _{max}
1276.8	24	R, OL, CO	12.5mg/1000mg 5mg/1000mg	Low	18.5 - 29.9	18 - 50	Caucasian	AUC _{0-infty} , C _{max}
1276.9	16	R, OL, CO	5mg EMPA twice daily compared to 10mg EMPA daily ¹	Low	18.5 - 29.9	18 – 50	Caucasian	AUC _{0-24,ss} , C _{max,ss}
1276.23	96	R, OL, CO	12.5mg/500mg 12.5mg/850mg 5mg/500mg 5mg/850mg	Low	19 - 24	18 – 40	Asian	AUC _{0-infty} , C _{max}
1276.24	32	R, OL, CO	12.5mg/500mg	Low	18.5 - 29.9	18 - 50	Predominantly Caucasian	AUC _{0-tz} , C _{max} (metformin only)

Source: compiled during the evaluation.

¹Trial 1276.9 assessed bioequivalence of 5mg empagliflozin twice daily to empagliflozin 10mg once daily.

Abbreviations: FDC, fixed dose combination; IR, immediate release; BMI, body mass index; R, randomised; OL, open-label; CO, cross over; AUC_{0-infty}, area under the concentration-time curve of the analyte in plasma over the time from 0 to infinity; C_{max}, maximum plasma concentration; AUC_{0-tz}, area under the plasma concentration-time curve from time 0 to time t_z of the last measurable concentration; C_{max,ss}, maximum measured concentration of the analyte in plasma at steady state.

Comparative effectiveness

6.8 The results of bioequivalence study 1276.9, which compared empagliflozin 10mg once daily to empagliflozin 5mg twice daily are presented in Table 3.

Table 3: Bioequivalence of empagliflozin 5mg twice daily to empagliflozin 10mg daily in healthy adults

Trial	Regimes compared	Geometric mean ratio, % (90% CI)	
		AUC _{0-24,ss}	
1276.9	Empagliflozin 5mg twice daily	[REDACTED]	
	Empagliflozin 10mg daily		

Source: Table B.8.1, p254 of the submission.

Abbreviations: CI, confidence interval; AUC, area under the curve; ss, steady state; C_{max}, maximum measured concentration of the analyte in plasma; NA, not applicable

- 6.9 The results of the bioequivalence studies comparing the FDCs to their individual components are presented in Table 4.

Table 4: Bioequivalence of empagliflozin/metformin FDCs to individual components in healthy adults

Trial	FDC	Components tested	Food state	Geometric mean ratio, % (90% CI)	
				AUC _{0-infty}	C _{max}
1276.5	12.5mg/1000mg	Empagliflozin 12.5mg	Fasted	[REDACTED]	
		Metformin 1000mg			
1276.6	12.5mg/500mg	Empagliflozin 12.5mg	Fed	[REDACTED]	
		Metformin 500mg			
	5mg/500mg	Empagliflozin 5mg	Fed	[REDACTED]	
		Metformin 500mg			
1276.7	12.5mg/850mg	Empagliflozin 12.5mg	Fed	[REDACTED]	
		Metformin 850mg			
	5mg/850mg	Empagliflozin 5mg	Fed	[REDACTED]	
		Metformin 850mg			
1276.8	12.5mg/1000mg	Empagliflozin 12.5mg	Fasted	[REDACTED]	
		Metformin 1000mg			
	12.5mg/1000mg	Empagliflozin 12.5mg	Fed	[REDACTED]	
		Metformin 1000mg			
	5mg/1000mg	Empagliflozin 5mg	Fed	[REDACTED]	
		Metformin 1000mg			
1276.23	5mg/500mg	Empagliflozin 5mg	Fasted	[REDACTED]	
		Metformin 500mg			
	5mg/850mg	Empagliflozin 5mg	Fasted	[REDACTED]	
		Metformin 850mg			
	12.5mg/500mg	Empagliflozin 12.5mg	Fasted	[REDACTED]	
		Metformin 500mg			
	12.5mg/850mg	Empagliflozin 12.5mg	Fasted	[REDACTED]	
		Metformin 850mg			
1276.24	12.5mg/500mg	Empagliflozin 12.5mg	Fed	NR	
		Metformin 500mg		NR	

Source: Tables B.8.1, p254; B.6.13, p173; B.6.15, p175 of the submission.

Abbreviations: FDC, fixed dose combination; CI, confidence interval; AUC, area under the curve; infty, infinity; C_{max}, maximum measured concentration of the analyte in plasma; NR, not reported.

- 6.10 Sixteen-week HbA1c results for trial 1276.10, which compared the efficacy of twice daily to once daily dosing of empagliflozin (+ metformin), were consistent with non-inferiority, using the pre-specified non-inferiority margin of 0.35%.
- 6.11 Indirect comparisons between empagliflozin and dapagliflozin (with metformin as background therapy) were previously presented as part of the empagliflozin dual therapy submission at the July 2014 PBAC meeting.

Clinical claim

- 6.12 The submission claimed that the empagliflozin/metformin FDC is bioequivalent to the individual components taken concomitantly. This claim has been assessed by the TGA delegate who considered that bioequivalence had been demonstrated for each of the FDC tablets and their co-administered individual components.
- 6.13 The submission also claimed that empagliflozin (+ metformin) was non-inferior to the secondary comparator dapagliflozin (+ metformin) in terms of efficacy and safety. While there have been minor updates to the included trials and trial datasets, the results remain consistent with those previously presented at the July 2014 PBAC meeting.
- 6.14 The PBAC considered that the clinical claim was adequately supported.

Economic analysis

- 6.15 The submission presented a cost-minimisation analysis. The equi-effective doses for each of the FDCs are summarised in Table 5. These were consistent with the doses used to demonstrate bioequivalence.

Table 5: Equi-effective doses for the individual components of each FDC

Empagliflozin/metformin FDC	Equi-effective doses
5mg/500mg twice daily	Empagliflozin 10mg daily/metformin 500mg twice daily
5mg/850mg twice daily	Empagliflozin 10mg daily/metformin 850mg twice daily
5mg/1000mg twice daily	Empagliflozin 10mg daily/metformin 1000mg twice daily
12.5mg/500mg twice daily	Empagliflozin 25mg daily/metformin 500mg twice daily
12.5mg/850mg twice daily	Empagliflozin 25mg daily/metformin 850mg twice daily
12.5mg/1000mg twice daily	Empagliflozin 25mg daily/metformin 1000mg twice daily

Source: Table D.1.1 of the submission.

- 6.16 Table 6 summarises the proposed prices for the FDC tablets and their individual components. For each of the FDCs, the approved ex-manufacturer price per day was neutral compared to the daily cost of the individual components combined. There was a small reduction in the DPMQ for each FDC compared to the summed individual components.

Table 6: Empagliflozin, metformin (immediate release) and FDC prices

Resource item	Max. Qty	DPMQ	AEMP	AEMP/unit
PBS listed individual components				
Empagliflozin 10mg	30	\$60.97	\$47.01	\$1.57
Empagliflozin 25mg	30	\$60.97	\$47.01	\$1.57
Metformin IR 500mg	100	\$13.42	\$2.79	\$0.03
Metformin IR 850mg	60	\$13.42	\$2.79	\$0.05
Metformin IR 1000mg	90	\$15.65	\$4.86	\$0.05
Empagliflozin/metformin FDC				
Empagliflozin 5mg + metformin 500mg	60	\$62.76	\$48.68	\$0.81
Empagliflozin 5mg + metformin 850mg	60	\$63.96	\$49.80	\$0.83
Empagliflozin 5mg + metformin 1000mg	60	\$64.45	\$50.25	\$0.84
Empagliflozin 12.5mg + metformin 500mg	60	\$62.76	\$48.68	\$0.81

Resource item	Max. Qty	DPMQ	AEMP	AEMP/unit
Empagliflozin 12.5mg + metformin 850mg	60	\$63.96	\$49.80	\$0.83
Empagliflozin 12.5mg + metformin 1000mg	60	\$64.45	\$50.25	\$0.84

Source: Table D.2.1 of the submission.

Abbreviations: Max. Qty, maximum quantity; DPMQ, dispensed price for maximum quantity; AEMP, agreed ex-manufacturer price; FDC, fixed dose combination; IR, immediate release.

Drug cost/patient/year

- 6.17 Table 7 summarises the drug costs for a single patient for one year (based on 12.167 [=365/30] scripts per year).

Table 7: FDC drug costs per year

FDC (Empagliflozin/metformin)	Cost/patient/year
5mg/500mg	\$764
5mg/850mg	\$778
5mg/1000mg	\$784
12.5mg/500mg	\$764
12.5mg/850mg	\$778
12.5mg/1000mg	\$784

Estimated PBS usage & financial implications

- 6.18 This submission was not considered by DUSC. The financial analysis was based on a market share approach where a proportion of the patients taking a sodium glucose cotransporter 2 (SGLT2) inhibitor and metformin switch to the empagliflozin/metformin FDC.
- 6.19 Future SGLT2 inhibitor dual therapy uptake rates were predicted using historical monthly dipeptidyl peptidase-4 (DPP-4) inhibitor uptake rates (matched for time since PBS listing), derived from Medicare 10% sample data. The proportion of patients using a SGLT2 inhibitor/metformin FDC was estimated from the corresponding historical proportion of patients using a DPP-4 inhibitor/metformin FDC. The total estimated SGLT2 inhibitor/metformin FDC population was divided between the empagliflozin and dapagliflozin FDCs using a market share approach.
- 6.20 The estimated utilisation and financial implications associated with listing the FDC on the PBS are summarised in Table 8.

Table 8: Estimated empagliflozin/metformin FDC use and net financial implications for the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Total estimated SGLT2 + metformin prescriptions	██████	██████	██████	██████	██████
FDC share of SGLT2 + metformin market	██████	██████	██████	██████	██████
Empagliflozin/metformin FDC share of SGLT2/metformin FDC market, %	██████	█	█	█	█
Empagliflozin/metformin FDC prescriptions	██████	██████	██████	██████	██████
Empagliflozin/metformin FDC	██████	██████	██████	██████	██████

	Year 1	Year 2	Year 3	Year 4	Year 5
prescriptions (adjusted for pack size)					
Total cost empagliflozin/metformin FDC prescriptions (less co-payments)					
Cost to PBS/RPBS	\$	\$	\$	\$	\$
Total cost prescriptions to be replaced by empagliflozin/metformin FDC (less co-payments)					
Cost to PBS/RPBS	\$	\$	\$	\$	\$
Net financial implications of listing FDC					
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$

¹Market share estimated at █% for the first month of year 1, increasing incrementally each month to █% at the end of year 1. Abbreviations: SGLT2, sodium-glucose cotransporter 2; FDC, fixed dose combination; DPMQ, dispensed price for maximum quantity.

Source: Tables E.1.2, p275; E.1.3, p276; E.1.7, p280; E.2.1, p282; E.2.2, p283; E.2.3, p285; E.2.4, p286; E.3.1, p288; E.3.2, p289; E.3.3, p291; E.3.4, p292; E.4.1, p293 of the submission.

6.21 The submission estimated a saving of \$█ in the first year following listing, increasing to a saving of \$█ by year 5, resulting in a cumulative saving of less than \$10 million per year over the first 5 years. In general, substitution of empagliflozin/metformin FDC for the individual components resulted in a lower net cost to the PBS/RPBS, predominantly due to a reduction in anticipated mark-ups and dispensing fees which more than offset the decrease in co-payments received.

6.22 The utilisation and financial estimates were uncertain due to the following issues:

- The submission provided summary level data for the Medicare 10% sample used in the submission. No details of how the original Medicare data had been adapted for use in the submission were provided. The Pre-Sub-Committee Response (PSCR) (p1-2) reiterated the methodology used for this analysis.
- Market share projections for the dapagliflozin and empagliflozin FDCs are uncertain, especially given differences in dosing regimens, metformin release profiles, and the unclear timing of PBS listings. The PSCR (p2) stated that the dapagliflozin/metformin XR FDC (expected to compete with the empagliflozin/metformin FDC for market share) is now scheduled to be PBS listed in October 2015. The financial projections included in the submission had assumed listing in August 2015.
- Although the de-listing of canagliflozin from the PBS schedule was factored in to the market share assumptions, future SGLT2 inhibitor market dynamics following canagliflozin removal are inherently uncertain.
- There may be additional costs to the PBS derived from:
 - general patients previously self-funding metformin therapy who switch to the FDC,
 - patients prescribed a FDC and additional metformin concurrently.
- The assumption that SGLT2 dual therapy growth rates will mirror historical DPP-4 dual therapy growth, and that SGLT2/metformin FDC use will mirror historical DPP-4/metformin FDC may not be appropriate.

7 PBAC Outcome

7.1 The PBAC recommended empagliflozin/metformin FDC on a cost-minimisation basis with empagliflozin and metformin taken concomitantly. The equi-effective doses were empagliflozin 5mg/metformin 500mg twice daily and empagliflozin 10mg daily and metformin 500mg twice daily taken concomitantly.

- 7.2 The PBAC noted that positive recommendations were also made at the November 2015 meeting for empagliflozin in triple oral combination with metformin and a sulfonyleurea and in combination with insulin. The PBAC therefore advised that the restriction for empagliflozin/metformin FDC should include use for those indications.
- 7.3 The PBAC also recommended that the restriction permit a patient who had previously demonstrated that their diabetes was unable to be controlled with metformin or a sulfonyleurea to access PBS subsidised empagliflozin without the need to requalify. The PBAC noted that this was consistent with the restriction for dapagliflozin.
- 7.4 The PBAC considered that there was no reason to exempt empagliflozin/metformin FDC from the Safety Net 20 Day Rule.
- 7.5 The PBAC advised that empagliflozin/metformin FDC is suitable for prescribing by Nurse Practitioners for Continuing Therapy Only.
- 7.6 Under Section 101(3BA) of the *National Health Act 1953*, the PBAC advised that empagliflozin/metformin FDC should be treated as interchangeable on an individual patient basis with dapagliflozin/metformin FDC.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
EMPAGLIFLOZIN/METFORMIN Oral tablet, 5mg/500mg	60	5	Jardiancemet®/ Jardiamet® Boehringer Ingelheim
EMPAGLIFLOZIN/METFORMIN Oral tablet, 5mg/850mg	60	5	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 5mg/1000mg	60	5	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 12.5mg/500mg	60	5	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 12.5mg/850mg	60	5	
EMPAGLIFLOZIN/METFORMIN Oral tablet, 12.5mg/1000mg	60	5	

Authority required (Streamlined):

Dual therapy for Type 2 diabetes.

1. Empagliflozin/metformin

Category / Program	GENERAL – General Schedule (Code GE)
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Public Summary Document – November 2015 PBAC Meeting

Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with metformin; 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 despite treatment with metformin.
Population criteria:	-
Foreword	-
Definitions	-
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 treatment with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor is initiated. 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. 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 result 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. 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.
Administrative Advice	The fixed dose combination is not PBS-subsidised for use, as initial therapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.
Cautions	-

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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
Episodicity:	-
Severity:	-
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	Patient must have previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and empagliflozin.
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
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. The fixed dose combination is not PBS-subsidised for use, as initial therapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.
Cautions	-

2. Empagliflozin/metformin (triple therapy)

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
Episodicity:	-

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Severity:	-
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
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 optimal doses of dual oral therapy;</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 inhibitor despite treatment with optimal doses of dual oral therapy.</p>
Population criteria:	-
Foreword	-
Definitions	-

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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 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 (b) Had red cell transfusion within the previous 3 months</p> <p>The result 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>A patient whose diabetes was previously demonstrated unable to be controlled with metformin or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.</p>
<p>Administrative Advice</p>	<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: The fixed dose combination is not PBS-subsidised for use, as initial therapy 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 two of either: a gliptin, a glitazone or an SGLT2 inhibitor.</p>
<p>Cautions</p>	<p>-</p>

3. Empagliflozin/metformin (insulin add-on)

<p>Category / Program</p>	<p>GENERAL – General Schedule (Code GE)</p>
<p>Prescriber type:</p>	<p><input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input checked="" type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
<p>Episodicity:</p>	<p>-</p>
<p>Severity:</p>	<p>-</p>
<p>Condition:</p>	<p>Diabetes mellitus type 2</p>
<p>PBS Indication:</p>	<p>Diabetes mellitus type 2</p>

Public Summary Document – November 2015 PBAC Meeting

Treatment phase:	-
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<p>The treatment must be in combination with insulin, 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>
Population criteria:	-
Foreword	-
Definitions	-
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 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 result 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>

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), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.
Cautions	-

9 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.

10 Sponsor's Comment

The sponsor had no comment.