6.07 EMPAGLIFLOZIN
oral tablet, 10mg, 25mg
Jardiance®, Boehringer Ingelheim

1 Purpose of Application

1.1 The submission sought to extend the current PBS listing of empagliflozin 10mg and 25mg tablets to include an Authority Required (Streamlined) listing for the treatment of type 2 diabetes in combination with insulin, with or without metformin.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
EMPAGLIFLOZIN 10 mg tablet, 30	30	5	$60.97	Jardiance	Boehringer Ingelheim
EMPAGLIFLOZIN 25 mg tablet, 30	30	5	$60.97	Jardiance	Boehringer Ingelheim

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	-
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	The treatment must be in combination with insulin, AND Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a 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 Patient must have, or have had, whereHbA1c 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. ~~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.~~ ~~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.~~
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 gliptin, a glitazone, a glucagon-like peptide-1 or an 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.*

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:** 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.

2.2 The listing was requested on a cost minimisation basis compared to dapagliflozin.

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

3 Background

3.1 TGA status at time of PBAC consideration: Empagliflozin (10 and 25mg) was TGA registered on 17 April 2014 as an adjunct to diet and exercise in patients with Type 2 diabetes as monotherapy for whom metformin is otherwise indicated but considered inappropriate due to intolerance, and as add-on combination therapy with other glucose-lowering medicinal products including insulin.

3.2 Empagliflozin (Jardiance) 10mg and 25mg is currently listed on the PBS for dual oral therapy for the treatment of Type 2 diabetes in combination with metformin or a sulfonylurea (July 2014).

3.3 The starting dose for empagliflozin is 10mg daily. In patients tolerating empagliflozin 10mg and requiring additional glycaemic control, the dose can be increased to 25mg daily.

3.4 Empagliflozin has not previously been considered by PBAC in combination with insulin for Type 2 diabetes.

3.5 There were two concurrent submissions for empagliflozin in type 2 diabetes: empagliflozin in triple oral therapy; and empagliflozin plus metformin fixed dose combinations. 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 in combination with insulin, with or without metformin when therapy with insulin (± metformin) does not provide adequate glycaemic control.

4.2 Alternative agents for the treatment of type 2 diabetes in combination with insulin include diabetes medicines, both listed and not listed on the PBS:

- Up-titration of basal insulin
- Pre-mixed and rapid acting insulins
- Oral diabetes medicines i.e. sulfonylureas, other DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, pioglitazone and acarbose; and
- Fixed dose combinations of oral diabetes medicines with metformin (where available).

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

5 Comparator

5.1 The submission nominated dapagliflozin, PBS listed for use in combination with insulin (± metformin) on 1 April 2015, as the main comparator. This was the appropriate comparator. The submission also nominated exenatide and insulin up-titration or intensification as secondary comparators.

5.2 The PBAC considered dapagliflozin to be the appropriate 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 The submission was based on an indirect analysis comparing empagliflozin 10mg and 25mg plus insulin (Trials 1245.33, 1245.49, and 1245.36) with dapagliflozin plus insulin (Trial CT-006), using placebo plus insulin as the common comparator. The ESC considered the indirect comparisons to be appropriate.

6.4 The submission also presented two further indirect comparisons as supportive analyses for the clinical comparison, not used in the economic analysis:

- Empagliflozin 10mg and 25mg with insulin (Trials 1245.33 and 1245.49) versus exenatide with insulin (Trial GWCO) via placebo with insulin.

- Empagliflozin 25mg plus insulin (Trials 1245.33 and 1245.49) vs insulin intensification (Trial GWDM) via exenatide plus insulin, assuming non-inferiority of empagliflozin and exenatide.

6.5 Details of the trials presented in the submission are provided in Table 1.

Table 1 : Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Randomised trials used in the indirect comparisons		
Empagliflozin + insulin vs placebo + insulin		
Trial 1245.33	A phase IIb, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 10773 (10 mg and 25 mg) administered orally, once daily over 78 weeks in type 2 diabetic patients receiving treatment with basal insulin (glargine, detemir, or NPH insulin only) with or without concomitant metformin and/or sulfonylurea therapy and insufficient glycaemic control (NCT01011868)	11 January 2013
	Rosenstock J, Jelaska A, Kim G, Broedl UC, Woerle HJ. Empagliflozin as add-on to basal insulin for 78 weeks improves glycaemic control with weight loss in patients with Type 2 diabetes: A phase III, randomised, double-blind trial [POSTER]	*Diabetic Medicine* 2014; 31 (Suppl. 1):64
	Rosenstock J, Jelaska A, Wang F, Kim G, Broedl UC, Woerle HJ. Empagliflozin as add-on to basal insulin for 78 weeks improves glycaemic control with weight loss in insulin-treated type 2 diabetes	*Diabetes* 2013; 62 (Suppl. 1):A285
	Rosenstock J, Jelaska A, Wang F, Kim G, Broedl UC, Woerle HJ. Empagliflozin as add-on to basal insulin for 78 weeks improves glycaemic control with weight loss in insulin-treated type 2 diabetes mellitus	*Diabetologia* 2013; 56 (Suppl. 1):S372
Trial 1245.49	A phase III, randomized, double-blind, placebo-controlled, parallel group safety and efficacy study of BI 10773 (10 mg and 25 mg administered orally once daily) during 52 weeks in patients with type 2 diabetes mellitus and insufficient glycaemic control on MDI insulin regimen alone or with metformin (NCT01306214)	20 September 2013
	Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, Broedl UC; EMPA-REG MDI Trial Investigators. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycaemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes.	*Diabetes Care* 2014; 37 (7):1815-23
Trial 1245.36	A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg and 25 mg administered once daily) as add on to pre-existing antidiabetic therapy over 52 weeks in patients with type 2 diabetes mellitus and renal impairment and insufficient glycaemic control (NCT01164501)	07 January 2013
	Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, Broedl UC; EMPA-REG RENAL trial investigators. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial.	*Lancet Diabetes Endocrinology* 2014; 2 (5):369-84
Dapagliflozin + insulin vs placebo + insulin		
CT-006	A 24-week international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 80-week extension period to	August 2011

Trial ID	Protocol title/ Publication title	Publication citation
	evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycaemic control on insulin. Report for the 24-week short-term treatment period plus 24-week long-term extension period I and 56-week long-term extension period II. (NCT00673231)	
	Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S; Dapagliflozin 006 Study Group. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years.	*Diabetes, Obesity and Metabolism* 2014; 16 (2):124-36
	Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S; Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial.	*Annals of Internal Medicine* 2012; 156 (6):405-415
	Wilding JPH, Woo V, Pahor A, Sugg J, Langkilde A, Parikh S (2010) Effect of dapagliflozin, a novel insulin-independent treatment, over 48 weeks in patients with type 2 diabetes poorly controlled with insulin [POSTER]	*Diabetologia* 2010; 53 (Suppl. 1): S348
Exenatide + insulin vs placebo + insulin		
GWCO	A randomized trial comparing exenatide with placebo in subjects with type 2 diabetes on insulin glargine with or without oral antihyperglycemic medications (NCT00765817).	June 2010
	Rosenstock J, Shenouda SK, Bergenstal RM, Buse JB, Glass LC, Heilmann CR, Kwan AYM, MacConell LA, Hoogwerf BJ. Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimised insulin glargine in patients with type 2 diabetes.	*Diabetes Care* 2012; 35 (5):955-958
	Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AYM, Hoogwerf BJ, Rosenstock J. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes.	*Annals of Internal Medicine* 2011; 154 (2): 103-112
	Wintle M, Pencek R, Han J, Miller S, Buse J. Addition of fixed-dose exenatide to insulin glargine therapy improved glycaemic control without increasing hypoglycaemia or weight gain across a range of insulin titration.	*Diabetologia* 2012; 55 (Suppl. 1):S331
	Buse J, Glass L, Heilmann C, Shenouda S, Kwan AYM, Macconell L, Hoogwerf B. Weight change in placebo and exenatide (BID)-treated subjects with type 2 diabetes on insulin glargine: Effects of sex, diabetes duration, baseline A1C, and insulin dose. [POSTER]	*Diabetes* 2011; 60 (Suppl. 1):A266-A267
	Bergenstal RM, Buse JB, Glass LC, Heilmann CR, Lewis MS, Kwan AYM, Hoogwerf BJ, Rosenstock J. Exenatide added to insulin glargine-treated patients with type 2 diabetes provided excellent fasting and postprandial control with weight loss and no increased risk of hypoglycaemia.	*Diabetologia* 2010; 53: S37
	Buse JB, Han J, Miller S, Macconell L, Pencek R, Wintle M. Addition of exenatide BID to insulin glargine: A post-hoc analysis of the effect on glycemia and weight across a range of insulin titration.	*Current Medical Research and Opinion* 2014; 30 (7): 1209-1218
Exenatide + insulin vs insulin optimisation		
GWDM	A randomized trial comparing two therapies: Basal insulin glargine,	August 2013

Trial ID	Protocol title/ Publication title	Publication citation
	exenatide and metformin therapy (BET) or basal insulin glargine, bolus insulin lispro and metformin therapy (BBT) in subjects with type 2 diabetes who were previously treated by basal insulin glargine with either metformin or metformin and sulfonylurea (4b: basal insulin glargine, exenatide BD, and metformin therapy or basal insulin glargine, bolus insulin lispro and metformin therapy (NCT00960661). Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, de Vries D, Hoogwerf BJ, MacConell L, Wolffenbuttel BH; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimised basal insulin in type 2 diabetes. Diabetes Care. 2014 Oct; 37(10):2763-73.	*Diabetes Care* 2014; 37 (10):2763-2773

Source: Table B.5 (pp.40-41) of the submission, Table 3 (pp.7-8) of Appendix 7 of the submission, relevant clinical study reports (CSR) and publications

6.6 The key features of the direct randomised trials are summarised in Table 2.

Table 2 : Key features of the included evidence (indirect comparison)

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Empagliflozin + insulin versus placebo plus insulin					
1245.33	494	Randomised, double-blind. 18 weeks (primary) 78 weeks (secondary)	Low	HbA1c 7.0-10.0% treated with basal glargine or detemir insulin (≥20 IU/day) or NPH insulin (≥14 IU/day)	Change in HbA1c, weight, FPG, daily insulin dose, blood pressure from baseline to endpoint
1245.49	566	Randomised, double-blind. 18 weeks (primary) 52 weeks (secondary)	Low	HbA1c 7.5-10.0% treated with both basal and rapid acting insulin (>60IU/day)	Change in HbA1c, weight, FPG, daily insulin dose, blood pressure from baseline to endpoint
1245.36[a]	738	Randomised, double-blind. 24 weeks (primary) 52 weeks (secondary)	Low	HbA1c 7.0-10.0% pre-treated with any antidiabetic therapy excluding SGLT-2 inhibitors	Change in HbA1c from baseline to endpoint
Dapagliflozin plus insulin versus placebo plus insulin					
CT-006	808	Randomised, double-blind. 24 weeks (primary) 48 and 104 weeks (secondary)	Low	HbA1c 7.5-10.5% on stable insulin ≥30units/day.	Change in HbA1c, weight, FPG, daily insulin dose, blood pressure from baseline to endpoint
Exenatide plus insulin versus placebo plus insulin					
GWCO	261	Randomised, double blind 30 weeks	Low	HbA1c 7.1-10.5% on stable insulin glargine ≥20units/day	Change in HbA1c, weight, FPG, daily insulin dose, blood pressure from baseline to endpoint
Exenatide plus insulin versus insulin optimisation					
GWDM	627	Randomised, open label, active control; 30 weeks	Low		Change in HbA1c from baseline to endpoint

[a]Only a subgroup of patients using insulin were included in the main analyses
Source: compiled during the evaluation

6.7 The baseline characteristics of the trial populations were broadly similar. However, all trials excluded patients with a significant history of cardiovascular, degrees of renal or hepatic disease, whilst the proposed PBS population will include patients with these conditions.

6.8 Use of background oral diabetes medicines differed between trials. Trial 1245.33 included metformin and/or a sulfonylurea, Trial 1245.49 included metformin only, and Trials 1245.36 and CT-006 included any oral diabetes medicines. Rates of use of background oral therapies varied between trials from approximately 50-100% of patients.

6.9 There were substantial differences in baseline mean daily insulin dose, insulin type and insulin titration protocols between trials. Trial 1245.33 allowed basal insulin only and had a lower mean dose overall at baseline. Trial 1245.49 and Trial CT-006 were most comparable in terms of insulin type and mean daily dose. These differences limited the exchangeability between the empagliflozin trials used in the meta-analysis, and the exchangeability between the meta-analysed results of the empagliflozin trials and the dapagliflozin trial.

6.10 Trial designs and objectives varied between trials. Trial CT-006 and Trial 1245.49 were most similar in terms of design and objectives, which were to assess the impact of adding an SGLT2 inhibitor to a regimen of insulin with or without oral diabetes medicines. Trial 1245.33 assessed the effect of adding empagliflozin to basal insulin only, and the objective of Trial 1245.36 was to examine the impact of adding empagliflozin to a range of diabetes therapies in patients with varying levels of renal impairment.

Comparative effectiveness

6.11 Table 3 summarises the results of change in HbA1c from baseline in the empagliflozin and dapagliflozin trials in combination with insulin, and the indirect comparison between these treatments over 18-24 weeks.

Table 3: Results of mean change in HbA1c from baseline across randomised trials (indirect comparison): empagliflozin + insulin versus dapagliflozin + insulin

Trial	Empagliflozin	Placebo	Dapagliflozin	Mean difference (95% CI)
Empagliflozin 25mg vs. dapagliflozin 10mg (short-term HbA1c outcomes)				
1245.33, N = 242 (18 weeks)	-0.71 (0.76)	-0.01 (0.78)	-	-0.70 (-0.89, -0.51)
1245.49, N = 377 (18 weeks)	-1.02 (0.69)	-0.50 (0.78)	-	-0.52 (-0.63, -0.41)
1245.36 MILD, N = 78 (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
1245.36 MOD, N = 211 (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
CT-006, N = 339 (24 weeks)	-	-0.39 (0.72)	-0.97 (0.67)	-0.58 (-0.73, -0.43)
Meta-analysis of empagliflozin trials [WMD (95% CI)] I^2 = 59%				[redacted]
Indirect estimate of effect, results < 0 favour empagliflozin [WMD (95% CI)]				[redacted]
Empagliflozin 10mg vs. dapagliflozin 10mg (short-term HbA1c outcomes)				
1245.33, N = 242 (18 weeks)	-0.57 (0.8)	-0.01 (0.78)	-	-0.56 (-0.75, -0.37)
1245.49, N = 377 (18 weeks)	-0.94 (0.68)	-0.50 (0.78)	-	-0.44 (-0.58, -0.30)
1245.36 MILD, N = 78 (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
1245.36 MOD, N = 211 (24 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
CT-006, N = 339 (24 weeks)	-	-0.39 (0.72)	–0.97 (0.67)	-0.58 (-0.73, -0.43)
Meta-analysis of empagliflozin trials [WMD (95% CI)] I^2 = 0%				[redacted]
Indirect estimate of effect, results < 0 favour empagliflozin [WMD (95% CI)]				[redacted]

Source: Table B.39, pp. 125-126 of the submission; and Table 1, p. 5 of Appendix 6 of the submission
Abbreviations: WMD, weighted mean difference, SD, standard deviation, CI, confidence interval, MILD, mild renal impairment, MOD, moderate renal impairment.

6.12 The addition of empagliflozin 10mg or 25mg or dapagliflozin 10mg to background insulin therapy (± other oral diabetes therapies) produced significant reductions in HbA1c compared to placebo with insulin over 18-24 weeks. Results were consistent over 48-78 weeks.

6.13 In the indirect comparisons empagliflozin 10mg and 25mg demonstrated non-inferiority to dapagliflozin 10mg over 18-24 weeks. The upper limit of the 95% confidence interval was less than the pre-specified non-inferiority margin of 0.4%. Non-inferiority was also demonstrated over 48-78 weeks. The ESC considered the use of indirect comparisons appropriate to demonstrate equi-effective doses in this instance. The ESC viewed the pre-specified non-inferiority margin of 0.4% as reasonable, and recalled that the PBAC had generally accepted non-inferiority margins for HbA1c of 0.3% and/or 0.4%.

Comparative harms

6.14 Compared to placebo, both empagliflozin and dapagliflozin were associated with higher rates of hypoglycaemia, urinary tract infections and genital infections. Generally, the hypoglycaemia events did not require either non-medical or medical assistance. Similar proportions of patients experienced adverse events in the empagliflozin 10mg and 25mg arms.

6.15 A TGA communication released on 13 August 2015 warned that use of SGLT2 inhibitors, empagliflozin, dapagliflozin and canagliflozin may lead to ketoacidosis.

Clinical claim

6.16 The submission described empagliflozin 10mg and 25mg as non-inferior in terms of comparative effectiveness and similar in terms of comparative safety over dapagliflozin 10mg, when used in combination with insulin in the treatment of type 2 diabetes mellitus.

6.17 The PBAC considered that the clinical claim was adequately supported.

6.18 The PBAC recalled that it had previously accepted non-inferiority between empagliflozin and dapagliflozin in terms of comparative safety in dual oral therapy (July 2014 empagliflozin PSD).

Economic analysis

6.19 Cost-minimisation analysis. The equi-effective doses in the submission were:

Empagliflozin 10mg or 25mg = dapagliflozin 10mg

These estimates were based on the indirect analysis comparing empagliflozin and dapagliflozin. The PBAC has previously considered that empagliflozin 25mg is equi-effective to dapagliflozin 10mg [July 2014 Empagliflozin (dual therapy) PSD]. Due to the chronic nature of Type 2 diabetes, treatment is expected to be life-long.

6.20 The submission proposed a flat pricing structure for empagliflozin 10mg and 25mg, based on the listed price of dapagliflozin 10mg and similar to the listing for empagliflozin 10mg and 25mg in dual therapy (as at 1 July 2015).

Drug cost/patient/year: $[redacted]

6.21 At the requested DPMQ of $[redacted] for a 30 pack of empagliflozin 10mg or 25mg, the drug cost per patient per year for empagliflozin was estimated to be $[redacted] (assuming 12.17 packs per year). The DPMQ for dapagliflozin 10mg is $[redacted] for a 28 pack, with a drug cost per patient per year of $[redacted] (assuming 13.04 packs per year).

Estimated PBS usage & financial implications

6.22 This submission was not considered by DUSC. The submission presented a market share approach, with estimates based on extrapolated trends of use of any therapy with insulin (excluding triple therapy, which was included in the submission for empagliflozin triple oral therapy) derived from an analysis of the 10% Medicare sample. The submission also assumed the likely uptake of sodium glucose transporter-2 (SGLT2) inhibitors of the total insulin therapy market and substitution patterns.

6.23 Table 4 summarises the estimated extent of use and financial implications associated with listing empagliflozin in combination with insulin.

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Total number of PBS/RPBS SGLT2 inhibitor scripts (without empagliflozin)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of SGLT2 inhibitor scripts (with empagliflozin)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empagliflozin market uptake from SGLT2 inhibitors	[redacted]%[b]	[redacted]%	[redacted]%	[redacted]%	[redacted]%
- Empagliflozin 10mg (56% of total empagliflozin utilisation)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Empagliflozin 25mg (44% of total empagliflozin utilisation)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total empagliflozin scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS (less patient co-payments)					
Total cost of SGLT2 inhibitor market to PBS/RPBS net of patient co-payments (without empagliflozin)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost of SGLT2 inhibitor market to PBS/RPBS net of patient co-payments (with empagliflozin)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

[a]Number of prescriptions when empagliflozin is included in triple therapy market is slightly less due to larger pack size (30 pack) vs dapagliflozin (28 pack)
[b]In Year 1, market share of empagliflozin increases by approximately [redacted]% per month starting at [redacted]% at 1 April 2016 increasing to [redacted]% by 30 March 2017
[c]Assumption by sponsor
Abbreviations: SGLT2=sodium-glucose cotransporter 2
Source: Tables E.2-1 to E.2-4, E.3-1 to E.3-4, and E.4-1 of the submission

The redacted table above shows that the number scripts for empagliflozin is estimated to be 10,000 – 50,000 per year at a net cost to the PBS of less than $10 million per year.

6.24 The submission estimated that the listing of empagliflozin in combination with insulin will result in a small additional cost to the PBS. The estimate may not be reliable given the following issues:

- The 10% Medicare sample analysis used to estimate the total type 2 diabetes market in combination with insulin therapy was not provided and could not be verified. The Pre-Sub-Committee Response (PSCR) (p.2) reiterated the methodology used for this analysis, and expressed a willingness to provide the

raw 10% Department of Human Services data set should the PBAC consider this informative.

- Possible underestimates of the number of people with type 2 diabetes taking insulin therapy. The PSCR (p.3) argued that including the triple therapy insulin containing regimens in the estimation of the net impact to the PBS/RPBS of this submission would lead to double counting, across the sponsor's concurrent submission for empagliflozin triple combination therapy.
- Empagliflozin may increase the SGLT-2 inhibitor market in type 2 diabetes, as it offers dose titration and has slightly different characteristics (in precautions and contraindications as per product information) to dapagliflozin, allowing for use in a wider population depending on renal function, hepatic function and age. The PSCR (p.2) argued that the only difference between empagliflozin and dapagliflozin in terms of contraindications relates to renal function, with a stricter threshold for dapagliflozin compared with empagliflozin, and that any patients not eligible for treatment with dapagliflozin based on renal function are expected to be treated with empagliflozin, substituting with the SGLT2 inhibitor market. The ESC did not agree that these patients would be substituting within the existing SGLT2 inhibitor market and considered that the listing of empagliflozin had the potential to expand the market. Furthermore, the ESC also noted that dapagliflozin initiation is contraindicated in the over 75 years age group.

6.25 The 10 mg and 25 mg doses have very similar effects in the clinical trials, and the PBAC has previously accepted these as equi-effective doses. However, this has new clinical relevance in light of the sponsor's concurrent submission to the PBAC for a fixed dose combination of empagliflozin with metformin [item 5.06 refers], which includes a 12.5mg / 1000mg metformin dosing. In practice, the ESC expects that the 12.5mg /1000mg metformin FDC would be an effective, and preferred, once daily prescription. This would have follow-on implications for the FDC proposed maximum quantity of 60 tablets, as this equates to two months' supply if taken once daily, rather than the one months' supply suggested by the PBAC Guidelines. The PBAC noted that the sponsor in its Pre-PBAC response did not accept the ESC advice that a dosing of 12.5 mg / 1000 mg FDC would be sufficient as a one per day dose. The PBAC considered that the preferred prescription would be empagliflozin 12.5 mg / 1000 mg metformin per day plus 1000 mg of metformin.

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

7 PBAC Outcome

7.1 The PBAC recommended the PBS listing of empagliflozin in combination with insulin on a cost minimisation basis with dapagliflozin. The equi-effective doses were empagliflozin 10mg or 25mg and dapagliflozin 10mg.

7.2 The PBAC considered that there was no reason to exempt the empagliflozin from the Safety Net 20 Day Rule.

7.3 The PBAC advised that empagliflozin is suitable for prescribing by Nurse Practitioners for continuing therapy only.

7.4 Under Section 101(3BA) of the *National Health Act 1953,* the PBAC advised that

empagliflozin should be treated as interchangeable on an individual patient basis with dapagliflozin.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
EMPAGLIFLOZIN 10 mg tablet, 30	30	5	Jardiance	Boehringer Ingelheim
EMPAGLIFLOZIN 25 mg tablet, 30	30	5	Jardiance	Boehringer Ingelheim

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	-
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	-
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	The treatment must be in combination with insulin, AND Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a 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 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.

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 gliptin, a glitazone, a glucagon-like peptide-1 or an 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.
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:** 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.

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.