

5.4 EMPAGLIFLOZIN, oral tablet, 10 mg, 25 mg, Jardiance[®], Boehringer Ingelheim Pty Ltd

1 Purpose of Application

- 1.1 This submission seeks an Authority required listing for empagliflozin (Jardiance[®]) for the treatment of type 2 diabetes in combination with metformin or a sulfonylurea.

2 Requested listing

- 2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
EMPAGLIFLOZIN, ORAL TABLET, 10 MG.	30	5	JARDIANCE [®]	Boehringer Ingelheim
EMPAGLIFLOZIN ORAL TABLET, 25 MG.	30	5		

Authority required

Dual therapy with metformin or a sulfonylurea in patients unable to be adequately controlled by treatment with metformin and a sulfonylurea.

- 2.2 The evaluation noted that, following the change of gliptins to an earlier position in the PBS-subsidised treatment algorithm, (namely, second-line treatment), the current review of the restrictions of third line treatment options will alter the relative positioning of the gliptins and gliflozins in the treatment algorithm for type 2 diabetes, including the possibility that patients will be required to trial a gliptin prior to subsidised use of a gliflozin.
- 2.3 The Department's proposed amendments to the restrictions for PBS-subsidised third-line treatments for type 2 diabetes and sponsor responses to consultation on the proposed changes were considered by PBAC in a separate item on this agenda.
- 2.4 Listing is requested on a cost-minimisation basis compared to dapagliflozin and canagliflozin.

For PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Empagliflozin was recommended for inclusion on the ARTG at the 4 April 2014 meeting of the Advisory Committee on Prescription Medicines (ACPM). The ESC noted that the TGA indication was broader than the proposed restriction, as it included treatment with a dipeptidyl peptidase-4 (DPP-4) inhibitor (gliptin).
- 3.2 Empagliflozin has not previously been considered by the PBAC.

4 Clinical place for the proposed therapy

- 4.1 When diet, exercise and metformin monotherapy are inadequate in controlling blood glucose, current treatment guidelines for type II diabetes recommend adding a sulfonylurea. If dual therapy with metformin and a sulfonylurea is unsuccessful, treatment options include addition of: insulin, glucagon like peptide 1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins), thiazolidinediones (TZDs) (glitazones), or an SGLT-2 inhibitor (gliflozin).
- 4.2 The submission proposed that the place in therapy of empagliflozin is an alternative treatment option to the two currently listed gliflozin (dapagliflozin and canagliflozin).

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

5 Comparator

- 5.1 The submission nominated dapagliflozin and canagliflozin as the main comparators. The main argument provided in support of the comparators is that empagliflozin is a pharmacological analogue of both canagliflozin and dapagliflozin. The submission nominated sitagliptin as a supplementary comparator. However, dapagliflozin and canagliflozin have only recently been PBS-listed (December 2013) and are yet to establish a market. Therefore, it is possible that empagliflozin will substitute for gliptins. Sitagliptin (the most widely used gliptin) may therefore also be an appropriate main comparator. The previous dapagliflozin and canagliflozin submissions nominated sitagliptin as the main comparator.
- 5.2 The ESC considered that dapagliflozin and canagliflozin were the appropriate comparators as they are drugs of same pharmacological class and that the gliptins are now listed in an earlier line of therapy.

For PBAC's view, see section 7 "PBAC outcome"

6 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.

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

Clinical trials

- 6.3 A head-to-head trial of empagliflozin and sitagliptin was identified by the submission. Trial 1245.10 is a double-blind trial that compared empagliflozin 10 mg and 25 mg in combination with metformin with placebo plus metformin; and included an open label sitagliptin with metformin arm for sensitivity. The submission argued that the open label design means that the trial does not represent a true head-to-head comparison of empagliflozin and sitagliptin and exposes the results to bias. The submission acknowledged that the objective outcome of HbA1c lessens the risk of bias however safety outcomes are more likely to be subject to bias.

6.4 The submission is based on a series of indirect comparisons of empagliflozin and its comparators sitagliptin, canagliflozin and dapagliflozin:

Using placebo plus metformin as the common comparator:

- Empagliflozin 25mg plus metformin versus sitagliptin 100mg plus metformin;
- Empagliflozin 25 mg plus metformin versus dapagliflozin 10 mg plus metformin;
- Empagliflozin 10 mg plus metformin versus dapagliflozin 10 mg plus metformin;
- Empagliflozin 25 mg plus metformin versus canagliflozin 300 mg plus metformin;
- Empagliflozin 10 mg plus metformin versus canagliflozin 300 mg plus metformin;
- Empagliflozin 25 mg plus metformin versus canagliflozin 100 mg plus metformin;
- Empagliflozin 10 mg plus metformin versus canagliflozin 100 mg plus metformin.

Using a sulfonylurea plus metformin as the common comparator:

- Empagliflozin 25 mg plus metformin versus sitagliptin 100 mg plus metformin;
- Empagliflozin 25 mg plus metformin versus dapagliflozin 10 mg plus metformin;
- Empagliflozin 25 mg plus metformin versus canagliflozin 300 mg plus metformin.

6.5 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission for empagliflozin and its comparators sitagliptin, canagliflozin and dapagliflozin

Trial ID	Protocol title/ Publication title	Publication citation
Common reference using placebo+metformin		
EMPA+MET vs. PBO+MET (+OL SITA+MET)		
Study 1245.10	A Phase II, Randomised, Parallel Group Safety, Efficacy, and Pharmacokinetics Study of BI 10773 (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg) 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 Glycaemic Control Despite Metformin Therapy. NCT00749190 Rosenstock 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	Internal study report September 2010 Diabetes Obes Metab 2013; 15(12):1154-60
EMPA+MET vs. PBO+MET		
Study 1245.23	Trial 1245.23. A Phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg, 25 mg) 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.	Internal study report September 2012
Study 1245.31	Trial 1245.31. A Phase III double-blind, extension, placebo-controlled parallel group safety and efficacy trial of BI 10773 (10 and 25 mg 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 December 2012
SITA+MET vs. PBO+MET		
Bergental 2012	Bergental et al. Efficacy and Safety of Taspoglutide Versus Sitagliptin for Type 2 Diabetes Mellitus (T-Emerge 4 Trial). Bergental et al. Once weekly taspoglutide, a human GLP-1 analog, is superior to sitagliptin in improving glycemic control and weight loss in patients with type 2 diabetes (T2D): results from the T-emerge 4 trial.	Diabetes Ther 2012; 3:13 Diabetes 2010b; 59(Suppl 1):A16
Charbonnel 2006	Charbonnel et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone.	Diabetes care 2006; 29:2638-2643
Nucci 2011	Nucci et al. The sodium glucose co-transporter-2 (SGLT2) inhibitor, PF04971729, provides multi-faceted improvements in diabetic patients inadequately controlled on metformin [Abstract].	Diabetologia. 2011; 54(Suppl 1):S347.
Raz 2008	Raz et al. Efficacy and safety of sitagliptin added to ongoing metformin	Current Medical

Trial ID	Protocol title/ Publication title	Publication citation
	therapy in patients with type 2 diabetes.	Research and Opinion 2008; 24:537-550.
Scott 2008	Scott et al. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes.	Diabetes Obes Met 2008; 10(10):959-969
Yang 2012	Yang et al. The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes.	Journal of Diabetes 2012; 4(3):227-237
SITA+MET vs. CANA+MET vs. PBO+MET		
CANTATA-D	A randomised, double-blind, placebo and active-controlled, 4-arm, parallel group, multicentre study to evaluate the efficacy, safety and tolerability of canagliflozin in the treatment of subjects with type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy. NCT01106677 Lavalle-Gonzalez et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Nicolle, L. E., Capuano, G., Ways, K., & Usiskin, K. Effect of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study. Nyirjesy et al. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor.	ClinicalTrials.gov Diabetologia 2013; 56:2582–2592. Current Medical Research and Opinion 2012; 28(7):1167-1171. Current Medical Research and Opinion 2012; 28(7): 1173-1178.
Rosenstock 2012	Rosenstock et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes.	Diabetes Care 2012; 35:1232–1238.
DAPA+MET vs. PBO+MET		
Study CT-003	A 16-week, multicentre, randomised, double-blind, placebo-controlled phase III study to evaluate the safety and efficacy of dapagliflozin 2.5 mg BID, 5 mg BI and 10 mg QD versus placebo in patients with type 2 diabetes who are inadequately controlled on metformin-IR monotherapy (NCT01217892)	ClinicalTrials.gov
Study CT-012	A 24-week, Multicentre, Int., Double blind, Rand., Parallel group, Plac.-Controlled, Phase III Study With a 78-week Ext.Per. to Evaluate the Effect of Dapagliflozin in Combination With Metformin on Body Weight in Subjects With Type2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin Alone. NCT00855166. Bolinder 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. Ljunggren 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. Bolinder 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.	ClinicalTrials.gov J Clin Endocrinol Metab. 2012; 97:1020-31 Diabetes Obes Metab 2012;14:990-9 Diabetes Obes Metab 2014; 16:159–169.
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 et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Bailey et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomised, double-blind, placebo-controlled 102-week trial.	ClinicalTrials.gov Lancet 2010; 375: 2223-2233 BMC Med. 2013; 11:43
Common reference using sulfonylurea+metformin		
EMPA+MET vs SU+MET		
Trial 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	Internal study report January 2013

Trial ID	Protocol title/ Publication title	Publication citation
	metformin treatment. Ridderstrale 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(1): 129-139
SITA+MET vs SU+MET		
Koren 2012	Koren et al 2012. The effect of sitagliptin versus glibenclamide on arterial stiffness, blood pressure, lipids, and inflammation in type 2 diabetes mellitus patients.	Diabetes Technology and Therapeutics. 2012; 14(7): 561-567
Nauck 2007	Nauck MA et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial.	Diabetes Obes Met 2007; 9(2):194-205
Seck 2010b	Arechavaleta R et al 2011. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: A randomized, double-blind, non-inferiority trial.	Diabetes Obes Met 2011; 13(2):160-168
Srivastava 2012	Srivastava et al 2012. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone.	Journal of Association of Physicians of India 2012; 60(3):27-30.
DAPA+MET vs SU+MET		
Trial CT-004	A 52-Week International, Multicentre, 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 et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, 52-week, double-blind, active-controlled non-inferiority trial.	ClinicalTrials.gov Diabetes Care 2011; 34:2015-22
CANA+MET vs SU+MET		
CANTATA-SU	A Randomised, Double-Blind, 3-Arm Parallel Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy. NCT00968812. Cefalu et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial.	ClinicalTrials.gov Lancet. 2013, 382(9896): 941-950.

Source: Table B.7 (pp44-47), Table 5 (pp12-15) Attachment 5 of the submission.

Abbreviations: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; MET, metformin; PBO, placebo; SITA, sitagliptin; SU, sulfonylurea

6.6 The key features of the randomised trials are summarised in the table below.

Key features of the included evidence – indirect comparison

Trial ID	Design/duration/participant numbers	Risk of bias	Patient population	Primary Outcome(s)
Common reference using placebo+metformin				
EMPA+MET vs PBO+MET(+OL SITA+MET)				
Study 1245.10	R, DB, PC (12-week) EMPA 10mg (N=71), EMPA 25mg (N=70), OL SITA 100mg (N=71), PBO (N=71), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 12
EMPA+MET vs. PBO+MET				
Study 1245.23	R, DB, PC (24-week) EMPA 10mg (N=217), EMPA 25mg (N=213), PBO (N=207), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 24

Trial ID	Design/duration/participant numbers	Risk of bias	Patient population	Primary Outcome(s)
SITA+MET vs. PBO+MET				
Bergental 2012	R, DB, PC, AC (24-week) SITA 100mg (N=177), PBO (N=90), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 24
Charbonnel 2006	R, DB, PC (24-week) SITA 100mg (N=464), PBO (N=237), added to MET	Unclear	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 24
Nucci 2011 [abstract]	R, DB, PC (12-week) SITA 100mg, PBO, added to MET (total N=328)	Unclear	Type 2 diabetes patients on metformin	Change in HbA1c from baseline to week 12
Raz 2008	R, DB, PC (30-week) SITA 100mg (N=96), PBO (N=94), added to m MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 18
Scott 2008	R, DB, PC, AC (18-week) SITA 100mg (N=94), PBO (N=92), added to MET	Unclear	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 18
Yang 2012	R, DB, PC (24-week) SITA 100mg (N=197), PBO (N=198), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 24
SITA+MET vs. CANA+MET vs. PBO+MET				
CANTATA-D	R, DB, PC (26 weeks), AC (52 weeks) CANA 100mg (N=368), CANA 300mg (N=367), SITA 100mg (N=366), PBO (N=183), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 26
Rosenstock 2012	R, DB, PC, AC (26/52-week) CANA 100mg (N=64), CANA 300mg (N=64), SITA 100mg (N=65), PBO (N=65), added to MET	Unclear	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 12
DAPA+MET vs PBO+MET				
Study CT-003	R, DB, PC (16-week) DAPA 10mg (N=99), PBO (N=101), added to MET	Unclear	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 16
Study CT-012	R, DB, PC (24-week) DAPA 10mg (N=89), PBO (N=91), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in total body weight from baseline to week 24
Study CT-014	R, DB, PC (24-week) DAPA 2.5 mg (N=137), DAPA 5 mg (N=137), DAPA 10 mg (N=135), PBO (N=137), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change from baseline in HbA1c at week 24
Common reference using sulfonylurea+metformin				
EMPA+MET vs SU+MET				
Trial 1245.28	R, DB, AC (104-week) EMPA 25mg (N=769), glimepiride 1 to 4 m/day(N=780), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change from baseline in HbA1c after 104 weeks of treatment
SITA+MET vs SU+MET				
Koren 2012	R, P, OL, CO (28-week) Participant numbers: SITA 100mg, glibenclamide (5 mg & titrated as needed), added to MET (total N=40)	High	Type 2 diabetes patients inadequately controlled on metformin	Change from baseline to week 12 for cardiovascular risk factors
Nauck 2007	R, DB, AC (52-week) SITA 100 mg (N = 588), glipizide 5 - 20 mg (N =584), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline at week 52
Seck 2010b	R, DB, AC (30-week) SITA 100 mg (n = 516), glimepiride 1- 6 mg) (n = 519), added to MET	Low	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline at week 30

Srivastava 2012	R, AC (18-week) SITA 50/100-200 mg, glimepiride 1/2 - 4mg per day. (total N=50), added to MET	High	Type 2 diabetes patients inadequately controlled on metformin	Change in HbA1c from baseline to week 52
DAPA+MET vs SU+MET				
Trial CT-004	R, DB, AC (52-week) DAPA 2.5- 10mg (n = 406), glipizide 5-20mg) (n = 408), added to MET	Low	Type 2 diabetes pts inadequately controlled on metformin	Change in HbA1c from baseline to week 52
CANA+MET vs SU+MET				
CANTATA-SU	R, DB, AC (52-week) CANA 100 mg (N=483), CANA 300 mg (N=485), glimepiride 1- 6/8 mg) (N=482), added to MET	Low	Type 2 diabetes pts inadequately controlled on metformin	Change in HbA1c from baseline to week 52

Note: In studies with multiple arms and comparators table includes only arms of trials relevant to the submission
 Source: from individual trial reports & publications provided in the relevant references & attachments of the submission.
 Abbreviations: AC, active controlled; CANA, canagliflozin; DAPA, dapagliflozin; DB, double blind; EMPA, empagliflozin; HbA1c, glycosylated haemoglobin; MET, metformin; OL, open label; P, prospective; PC, placebo controlled; PBO, placebo; SU, sulfonylurea; OL=open label; R=randomised; CO= crossover trial; SITA= sitagliptin

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

Comparative effectiveness

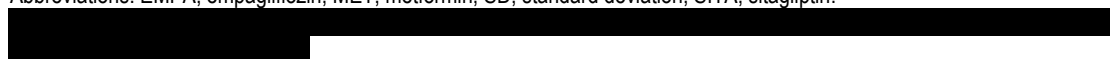
6.7 The evaluation noted that no data are presented to support the requested listing for empagliflozin in combination with a sulfonylurea. The PSCR (p2) stated that the approved TGA indication allows empagliflozin to be used as an add-on therapy. The ESC noted that the approved TGA indication is more broad compared to the requested PBS indication, and that this has been acknowledged by the sponsor.

6.8 The result of the head-to-head comparison of empagliflozin 25 mg and open-label sitagliptin 100 mg, in combination with metformin is summarised below.

Study 1245.10: comparison of empagliflozin and (open-label) sitagliptin with metformin

	EMPA 25mg+MET N=70	SITA 100mg+MET N=71	Mean difference (95% CI)
Mean (SD) change from baseline in HbA1c	██████████	██████████	██████████

Source: Table 45, p129 Attachment 5 of the submission
 Abbreviations: EMPA, empagliflozin; MET, metformin; SD, standard deviation; SITA, sitagliptin.



6.9 There was no statistically significant difference between empagliflozin 25 mg and sitagliptin 100 mg, both in combination with metformin. The results are consistent with non-inferiority using the nominated 0.4% non-inferiority margin. The submission does not present results comparing empagliflozin 10 mg with sitagliptin 100 mg.

6.10 The results of the indirect analyses using placebo plus metformin as the common comparator are summarised below. The submission appropriately considers these analyses as the primary analyses, due to the limited exchangeability between the trials included in the indirect analyses with a sulfonylurea and metformin as the common comparator (differences in the sulfonylurea used and the allowed sulfonylurea doses).The submission arbitrarily divides results into short term (12-16 weeks), medium term (18-30 weeks) and long term (52-104 weeks).

Mean change from baseline in HbA1c (%)

Comparison Time period	Empagliflozin+metformin mean difference (95% CI)	Comparator+metformin mean difference (95% CI)	WMD (95% CI) WMD<0 favours EMPA
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Empagliflozin versus sitagliptin with metformin (placebo plus metformin common comparator)			
	EMPA 25mg+MET	SITA 100mg+MET	
Short term (12 weeks)	██████████	██████████	██████████
Medium term (18-30 weeks)	-0.64 (-0.78, -0.50)	██████████	██████████
Empagliflozin versus dapagliflozin with metformin (placebo plus metformin common comparator)			
	EMPA 25mg+MET	DAPA 10mg+MET	
Short term (12-16 weeks)	██████████	-0.29 (-0.45, -0.13)	██████████
Medium term (24 weeks)	-0.64 (-0.78, -0.50)	██████████	██████████
Long term (52-102 weeks)	-0.70 (-0.84, -0.56)	██████████	██████████
	EMPA 10mg+MET	DAPA 10mg+MET	
Short term (12-16 weeks)	██████████	-0.29 (-0.45, -0.13)	██████████
Medium term (24 weeks)	-0.57 (-0.71, -0.43)	██████████	██████████
Long term (52-102 weeks)	-0.62 (-0.76, -0.48)	██████████	██████████
Empagliflozin versus canagliflozin with metformin (placebo plus metformin common comparator)			
	EMPA 25mg+MET	CANA 300mg+MET	
Short term (12 weeks)	██████████	-0.70 (-0.82, -0.58)	██████████
Medium term (24-26 weeks)	-0.64 (-0.78, -0.50)	-0.76 (-0.90, -0.63)	██████████
	EMPA 10mg+MET	CANA 300mg+MET	
Short term (12 weeks)	██████████	-0.73 (-0.98, -0.48)	██████████
Medium term (24-26 weeks)	-0.57 (-0.71, -0.43)	-0.76 (-0.90, -0.63)	██████████

Source: compiled during the evaluation

Abbreviations: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; MET, metformin; SITA, sitagliptin; WMD, weighted mean difference

- 6.11 The evaluation noted that the results of the indirect analyses comparing empagliflozin (10 mg and 25 mg) with its comparators sitagliptin, dapagliflozin and canagliflozin are consistent with non-inferiority using the 0.4% non-inferiority margin nominated in the submission. However, results favoured canagliflozin with some outcomes failing the more stringent non-inferiority margin of 0.3%.
- 6.12 The short term analyses include results measured at 12 weeks, which may not be sufficient for patients to achieve optimal glycaemic control. For the medium term analyses there are large differences in the common comparator arms for the sitagliptin comparison and large placebo responses in the dapagliflozin trials (-0.3%), suggesting the trials may not be exchangeable. The long term analyses against dapagliflozin may not be reasonable as they compare results at 52 versus 102 weeks and the dapagliflozin trial had small patient numbers.

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

Comparative harms

- 6.13 In the empagliflozin trials, empagliflozin with metformin was associated with higher rates of genital infections compared with metformin alone or metformin plus a sulfonylurea.

6.14 Indirect comparisons of a limited number of safety outcomes were presented in the submission. Empagliflozin plus metformin was associated with a statistically significantly lower proportion of patients with any adverse event compared with dapagliflozin plus metformin, at 24 weeks, but not at 52-102 weeks. There were no statistically significant differences between treatments in adverse events of special interest (hypoglycaemia, genital infections and urinary tract infections) however no data were presented versus sitagliptin. The results based on indirect comparisons are of limited value and should be interpreted with caution, given differences in definitions of adverse events, different time points and wide confidence intervals.

6.15 The ESC noted that there are limited long-term safety data for empagliflozin.

Benefits/harms

6.16 A summary of the comparative benefits and harms for empagliflozin versus comparator drugs (sitagliptin, dapagliflozin and canagliflozin) is presented below.

Summary of comparative benefits and harms for empagliflozin and comparator drugs (sitagliptin, dapagliflozin and canagliflozin): Data from medium term analyses; 18-30 weeks' duration

Benefits: Mean change in HbA1c						
Comparison Trials	Active treatment group		Common reference		Active treatment vs. common reference Mean difference (95% CI)	Indirect comparison: Mean difference (95% CI)
	n	Mean difference (SD)	n	Mean difference (SD)		
Empagliflozin 25mg+metformin vs. sitagliptin 100mg+metformin (placebo+metformin common comparator)						
EMPA 25mg+MET vs PBO+MET						
1245.23	213	-0.77 (0.73)	207	-0.13 (0.719)	-0.64 (-0.78, -0.50)	
SITA 100mg+MET vs PBO+MET						
Meta-analysis of sitagliptin 100mg+metformin vs placebo+metformin ^a						
Empagliflozin 25mg+metformin vs dapagliflozin 10mg+metformin (placebo+metformin common comparator)						
EMPA 25mg+MET vs PBO+MET					-0.64 (-0.78, -0.50)	
DAPA 10mg+MET vs PBO+MET						
Meta-analysis of dapagliflozin 10mg+metformin vs placebo+metformin ^b						
Empagliflozin 10mg+metformin vs dapagliflozin 10mg+metformin (placebo+metformin common comparator)						
EMPA 10mg+MET vs PBO+MET						
1245.23	217	-0.70 (0.74)	207	-0.13 (0.72)	-0.57 (-0.71, -0.43)	
DAPA 10mg+MET vs PBO+MET						
Empagliflozin 25mg+metformin vs canagliflozin 300mg+metformin (placebo+metformin common comparator)						
EMPA 25mg+MET vs PBO+MET					-0.64 (-0.78, -0.50)	
CANA 300mg+MET vs PBO+MET						
CANT ATA-D	360	-0.94 (0.77)	181	-0.18 (0.76)	-0.76 (-0.90, -0.63)	
Empagliflozin 10mg+metformin vs canagliflozin 300mg+metformin (placebo+metformin common comparator)						
EMPA 10mg+MET vs PBO+MET					-0.57 (-0.71, -0.43)	
CANA 300mg+MET vs PBO+MET					-0.76 (-0.90, -0.63)	
Harms						
Compar	Active	Common	OR	Event rate/100 patients		RD

ison Trials	treatment group	reference	(95% CI)	Active treatment group	Common reference	(95% CI)
Discontinuations due to adverse events						
Empagliflozin 10/25mg+metformin vs sitagliptin 100mg+metformin (placebo+metformin common comparator)						
Indirect comparison: 1245.23 and meta-analysis of Charbonnel 2006, Raz 2008, Scott 2008 and Yang 2012				21/851 (2.5)	14/620 (2.3)	NE
Empagliflozin 25mg+metformin vs dapagliflozin 10mg+metformin (placebo+metformin common comparator)						
Indirect comparison: 1245.23 and meta-analysis of CT-012 and CT-014				8/226 (3.5)	5/228 (2.2)	NE
Empagliflozin 25mg+metformin vs canagliflozin 300mg+metformin (placebo+metformin common comparator)						
Indirect comparison: 1245.23 and CANTATA-D				6/367 (1.6)	7/183 (3.8)	NE
Genital infections						
Empagliflozin 25mg+metformin vs dapagliflozin 10mg+metformin (placebo+metformin common comparator)						
Indirect comparison of 1245.23 and meta-analysis of CT-012 and CT-014				11/226 (4.9)	7/228 (3.1)	NE
Urinary tract infections						
Empagliflozin 25mg+metformin vs dapagliflozin 10mg+metformin (placebo+metformin common comparator)						
Indirect comparison of 1245.23 and meta-analysis of CT-012 and CT-014				9/214 (4.2) 13/367 (3.5)	8/206 (3.9) 7/228 (3.1)	NE
Empagliflozin 25mg+metformin vs canagliflozin 300mg+metformin (placebo+metformin common comparator)						
Indirect comparison: 1245.23 and CANTATA-D				9/214 (4.2) 13/367 (3.5)	8/206 (3.9) 4/183 (2.2)	NE

Source: compiled during the evaluation

Abbreviations: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; MET, metformin; NE, not estimated; PBO, placebo; SD, standard deviation; SITA, sitagliptin; OR, odds ratio; RD, risk difference.

^a Chi-square for heterogeneity: p=not reported; I² statistic=66%

^b Chi-square for heterogeneity: p=0.04; I² statistic=77%

Figures in italics have been updated from the pre-PBAC response

- 6.17 On the basis of the indirect evidence presented in the submission, the comparison of empagliflozin resulted in:
- A similar effect on HbA1c over 30 weeks compared to sitagliptin, dapagliflozin and canagliflozin.
 - Similar odds of discontinuing due to adverse events, genital infections and urinary tract infections at 18-30 weeks compared to sitagliptin, dapagliflozin and canagliflozin. The submission considers that empagliflozin is non-inferior in terms of safety to the comparator drugs.

For PBAC's view, see section 7 "PBAC outcome"

Clinical claim

- 6.18 The submission claimed that empagliflozin is non-inferior to sitagliptin, canagliflozin and dapagliflozin in terms of comparative efficacy and safety. The ESC considered the non-inferiority claim to dapagliflozin and canagliflozin to be reasonable.
- 6.19 The sitagliptin and dapagliflozin comparisons were generally consistent with non-inferiority in terms of mean change in HbA1c. The canagliflozin analyses were consistent with non-inferiority using the 0.4% non-inferiority margin, however non-inferiority was not consistently met using the more stringent 0.3% margin.
- 6.20 The ESC noted that empagliflozin appeared to have a similar safety profile to dapagliflozin and canagliflozin, however, there are inadequate data to determine comparative event rates.

- 6.21 The PBAC considered that the claim of non-inferior comparative effectiveness to canagliflozin and dapagliflozin was reasonable.
- 6.22 The PBAC noted the higher rates of genital infections and urinary tract infections reported in the empagliflozin with metformin trials compared with metformin alone or metformin plus a sulfonylurea and considered that these adverse events are a gliflozin class effect and are related to the increased levels of glucose in urine.
- 6.23 The PBAC considered that, overall, the claim of non-inferior comparative safety to dapagliflozin was reasonable on the basis of the adverse events comparison of empagliflozin plus metformin with dapagliflozin plus metformin at 52-102 weeks and on the information provided in the pre-PBAC response.

Economic analysis

- 6.24 The submission presented a cost-minimisation analysis. This is consistent with the clinical claim of non-inferiority of empagliflozin to dapagliflozin and canagliflozin.
- 6.25 The equi-effective doses are estimated by the submission as:
- Empagliflozin (10mg or 25mg) is equi-effective to canagliflozin 100mg. The ESC noted that empagliflozin does not require any dose adjustments in patients with renal inefficiency, whereas efficacy of canagliflozin is dependent on renal function in which 100 mg canagliflozin is recommended for patients with eGFR of 45 to < 60 mL/min/1.73m)
 - Empagliflozin (10mg or 25mg) is equi-effective to canagliflozin 300 mg.
 - Empagliflozin (10mg or 25mg) is equi-effective to dapagliflozin (10mg).
- 6.26 The submission does not propose equi-effective doses of empagliflozin and sitagliptin. Based on the analyses presented in the submission, empagliflozin 25mg may be equivalent to sitagliptin 100mg.

Empagliflozin proposed price and prices of comparators (sitagliptin, dapagliflozin and canagliflozin)

Product	Max Quantity	Ex-manufacturer	DPMQ
Sitagliptin 100mg ^a	28	\$44.34	\$59.07
Dapagliflozin 10mg	28	\$70.72	\$90.27
Canagliflozin 100mg	30	\$75.97	\$96.48
Canagliflozin 300mg	30	\$75.97	\$96.48
Empagliflozin 10mg	30	\$75.97	\$96.48
Empagliflozin 25mg	30	\$75.97	\$96.48

Source: Table D.3, p337 of the submission

Abbreviations: DPMQ, dispensed price per maximum quantity

^a On 1 April 2014, the DPMQ of sitagliptin was reduced from \$90.81 to \$59.07 and its restriction revised to remove the requirement that patients be contraindicated or intolerant to a combination of metformin and a sulfonylurea

- 6.27 The PBAC considered that, consistent with the approach taken with the other PBS-subsidised gliflozins, the equi-effective doses should be: empagliflozin 25 mg to canagliflozin 300 mg and dapagliflozin 10 mg.

Drug cost/patient/year}; \$1173.84

- 6.28 The cost per patient per year of empagliflozin is \$1,173.84. (= \$96.48/30x365). This is the same as the drug cost/patient/year for canagliflozin; for dapagliflozin the drug cost/patient/year is \$1,260.81; and for sitagliptin \$770.02. The ESC noted that empagliflozin has a flat pricing structure for 10 mg and 25 mg, as for canagliflozin

- 6.34 The ESC considered that the market uptake of empagliflozin was currently difficult to estimate because canagliflozin and dapagliflozin were newly PBS listed (December 2013) and the recent amendment to the PBS restrictions of gliptins took effect on 1 April 2014. Overall, the ESC considered adding another gliflozin on the PBS was unlikely to increase the substitution of a gliptin to a gliflozin, and any risk would be mitigated by a risk share agreement.

Financial Management – Risk Sharing Arrangements

- 6.35 At the July 2013 meeting, the PBAC recommended that a risk share arrangement (RSA) should be put in place for canagliflozin and dapagliflozin, “in order to manage the risk of possible usage outside the third line setting proposed by the sponsor” (July 2013 Public Summary Documents for dapagliflozin and for canagliflozin). The Public Summary Documents state that any other gliflozin listed on the PBS for use in the third line setting should be required to join the same RSA. The ESC noted that the PSCR (p4) states that it accepts that the sponsor will enter the existing risk share arrangement of dapagliflozin and canagliflozin.
- 6.36 The PBAC noted the shifting PBS-subsidised treatment algorithm for Type II diabetes mellitus and that the gliflozins are yet to establish their market share and true clinical place. The PBAC further noted that the shift of the gliptins to the second-line setting for subsidy purposes is expected to reduce the potential number of patients eligible for treatment with PBS subsidised third-line treatments, and thereby requires a re-evaluation of the caps in the existing RSA.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority required listing of empagliflozin for the third-line treatment of Type II diabetes in combination with metformin or a sulfonylurea.
- 7.2 The PBAC considered, among other matters, that the cost-effectiveness of empagliflozin would in its assessment be acceptable if it were cost-minimised against dapagliflozin and canagliflozin in terms of effectiveness, and dapagliflozin in terms of safety, and the measures below were implemented to contain risks associated with the cost of the drug to the PBS:
- Empagliflozin should join the same risk share as the other third-line PBS subsidised gliflozins, noting that re-evaluation of the caps in the existing RSA is required following the shift of the gliptins to the second-line setting for subsidy purposes, and the potential for the Government to incur additional costs should patients received 2 x 10 mg empagliflozin tablets in place of 1 x 25 mg tablet.
- 7.3 The equi-effective doses are empagliflozin 25 mg to canagliflozin 300 mg and dapagliflozin 10 mg.
- 7.4 The PBAC recommended that the PBS restriction of empagliflozin should be the same as the current restriction for dapagliflozin and canagliflozin. Subject to any issue raised by the sponsor, the PBS restriction of empagliflozin should also be amended in accordance with any changes to the restrictions for dapagliflozin and canagliflozin arising from the PBAC’s recommendations in relation to the review of the restrictions for the PBS subsidised third-line treatments for Type II diabetes (see separate agenda item).

- 7.5 The PBAC considered the choice of dapagliflozin and canagliflozin as comparators to be reasonable.
- 7.6 From the data presented in the indirect analyses comparing empagliflozin (10 mg and 25 mg) with its comparators, dapagliflozin and canagliflozin, the PBAC accepted the non-inferiority of empagliflozin in terms of effectiveness using a non-inferiority margin of 0.4% for HbA1c.
- 7.7 Overall, the PBAC accepted the non-inferiority of empagliflozin to dapagliflozin in terms of comparative safety.
- 7.8 Advice to the Minister under Section 101(3BA) of the *National Health Act*
The PBAC advised the Minister that under Section 101(3BA) of the *National Health Act*, empagliflozin should be treated as interchangeable on an individual patient basis with dapagliflozin and canagliflozin.
- 7.9 The PBAC advised that empagliflozin is suitable for prescribing by nurse practitioners for continuation therapy only where the patient is initiated by a medical practitioner.
- 7.10 The PBAC recommended that the Safety Net 20 Day Rule should apply.

Outcome:

Recommended.

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
EMPAGLIFLOZIN			Jardiance	BY
Empagliflozin 10 mg tablet, 30	1	5		
Empagliflozin 25 mg tablet, 30	1	5		

Condition/ Indication:	Diabetes mellitus type 2
Restriction:	Authority required
Clinical criteria	<p>The treatment must be in combination with metformin; OR The treatment must be in combination with a sulfonylurea,</p> <p>AND</p> <p>The condition must not be able to be adequately controlled by treatment with metformin and 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 (GLP1) or a sodium-glucose co-transporter 2 (SGLT2) inhibitor); 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, glitazone, glucagon-like peptide-1 or an SGLT2 inhibitor</p>
Prescriber	The date and level of the qualifying HbA1c measurement must be, or must have been,

<p>Instructions</p>	<p>documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a GLP1 or an SGLT 2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, glitazone, 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 GLP1 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>This drug is not PBS subsidised for use in combination with metformin and a sulfonylurea (triple oral therapy), as monotherapy or in combination with insulin, a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.</p>

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.