

6.03 DAPAGLIFLOZIN
10 mg tablet, 28,
Forxiga®, AstraZeneca Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission sought an Authority Required (Streamlined) listing for dapagliflozin 10mg tablets for the treatment of patients with type 2 diabetes mellitus (T2DM) in combination with metformin and a sulfonylurea (MET + SU).
- 1.2 At its November 2014 meeting, the PBAC stated that it “would welcome submissions for PBS listing of the triple oral therapy combination of metformin + sulfonylurea + SGLT2 inhibitor” (PBAC Ratified Minutes Type 2 Diabetes Medicines Post-Market Review, Para 5.7). This was based on a Network Meta-Analysis (NMA) of triple therapy trials included in the ‘Comparative Safety and Effectiveness of Type 2 Diabetes Medicines: Final Report September 2014’ prepared for the Post Market Review of Diabetes Medicines that indicated “that of the triple oral therapy options, metformin + sulfonylurea + SGLT2 inhibitor provided the largest reductions in HbA1c and likely important weight loss. The Committee also noted small reductions in systolic and diastolic blood pressure associated with the use of SGLT2 inhibitors.” However, the NMA did not include data on dapagliflozin triple oral therapy. Efficacy of SGLT2 inhibitors was informed by a trial of canagliflozin versus sitagliptin, on a background of MET+SU. The evaluation considered that the NMA may not be applicable to dapagliflozin triple oral therapy.

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	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DAPAGLIFLOZIN dapagliflozin 10 mg tablet, 28	1	5	TBA	Forxiga AZ

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority required (Streamlined)
Clinical criteria:	<p>The treatment must be in combination with metformin, AND The treatment must be in combination with a sulfonylurea 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 maximally tolerated doses of metformin and a sulfonylurea; 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 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.</p>
Prescriber Instructions	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time 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: (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 results 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	<i>Dapagliflozin 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'</i>

- 2.2 The PBAC noted the sponsor's request, in its pre-PBAC response, for a listing for the dapagliflozin+metformin XR fixed dose combination (FDC) for use in combination with sulfonylurea so as to align the restrictions between dapagliflozin and the FDC, noting that the FDC was recommended for use in the dual therapy setting in July 2014, but is yet to be listed.
- 2.3 Listing was requested on a cost-minimisation (including cost-offsets) basis compared to insulin glargine as the main comparator and exenatide as the secondary comparator.

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

3 Background

- 3.1 Dapagliflozin was TGA registered on 22 October 2012 for use in patients with T2DM: as monotherapy in patients for whom MET is not tolerated; initial combination therapy with MET; and add-on combination therapy with MET, SU, dipeptidyl peptidase-4 (DPP4) inhibitor or insulin.
- 3.2 On 4 March 2015, the registered indications were extended to include use in triple therapy with MET+SU.
- 3.3 The submission was lodged under the TGA/PBAC parallel process. At the time of evaluation, the Clinical Evaluator's Report and draft Product Information (PI) were available.
- 3.4 Dapagliflozin is currently PBS-listed as a second-line treatment in combination with MET or SU. In November 2014, the PBAC recommended dapagliflozin for use in combination with insulin. The PBAC has not previously considered listing dapagliflozin for use in combination with MET+SU.
- 3.5 The table below summarises previous PBAC considerations of T2DM triple therapy.

Relevant PBAC considerations of triple combination therapies for T2DM

Meeting	Item	Recommendation	Basis for listing/reasons for not recommending
Triple therapy with MET+SU			
Nov 2007	Pioglitazone		Cost-minimised to rosiglitazone
Nov 2008	Exenatide (with MET and/or SU)	Recommended	Cost-minimised to insulin glargine taking account of the higher costs of initiation and titration of insulin glargine. Equi-effective doses: exenatide 9.07mcg bd and insulin glargine 24.93 IU/day when used in triple therapy with MET and SU. The 2mg once weekly formulation was recommended in Nov 2013, cost-minimised to exenatide 10mcg bd
July 2012	Linagliptin	Not recommended	Insufficient evidence to accept the submission's clinical claim that linagliptin triple therapy is non-inferior in terms of comparative effectiveness to pioglitazone triple therapy.
Mar 2013	Liraglutide in dual/triple therapy	Recommended (not progressed by sponsor)	Cost-minimised to exenatide (BD). The PBAC did not accept the sponsor's claim of cost-offsets for one less needle per day (March 2013 Public Summary Document, Liraglutide).
July 2013	Vildagliptin	Not recommended	The PBAC did not accept pioglitazone as the appropriate comparator in view of concerns about adverse cardiovascular events and its diminishing use in the clinical treatment algorithm for T2DM.
July 2014	Lixisenatide (dual therapy with MET & triple therapy with MET+SU)	Not recommended	Cost-minimisation to exenatide was sought. The PBAC considered that non-inferiority to exenatide was not adequately established. 'The lower limit of the 95% CI (0.08%) did not include the null and so the results of the indirect comparison suggested with a high degree of certainty that lixisenatide is worse than exenatide 10mcg BD at lowering HbA1c. Further to this, whether a MCID margin of 0.3% or 0.4% is used to determine if the results are clinically significant, the PBAC noted that the upper limit of the 95% CI (0.62%) suggested that lixisenatide may be clinically worse than exenatide 10mcg BD. (July 2014 Public Summary Document, Lixisenatide Item 5.9.

Source: compiled during evaluation

Abbreviation: MET= metformin, SU= sulphonylurea, FDC= fixed dose combination, XR= extended release

4 Clinical place for the proposed therapy

- 4.1 T2DM is a chronic disease characterised by hyperglycaemia. Diet and exercise are the first steps in managing the disease, followed by the addition of metformin. When this is inadequate in controlling blood glucose, treatment guidelines generally recommend adding a sulphonylurea as the standard approach. Dapagliflozin and DPP-4 inhibitors ('gliptins') are now PBS-listed in this setting. If dual therapy is unsuccessful, insulin can be added. Other options include glucagon like peptide 1 (GLP-1) receptor agonists, thiazolidinediones ('glitazones') or acarbose.
- 4.2 The submission proposed dapagliflozin triple therapy in combination with MET+SU as an alternative treatment option, with a different mechanism of action, to the currently available antidiabetic agents.
- 4.3 The ESC noted that the following medicines are currently PBS-subsidised in triple therapy in combination with MET+SU: insulin, GLP-1 receptor agonists (e.g. exenatide), thiazolidinediones ('glitazones') and acarbose. Given these options, the ESC considered there may be use of dapagliflozin, along with gliptins, in triple oral

therapy in clinical practice. Such use may be occurring in the private market, or as PBS-subsidised therapy despite being outside the restrictions. The February 2013 DUSC analysis showed extensive use of gliptin + MET + SU, despite gliptins not being subsidised for use in this combination.

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

5 Comparator

- 5.1 The submission nominated insulin glargine as the main comparator and exenatide as a secondary comparator.

For more detail on 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 and welcomed the input from health care professionals (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dapagliflozin triple oral therapy including potential weight loss and blood pressure lowering, that it avoids the need for injectable agents which may be difficult for patients to commence and offers increased choice which may allow greater individualisation of treatment.

Clinical trials

- 6.3 The submission was based on two indirect comparisons comparing:
- dapagliflozin and insulin glargine, in combination with MET+SU; and
 - dapagliflozin and exenatide, in combination with MET+SU.
- An indirect comparison of dapagliflozin and vildagliptin, in combination with MET+SU, was included in an attachment to the submission.
- 6.4 Details of the trials presented in the submission are provided below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Dapagliflozin vs. placebo, both in combination with metformin and a sulfonylurea		
Trial CT005	A 24-week, multicentre, randomised, double-blind, placebo-controlled, international phase III Study with a 28-week extension period to evaluate the safety and efficacy of dapagliflozin 10mg once daily in patients with Type 2 diabetes who have inadequate glycaemic control on a background combination of metformin and sulfonylurea. Report for the 24-week short-term treatment period. Grandy, "Weight-related quality of life and treatment satisfaction among type 2 diabetes mellitus patients treated with dapagliflozin in triple-therapy regimen." Matthaei, "Improvement in glycaemic control and reduction in body weight over 52 weeks with dapagliflozin as add-on therapy to metformin plus sulphonylurea." Matthaei, "Improvement in glycaemic control and reduction in body weight over 52 weeks with dapagliflozin as add-on therapy to metformin plus sulfonylurea." Matthaei, "Dapagliflozin improves glycaemic control and reduces body weight as add-on therapy to metformin plus sulphonylurea." Sternhufvud, "Change in quality of life (EQ-5D) among type 2 diabetes mellitus patients inadequately controlled with metformin plus sulfonylurea and treated with dapagliflozin as triple therapy regimen for 24 weeks."	18 July 2013 Diabetes 2014 63: A204-A205 Diabetologia 2014a: 57(1): S347 Diabetes 2014b 63: A70-A71. Diabetologia 2013 56: S374-S375. Value in Health 2014 17(3): A257.
Russell-Jones 2009	Russell-Jones et al. "Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 MET+SU): A randomised controlled trial."	Diabetologia 2009 52(10): 2046-2055.
Trial 115	A Phase 3, Randomized, Double-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA1c) of Exenatide Given Twice Daily in Subjects With Type 2 Diabetes Mellitus Treated With Metformin and a Sulfonylurea. Kendall, "Effects of exenatide (exendin-4) on 6glycaemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea." Blonde, "Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes." Riddle, "Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin." Fineman, "Effect on glycaemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes."	27 April 2004 Diabetes Care 2005 28(5): 1083-1091. Diabetes, Obesity and Metabolism 2006 8(4): 436-447. Diabetes/Metabolism Research and Reviews 2006 22(6): 483-491. Diabetes Care 2003 26(8): 2370-2377.

Source: Table B.3, pB34-B35 of the submission

6.5 The submission also presented two network meta-analyses (NMA) as supportive evidence. One of these was the NMA of triple therapy trials included in the Post Market Review of Diabetes medicines. Overall, the NMAs included trials that are not applicable to dapagliflozin, the proposed PBS listing and/or the population requested in the submission.

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

Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Dapagliflozin vs placebo					
CT005	218	RCT, DB, MC 24 wks with a 28 wk extension	Low	HbA1c 7-10.5% on stable MET dose \geq 1500mg/day and maximum tolerated dose of SU (at least 50% of maximum dose)	HbA1c
Insulin glargine vs placebo					
Russell-Jones 2009	581 (n=349 for insulin glargine and placebo arms)	R, MC 26 weeks OL for insulin glargine treatment arm	Low	HbA1c 7.0-10% on oral glucose-lowering drug combination therapy (95% of trial population on combination therapy).	HbA1c and weight
Exenatide vs placebo					
Trial 115	734 (n=488 for exen 10mcg and placebo arms)	R, DB, MC 30 weeks	Low	HbA1c 7.5-11% on stable MET dose \geq 1500mg/day and maximally effective dose of SU	HbA1c

Source: Compiled during the evaluation
Abbreviation: DB=double blind; MC=multi-centre; OL=open label; R=randomised

6.7 Differences were noted in SU doses administered within and between trials. Higher doses were administered in the placebo compared with active treatment arms in Trial 115 and Russell-Jones 2009, but comparable doses were administered in the placebo compared with active treatment arm in CT005.

The trials included in the indirect comparisons also differed with respect to:

- MET doses (due to different starting doses and dose titration protocols);
- baseline characteristics, especially HbA1c;
- trial duration (ranging from 24-30 weeks); and
- HbA1c changes from baseline in the placebo arm between the three trials.

The differences between trials were more apparent for the CT005 and 115 trials, suggesting that the trials are not exchangeable and that the indirect comparison of dapagliflozin and exenatide may not be valid.

6.8 The submission attempted to adjust for these differences by conducting two sensitivity analyses using alternative data from Trial 115:

- '24; ITT': The results at 24 weeks (rather than 30 weeks) so that the duration of treatment was the same as the dapagliflozin trial; and
- '30 Max SU': Patients who took the maximally effective dose of sulfonylurea, which was a pre-specified subgroup in the trial. The submission stated that the dosing of SU in the Max SU subgroup is more reflective of Australian treatment patterns, and is similar to the mean SU dose in Trial CT005. However, SU dosing variation remained within trial.

The large differences in placebo response also remained with both these analyses. These differences impact on the interpretation of the results and may preclude a meaningful indirect comparison with exenatide.

- 6.9 The submission used a non-inferiority margin of 0.5% change in HbA1c for the indirect comparison. The PBAC and international regulatory agencies have generally accepted non-inferiority margins for HbA1c of 0.3% and/or 0.4%. The evaluation considered that the submission's use of a higher non-inferiority margin was not adequately justified.
- 6.10 The ESC considered that a non-inferiority margin of 0.5% change in HbA1c was not appropriate because changes in HbA1c of greater than 0.4% may lead to clinically important differences in patient outcomes. The ESC further noted that the PBAC has generally accepted non-inferiority margins between 0.3% and 0.4%, and has not previously accepted a non-inferiority margin of 0.5% change in HbA1c for the primary analysis of a submission. The ESC considered that it may be clinically inappropriate to accept a non-inferiority margin of greater than 0.4% change in HbA1c. The ESC noted that the heterogeneity between the trials used in the indirect comparison would affect the precision of the estimate of change in HbA1c, but noted that it was difficult to determine the magnitude and direction of any bias.

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

Comparative effectiveness

- 6.11 The table below presents the results of change in HbA1c in the dapagliflozin, insulin glargine and exenatide trials and the indirect comparisons between treatments.

Mean change in HbA1c from baseline to week 24/26/30: dapagliflozin vs insulin glargine, dapagliflozin vs exenatide, as add-on therapy to metformin and sulphonylurea

Trial ID	Comparison	Week; population	LS mean change from baseline (s.e.)		Difference in LS mean change (95% CI)
			Active Treatment	Placebo	
Trial CT005	Dapagliflozin vs Placebo	24; FAS	-0.86 (0.07)	-0.17 (0.07)	-0.69 (-0.89, -0.49)
Russell-Jones (2009)	Insulin glargine vs Placebo	26; ITT	-1.09 (0.09)	-0.24 (0.11)	-0.85 (-1.04, -0.66)
Trial 115	Exenatide vs Placebo	30; ITT	-0.88 (0.08)	0.12 (0.08)	-1.00 (-1.20, -0.80)
		24; ITT	-1.04 (0.08)	0.06 (0.08)	-1.10 (-1.29, 0.92)
		30; Max SU	-1.05 (0.12)	-0.03 (0.11)	-1.02 (-1.30, -0.73)
Indirect comparisons					
Dapagliflozin vs Insulin glargine				24/26	0.16 (-0.11, 0.43)
				24/30	0.31 (0.03, 0.59)
Dapagliflozin vs Exenatide				24/24	0.41 (0.14, 0.68)
				24/30 Max SU	0.33 (-0.02, 0.68)

Source: Table B.24, pB97 of the submission

Abbreviations: CI, Confidence interval; FAS, Full analysis set; ITT, Intention to Treat; HbA1c, Glycosylated haemoglobin; LS, least squares; Max, maximum; PP, Per protocol; SE., standard error; SU, sulphonylurea; vs, versus; Wk, week.

Bolded figures are not non-inferior at the submission's nominated non-inferiority margin of 0.5% change in HbA1c.

- 6.12 Patients treated with dapagliflozin, insulin glargine and exenatide all achieved statistically significant reductions in HbA1c compared with placebo.
- 6.13 The indirect comparisons indicated that the criterion for non-inferiority of dapagliflozin versus insulin glargine was met when a margin of 0.5% is considered; however, non-inferiority was not met at a non-inferiority margin of 0.4%.
- 6.14 Dapagliflozin failed to meet the non-inferiority criterion versus exenatide when a margin of 0.5% (and 0.4%) was considered in all three of the comparisons between dapagliflozin and exenatide that were conducted in the submission:
- HbA1c measured at the end of the respective trials (24 vs 30 weeks);
 - HbA1c measured at 24 weeks in both trials; or
 - HbA1c measured at 24 weeks in CT005 and measured at 30 weeks in the Max SU sub-group of Trial 115. The submission states this is most likely due to the small number of subjects included in this analysis (109 patients in the dapagliflozin arm of CT005 and ~120 in the exenatide Max SU group).
 - Moreover, the results comparing the FAS/ITT populations at 24/30 and 24/24 of CT005 and Trial 115 suggested that dapagliflozin may be inferior to exenatide.
- 6.15 The table below presents the results of change in total body weight (kg).

Mean change in total body weight (kg) from baseline to Week 24/26/30: dapagliflozin vs insulin glargine, dapagliflozin vs exenatide, as add-on therapy to MET+ SU

Trial ID	Comparison	Week; population	Mean change in total body weight (kg) from baseline (s.e.)		Difference in LS mean change (95% CI)
			Active Treatment	Placebo	
Trial CT005	Dapagliflozin vs Placebo	24, FAS	-2.65 (0.26)	-0.58 (0.26)	-2.07 (-2.79, -1.35)
Russell-Jones (2009)	Insulin glargine vs Placebo	26; ITT	1.60 (0.33)	-0.42 (0.39)	2.02 (1.02, 3.02)
Trial 115	Exenatide vs Placebo	30; ITT	-1.60 (0.21)	-0.90 (0.21)	-0.70 (-1.30, -0.20)
		30; Max SU	-1.7 (0.27)	-0.8 (0.24)	-0.90 (-1.60, -0.20)
Indirect comparisons					
Dapagliflozin vs Insulin glargine				Wk24/26	-4.09 (-5.33, -2.85)
Dapagliflozin vs Exenatide				Wk24/30	-1.37 (-2.27, -0.47)
				Wk 24/30 Max SU	-1.17 (-2.18, -0.16)

Abbreviations: CI, Confidence interval; FAS, Full analysis set; ITT, intention to treat; LS, least squares; Max, maximum; s.e., standard error; SU, sulfonylurea; Wk, week.

Source: Table B.25, pB97-B98 of the submission

- 6.16 Treatment with dapagliflozin was associated with a statistically significant net improvement in body weight for the comparison with both insulin and exenatide. The submission claimed that the difference was clinically meaningful for the comparison with insulin based on the statement in the RACGP ‘General practice management of type 2 diabetes, 2014–15’ Guidelines that weight loss of >2-3kg may result in a clinically meaningful reduction in systolic blood pressure. The PBAC has previously expressed a preference for evidence relating to changes in body weight to be from properly designed weight loss or quality of life studies.

- 6.17 The evaluation had stated that, based on the evidence presented in the submission, it was unclear what proportion of weight loss was attributable to reductions in body fat versus lean body mass (including fluid loss). The PBAC noted a study by Bolinder et al 2012, which showed that a significant proportion of the weight loss associated with dapagliflozin, when used in combination with metformin (dual therapy), resulted from a reduction in total-body fat mass.¹

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

Comparative harms

- 6.18 No statistically significant differences between dapagliflozin and placebo or insulin glargine and placebo were observed in terms of the adverse events reported. A statistically significantly greater proportion of patients treated with exenatide 10mcg experienced at least one adverse event compared with placebo. There was no statistically significant difference in patients experiencing at least one significant adverse event between dapagliflozin and insulin (OR=0.16: 95% CI [0.02, 1.63]) or exenatide (OR 0.21: 95% CI [0.02, 2.10]). However, for some of the safety outcomes there were substantial differences in adverse events rates between the common comparator (placebo) arms, including the comparison with exenatide for the outcome of patients experiencing at least one adverse event. The dapagliflozin and exenatide trials do not appear to be exchangeable for safety outcomes.
- 6.19 There was no statistically significant difference between dapagliflozin and either insulin or exenatide in the number of patients who experienced at least one hypoglycaemic event. The submission acknowledged that there are substantial variations in the control group event rates for hypoglycaemia between the trials (3.7% versus 12.6% versus 16.7%). This may be due to differences in SU dosing, definitions of hypoglycaemia and reporting of hypoglycaemia. The trials do not appear to be exchangeable for hypoglycaemia outcomes.
- 6.20 While there was no increase in rates of urinary tract infections (UTIs) with dapagliflozin compared to insulin glargine or exenatide, this appeared to be driven by the high rates of UTIs in the placebo arm of CT005. It is unclear why the rate of UTIs was substantially higher in the placebo arm of CT005 than the placebo arms of Russell-Jones and Trial 115.
- 6.21 Dapagliflozin was associated with more events suggestive of a genital infection than placebo. The submission does not present an indirect comparison of the risk of genital infections between dapagliflozin and insulin glargine or exenatide because event rates were not reported in Russell-Jones 2009 and Trial 115.
- 6.22 A summary of the comparative harms for dapagliflozin versus insulin glargine and exenatide is presented below.

¹ Bolinder 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 glycaemic control on metformin. *J Clin Endocrinol Metab.* 2012; 97(3):1020-31.

Summary of comparative harms for dapagliflozin and insulin glargine and exenatide

Harms								
	Active Tx n/N (%)	PBO n/N (%)	RR (95% CI)	Event rate/100 patients				RD (95% CI)
				DAPA	Insu- in	EXE	PBO	
Adverse event (at least one): indirect comparison								
Trial CT005: DAPA ^b	53/109 ^b (48.6%)	56/109 ^b (51.4%)	0.95 (0.73, 1.23)	49	-	-	51	-2.8% (-16.0%, 10.5%)
Russell-Jones (2009) insulin	127/232 (54.7%)	64/114 (56.1%)	0.98 (0.80, 1.19)	-	55	-	56	-1.4% (-12.5%, 9.7%)
Trial 115 EXE	224/241 (92.9%)	203/247 (82.2%)	1.13 (1.06, 1.21)	-	-	93	82	10.8% (5.0%, 16.5%)
Indirect comparison: DAPA vs Insulin glargine			0.97 (0.70, 1.35)	-				-1.4% (-18.7%, 16.0%)
Indirect comparison: DAPA vs EXE			0.84 (0.64, 1.10)	-				-13.5% (-28.0%, 1.0%)
Significant adverse event (at least one): indirect comparison								
Trial CT005: DAPA ^b	1/109 (0.9%)	6/109 (5.5%)	0.17 (0.02, 1.36)	1	-	-	6	-4.6% (-9.2%, 0.1%)
Russell-Jones (2009) insulin	16/232 (6.9%)	8/114 (7.0%)	0.98 (0.43, 2.23)	-	7	-	7	-0.1% (-5.8%, 5.6%)
Trial 115 EXE	11/241 (4.6%)	15/247 (6.1%)	0.75 (0.35, 1.60)	-	-	5	6	-1.5% (-5.5%, 2.5%)
Indirect comparison: DAPA vs Insulin			0.17 (0.02, 1.62)	-				-4.5% (-11.8%, 2.9%)
Indirect comparison: DAPA vs EXE			0.22 (0.02, 2.07)	-				-3.1% (-9.2%, 3.0%)

Abbreviations: Tx = treatment; DAPA = dapagliflozin; EXE = exenatide; ITT = intention to treat; LS = least squares; PBO = placebo; RD = risk difference; RR = risk ratio; SE = standard error; FAS = Full Analysis Set. CI, confidence interval; n, number with event; Max, maximum; N, number in group; SU, sulfonylurea; vs, versus; Wk, week.

^b Safety Analysis Set was used for safety outcomes of CT005.

Source: Table B.23, B.24 and B.33, pB91-B105 of the submission

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

Clinical claim

6.23 The submission described dapagliflozin 10mg/day, in combination with MET+SU, as non-inferior to both insulin glargine 24 IU/day and exenatide 10mcg BD in terms of comparative efficacy relating to glycaemic control, as measured by HbA1c. The evaluation considered that the claim with respect to the comparative efficacy of dapagliflozin and insulin glargine is only supported when considering a non-inferiority margin of 0.5% for change in HbA1c. Non-inferiority of dapagliflozin compared with insulin glargine is not supported when considering a margin of 0.4%; and non-inferiority of dapagliflozin and exenatide is not supported when considering a non-inferiority margin of 0.4 or 0.5% and in fact, there are indications that dapagliflozin may be inferior to exenatide. The evaluation also noted there was significant heterogeneity between the trials, particularly in the trials comparing dapagliflozin and exenatide to placebo, as demonstrated by the large variation in placebo responses; thus this indirect comparison may not be valid.

6.24 The ESC considered that the submission's claim of non-inferiority against insulin glargine may be reasonable. While the non-inferiority criterion of 0.4% change in HbA1c was not met, the analysis approached non-inferiority (upper bound of the 95%

CI was 0.43%). This ESC considered that changes in HbA1c of greater than 0.4% may lead to clinically important differences in patient outcomes, and noted that it was difficult to determine the magnitude and direction of any bias inherent in the indirect comparison. However, the ESC acknowledged the clinical need for an oral regimen in triple therapy.

- 6.25 However, the ESC considered that the submission's claim of non-inferiority against exenatide was not adequately supported. The non-inferiority criterion of 0.4% change in HbA1c was not met for any of the analyses presented. For the primary analysis (FAS/ITT population at 24/30 weeks) the upper bound of the 95% CI was 0.59 [mean difference in HbA1c: 0.31% (95% CI: 0.03, 0.59)]. Moreover, results from the two of the three analyses presented against exenatide (i.e. the analyses comparing the FAS/ITT populations at 24/30 and 24/24 of CT005 and Trial 115) suggest that dapagliflozin may be inferior to exenatide because the 95% CI does not include null.
- 6.26 The submission described dapagliflozin 10mg/day, in combination with MET+SU, as having a different safety profile to both insulin glargine 24 IU/day and exenatide 10mcg BD, but as non-inferior with respect to comparative safety as measured by the occurrence of hypoglycaemic events, adverse events, significant adverse events and discontinuations due to adverse events. The evaluation considered that the claim with respect to the comparative safety of dapagliflozin and insulin glargine is reasonably well supported by the data presented in the submission for some of the safety outcomes. The dapagliflozin and exenatide results for adverse events are not comparable given the large differences in the placebo arms of CT005 and Trial 115, and the lack of exchangeability in terms of adverse event reporting between the two trials. Rates of hypoglycaemia are particularly difficult to compare between dapagliflozin and both insulin glargine and exenatide.
- 6.27 The PBAC considered that the claim of non-inferior comparative effectiveness to insulin glargine was reasonable.
- 6.28 The PBAC accepted that dapagliflozin has a different safety profile to insulin glargine and considered that the claim of non-inferior comparative safety was reasonable.
- 6.29 The PBAC did not accept the claim of non-inferior comparative effectiveness and safety to exenatide.

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

Economic analysis

- 6.30 The submission presented a cost-analysis versus insulin glargine and exenatide including drug acquisition costs and costs of healthcare resource consumption. The equi-effective doses were estimated as dapagliflozin 10mg (oral) and exenatide 20mcg (subcutaneous) and insulin glargine 24 IU/day (subcutaneous). The equi-effective doses were derived from an indirect comparison using trials that are not exchangeable, particularly for the exenatide comparison. The ESC considered the equi-effective doses based on trial data to be reasonable for the comparison with insulin, but not for exenatide.
- 6.31 The evaluation considered that it may be more appropriate to conduct the cost-minimisation analysis against insulin glargine only, given that non-inferiority has not been adequately demonstrated for the comparison with exenatide.
- 6.32 The cost-analysis derived the requested price of dapagliflozin from the following avoided costs:
- (i) drug costs - insulin glargine or exenatide;
 - (ii) cost of test strips, needles, GP and endocrinologist consultations and diabetes educator visits associated with insulin or exenatide; and
 - (iii) cost of reduced use of antihypertensive medicines compared with treatment with insulin glargine.

Cost-analysis: derived price for dapagliflozin based on avoided costs associated with treatment with insulin glargine and exenatide

Description	Dapagliflozin	Insulin glargine	Exenatide
Drug cost	-	\$338.68	\$1,160.94
<i>Treatment initiation</i>			
GP consultations	\$ (1/year)	\$37.05 (1/year)	\$37.05 (1/year)
Endocrinologist consultations	\$ (0/year)	\$85.55 (1/year)	\$0.00 (0/year)
Diabetes educator visits	\$ (0/year)	\$86.35 (1/year)	\$86.35 (1/year)
<i>Treatment titration to stabilisation</i>			
GP consultations	\$ (1/year)	\$0.00 (0/year)	\$37.05 (1/year)
Diabetes educator visits	\$ (0/year)	\$253.20 (4/year)	\$0.00 (0/year)
Blood glucose monitoring (glucose indicator test strip)	\$ (1/day)	\$297.19 (2/day)	\$148.60 (1/day)
Needles for insulin pen	\$ (0/day)	\$47.45 (1/day)	\$94.90 (2/day)
Reduced use of antihypertensive medicines with dapagliflozin compared with insulin	-	\$0.00	-
Derived price for dapagliflozin, 10mg, 28			
Total cost of treatment	\$	\$1,145.47	\$1,564.89
Incremental cost (compared with dapagliflozin)	-	\$922.78	\$1342.19
Derived price for dapagliflozin (DPMQ)	-	\$70.74	\$102.89
Weighted price (and weightings) for dapagliflozin (DPMQ)	\$	(75.8%)	(24.2%)

Source: compiled during the evaluation

Figures in italics are changes to the cost-analysis agreed to in the PSCR.

- 6.33 The cost-analysis did not include any incremental cost for monitoring and managing genital and urinary tract infections (UTIs) due to treatment with dapagliflozin. These

costs were included for the listing of dapagliflozin use in dual therapy with MET or SU; and the PBAC recently considered that these additional costs should be considered for dapagliflozin in combination with insulin versus up-titrated insulin (November 2014 PBAC Minutes, dapagliflozin).

- 6.34 The evaluation considered that for the comparison with insulin glargine, the claimed cost-offsets are likely overestimates:
- The assumption that treatment with insulin requires referral to an endocrinologist, and five additional diabetes educator visits per year was inadequately justified.
 - The assumed 50% reduction in antihypertensive medicine doses was based on blood pressure reductions observed in the indirect comparison and a meta-analysis of the effect of using lower dose combination antihypertensive regimens that does not support the proposed dose reductions. The same methodology was used in the November 2014 submission for dapagliflozin with insulin. However, following the ESC advice, the sponsor agreed to the removal of this offset (November 2014 PBAC Minutes, dapagliflozin). The PSCR (p4) accepted the removal of this cost-offset from the pricing derivation.
 - The unit price for glucose test strips was based on the PBS listed price (of \$53.50 per 100 strips), however, around 90% of patients obtain glucose testing strips through the National Diabetes Services Scheme (NDSS) (<http://www.pbs.gov.au/info/reviews/diabetes-stage-one-report>, Table 1). According to the NDSS, the price of a 100 pack of strips is \$39.29 (including patient co-payment). The PSCR (p4) agreed to weight the costs of test strips between PBS and NDSS use.
- 6.35 For the comparison with exenatide, the evaluation considered the requested price of dapagliflozin may be inadequately justified because non-inferiority had not been adequately demonstrated. The evaluation considered that it may be more appropriate to conduct the cost-analysis against insulin glargine only. The ESC considered this reasonable.
- 6.36 As the ESC did not agree with the non-inferiority claim to exenatide, the ESC did not provide advice to the PBAC on cost-offsets for dapagliflozin versus exenatide.
- 6.37 The ESC noted that the submission based its non-insulin offset calculations on the initial year of treatment and then assumed that the same non-insulin offsets achieved in the first year of therapy will be reproduced in every year of therapy. This was not considered to be an appropriate assumption for the costs that are avoided on initiation of treatment, and may also not be an appropriate assumption for some of the offsets that are avoided in the stabilization phase of treatment. The established method of dealing with this issue is to pro rata “one-off” costs over a period of treatment, usually a number of years for chronic therapies.

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

Drug cost/patient/year: \$ [REDACTED].

- 6.38 At the requested DPMQ of \$ [REDACTED] for a 28 tablet pack of dapagliflozin, the drug cost per patient per year for dapagliflozin is \$ [REDACTED] (assuming 13.04 packs per year).

- 6.39 The PSCR stated that if dapagliflozin is listed for use in combination with MET+SU, it is “expected to have three PBS indications (dual therapy, triple therapy and add-on to insulin) [REDACTED]”
- 6.40 The ESC noted that it was not intuitive to have differential pricing between the dual therapy and triple therapy indications because if a patient’s HbA1c is not adequately controlled on metformin plus dapagliflozin and a sulfonylurea is added, then the Commonwealth price for the dapagliflozin would increase from the dual therapy price to the triple therapy price.

Estimated PBS usage & financial implications

- 6.41 This submission was not considered by DUSC. The submission presented a market share approach, with estimates of use based on the assumption that current trends of use of triple therapy agents will continue in line with current trends. The submission distinguished between not expecting the listing of dapagliflozin to grow the total triple therapy market versus the listing growing the “reimbursed market”. For the purposes of estimating the net cost to the PBS, however, the requested listing of dapagliflozin is expected to increase the current triple therapy market.
- 6.42 The ESC noted that the PSCR accepted the removal of the use of anti-hypertensives from the cost-offset analysis and agreed to a weighted cost of blood glucose test strips. The ESC noted that these changes will slightly alter the estimated financial implications.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market share	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Packs ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/government					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net non-drug and antihypertensive medicine cost ^b	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Estimated total net cost					
Net cost to PBS/RPBS/government	-\$ [REDACTED]*	-\$ [REDACTED]*	-\$ [REDACTED]*	-\$ [REDACTED]*	-\$ [REDACTED]*

^a Assuming 13.04 per year as estimated by the submission.

^b Including costs offsets related to reduced use of antihypertensive medicines and insulin glargine and exenatide administration and management, specifically: blood glucose test strips, needles, GP and endocrinologist consultations and diabetes educator visits avoided.

* Figures based on original price presented in the submission. Changes accepted in the PSCR will slightly alter these figures.

Source: compiled during the evaluation

- 6.43 At year 5, the estimated number of packs dispensed was over 200,000 per year and the net cost to the PBS/RPBS would be approximately \$10-\$20 million per year.
- 6.44 The submission estimated that listing dapagliflozin for triple therapy will have a net cost to the PBS but a net save to government health budgets overall. The net save is likely to be an overestimate.

- The cost-offsets included in the estimates of financial implications to government are based on those calculated in the cost-analysis and are unlikely to be fully realised.
- In addition, the submission claimed that, in theory, the listing of dapagliflozin for triple therapy should be cost neutral to government but that the estimated cost saving estimate “is not unexpected in the context of a budget analysis where the complexity necessitates a number of assumptions” (p.E-171). That is, the estimated cost saving to overall government health budgets, of less than \$10 million in Year 1, and increasing to less than \$10 million in Year 5, is an overestimate.

6.45 Some of the cost-offsets included in the estimates of financial implications to Government are not costs to the Commonwealth.

7 PBAC Outcome

7.1 The PBAC recommended the listing of dapagliflozin for the treatment of type 2 diabetes mellitus in combination with metformin and a sulfonylurea (referred to as “triple oral therapy”). The recommendation was formed on the basis of a cost analysis compared with insulin (including drug acquisition costs and costs of healthcare resource consumption). The equi-effective doses are dapagliflozin 10mg (oral) and insulin glargine 24 IU/day (subcutaneous).

7.2 The PBAC accepted that dapagliflozin used in combination with metformin and a sulfonylurea is non-inferior to insulin in combination with metformin and a sulfonylurea.

7.3 The PBAC considered that there is a clinical need for an oral regimen in triple therapy, noting the advantages to patients of regimens that do not require injections.

7.4 The PBAC considered that insulin glargine was the appropriate main comparator, and exenatide was an appropriate secondary comparator.

7.5 The PBAC considered that the appropriate non-inferiority margin for change in HbA1c is 0.4%, or lower. The PBAC agreed with the ESC that changes in HbA1c of greater than 0.4% may lead to clinically important differences in patient outcomes.

7.6 The PBAC noted that using a 0.4% non-inferiority margin, dapagliflozin failed to meet the non-inferiority criteria versus insulin glargine in the indirect comparison presented. However, the Committee considered that, on balance, non-inferiority to insulin glargine could be accepted. In forming this view, the PBAC considered the following factors:

- the clinical need for an oral regimen in the triple therapy setting
- dapagliflozin triple oral therapy may have some clinical advantages including small reductions in body weight and small improvements in systolic blood pressure; and
- the upper bound of the 95% confidence interval was 0.43% and thus approached non-inferiority (% change in HbA1c of 0.16 [95% CI: -0.11, -0.43]). The PBAC agreed with the ESC that the heterogeneity between the trials for insulin and dapagliflozin would affect the precision of the estimate of change in HbA1c, noting that it was difficult to determine the magnitude and direction of

any bias inherent in the indirect comparison.

- 7.7 The PBAC considered that dapagliflozin has a different, but not worse, safety profile than insulin glargine as measured by the occurrence of adverse events, significant adverse events and discontinuations due to adverse events.
- 7.8 The PBAC considered that the increased incidence of UTIs and genital infections observed with dapagliflozin in dual therapy (with metformin or a sulfonylurea) was also likely to occur in the triple therapy setting. While the indirect comparison indicated that there was no statistically significant difference in the incidence of UTIs between dapagliflozin and insulin glargine in the triple therapy setting, the PBAC considered that this may have been driven by the high rates of UTIs in the placebo arm of the dapagliflozin trial (CT005). Further, while an indirect comparison couldn't be conducted for genital infections, the PBAC noted that dapagliflozin is associated with a higher rate of genital infections compared with placebo.
- 7.9 With regard to the comparison against exenatide, the PBAC considered that the indirect comparison was not interpretable due to the significant differences between the dapagliflozin and exenatide trials, including in patient baseline characteristics and doses of background therapies (particularly sulfonylurea doses). This heterogeneity was demonstrated by the large variation in placebo responses between the dapagliflozin trial (CT005) and the exenatide trial (Trial 115). Therefore, the PBAC could not reach a conclusion regarding the comparative efficacy and safety of dapagliflozin and exenatide (both in combination with metformin and a sulfonylurea).
- 7.10 Therefore, the PBAC agreed with the ESC that it would be appropriate to conduct the cost analysis against insulin glargine only.
- 7.11 The PBAC provided the following comments as to the suitability of each of the cost-offsets claimed in the submission compared to insulin glargine.

PBAC recommendation on each cost-offset presented in the submission (compared to insulin glargine)

Cost-offset claimed in the submission	PBAC recommendation
GP consultation of 1 more/year for initiation phase and 1 more/year for titration phase	The PBAC did not accept the claim of one additional GP consultation in either phase because no evidence was provided to justify the change in the number of GP visits.
Endocrinologist visit of 1 less/year	The PBAC did not accept one less endocrinologist consultation as it was inadequately supported. The PBAC noted that this cost offset was based on a study of practice patterns observed at Westmead hospital in Sydney. However this study was conducted five years ago. The PBAC considered that the number of endocrinologist visits may have changed since this time.
Diabetes educator visits of 1 less/year for initiation and 4 less/year for titration	The PBAC did not accept that there would be 5 less diabetes educator visits (1 at initiation and 4 for titration) every year, as patients are likely to continue to be referred to a diabetes educator for diabetes related issues other than injection technique and insulin dose titration. However the PBAC considered that a cost offset for one less diabetes educator visit a year would be reasonable.
Glucose test strips of 1 less/day	The PBAC accepted the cost offset for one less glucose indicator strip per day and noted that the sponsor had agreed to weight the cost of test strips between PBS and NDSS use.
Needles of 1 less/day	The PBAC accepted the cost offset of one less needle per day.
Anti-hypertensive medicines	The PBAC noted that the PSCR accepted the removal of this cost-offset from the pricing derivation.
Urinary tract and genital infections	The PBAC recommended that the costs of monitoring adverse events (including additional visits to the doctor, treatment with antibiotics and antifungals, and mid-stream urine testing) that were included for dapagliflozin in the dual setting should be applied to dapagliflozin in the triple oral therapy setting.

- 7.12 The PBAC considered that the appropriate process for consideration of the sponsor's request, made in the pre-PBAC response, to extend the listing of the dapagliflozin plus metformin XR fixed dose combination to the triple oral therapy setting would be through a minor submission.
- 7.13 The PBAC advised that the NOTE in the current restriction of dapagliflozin dual therapy will need to be amended to allow for triple oral combination therapy.
- 7.14 The PBAC advised that dapagliflozin is suitable for prescribing by nurse practitioners.
- 7.15 The PBAC recommended that the Safety Net 20 Day Rule should not apply as it does not apply to the current dapagliflozin listings.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

Public Summary Document – March 2015 PBAC Meeting

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
DAPAGLIFLOZIN dapagliflozin 10 mg tablet, 28	1	5	TBA	Forxiga	AZ

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	Authority required (Streamlined)
Clinical criteria:	<p>The treatment must be in combination with metformin, AND The treatment must be in combination with a sulfonylurea 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 maximally tolerated doses of metformin and a sulfonylurea; 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 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.</p>
Prescriber Instructions	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time 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: (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 results 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	<i>Dapagliflozin 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'</i>

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.

9 Sponsor's Comment

The Sponsor had no comment.