

7.4 DAPAGLIFLOZIN

Tablet; 10 mg;

Forxiga®; AstraZeneca Australia Pty Ltd.

Corrigendum

Replaced the November 2014 ratified PBAC minutes for dapagliflozin with the following revised minutes (Sections 7.6 – 7.10 are revised, replacing previous paragraphs).

1 Purpose of Application

- 1.1 The resubmission sought an Authority required listing of dapagliflozin 10 mg tablets for the treatment of type 2 diabetes (T2D) in combination with insulin. The first submission for this listing was considered by the PBAC at the March 2012 meeting and rejected on the basis of uncertain comparative clinical effectiveness (PBAC Minutes para.5.3.32, p.44).

2 Requested listing

- 2.1 The abridged requested listing is shown below:

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

Authority Required (STREAMLINED)

Diabetes mellitus type 2

Clinical criteria:

The treatment must be in combination with insulin,

AND

Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR

Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.

- 2.2 The listing was requested on a cost minimisation basis compared to up-titration or intensification of insulin therapy.
- 2.3 The requested listing was similar in scope to the March 2012 submission.

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

3 Background

3.1 Dapagliflozin was TGA registered on 22 October 2012 as an adjunct to diet and exercise in patients with type 2 diabetes as monotherapy for whom metformin is otherwise indicated but not tolerated, initial combination therapy with metformin and combination therapy with other anti-hyperglycaemic agents.

3.2 Dapagliflozin with insulin was previously rejected by the PBAC at the March 2012 meeting.

Summary of the previous submission and current resubmission

	Dapagliflozin, March 2012	Current resubmission
Requested PBS listing	<ul style="list-style-type: none"> Authority Required (Streamlined) - Combination therapy with insulin. <p>PBAC Comment: Streamlined Authority was not appropriate as dapagliflozin was a “first in class” agent with a novel mode of action, with possible use outside the requested indication (para.5.2.27).</p>	<ul style="list-style-type: none"> Authority Required - Diabetes mellitus type 2. The treatment must be in combination with insulin.
Requested price	<ul style="list-style-type: none"> ██████████ DPMQ. 	<ul style="list-style-type: none"> ██████████ DPMQ.
Main comparator	<ul style="list-style-type: none"> Pioglitazone. <p>PBAC Comment: Insulin should be included as an additional appropriate comparator, given reduction in insulin may be the objective of therapy in some patients (para.5.2.28).</p>	<ul style="list-style-type: none"> Insulin up-titration or intensification. Exenatide as secondary comparator.
Clinical evidence	<ul style="list-style-type: none"> An indirect comparison of dapagliflozin versus pioglitazone (in combination with insulin) using placebo (in combination with insulin) as a common comparator; one dapagliflozin trial (CT-006) and pooled results from two pioglitazone trials (Mattoo 2005 and in sensitivity analysis, Rosenstock 2002). <p>PBAC Comment: The PBAC noted substantial differences between the treatment of comparator arms between trials, added additional uncertainty to the indirect comparison. The exclusion of Rosenstock (2002) was inappropriate as it was the pivotal trial in the resubmission for listing pioglitazone for combination therapy with insulin (para.5.2.29-30).</p>	<ul style="list-style-type: none"> An informal multi-step indirect comparison of dapagliflozin and up-titrated insulin (in combination with insulin) using exenatide and various insulin regimens as common comparators; one dapagliflozin trial (CT-006) and pooled results from two exenatide trials (GWCO and GWDM).
Key effectiveness data	<ul style="list-style-type: none"> Difference in change in HbA1c from baseline, dapagliflozin vs pioglitazone -0.05, 95% CI (-0.29, 0.19), satisfying the non-inferiority margin of 0.35%. Including Rosenstock (2002), 0.16; 95% CI (-0.30, 0.68), not satisfying the non-inferiority margin of 0.35%. <p>PBAC Comment: The PBAC noted that only the pivotal analysis (excluding all pioglitazone trials other than Mattoo 2005) showed dapagliflozin was non-inferior to pioglitazone. Sensitivity analysis including Rosenstock 2005 with Mattoo, showed dapagliflozin did not satisfy the non-inferiority margin of 0.40%. Therefore, the PBAC was not convinced that dapagliflozin was non-inferior to pioglitazone in combination with insulin (para.5.2.31-32).</p>	<ul style="list-style-type: none"> Difference in change in HbA1c from baseline, dapagliflozin vs exenatide 0.11, 95% CI (-0.17, 0.39), satisfying the non-inferiority margin of 0.40%. Using MMRM analysis 0.16; 95% CI (0.13, 0.46), not satisfying the non-inferiority margin of 0.40%. Assumed exenatide equivalence to up-titrated insulin 37.5 units/day in Trial GWDM is applicable to dapagliflozin.

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	Dapagliflozin, March 2012	Current resubmission
Key safety data	<ul style="list-style-type: none"> Dapagliflozin was associated with an increased incidence of genital infection (particularly in women), urinary tract infection and uncertainty about long term safety, particularly due to possible signals for breast and bladder cancer. <p>PBAC Comment: The PBAC noted these safety concerns and considered there was insufficient evidence to support the claim of non-inferiority in terms of comparative safety (para.5.2.35-36).</p>	<ul style="list-style-type: none"> Unchanged from the previous submission.
Clinical claim	<ul style="list-style-type: none"> Non-inferiority to pioglitazone (in combination with insulin). <p>PBAC Comment: The PBAC was not convinced that dapagliflozin was non-inferior to pioglitazone in combination with insulin in terms of clinical efficacy or safety (para.5.2.31-32 & 5.2.36).</p>	Equivalence to 37.5 units of insulin per day; non-inferiority to exenatide (BD) (in combination with insulin).
Economic evaluation	<ul style="list-style-type: none"> Cost-minimisation with equi-effective doses: dapagliflozin 10mg = pioglitazone 30mg. <p>PBAC Comment: The PBAC considered the requested price of dapagliflozin based on the cost minimisation and F1 formulary price of pioglitazone was not justified (para.5.2.37).</p>	<ul style="list-style-type: none"> Cost-minimisation with equi-effective doses: dapagliflozin 10mg = exenatide 19.3µg = 37.5 units of insulin per day. Cost analysis estimating cost offsets to the MBS of ██████████ over 5 years.
Number of patients	<ul style="list-style-type: none"> Not estimated. 	<ul style="list-style-type: none"> ██████████ in Year 1 increasing to ██████████ in Year 5.
Estimated cost to PBS	<ul style="list-style-type: none"> Drug cost to PBS of ██████████ in Year 1 increasing to ██████████ in Year 5 for a total of ██████████ over the first 5 years of listing. A net savings of ██████████ in Year 1 increasing to a savings of ██████████ in Year 5 for a total savings of ██████████ over the first 5 years of listing. <p>PBAC Comment: The PBAC considered the submission's estimates were uncertain, given the safety concerns related to thiazolidinediones and dapagliflozin, the failure to consider patients with renal disease and the cost to the PBS if dapagliflozin was listed at the F2 formulary price of pioglitazone (para.5.2.26).</p>	<ul style="list-style-type: none"> Drug cost to PBS of ██████████ in Year 1 increasing to ██████████ in Year 5 for a total of ██████████ over the first 5 years of listing. A net cost of ██████████ in Year 1 increasing to ██████████ in Year 5 for a total of ██████████ over the first 5 years of listing.
PBAC decision	<ul style="list-style-type: none"> Rejected on the basis of an inadequate comparison across appropriate comparators and uncertain comparative clinical effectiveness (para.5.2.38). 	-

Source: Compiled during the evaluation

4 Clinical place for the proposed therapy

- 4.1 Type 2 diabetes is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, insufficient insulin secretion or both. Diet and exercise are the first steps in managing the disease, followed by initiation of drug therapy with metformin, or metformin with a sulfonylurea (if tolerated). Further treatment options include the addition of insulin, a glucagon like peptide 1 (GLP-1) analogue, a dipeptidyl peptidase-4 (gliptin) inhibitor, a thiazolidinediones (TZD), or a sodium glucose transporter 2 (SGLT-2) inhibitor, alone or in combinations.

- 4.2 The resubmission proposed dapagliflozin will be used in patients treated with insulin, after failure of maximum tolerated doses of oral diabetes medicines, in place of insulin up-titration or intensification.
- 4.3 The ESC noted that the resubmission does not exclude combination with metformin or a sulfonylurea, resulting in the possible use in dual or triple therapies with insulin. The DUSC considered that the use of dapagliflozin and insulin in a triple combination with metformin was clinically appropriate and should not be excluded.
- 4.4 The ESC also noted that dapagliflozin is contraindicated in patients with an eGFR<60 mL/min/1.73m² and that it is not for use in patients aged over 75 years.

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

5 Comparator

- 5.1 Up-titration or intensification of insulin. The ESC advised that this is the appropriate comparator. The resubmission also nominates exenatide and lixisenatide as secondary comparators. Exenatide may be an appropriate secondary comparator, but is not currently listed on the PBS for use in combination with insulin for diabetes mellitus type 2. Lixisenatide is not listed on the PBS and is not considered as an appropriate secondary comparator.
- 5.2 The ESC acknowledged the comment in the Pre-Sub-Committee Response (PSCR, p1) that the PBAC has previously expressed that up-titration insulin would be a specific comparator for dapagliflozin in this indication from the March 2012 PBAC submission.

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 (2) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with dapagliflozin in combination with insulin including better glycaemic control with lower insulin dose and weight loss.

Clinical trials

- 6.3 The submission is based on a multi-step informal indirect analysis comparing dapagliflozin to exenatide (in combination with insulin), then assuming reductions in up-titration of insulin observed in patients treated with exenatide (in combination with

insulin glargine) in the clinical trials are applicable to dapagliflozin, as illustrated below.

1. Indirect comparison of dapagliflozin + insulin (Trial CT-006) vs exenatide + insulin (GWCO) using placebo + insulin as a common comparator (i.e. a formal indirect comparison);
2. Insulin up-titration avoided with exenatide in Trial GWDM (exenatide + long-acting insulin vs long-acting + fast-acting insulin) is assumed to be applicable to dapagliflozin (i.e. an informal indirect comparison).

6.4 Details of the trials presented in the resubmission are provided in the following table.

Trials and associated reports presented in the resubmission

Trial ID	Protocol title	Publication citation
Randomised trials used in the indirect comparisons		
Study 006 (CT-006)	A 24-week international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 80-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycaemic control on insulin. Report for the 24-week short-term treatment period plus 24-week long-term extension period I and 56-week long-term extension period II. (NCT00673231). Wilding et al. Effect of dapagliflozin, a novel insulin-independent treatment, over 48 weeks in patients with type 2 diabetes poorly controlled with insulin.	CSR Date: August 2011. Diabetes Care 2010; 32(9): 1656-62.
GWCO	A randomized trial comparing exenatide with placebo in subjects with type 2 diabetes on insulin glargine with or without oral anti-hyperglycaemic medications. (NCT00765817). Bergenstal et al. Exenatide added to insulin glargine-treated patients with type 2 diabetes provided excellent fasting and postprandial control with weight loss and no increased risk of hypoglycaemia.	CSR Date: June 2010. Diabetologia 2010; 53: S37.
GWDM	A randomized trial comparing two therapies: Basal insulin glargine, exenatide and metformin therapy (BET) or basal insulin glargine, bolus insulin lispro and metformin therapy (BBT) in subjects with type 2 diabetes who were previously treated by basal insulin glargine with either metformin or metformin and sulfonylurea (4b: basal insulin glargine, exenatide BD, and metformin therapy or basal insulin glargine, bolus insulin lispro and metformin therapy). Diamant et al. Exenatide BD vs. Insulin Lispro TDS Added to Titrated Insulin Glargine QD in Metformin-Treated T2DM Patients Resulted in Similar Glycemic Control but Weight Loss and Less Hypoglycaemia (Conference abstract).	CSR Date: August 2013. Diabetes 2013; 62:A17-A18.
Supplementary randomised trials		
GetGoal-L	A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin.	Date: September 2011.

Trial ID	Protocol title	Publication citation
	Riddle et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L).	Diabetes Care 2013; 36(9): 2489-96.
GetGoal-L-Asia	A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin with or without sulfonylurea Seino Y, Min KW, et al. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia).	CSR Date: July 2011. Diabetes, Obesity and Metabolism 2012; 14(10): 910-917.

Source: Table B.6, pp.B13-16 of the resubmission, relevant Clinical Study Reports (CSR) and publications.
Abbreviations: BD, twice daily; CSR, Clinical Study Report.

6.5 The key features of the direct randomised trials are summarised in the following table.

Key features of the included evidence (indirect comparison)

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Dapagliflozin + stable basal insulin (mixed regimens) vs placebo + stable basal insulin (mixed regimens)					
CT-006	808	R, DB, MC, 24 wks with 48 wk and 104 wk extensions	Low	HbA1c 7.5-10.5% on stable insulin ≥30units/day	Change in HbA1c, weight, FPG, blood pressure from baseline to endpoint
Exenatide + optimised insulin glargine vs placebo + optimised insulin glargine					
GWCO	261	R, DB, MC, 30 wks	High	HbA1c 7.1-10.5% on stable insulin glargine ≥20units/day	Change in HbA1c, weight, FPG, blood pressure from baseline to endpoint
Exenatide + optimised insulin glargine vs optimised insulin lispro + optimised insulin glargine					
GWDM	627	R, OL, AC, prospective 30 wks	Low	HbA1c 7.0-10.0% on stable insulin glargine ≥20units/day	Change in HbA1c, weight, FPG, blood pressure from baseline to endpoint
Exenatide + optimised insulin glargine vs optimised insulin lispro + optimised insulin glargine					
GetGoal-L	496	R, DB, MC 24 wks	Low	HbA1c 7-10% on stable basal insulin ≥30 units/day ± metformin	Change in HbA1c, weight, FPG, blood pressure from baseline to endpoint
GetGoal-L-Asia	311	R, DB, MC 24 wks	Low	HbA1c 7-10% on stable basal insulin ≥10 units/day ± sulfonylurea	Change in HbA1c, weight, FPG, blood pressure from baseline to endpoint

Source: compiled during the evaluation.

Abbreviations: AC, active control; BD, twice daily; DB, double blind; FPG, fasting plasma glucose; MC, multi-centre; OL, open label; R, randomised.

6.6 There were substantial differences in baseline population characteristics and prior treatment regimens between trials (particularly CT-006 compared to GWCO and GWDM), with metformin use higher in trials GWDM (100%) and GWCO (82%) compared to CT-006 (44%). Insulin regimens vary substantially between trials in terms of types of insulin permitted, baseline doses, initial titration at the introduction

of the trial drug, ongoing titration throughout the treatment phase and rescue protocols.

- 6.7 GetGoal-L Asia differed from the other included trials in terms of baseline mean BMI, baseline mean daily insulin dose, prior and ongoing use of sulfonylureas and race, and was not sufficiently comparable with the other trials to justify inclusion in the indirect analysis.
- 6.8 The trials used in the multi-step indirect analysis are not comparable and the resubmission acknowledges that a formal indirect comparison was not appropriate due to non-exchangeability of the trials.
- 6.9 The ESC acknowledged the Pre-Sub-Committee Response's (PSCR, p1) comment that the PBAC has previously advised that up-titration of insulin would be a specific comparator for dapagliflozin in this indication, from the March 2012 PBAC submission. Overall, the ESC considered that the multi-step indirect comparison across three trials was limited by between-trial heterogeneity, particularly due to the baseline characteristics of trial participants.
- 6.10 The ESC further noted that the indirect comparison is sensitive to the method used to impute missing trial data. The non-inferiority of dapagliflozin versus exenatide (in combination with insulin) in the indirect analysis comparing Trial CT-006 with Trial GWCO is dependent on whether missing data for Trial CT-006 are analysed using last observation carried forward (LOCF) or mixed-effects model repeated measures (MMRM) imputation. As this represents a key component of the non-inferiority argument, greater justification for the preference for LOCF over a probabilistic imputation method such as MMRM would permit a more informed assessment of whether non-inferiority has actually been established at this particular stage of the indirect comparison.

Comparative effectiveness

- 6.11 Indirect analysis of dapagliflozin vs exenatide (trials CT-006 and GWCO) and the direct comparison between exenatide and insulin up-titration (Trial GWDM).

Results of mean change in HbA1c (%) from baseline (indirect analysis dapagliflozin vs exenatide)

Trial ID	Dapagliflozin + insulin HbA1c% (SE) N=194	Placebo + insulin HbA1c% (SE) N=193	Placebo + optimised glargine HbA1c% (SE) N=112	Exenatide + optimised glargine HbA1c% (SE) N=100	Difference in LS mean change in HbA1c% (95% CI)
CT-006	-0.9 (0.515)	-0.3 (0.0521)	-	-	-0.6 (-0.74, -0.45)
GWCO	-		-1.0 (0.09)	-1.71 (0.09)	-0.71 (-0.95, -0.47)
Indirect comparison					0.11 (-0.17, 0.39)

Source: Table B.20, p.B78 and Table B.39, p.B104 of the resubmission.

Abbreviations: LS, least square means; SE, standard error.

Results of LS mean change in HbA1c from baseline (exenatide vs up-titrated insulin)

	Optimised lispro + optimised glargine HbA1c% (SE) N=276	Exenatide + optimised glargine HbA1c% (SE) N=265	Difference in LS mean change in HbA1c% (95% CI)
GWDM	-1.07 (0.05)	-1.1 (0.05)	-0.03 (-0.16, 0.11)

Source: Table B.20, p.B78 of the resubmission.

Abbreviations: LS, least square means; SE, standard error.

Results of mean change in insulin dose (units/day) from baseline (indirect comparison)

Trial ID	Dapagliflozin + insulin Insulin U/day (SE) N=194	Placebo + insulin Insulin U/day (SE) N=193	Placebo + optimised glargine Insulin U/day (SE) N=112	Exenatide + optimised glargine Insulin U/day (SE) N=100	Difference in mean change in units/day (95% CI)
CT-006	-1.16 (0.935)	5.08 (0.943)	-	-	-6.23 (-8.84, -3.63)
GWCO	-	-	19.71 (2.1)	13.19 (2.2)	-6.52 (-12.24, -0.79)
Indirect comparison					0.29 (-5.98, 6.56)

Source: Table B.23, p.B84 and Table B.45, p.B10 of the resubmission.

Abbreviations: U, units of insulin; SE, standard error.

† A mean reduction of 10.3units/day of glargine and an increase of 42.1units/day of lispro.

Results of mean change in insulin dose (units/day) from baseline (exenatide vs up-titrated insulin)

	Optimised lispro + optimised glargine Insulin units/day (SE) N=315	Exenatide + optimised glargine Insulin units/day (SE) N=312	Difference in mean change in units/day (95% CI)
GWDM	-31.8 (3.609)	-4.4 (2.388)	-36.2 (-43.5, -27.7)

Source: Table B.23, p.B84 of the resubmission.

Abbreviations: U, units of insulin; SE, standard error.

- 6.12 There was no statistically significant difference in mean change in HbA1c between dapagliflozin 10mg once daily and exenatide 10ug BD (in combination with insulin) in the indirect analysis. The upper bound of the 95% confidence interval of the indirect comparison (0.39) was less than the pre-specified non-inferiority margin of 0.40%. Using the MMRM analyses from both the CT-006 and GWCO trials the result of the indirect analysis conducted during the evaluation is less favourable to dapagliflozin (0.16; 95% CI: -0.13, 0.46) and the upper bound of the 95% confidence interval no longer satisfies the pre-specified non-inferiority margin of 0.40%.
- 6.13 Trial GWDM shows no statistically significant difference in mean change in HbA1c between exenatide 10ug twice daily and insulin lispro three times daily (in combination with insulin glargine).
- 6.14 The trials used in the indirect analysis were not comparable and there were substantial differences in treatment regimens between common comparator arms. The resulting differences in response across the common comparator arms of the trials may bias the indirect analysis in favour of dapagliflozin.
- 6.15 There was no statistically significant difference in mean change in insulin dose between dapagliflozin 10mg once daily and exenatide 10µg twice daily (in combination with insulin). There was a large difference in the magnitude of the mean change in insulin dose between the placebo + insulin arms across trials CT-006 and GWCO which may be the result of optimisation of glargine during the treatment phase of Trial GWCO and maintenance of stable pre-trial insulin regimens in Trial CT-006.
- 6.16 In Trial GWDM patients treated with exenatide and insulin glargine reported a reduction in glargine use of 4.4units/day while patients treated with insulin glargine and lispro reported a reduction in glargine use of 10.3units/day and an increase in lispro use of 42.1units/day, an overall increase of 31.8units/day. This result showed a statistically significant difference in mean change in insulin use between exenatide

10µg twice daily and insulin lispro three times daily (in combination with insulin glargine) of 36.2units/day.

- 6.17 Given the similar reductions in HbA1c achieved by patients treated with dapagliflozin and exenatide (in combination with insulin) in the indirect analysis (trials CT-006 and GWCO), the resubmission suggests a similar reduction in insulin dose as seen with exenatide in Trial GWDM can be expected in patients treated with dapagliflozin. While the data suggest insulin dose may be reduced in patients taking dapagliflozin, given differences in mode action between dapagliflozin and exenatide, the magnitude of these reductions is not certain. No formal indirect analysis is presented and the resubmission acknowledges that the trials are not exchangeable.

Comparative harms

- 6.18 Patients treated with dapagliflozin were less likely to experience treatment emergent adverse events compared to patients treated with exenatide (OR 0.67: 95% CI [0.33, 1.37]), and more likely to experience serious adverse events (OR 1.59: 95% CI [0.47, 5.38]), but these differences were not statistically significant. Discontinuation of treatment related to an adverse event was low across all trials but slightly higher in exenatide treated patients compared to dapagliflozin.
- 6.19 Patients treated with dapagliflozin were more likely to experience hypoglycaemia events (OR 1.34: 95% CI [0.68, 2.65]), and more likely to experience urinary tract infections (OR 4.25: 95% CI [0.31, 58.2]) and genital infections (OR 27.84: 95% CI [1.09, 710.5]) compared to exenatide, but only the difference in genital infections was statistically significant. Patients treated with exenatide were more likely to experience nausea (OR 0.06: 95% CI [0.02, 0.49]) and vomiting (OR 0.38: 95% CI [0.03, 5.19]) compared to those treated with dapagliflozin.

Benefits/harms

- 6.20 A summary of the comparative benefits and harms for dapagliflozin versus exenatide (secondary comparator) and insulin up-titration is presented in the following table.

Summary of comparative benefits and harms for dapagliflozin and exenatide

Benefits							
	Active treatment group			Common reference ^a			Indirect comparison: Mean difference (95% CI) dapagliflozin vs comparator
	n	Mean Δ baseline HbA1c	SE	n	Mean Δ baseline HbA1c	SE	
Mean change from baseline in HbA1c							
Dapagliflozin + stable insulin vs exenatide + optimised glargine via stable insulin/optimised glargine							
CT-006	194	-0.9	0.515	193	-0.3	0.521	-0.11
GWCO	100	-1.71	0.09	112	-1.0	0.09	(-0.17, 0.39)
Exenatide + optimised glargine vs optimised lispro + optimised glargine via optimised glargine							
GWDM	265	-1.1	0.05	276	-1.07	0.05	-0.03 (-0.16, 0.11)
Mean change from baseline in insulin dose (units/day)							
Dapagliflozin + stable insulin vs exenatide + optimised glargine via stable insulin/optimised glargine							
CT-006	194	-1.16	0.935	193	5.08	0.943	0.29
GWCO	100	13.19	2.2	112	19.71	2.1	(-5.98, 6.56)

Exenatide + optimised glargine vs optimised lispro + optimised glargine via optimised glargine								
GWDM	312	-4.4	2.388	315	-31.8	3.609	-36.2 (-43.5, -27.7)	
Harms								
Hypoglycaemia: indirect comparison								
	Dapa ^b	PBO ^a	Exe ^b	OR (95% CI)	Event rate/100 patients			RD (95% CI)
					Dapa ^b	PBO ^a	Exe ^b	
CT-006	88/197	83/196	-	1.10 (0.74, 1.64)	45	42	-	NR
GWCO	-	35/122	34/137	0.82 (0.47, 1.42)	-	29	25	NR
Indirect comparison				1.34 (0.68, 2.65)	-			NA
Genital infections: indirect comparison								
	Dapa ^c	PBO ^a	Exe ^c	OR (95% CI)	Event rate/100 patients			RD (95% CI)
					Dapa ^c	PBO ^a	Exe ^c	
CT-006	18/197	4/196	-	4.88 (1.62, 14.69)	9.2	4	-	NR
GWCO	-	2/122	0/137	0.18 (0.0, 3.69)	-	1.6	0	NR
Indirect comparison				27.84 (1.09, 710.51)	-			NA
Urinary tract infections: indirect comparison								
	Dapa ^b	PBO ^a	Exe ^b	OR (95% CI)	Event rate/100 patients*			RD (95% CI)
					Dapa ^b	PBO ^a	Exe ^b	
CT-006	11/197	6/196	-	1.87 (0.68, 5.17)	5.6	3	-	NR
GWCO	-	2/122	1/137	0.44 (0.04, 4.93)	-	1.6	0.7	NR
Indirect comparison				4.25 (0.31, 58.18)	-			NA

Source: Compiled during the evaluation.

Abbreviations: Dapa, dapagliflozin; Exe, exenatide; PBO, placebo.

^a Placebo arms were not comparable and included active comparators in trial GWCO.

^b All treatment and placebo arms included concurrent insulin regimens.

- 6.21 On the basis of indirect, multistep comparison of dapagliflozin and up-titrated insulin presented in the resubmission (using the comparison of dapagliflozin in combination with stable insulin and exenatide with optimised insulin), patients treated with dapagliflozin may get approximately a 0.11% smaller reduction in HbA1c over 24-30 weeks. No long-term outcome data were provided.
- 6.22 On the basis of the indirect comparison, for every 100 patients treated with dapagliflozin + stable insulin in comparison to exenatide + optimised insulin, approximately 5 additional patients would have a genital infection during 24-30 weeks.

Clinical claim

- 6.23 The submission describes dapagliflozin in combination with insulin as non-inferior in terms of comparative effectiveness compared with exenatide, equivalent to 37.5 units of insulin and different but no worse than exenatide or insulin in terms of comparative safety. The ESC considered that this claim is not adequately supported in terms of comparative effectiveness with exenatide and up-titration of insulin, but may be justified in terms of comparative safety. The PBAC considered that the overall claim of non-inferiority may be justified in this case (see below for further consideration).
- 6.24 The equivalence of dapagliflozin to a known dose of insulin up-titration is based on a multi-step informal indirect analysis. The resubmission acknowledges that lack of exchangeability between trials means a formal indirect comparison between dapagliflozin and insulin up-titration is not appropriate. Therefore, in the final step of

the multi-step informal indirect analysis insulin up-titration avoided by patients treated with exenatide is assumed to be applicable to dapagliflozin.

- 6.25 The claim of non-inferiority with exenatide is based on an indirect comparison of dapagliflozin versus exenatide (BD) using trials that are not comparable in terms of baseline insulin used, insulin used during the treatment phase, insulin titration protocols used during the treatment phase and management of hyperglycaemia.
- 6.26 The non-inferiority of dapagliflozin versus exenatide (in combination with insulin) is borderline in the indirect analysis comparing the CT-006 LOCF results with the GWCO MMRM results (upper confidence interval of 0.39% versus a non-inferiority margin of 0.40%). Using the MMRM analyses for both dapagliflozin and exenatide, dapagliflozin fails to satisfy the non-inferiority margin of 0.40%.
- 6.27 The PSCR (p2) claims the different methods of imputation result in similar conclusions, but does acknowledge that the result of non-inferiority is sensitive to the method. Depending upon the pattern of missing data, LOCF correction can inflate Type 1 error rates and introduce bias in treatment effect estimates relative to the MMRM model approach, particularly where data is missing not at random (MNAR). Whilst LOCF performance may be comparable to MMRM imputation where data is missing completely at random (MCAR) or missing at random (MAR) it is unlikely that the missing trial data in this instance follows a random pattern. More detail around how LOCF was assessed as the preferred approach over MMRM would permit a more informed assessment of whether non-inferiority has actually been established at this particular stage of the indirect comparison. The PBAC acknowledged the potential differences between the methods of imputation. The Committee considered that in this case, on balance, non-inferiority might be accepted, given the difficulties of trying to create and interpret a formal indirect comparison between dapagliflozin and up-titrated insulin compared to the use of insulin in practice.

Economic analysis

- 6.28 The resubmission presents a cost-minimisation and a cost analysis. The equi-effective doses are estimated as dapagliflozin 10mg once daily tablet and exenatide (BD) 19.3 µg/day by subcutaneous injection and insulin up-titration 37.5 units/day by subcutaneous injection (mixed insulin regimens). The ESC advised that the equi-effective doses are derived from a multi-step informal indirect comparison (dapagliflozin vs exenatide vs insulin up-titration) using trials that are not comparable due to differences in baseline patient characteristics as well as insulin and oral diabetes treatment regimens, which may bias the calculation of the equi-effective doses in favour of dapagliflozin. Insulin doses in Trial GWDM are inappropriately derived from the difference in change from baseline insulin dose in the ITT population instead of the steady state doses reported at the trial end-point, as recommended in the PBAC Guidelines (v4.4, p.208).
- 6.29 The ESC further advised that the 1 Aug 2014 Therapeutic Relativity Sheet lists the equi-effective doses of exenatide and glargine in T2D as; (i) exenatide 18.14µg daily equi-effective to 24.93units/day of glargine in triple therapy; and (ii) exenatide 18.7µg daily equi-effective to 27.30units/day of glargine in dual therapy. These doses relativities suggest the equi-effective doses may be as follows; dapagliflozin 10mg

daily = exenatide 19.3µg daily = insulin glargine 26.5units/day (triple therapy) to 28.2units/day (dual therapy).

- 6.30 The cost minimisation and cost analysis derive the requested price of dapagliflozin from the costs of insulin up-titration avoided;
- (i) cost of long-acting (glargine), intermediate, fast-acting and intermediate and fast-acting insulin avoided;
 - (ii) cost of test strips, needles and diabetes educator visits associated with avoided up-titration events;
 - (iii) cost of treating the differential in hypoglycaemia events avoided;
 - (iv) cost of reduced use of antihypertensive medicines; and
 - (v) costs of adverse event management.
- 6.31 The cost of 37.5 units of each category of insulin is calculated using the current PBS list prices (DPMQ). Costs are weighted by the proportions of dispensed scripts for each category for all type 1 and type 2 diabetes patients (Medicare Australia PBS data). The resubmission notes that glargine is subject to a special price arrangement, and uses an estimated effective price in the analysis.
- 6.32 Dapagliflozin is expected to substitute subcutaneous injections of insulin and the related cost offsets included are based on those accepted by the PBAC in the March 2010 exenatide resubmission for dual therapy in T2D. However, the PBAC rejected cost offsets for subcutaneous injected drug administration in the March 2013 liraglutide submission for dual and triple therapy, and the ESC suggested these cost offsets should be adequately justified on a case by case basis.
- 6.33 While the offsets in the March 2010 exenatide resubmission were based on complete substitution of glargine, only a portion of glargine use is expected to be substituted by dapagliflozin in combination with insulin. Therefore, offsets related to initiation of fast-acting/intermediate and fast-acting insulin are assumed to be completely avoided while cost offsets related to long-acting and intermediate acting insulin are partially avoided.
- 6.34 The resubmission assumes that the statistically significant difference in event rates reported for exenatide compared to up-titrated insulin in Trial GWDM (12.5%) are applicable to dapagliflozin, given the non-inferiority of dapagliflozin to exenatide in change in HbA1c from baseline in the indirect analysis.
- 6.35 The ESC noted that in the PBAC's previous consideration on needle cost offsets associated with liraglutide, at its March 2013 meeting, the PBAC did not accept the sponsor's claim of cost offsets for one less needle per day compared with the comparator exenatide twice daily (Liraglutide Public Summary Document, March 2013). At its November 2013 meeting, whilst considering a submission for exenatide once weekly, the PBAC recalled that cost-offsets for reduced needle use had not been accepted in its consideration of liraglutide, but that in the case of exenatide once weekly the required needles were provided with the product, compared to liraglutide still requiring some needles be provided through the National Diabetes Services Scheme (NDSS), and as such the savings were more likely to be realised, although not to the extent claimed. Given that PBAC had not previously accepted the cost-offset claimed for differential needle use for liraglutide, and noting that the total

cost offset claimed in the case of exenatide (based on the assumption of 100% compliance with twice daily exenatide dosing and use of a new needle for each dose) was not substantiated by any data, the PBAC considered approximately 50% of that use would be a reasonable basis for a claimed offset.

- 6.36 The ESC considered that there would be no reduction in the number of nurse educator visits as the content of these visits is not specific to titration and additional visits would not be required simply to manage titration. The PBAC agreed with this advice.
- 6.37 The ESC advised that the estimated numbers of hypoglycaemia events are likely over-estimates as they are based on a meta-analysis including trial populations that may not be comparable to the Australian population (low body weight; high proportion of concomitant sulfonylurea use). The estimated cost of hypoglycaemia events is calculated separately for mild, moderate and severe events, assuming all severe events require hospitalisation, all moderate events are treated with intravenous glucagon, and mild events make up the remainder of all events. These assumptions are likely to overestimate the cost offsets associated with dapagliflozin. The PBAC agreed that the reduced offset attributed to dapagliflozin in the pre-PBAC response was reasonable.
- 6.38 The ESC also advised that reductions in systolic and diastolic blood pressure observed for dapagliflozin versus placebo (CT-006) and those observed for exenatide compared to up-titrated insulin (GWDM) and assumed to be applicable to dapagliflozin, are relied to support cost offsets for subsequent reductions in antihypertensive medicines. The assumed 50% reductions in antihypertensive medicine doses are based on a meta-analysis exploring the benefits of using lower dose combination antihypertensive regimens that does not support the proposed dose reductions. The PBAC noted that the sponsor had removed the claimed offset for antihypertensive medicines in its pre-PBAC response.
- 6.39 Cost of managing genital and urinary tract infections repeat the approach used to estimate these in the July 2013 resubmission for dapagliflozin in dual therapy (costs were estimated but not included in the economic analysis). The PBAC noted in consideration of that submission that the cost of monitoring events including additional visits to the doctor, treatment with antibiotics and antifungals, and mid-stream urine testing should be included.
- 6.40 The ESC considered that the costs of infections associated with dapagliflozin were considered likely underestimates as treatment is complicated in these patients and would require at least one health care visit. The PBAC agreed that the cost-offset associated with this offset should be double that proposed by the submission.

Drug cost/patient/year:

- 6.41 The net cost of treating a patient with dapagliflozin per patient per year is estimated by the submission to be [REDACTED]

Estimated PBS usage & financial implications

6.42 Estimated extent of use and financial implications are discussed in the DUSC advice on this item.

Financial estimates for the re-submission compared with previous submission

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Number treated - March 2012					
Number of scripts*					
Number of scripts - March 2012					
Uptake rate					
Uptake rate March 2012					
Estimated net cost to PBS/MBS					
Net cost to PBS					
Net cost to PBS March 2012					
Net savings to MBS					
Net cost to MBS March 2012					
Estimated total net cost					
Net savings PBS/MBS					
Net cost PBS/MBS Nov 2013					

Source: Table 8, Executive Summary of the Commentary, compiled during the evaluation

* Number of prescriptions corrected as noted in Pre-Sub-Committee Response

The redacted table above shows:

Estimated patient numbers: less than 10,000 per year in Year 1, increasing to 50,000 – 100,000 per year in Year 5;

Estimated scripts: 100,000 – 200,000 per year in Year 1, increasing to over 200,000 per year in Year 5;

Estimated financial impact: Savings of less than \$10 million per year in Year 1, increasing to savings of less than \$10 million per year in Year 5.

6.43 The DUSC considered the estimates presented in the submission to be overestimated. The main issues are as follows:

- The clinical place of dapagliflozin with insulin has not been adequately defined. This is needed to estimate the size of the population who will be treated with dapagliflozin in combination with insulin.
- The use of volume caps from the SGLT2 dual therapy risk share agreement is an unconventional starting point for a market share approach and is not in accordance with the PBAC guidelines.
- The assumption that pioglitazone utilisation between the dual therapy and combination with insulin indications from 2003 to 2008 can be extrapolated to current dapagliflozin use may not be reasonable. Many changes occurred in clinical practice over the study period that may have influenced medicine use patterns, including additional indications for glitazones and the availability of long acting insulins (2006). The type 2 diabetes treatment algorithm has undergone further change since the nominated study period, including the introduction of gliptins (2008) and dapagliflozin itself, such that the ratio of use for pioglitazone in 2003-2008 is not relevant to the current market.

- 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 realised.
 - Insulin substitution is likely overestimated.
 - Glucagon substitution is likely overestimated.
 - Antihypertensive therapy is not a relevant cost offset.
- 6.44 Overall, the DUSC considered that the resubmission's estimates of the number of dapagliflozin scripts over five years is substantially higher than estimated in the previous submission, and is most likely an overestimate.
- 6.45 The PBAC accepted the DUSC's advice with respect to the submission's estimates and noted that the estimates would also require revision to take account of its recommended revisions to the basis for pricing dapagliflozin.

Quality Use of Medicine

- 6.46 The ESC expressed concern about polypharmacy with another agent for use in combination with insulin. The ESC considered that the role of dapagliflozin in combination with insulin in clinical practice is unclear.

Financial Management – Risk Sharing Arrangements

- 6.47 The resubmission advises that a Risk Share Arrangement for dapagliflozin in restricted dual therapy, including pack volume caps based on predicted substitution patterns of the SGLT2s for the gliptins and other therapies in the dual therapy setting, may be terminated if a request for a 'true dual therapy' second line listing for dapagliflozin is approved

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of dapagliflozin for the treatment of type 2 diabetes in combination with insulin. The recommendation was formed on the basis of a cost-minimisation and cost-analysis derived from the costs of insulin up-titration avoided.
- 7.2 The PBAC considered that up-titrated insulin was the appropriate comparator but noted that clinical data clarifying the efficacy of dapagliflozin and insulin with and without concomitant metformin were not presented. The PBAC agreed with the DUSC that patients should not be prevented from taking metformin in combination with PBS subsidised dapagliflozin and insulin. In particular, the PBAC considered it clinically inappropriate for a patient being treated with metformin and insulin to have to discontinue the metformin in order to commence dapagliflozin.
- 7.3 The PBAC agreed with the ESC and the sponsor that the trials included in the informal indirect comparison lacked exchangeability and considered that, in addition, the patients in the clinical trial that included dapagliflozin were not representative of

the Australian population who would be treated through the PBS particularly in terms of their age at diagnosis and their ethnicity.

- 7.4 The PBAC noted the ESC's concerns about describing dapagliflozin, in combination with insulin, as non-inferior in terms of comparative effectiveness compared with exenatide and as having a different, but not worse, safety profile than exenatide or insulin in terms of the comparative safety. The PBAC acknowledged the differing views of the ESC and the Sponsor in terms of the result of non-inferiority being sensitive to the methods of imputation. However, the Committee considered that in this case, on balance, non-inferiority might be accepted, given the difficulties of trying to create and interpret a formal indirect comparison between dapagliflozin and up-titrated insulin compared to the use of insulin in practice.
- 7.5 On the other hand, the PBAC considered that the estimate of equi-effective doses from the multi-step informal indirect comparison was difficult to support due to the lack of interchangeability between the clinical trials. Hence the committee considered that the dose equivalence should be based on the established relativity between exenatide and insulin glargine as reflected in the 1 August 2014 Therapeutic Relativity Sheets: dapagliflozin 10 mg daily is equivalent to insulin glargine 26.5 units/day (triple therapy) and 28.2 units/day (dual therapy).
- 7.6 The PBAC agreed that all non-insulin costs associated with the use of fast/intermediate acting insulin can be avoided when a fast/intermediate acting insulin is replaced with dapagliflozin. The committee further considered that when a long/intermediate acting insulin is partially replaced with dapagliflozin, then only some of the costs associated with that insulin may be avoided.
- 7.7 However, the PBAC did not accept that all the non-insulin costs proposed by the submission as offsets were appropriate. In reaching the view that not all the offsets proposed were appropriate, the PBAC noted that the exenatide (BD) March 2010 submission nominated by the submission was not an entirely relevant precedent. In the exenatide submission it was assumed insulin would be completely replaced by exenatide. In the case of dapagliflozin, all patients, even those able to completely discontinue fast/intermediate acting insulin will remain on some insulin treatment. Dapagliflozin and exenatide have different mechanisms of action and thus the requirements for monitoring when switching from insulin to one of these drugs are not the same. Lastly, the Australian guidelines for managing diabetes have changed since 2010 with associated changes in the way diabetes nurse educators are used.
- 7.8 The PBAC noted that there is little data available on use of non-insulin consumables with different combinations of diabetes medicines, making it difficult to determine what offsets will be realised in clinical practice. The PBAC considered that, on balance, the following non-insulin cost offsets were appropriate for dapagliflozin (with insulin):
- an approximate 50% reduction in needle costs for patients receiving a fast or intermediate acting insulin is reasonable based on the previous consideration of exenatide (once weekly) in November 2013; and
 - a reduction in the use of blood glucose test strips for all patients of, on average, one test strip per day, is reasonable on the basis that patients will continue to use some insulin and will likely, at least initially on adding dapagliflozin, continue to test their blood glucose at the same frequency as before; but once they have

- been stabilised on dapagliflozin and insulin, they will be able to reduce by one the number of tests they conduct each day; and
- the cost offset for hypoglycaemia as proposed in the Pre-PBAC Response, and based on the advice of the ESC.
- 7.9 The PBAC agreed with the ESC that a cost offset for savings in anti-hypertensive medications is not appropriate as data from the meta-analysis exploring benefits of using lower dose combination anti-hypertensive regimens does not support the proposed dose reductions, and noted that the sponsor had accepted this approach in its Pre-PBAC Response.
- 7.10 The committee agreed with the ESC advice that “no reduction in the number of nurse educator visits” is appropriate irrespective of the type of insulin being replaced or the extent to which that insulin is replaced. In forming this view, the PBAC considered that the content of these visits is not specific to titration (as claimed by the submission), that the guidelines for nurse educator visits have changed since 2010 and that the addition of dapagliflozin to background insulin treatment may, in the short term, result in more frequent episodes of hypoglycaemia, with the possibility that more, rather than less, nurse educator visits are appropriate in this setting.
- 7.11 The PBAC considered that the cost of monitoring adverse events including additional visits to the doctor, treatment with antibiotics and antifungals, and mid-stream urine testing should be included as an offset. The PBAC agreed with the ESC that the cost-offset associated with this offset should be double that proposed by the submission.
- 7.12 The PBAC recommended that the Safety Net 20 Day Rule should apply for dapagliflozin in combination with insulin.
- 7.13 The PBAC recommended dapagliflozin (with insulin) is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners under Continuing Therapy Only.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

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

Authority Required (STREAMLINED)

Diabetes mellitus type 2

Clinical criteria:

The treatment must be in combination with insulin,

AND

Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR

Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.

Prescriber Instruction

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.

Prescriber Instruction

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.

Prescriber Instruction

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.

Prescriber Instruction

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.

Note

Continuing Therapy Only:

For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners

Note

Dapagliflozin is not PBS-subsidised for use in combination with metformin and a sulfonylurea (triple oral therapy), as monotherapy or in combination with a thiazolidinedione (glitazone), a dipeptidyl peptidase 4 inhibitor (gliptin) or a glucagon-like peptide-1.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.