

PUBLIC SUMMARY DOCUMENT

Product: Dapagliflozin, tablet, 10 mg, (as propanediol monohydrate), Forxiga[®]

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission sought an Authority Required (Streamlined) listing for the treatment of patients with type 2 diabetes in combination with metformin or a sulfonylurea.

2. Background

This drug had not previously been considered by the PBAC.

A separate submission requesting an Authority Required (Streamlined) listing for dapagliflozin for the treatment of type 2 diabetes, in combination with insulin, in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with insulin and oral anti-diabetic agents, or insulin alone where metformin is contraindicated, was also considered at the March 2012 PBAC meeting.

3. Registration Status

Dapagliflozin 10 mg tablets were TGA registered on 22 October 2012 for the following indications:

Monotherapy

Dapagliflozin is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.

Initial combination

Dapagliflozin is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels).

Add-on combination

Dapagliflozin is indicated in patients with type 2 diabetes mellitus to improve glycemic control:

- in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycemic control;
- in combination with a sulfonylurea (SU), when a SU alone with diet and exercise does not provide adequate glycemic control;
- in combination with insulin (alone or with one or both of metformin or a sulfonylurea [SU]) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

4. Listing Requested and PBAC's View

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).

Authority Required (STREAMLINED)

Dual oral combination therapy with metformin or a sulfonylurea.

Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of dapagliflozin despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The date and level of the qualifying HbA1c must be documented in the patient's medical records at the time treatment with dapagliflozin is initiated. The HbA1c must be no more than 4 months old at the time treatment with dapagliflozin is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:

- (a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or
- (b) red cell transfusion within the previous 3 months.

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of dapagliflozin therapy, must be documented in the patient's medical records.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

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 the addition of drug therapy with metformin. When diet and exercise modifications and metformin monotherapy is inadequate in controlling blood glucose, current treatment guidelines recommend adding a sulfonylurea. If dual therapy with metformin and a sulfonylurea is unsuccessful, insulin can be added. Other options include glucagon like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, or meglitinides.

The submission proposed that the place in therapy of dapagliflozin was as an alternative treatment option, with a different mechanism of action, to the currently available oral antidiabetic agents.

6. Comparator

The submission nominated sitagliptin as the main comparator. The PBAC agreed that sitagliptin was an appropriate comparator.

The submission identified pioglitazone as a potential secondary comparator, but could not identify any head-to-head trials or comparable studies suitable for an indirect analysis. The PBAC agreed that pioglitazone would be an appropriate secondary comparator.

7. Clinical Trials

The basis of the submission was three indirect comparisons of dapagliflozin and sitagliptin, as dual oral therapy with either metformin or a sulfonylurea (glipizide or glimepiride) with three different common references (metformin+placebo; metformin+glipizide, glimepiride+placebo). The submission included three dapagliflozin randomised controlled trials (RCTs) (CT-014, CT-004 and CT-005) and five sitagliptin RCTs (Charbonnel 2006, Scott 2008, Raz 2008, Merck 024, Hermansen 2007). The submission nominated a non-inferiority margin of 0.35% (change in HbA1c % from baseline, (i.e., the upper bound of the 95% confidence interval does not exceed +0.35%)), for the test of non-inferiority between dapagliflozin and sitagliptin. This was the pre-specified non-inferiority margin in trials CT-004 and Merck 024.

The PBAC recalled that previously, submissions have proposed minimum clinically important differences (MCIDs) ranging from 0.3% to 0.4% (HbA1c) as an appropriate non-inferiority margin for blood glucose reducing agents. The PBAC previously noted that a 0.3% difference in HbA1c in the regulatory guidance documents refers to both the non-inferiority margin and a clinically meaningful reduction in HbA1c (Liraglutide PSD, November 2010).

Details of the trials published at the time of submission are in the table below.

Trials and associated reports presented in the submission

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Metformin + placebo as common comparator		
Dapagliflozin + metformin vs metformin		
CT-014 Bailey CJ, et al. (2010).	Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial.	<i>The Lancet</i> (2010), 375 (9733): 2223-2233.
Sitagliptin + metformin versus metformin		
Charbonnel (2006)	Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone.	<i>Diabetes Care</i> (2006), 29(12): 2638-2643.
Scott (2008)	Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes.	<i>Diabetes, Obesity and Metabolism</i> (2008), 10(10): 959-969.
Raz (2008)	Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes.	<i>Current Medical Research and Opinion</i> (2008): 24(2): 537-550.

Metformin + glipizide as common comparator		
Dapagliflozin + metformin vs metformin + glipizide		
CT-004 Nauck M, et al. (2010)	Dapagliflozin vs glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin: 52-week results of a double-blind, randomised, controlled trial.	<i>Diabetologia</i> (2010), 53: S107 (abstract only).
Sitagliptin + metformin vs metformin + glipizide		
Merck 024	Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial.	<i>Diabetes, Obesity and Metabolism</i> (2007), 9(2): 194-205.
Glimepiride + placebo as common comparator		
Dapagliflozin + glimepiride vs glimepiride		
CT-005 Strojek KV, et al. (2010)	Efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus and inadequate glycaemic control on glimepiride monotherapy.	<i>Diabetologia</i> (2010), 53: S347-S348 (abstract only).
Sitagliptin + glimepiride vs glimepiride		
Hermansen, K et al (2007)	Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin.	<i>Diabetes, Obesity and Metabolism</i> (2007), 9(5): 733-745.

8. Results of Trials

Indirect analyses were presented for least squares mean reduction in HbA1c from baseline, proportion of patients reporting one or more episodes of hypoglycaemia and weight loss. The proportion of patients achieving a HbA1c <7% was not presented in the submission but data were extracted during the evaluation. The results are presented below.

Indirect comparison of LS mean change in HbA1c (%) from baseline (excluding data following rescue medication; LOCF)

Trial ID	LS mean change from baseline HbA1c % (95% CI)			Mean difference (95% CI)
	MET + Dapa	MET + Placebo	MET + Sita	
DOT with metformin vs metformin + placebo as common comparator (18-30 weeks)				
CT-014	-0.84 (-0.98, -0.70)	-0.30 (-0.44, -0.16)		-0.54 (-0.74, -0.34)
Charbonnel		-0.02 (-0.15, 0.10)	-0.67 (-0.77, -0.57)	-0.65 (-0.77, -0.53)
Raz		0.0 (-0.20, 0.30)	-1.0 (-1.20, -0.80)	-1.0 (-1.40, -0.70)
Scott		-0.22 (-0.36, -0.08)	-0.73 (-0.87, -0.60)	-0.51 (-0.70, -0.32)
	Sitagliptin meta-analysis ($I^2=59%$, $p=0.09$)			-0.65 (-0.84, -0.47)
	Dapagliflozin vs Sitagliptin (indirect)			0.11 (-0.17, 0.39)
	Sitagliptin meta-analysis (excluding Raz: $I^2=33%$, $p=0.22$)			-0.60 (-0.73, -0.47)
	Dapagliflozin vs Sitagliptin (Indirect excluding Raz)			0.06 (-0.18, 0.30)
DOT with metformin vs metformin + glipizide as common comparator (week 52)				
	MET + Dapa	MET + GLIP	MET + Sita	
CT-004	-0.52 (-0.69, -0.44)	-0.52 (-0.60, -0.44)		0.0 (-0.11, 0.11)
Merck 024		-0.51 (-0.60, -0.43)	-0.56 (-0.64, -0.47)	0.04 (-0.04, 0.13)
	Dapagliflozin vs Sitagliptin (indirect)			-0.04 (-0.18, 0.10)
DOT with metformin vs metformin + glipizide as common comparator (week 104)				
	MET + Dapa	MET + GLIP	MET + Sita	

CT-004	-0.32 (-0.42, -0.21)	-0.14 (-0.25, -0.03)		-0.18 (-0.33,-0.03)
Merck 024		-0.35 (-0.44, -0.26)	-0.33 (-0.42, -0.25)	0.01 (-0.08, 0.10)
Dapagliflozin vs Sitagliptin (indirect)				-0.19 (-0.36, -0.02)
DOT with glimepiride vs glimepiride + placebo as common comparator (week 24)				
	GLIM + Dapa	GLIM + Placebo	GLIM + Sita	
CT-005	-0.82 (-0.94, -0.70)	-0.13 (-0.26, -0.01)		-0.68 (-0.86, -0.51)
Hermansen		0.27 (0.09, 0.45)	-0.30 (-0.48, -0.12)	-0.57 (-0.82, -0.32)
Dapagliflozin vs Sitagliptin (indirect)				-0.11 (-0.41, 0.19)

Abbreviations: DOT = dual oral therapy; HbA1c = glycosylated haemoglobin; LS = least squares; MET = metformin; Dapa = dapagliflozin; Sita = sitagliptin; GLIP = glipizide; GLIM = glimepiride; LOCF = last observation carried forward.

Note: statistically significant results in bold.

There were no statistically significant differences between dapagliflozin and sitagliptin in dual oral therapy for reduction of HbA1c in the indirect analyses. The PBAC noted that the submission's nominated non-inferiority margin (0.35% change in HbA1c) was generally met except for the comparison using metformin + placebo as the common comparator (0.11 [95% CI: -0.17%, 0.39%]). The PBAC noted that the upper bound of this confidence interval was less than the 0.4% margin previously accepted by the PBAC, yet above the 0.3% non-inferiority margin referred to in regulatory guidance, and accepted by the PBAC in its March 2010 consideration of saxagliptin (Saxagliptin PSD, March 2010). The submission argued that this result related to the inclusion of the Raz (2008) trial (which reported a higher mean baseline HbA1c (>9%) than other included trials).

The adjusted mean change from baseline HbA1c over 102 weeks reported in Trial CT-014 showed a larger reduction in HbA1c in patients treated with dapagliflozin+metformin compared to metformin+placebo (-0.80: 95% CI [-1.08, -0.52]), but there were high discontinuation rates for both the dapagliflozin 10 mg + metformin and metformin alone trial arms (57/135, 25/137 patients continuing respectively).

The results for the proportion of patients achieving HbA1c less than 7% are presented in the table below.

Proportion of patients achieving HbA1c <7%

Trial ID	Treatment	Baseline HbA1c %	% HbA1c <7% n/N (%)	Difference from control %
DOT with metformin vs metformin + placebo as common comparator (18-30 weeks)				
CT-014	dapagliflozin + MET	7.9	58/132 (40.6%)	14.7%
	MET +placebo	8.1	33/134 (25.9%)	
Charbonnel	sitagliptin + MET	8.0	213/453 (47.0%)	28.7%
	MET +placebo	8.0	41/224 (18.3%)	
Scott	sitagliptin + MET	7.8	52/94 (55.0%)	17.0%
	MET +placebo	7.7	35/92 (38.0%)	
Raz (18wk)	sitagliptin + MET	9.3	13/96 (13.7%)	10.4%
	MET +placebo	9.1	3/94 (3.3%)	
DOT with metformin + metformin + glipizide as common comparator (week 52)				
CT-004	dapagliflozin + MET	7.7	27.4%	- 4.6%
	GLIP + MET	7.7	32.0%	
Merck 024	sitagliptin + MET	7.7	240/382 (63%)	3.9%
	GLIP + MET	7.6	242/411 (59%)	
DOT with glimepiride vs glimepiride + placebo as common comparator (week 24)				
CT-005	dapagliflozin + GLIM	8.1	49/150(32.7%)*	18.7%*
	GLIM +placebo	7.6	18/143(12.6%)*	

Trial ID	Treatment	Baseline HbA1c %	% HbA1c <7% n/N (%)	Difference from control %
Hermansen	sitagliptin + GLIM	8.4	11/102 (10.8%)	2.1%
	GLIM +placebo	8.4	9/103 (8.7%)	

Abbreviations: DOT = dual oral therapy; HbA1c = glycosylated haemoglobin; MET = metformin; GLIP = glipizide; GLIM = glimepiride; NR = not reported.

* updated in the Pre-Sub-Committee Response

With the exception of Raz (2008), the PBAC noted that smaller proportions of dapagliflozin + metformin treated patients achieved an HbA1c <7% (40.6%) compared to patients treated with sitagliptin + metformin in the metformin + placebo comparator trials (Charbonnel (47.0%), Scott (55.0%)). Fewer dapagliflozin + metformin treated patients achieved an HbA1c <7% (27.4%) compared to patients treated with glipizide + metformin (32%).

The results of the indirect comparison for the proportion of patients experiencing one or more hypoglycaemic events showed that statistically significantly fewer patients treated with dapagliflozin + glipizide reported one or more episodes of hypoglycaemia compared to patients treated with sitagliptin + glipizide. However, interpretation of these results was limited by the use of different definitions of hypoglycaemia with trials CT-014, CT-004 and CT-005 grouping major episodes, minor episodes and episodes suggestive of hypoglycaemia together. Highest hypoglycaemia event rates were reported in the glipizide+metformin arms of CT-004 and Merck 024 (40.4% and 32% respectively). The PBAC noted that glipizide is rarely used in Australia and this sulfonylurea has been associated with higher rates of hypoglycaemia and lower efficacy than gliclazide and other sulfonylureas more commonly used in Australian clinical practice.

Patients treated with dapagliflozin in combination with glipizide or glimepiride reported statistically significantly larger reductions in body weight over 24 and 52 weeks compared to patients treated with sitagliptin in combination with glipizide or glimepiride. However, the PBAC also noted that mean differences in changes in body weight were small (≤ 2.76 kg).

The PBAC noted there was evidence to suggest greater weight reduction with dapagliflozin than sitagliptin but that the reductions were small and inconsistent between trials. The PBAC considered that it was not clear whether weight loss was related to fluid depletion or reduced glucose load. The submission claimed that recent phase III clinical trials showed that treatment with dapagliflozin is associated with weight loss primarily due to decreased glycogen storage and sequestration as body fat. However, the PBAC noted that no evidence was presented to support this claim.

The PBAC noted that the indirect comparisons of adverse events (patients with at least one AE, patients with at least one SAE and AE leading to discontinuation) showed no statistically significant differences between dapagliflozin and sitagliptin. There were statistically significantly more patients with urinary tract and genital infections requiring treatment in dapagliflozin treated patients, particularly in women, in the clinical trials, with 6.9% of urinary tract infections and 28.8% not responding to initial standard treatment.

The PBAC noted that in July 2011, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee had noted safety concerns related to a higher incidence of bladder cancer, breast cancer, genital infections and urinary tract infections identified in Phase 2 and 3 dapagliflozin trials, concerns related to bone health and one incident of Hy's Law (drug

induced liver injury). Safety concerns regarding the number of patients treated with dapagliflozin reporting breast or bladder cancer in the clinical trials remain unresolved and it is uncertain whether dapagliflozin may act as a tumour promoter in patients with subclinical neoplasms. In addition, the FDA has recently requested further information from the sponsor to allow a better assessment of the benefit-risk profile for dapagliflozin.

For PBAC's view of these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described dapagliflozin in dual therapy with either metformin or a sulfonylurea as non-inferior in terms of comparative effectiveness and comparative safety over sitagliptin in dual therapy with either metformin or a sulfonylurea. The PBAC did not accept this claim. *See Recommendations and Reasons.*

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as dapagliflozin 10 mg/day and sitagliptin 100 mg/day based on the claimed non-inferiority in the fixed dose clinical trials and mean dose per day recommended in the product information documents.

The PBAC noted that the submission did not take into account the costs associated with treating adverse events. The PBAC considered that these costs should be included as part of the economic evaluation.

11. Estimated PBS Usage and Financial Implications

The submission estimated a cost-neutral listing over the first five years due to price parity with substituted agents.

The PBAC considered that a number of factors were likely to increase costs to the PBS including: a larger eligible population and difficulty in estimating the market due to a number of new agents added to the PBS in the past 12 months, safety concerns over the thiazolidinediones (TZDs), as well as costs associated with the treatment of adverse events.

12. Recommendation and Reasons

The PBAC considered that the requested Streamlined Authority listing was not appropriate as dapagliflozin is a "first in class" agent with a novel mode of action for the treatment of type 2 diabetes, and its efficacy is dependent on the patient's renal function (glomerular filtration rate).

The PBAC agreed that sitagliptin was an appropriate comparator.

The PBAC noted that the basis of the submission was three indirect comparisons of dapagliflozin and sitagliptin, as dual oral therapy with either metformin or a sulfonylurea (glipizide or glimepiride) with three different common references (metformin+placebo; metformin+glipizide, glimepiride+placebo). Non-inferiority was based on a minimum clinically important difference (MCID) nominated in the submission of 0.35% (change from baseline in HbA1c).

There were no statistically significant differences between dapagliflozin and sitagliptin in dual oral therapy for the primary outcome (reduction in HbA1c from baseline) in the indirect analyses. The PBAC noted that the submission's specified non-inferiority margin was generally met, except for the comparison using metformin + placebo as the common reference analysis (0.11% [95% CI -0.17%, 0.39%]). The upper bound of the 95% confidence interval is less than the 0.4% non-inferiority margin previously accepted by the PBAC, yet above the 0.3% non-inferiority margin referred to in regulatory guidance and accepted by the PBAC in its March 2010 consideration of saxagliptin (Saxagliptin PSD, March 2010).

The PBAC noted that the sensitivity analysis results presented in the submission excluded the Raz trial (2008), which reported a higher mean baseline HbA1c (>9%) than other included trials, and resulted in an upper bound of the dapagliflozin confidence interval of 0.3%. The PBAC considered that the exclusion of the Raz trial was not adequately justified as patients with an HbA1c >9% will still be eligible under the requested PBS listing. The PBAC further noted that the analysis conducted during the evaluation, of the difference in reduction in HbA1c, for dapagliflozin versus sitagliptin was 0.15% (95% CI -0.15%, 0.45%) which does not meet the submission's nominated non-inferiority margin.

The PBAC considered that many of the other issues arising from the submission for listing dapagliflozin in combination with insulin were also applicable to this submission for listing dapagliflozin in combination with metformin or a sulphonylurea:

- Lack of clinical outcome data – dapagliflozin is a first in class drug, but only has data on HbA1c and no evidence on clinical endpoints
- Uncertainty that dapagliflozin is not inferior in terms of glycaemic control
- Safety issues – particularly the increased risk of urinary and genital tract infections and uncertainty with a possible signal of breast cancer and bladder cancer.
- Likely to also substitute for cheaper drugs particularly sulphonylureas.

Based on the evidence presented, the PBAC considered there was insufficient evidence to accept the submissions clinical claim that dapagliflozin in dual therapy with either metformin or a sulphonylurea is non-inferior in terms of comparative effectiveness and comparative safety over sitagliptin in dual therapy with either metformin or a sulphonylurea.

The PBAC rejected the submission on the basis of uncertain comparative clinical effectiveness.

Recommendation:

Reject

13. 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.

14. Sponsor's Comment

The sponsor chose to make no further comment.