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 insulin.

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 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 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

Authority Required (STREAMLINED)
Combination therapy with insulin

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.

The date and level of the qualifying HbA1c must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 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 treatment with a gliptin, a glitazone or a glucagon-like peptide-1, 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 is as an alternative treatment option, with a different mechanism of action, to the currently available oral antidiabetic agents.

6. Comparator

The submission nominated pioglitazone as the main comparator. The PBAC considered that pioglitazone is not the only appropriate comparator, and that insulin should also be included as a comparator. *See Recommendation and Reasons.*

7. Clinical Trials

The submission presented an indirect comparison of dapagliflozin 10 mg/day + insulin (approximately 50% of patients also taking another oral anti-diabetic drug (OAD) versus pioglitazone 30 mg or 45 mg/day + insulin (dual therapy only), using placebo + insulin as a common comparator. The indirect analysis included one dapagliflozin randomised controlled trial (CT-006), three pioglitazone randomised controlled trials (Mattoo et al. 2005, Fernandez et al. 2008 and Henriksen et al. 2011) and one small pioglitazone open label study (N=39) that was terminated early due to lack of funds (Jacob et al. 2007). Details of the trials published at the time of submission are in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
Dapagliflozin + insulin vs placebo + insulin		
Trial CT-006 Soler NG et al.	Dapagliflozin lowered rate of insulin uptitration/trial discontinuation from lack of glycaemic control in 48-week trial of type 2 diabetes patients poorly controlled on insulin therapy.	*Diabetologia* (2010), 53: S348-S349. [abstract only]
Pioglitazone + insulin vs placebo + insulin		
Mattoo et al. (2005)	Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: Results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group trial.	*Clinical Therapeutics* (2005), 27(5): 554-567.
Jacob et al. (2007)	Weight gain in type 2 diabetes mellitus.	*Diabetes, Obesity and Metabolism* (2007), 9(3): 386-393.
Fernandez et al. (2008)	Addition of pioglitazone and ramipril to intensive insulin therapy in type 2 diabetic patients improves vascular dysfunction by different mechanisms.	*Diabetes Care* (2008), 31(1): 121-127.
Henriksen et al. (2011)	Efficacy and safety of the PPARgamma partial agonist balaglitazone compared with pioglitazone and placebo: a phase III, randomized, parallel-group study in patients with type 2 diabetes on stable insulin therapy.	*Diabetes Metab Res Rev* (2011), 27(4): 392-401.

The submission nominated a non-inferiority margin of 0.35% (i.e., the upper bound of the 95% confidence interval for difference in change in HbA1c does not exceed +0.35%) for the test of non-inferiority between dapagliflozin and pioglitazone in the indirect analyses of the primary outcome, change from baseline in HbA1c. The PBAC recalled that previously, submissions have proposed minimum clinically important differences (MCID) 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).

The submission relied on the indirect comparison including Mattoo (2005) only. Jacob (2007), Fernandez (2008) and Henriksen (2011) were excluded from the pivotal indirect analysis due to concerns of heterogeneity in the meta-analyses of the pioglitazone trials.

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

The results of the indirect comparison for change in HbA1c from baseline are presented in the table below.

Indirect comparison of LS mean change in HbA1c (%) from baseline

Trial ID	LS mean change from baseline HbA1c % (se)			Mean difference (95% CI)
	Dapa + insulin	Pbo + insulin	Pio + insulin	
Dapagliflozin + insulin vs placebo + insulin				
CT-006 (N=387)	-0.90 (0.05)	-0.30 (0.05)		**-0.60 (-0.74, -0.45)**
Pioglitazone + insulin vs placebo + insulin (meta-analyses)				
Mattoo (2005) (N=289)		-0.14 (0.08)	-0.69 (0.09)	**-0.55 (-0.75, -0.35)**
Jacob (2007) (N=39)		NR	NR	-0.60 (-1.34, 0.14)
Fernandez (2008) (N=20)		NR	NR	-0.30 (-0.92, 0.32)
Henriksen (2011) (N=208)		0.66 (0.16)	-0.56 (0.10)	**-1.22 (-1.69, -0.75)**
All pioglitazone trials (I^2=61%, p=0.05)				**-0.68 (-1.06, -0.31)**
Mattoo + Henriksen only (I^2=85%, p=0.01)				**-0.85 (-1.50, -0.20)**
Indirect analyses				**Dapa - Pio**
CT-006 vs All pioglitazone trials				0.08 (-0.33, 0.49)
CT-006 vs Mattoo + Henriksen				0.25 (-0.42, 0.92)
CT-006 vs Mattoo only (Pivotal analysis)				-0.05 (-0.29, 0.19)
Pioglitazone + insulin vs placebo + insulin (meta-analysis including Rosenstock)				
Mattoo (2005) (N=289)		-0.14 (0.08)	-0.69 (0.09)	**-0.55 (-0.75, -0.36)**
Rosenstock (2002) (N=375)*		-0.26 (0.08)	-1.26 (0.08)	**-1.0 (-1.28, -0.72)**
Mattoo + Rosenstock only				**-0.76 (-1.20, -0.32)**
Indirect analysis				**Dapa - Pio**
CT-006 vs Mattoo + Rosenstock				0.16 (-0.30, 0.68)

Abbreviations: Dapa = dapagliflozin; Pio = pioglitazone; HbA1c = glycosylated haemoglobin; LS = least squares; se = standard error.
*N=375 includes the 30mg pioglitazone and placebo arms only. This trial was inappropriately excluded in the submission.
Note: statistically significant results in bold.

For the primary outcome of change in HbA1c from baseline, there was no statistically significant difference between dapagliflozin and pioglitazone (in combination with insulin) in all three indirect analyses presented. Only the pivotal analysis (excluding all pioglitazone trials other than Mattoo 2005) met the submission's nominated non-inferiority margin of 0.35% (difference in change in HbA1c). The mean change in HbA1c over 48 weeks in Trial CT-006 versus placebo (-0.49%, 95% CI -0.67, -0.32) was consistent with the 24 week outcome.

However, the results of a sensitivity analysis comparing CT-006 with pooled estimates from Mattoo 2005 and Rosenstock 2002 showed that dapagliflozin did not meet the submission's nominated non-inferiority margin of 0.35%.

In the indirect comparison for mean change in bodyweight from baseline, there was a statistically significant difference in weight (change from baseline) between patients taking dapagliflozin or pioglitazone (in combination with insulin), primarily due to mean weight gains reported in patients taking pioglitazone (5.5 kg) and small mean weight loss reported in patients taking dapagliflozin (-1.67 kg). It was unclear what proportion of the weight loss reported by patients treated with dapagliflozin resulted from fluid diuresis compared to non-

fluid body mass. The PBAC was uncertain whether this difference would translate into cardiovascular or other health benefits.

There was no significant difference between dapagliflozin and pioglitazone (in combination with insulin) in the proportion of patients reporting one or more hypoglycaemic episodes. However, the definitions of hypoglycaemia and management of glycaemic control varied between trials, with Trial CT-006 using a strict protocol for up-titration or down-titration of insulin dose and Mattoo (2005) relying on study investigators to maintain glycaemic control.

An indirect analysis of Trial CT-006 and Mattoo 2005 showed a statistically significantly larger reduction in insulin utilisation in patients treated with pioglitazone compared to those treated with dapagliflozin (in combination with insulin). However, the PBAC considered the data presented were difficult to interpret given that 50% of dapagliflozin treated patients were taking other OADs while pioglitazone treated patients had all other OADs ceased.

The PBAC noted that indirect comparisons of adverse events (AE) (patients with at least one AE, patients with at least one severe adverse event (SAE) and AE leading to discontinuation) showed no statistically significant differences between dapagliflozin and pioglitazone (in combination with insulin). There were more patients with urinary tract and genital infections requiring treatment in dapagliflozin treated patients, particularly in women, in the clinical trials.

The PBAC noted that in July 2011, the US Food and Drug Administration'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, see Recommendation and Reasons.

9. Clinical Claim

The submission described dapagliflozin (in combination with insulin) as non-inferior in terms of comparative effectiveness and comparative safety to pioglitazone (in combination with insulin). The PBAC did not accept this claim. *See Recommendation and Reasons.*

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as dapagliflozin 10 mg/day and pioglitazone 30 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.

11. Estimated PBS Usage and Financial Implications

The submission used a market share approach to estimate use and financial implications to government.

The submission estimated the net cost per year to the PBS to be less than $10 million in Year 5.

The PBAC considered that the submission's estimates were uncertain given safety concerns with thiazolidinediones (TZDs), the safety concerns with dapagliflozin and the failure of the submission to consider the number of patients with renal disease unlikely to switch to dapagliflozin given the reduced efficacy at low glomerular filtration rates.

12. Recommendation and Reasons

The PBAC considered that the request for a Streamlined Authority listing, based on the current PBS listing for pioglitazone, 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 patients renal function. The PBAC also considered that there could be use outside the restriction with dapagliflozin used in addition to metformin in triple therapy with insulin.

The PBAC considered that pioglitazone alone, as an alternative oral anti-diabetic used in combination with insulin, is not the only appropriate comparator and that a percentage of the use of dapagliflozin would be in patients with the objective of reducing the dose of concomitant insulin, reducing hypoglycaemia and/or improving diabetes control. Therefore, insulin should also be included as a comparator.

The PBAC noted that the basis of submission was an indirect comparison of one trial of dapagliflozin plus insulin versus two trials of pioglitazone with insulin. The submission presents the primary outcome from Trial CT-006, change in HbA1c from baseline, and the key secondary outcomes, change in weight from baseline, difference in the proportion of patients experiencing one or more hypoglycaemic episodes and change in insulin utilisation from baseline. The PBAC noted that Trial CT-006 includes outcomes for dapagliflozin at 24 and 48 weeks, but no long term efficacy outcomes are presented. The PBAC noted that there were substantial differences in the treatment of the comparator arms between the dapagliflozin and pioglitazone trials giving additional uncertainty to the indirect comparison.

The PBAC did not consider there was strong basis for the selective inclusion/exclusion of trials in the pivotal indirect analysis particularly as this affected the statistical significance of the results. The PBAC noted that the Rosenstock trial (which was excluded) was the pivotal trial used in the resubmission for listing pioglitazone for combination therapy with insulin and the PBAC considered that its exclusion was inappropriate.

For the primary outcome of change in HbA1c from baseline from Trial CT-006, there was no statistically significant difference between dapagliflozin and pioglitazone (in combination with insulin) in all three indirect analyses presented. Only the pivotal analysis (excluding all pioglitazone trials other than Mattoo 2005) met the minimum clinically important difference (MCID) non-inferiority margin nominated in the submission of 0.35% (difference in change in HbA1c). The mean change in HbA1c over 48 weeks in Trial CT-006 versus placebo (-0.49%, 95% CI -0.67, -0.32) was consistent with the 24 week outcome.

However, the results of a sensitivity analysis comparing CT-006 with pooled estimates from Mattoo 2005 and Rosenstock 2002 show that dapagliflozin did not meet the submission's

nominated non-inferiority margin of 0.35%. Therefore, the PBAC was not convinced that non-inferiority of dapagliflozin compared with pioglitazone based on glycaemic control was demonstrated and considered that it remains unclear, for a first in class anti-diabetic agent, whether changes in HbA1c alone are sufficient to conclude non-inferiority with glitazones and other anti-glycaemic agents.

The PBAC noted that there was a statistically significant difference in weight (change from baseline) between patients taking dapagliflozin or pioglitazone (in combination with insulin). However, the Committee was uncertain whether this would translate into cardiovascular or other health benefits.

Although the PBAC noted that the results from Trial CT-006 show evidence of a clinical effect with dapagliflozin, the Committee remained uncertain as to how HbA1c changes will translate into clinical outcomes. The PBAC further noted that no clinical outcome data for dapagliflozin were presented on macrovascular and microvascular outcomes.

Although the indirect comparison did not show any statistically significant differences between dapagliflozin and pioglitazone (in combination with insulin) in relation to adverse events, the PBAC noted concerns remain about long term safety with dapagliflozin particularly the possible signal of breast cancer and bladder cancer and the increased risk of urinary and genital tract infections.

Based on the evidence presented, the PBAC considered there was insufficient evidence to accept the submissions clinical claim that dapagliflozin (in combination with insulin) is non-inferior in terms of comparative effectiveness and comparative safety to pioglitazone (in combination with insulin).

Therefore, the PBAC rejected the submission on the basis of an inadequate comparison across appropriate comparators and 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.