Public Summary Document

Product: Dapagliflozin, tablet, 10 mg, Forxiga®
Sponsor: Bristol-Myers Squibb Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission requested an Authority required listing for the treatment of patients with type 2 diabetes mellitus (T2DM) as dual oral combination therapy with metformin or a sulfonylurea.

2. Background

Dapagliflozin was first considered by the PBAC for use in T2DM at the March 2012 PBAC meeting in two parallel process submissions; (i) in dual oral therapy (DOT) with metformin or a sulfonylurea and (ii) in combination with insulin. Both applications were rejected by the PBAC on the basis of uncertain comparative effectiveness and uncertain cost effectiveness.

3. Registration Status

Dapagliflozin was TGA registered on 22 October 2012 for the following indications:

Monotherapy
As an adjunct to diet and exercise in patients with T2DM for whom metformin is otherwise indicated but not tolerated.

Initial combination
As initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with T2DM when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin mono-therapy (for example, high initial HbA1c levels).

Add-on combination
In patients with T2DM to improve glycaemic control:

- in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control;
- in combination with a sulfonylurea, when a sulfonylurea alone with diet and exercise does not provide adequate glycaemic control;
- in combination with insulin (alone or in combination with metformin and/or a sulfonylurea when existing therapy, along with diet and exercise, does not provide adequate glycaemic control.

4. Listing Requested and PBAC's View

Authority required
Dual oral combination therapy with metformin or a sulfonylurea.
T2DM, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a sodium glucose transporter 2 inhibitor, a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), or a glucagon-like peptide-1 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 a sodium glucose transporter 2 inhibitor, 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 sodium glucose transporter 2 inhibitor, 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 sodium glucose transporter 2 inhibitor, a gliptin, a glitazone, or a glucagon-like peptide-1, must be documented in the patient's medical records.

Note

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

The PBAC agreed that the restriction proposed by the submission appropriately limited use to the third line setting in combination with metformin or a sulfonylurea in patients whose diabetes, as measured by HbA1c, is not controlled on treatment with metformin and a sulfonylurea. However, the Committee recommended the restriction wording be modified to better reflect current clinical practice in which patients whose diabetes cannot be successfully managed with a combination of metformin and a sulfonylurea, irrespective of reason, are moved to dual therapy with metformin or a sulfonylurea, and a sodium glucose transporter 2 inhibitor, a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), or a glucagon-like peptide-1.

The PBAC also considered that an Authority required listing would be appropriate, as dapagliflozin is an agent in a new drug class.

The PBAC noted the recent Drug Utilisation Sub-Committee (DUSC) Analysis of Medicines for Type II Diabetes (April 2013 Special PBAC meeting), which showed substantial utilisation of gliptins as an add-on to metformin, without contraindication or intolerance to a sulfonylurea despite the PBS restriction. The Committee considered that it is not yet possible to determine if dapagliflozin will similarly be used outside of the third line restriction proposed by the submission but that the risk of such use could be managed through a risk share agreement *(see also Recommendations 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 receptor agonists, dipeptidyl peptidase-4 inhibitors, and thiazolidinediones.

The re-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

Sitagliptin 100 mg was the nominated comparator. The PBAC previously agreed that sitagliptin was an appropriate comparator for the third line setting.

7. Clinical Trials

The re-submission presented the same three indirect comparisons as presented in the March 2012 submission:

1. dual therapy with metformin, metformin+placebo as common comparator,
2. dual therapy with metformin, metformin+sulfonylurea (glipizide) as common comparator; and
3. dual therapy with sulfonylurea (glimepiride), sulfonylurea+placebo as common comparator.

An updated literature review identified six additional trials for inclusion in the metformin+placebo indirect comparison (Trial CT-003, Rosenstock 2011, Rosenstock 2012, Bergenstal 2012, Derosa 2012 and Yang 2012). No additional trials were identified for the indirect analyses with metformin+sulfonylurea and sulfonylurea+placebo as common comparators. New analyses presented in the re-submission were:

1. All key outcomes in the dual therapy with metformin, metformin+placebo as common comparator analysis,
2. A post-hoc subgroup analysis of patients with at least stage 3 chronic kidney disease in mean reduction in HbA1c from baseline (sensitivity analysis only),
3. The proportion of patients achieving an HbA1c of less than 7% for all three indirect comparisons;

Four trials (Derosa 2012, Raz 2008, Yang 2012 and Trial CT-003) were omitted from the re-submission's preferred base-case due to heterogeneity when included in the meta-analyses. The remaining results from the metformin+sulfonylurea (glipizide) and sulfonylurea+placebo comparator analyses were unchanged from the March 2012 submission.

The published trials and associated reports presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Common reference using placebo (as an add-on to metformin)		

Dapagliflozin as an add-on to metformin versus metformin		
Trial CT-014		
Bailey, CJ et al.	Dapagliflozin as an add-on to metformin lowers hyperglycaemia in type 2 diabetes patients inadequately controlled with metformin alone.	*Diabetologia* (2009); 52(S1): S76. [abstract only]
Bailey, CJ et al.	Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial.	*The Lancet* (2010); 375(9733): 2223-2233.
Bailey, CJ et al.	Sustained efficacy of dapagliflozin when added to metformin in type 2 diabetes inadequately controlled by metformin monotherapy.	*Diabetologia* (2011); 54: S67. [abstract only]
Trial CT-003	A 16-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Safety and Efficacy of Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD Versus Placebo in Patients with Type 2 Diabetes Who Are Inadequately Controlled on Metformin-IR Monotherapy.	Date of report 29 May 2012 ClinicalTrials.gov Identifier: NCT01217892
Trial CT-012		
Bolinder, J et al.	Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin.	*Journal of Clinical Endocrinology and Metabolism* (2012); 97(3): 1020-1031.
Bolinder, J et al.	Dapagliflozin produces long-term reductions in body weight, waist circumference and total fat mass in patients with type 2 diabetes inadequately controlled on metformin.	*Diabetologia* (2012); 55: S308. [abstract only]
Grandy, S et al.	Quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin for 24 weeks.	*Diabetes* (2012); 61: A600. [abstract only]
Ljunggren, O.	Dapagliflozin has no long-term effect on markers of bone turnover or bone mineral density in patients with inadequately controlled type 2 diabetes on metformin.	*Diabetologia* (2012); 55: S306-S307. [abstract only]
Ljunggren, O.	Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin.	*Diabetes, Obesity and Metabolism* (2012); 14(11):990-9. [abstract only]
Ingelgård, A.	Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin for 24 weeks.	*Diabetologia* (2012); 55: S320. [abstract only]
Sitagliptin as an add-on to metformin versus metformin		
Charbonnel et al	Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone.	*Diabetes Care* (2006); 29(12): 2638-2643.

Raz et al	Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes.	*Current Medical Research and Opinion* (2008); 24(2): 537-550.
Scott et al	Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes.	*Diabetes, Obesity and Metabolism* (2008); 10(10): 959-969.
Rosenstock, J et al.	Efficacy and safety of BI 10773, a new sodium glucose cotransporter-2 (SGLT-2) inhibitor, in type 2 diabetes inadequately controlled on metformin.	*Diabetes* (2011); 60: A271. [abstract only]
Seman, L et al.	ENCORE: Efficacy and safety of BI 10773, a new sodium glucose cotransporter- 2 (SGLT-2) inhibitor, in type 2 diabetes patients inadequately controlled on metformin.	*Diabetologia* (2011); 54: S67-S68. [abstract only]
Bergenstal et al	Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-Emerge 4 Trial).	*Diabetes Therapy* (2012); 3(1): 1-19.
Derosa et al	A randomized, double-blind, placebo-controlled trial evaluating sitagliptin action on insulin resistance parameters and (beta)-cell function.	*Expert Opinion on Pharmacotherapy* (2012a); 13(17): 2433-2442.
Derosa et al	Effects of a combination of sitagliptin plus metformin vs metformin monotherapy on glycemic control, (beta)-cell function and insulin resistance in type 2 diabetic patients.	*Diabetes Research and Clinical Practice* (2012b); 98(1): 51-60.
Rosenstock et al	Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes.	*Diabetes Care* (2012); 35(6): 1232-1238.
Yang et al	Sitagliptin added to ongoing metformin therapy in chinese patients with type 2 diabetes significantly enhances glycemic control.	*Diabetes* (2011); 60: A306. [abstract only]
Yang et al	The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes.	*Journal of Diabetes* (2012); 4(3): 227-237.
Brazg et al	Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and (beta)-cell function in patients with type 2 diabetes.	*Diabetes, Obesity and Metabolism* (2007); 9(2): 186-193.
Aaboe et al	Twelve weeks treatment with the DPP-4 inhibitor sitagliptin improves glycaemic control, but does not improve GLP-1 secretion, in patients with type 2 diabetes - A randomised trial.	*Diabetologia* (2009); 52(S1): S294.
Aaboe et al	Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus.	*Diabetes, Obesity and Metabolism* (2010); 12(4): 323-333.

NCT00875394	Study to Assess the Efficacy and Safety of Sitagliptin Added to the Regimen of Patients With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin (0431-189)	ClinicalTrials.gov Identifier: NCT00875394
Common reference using sulfonylurea (as an add-on to metformin)		
Dapagliflozin as an add-on to a metformin versus a sulfonylurea as an add-on to metformin		
Trial CT-004		
Nauck, M et al.	Dapagliflozin vs glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin: 52-week results of a double-blind, randomised, controlled trial.	*Diabetologia* (2010); 53: S107. [abstract only]
Nauck, M et al.	Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: A randomized, 52-week, double-blind, active-controlled noninferiority trial.	*Diabetes Care* (2011); 34(9): 2015-2022.
Del Prato, S et al.	Long-term efficacy and safety of add-on dapagliflozin vs add-on glipizide in patients with type 2 diabetes mellitus inadequately controlled with metformin: 2-year results.	*Diabetologia (2011); 54: S348. [abstract only]*
Sitagliptin as an add-on to a metformin versus a sulfonylurea as an add-on to metformin		
Merck 024		
Nauck, MA et al.	Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial.	*Diabetes, Obesity and Metabolism* (2007); 9(2): 194-205.
Seck, T et al.	Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: A 2-year study.	*International Journal of Clinical Practice* (2010a); 64(5): 562-576.
Seck, T et al.	Sitagliptin compared with the sulfonylurea glimepiride provides similar efficacy with less hypoglycemia and no weight gain when added to ongoing metformin therapy in patients with type 2 diabetes mellitus (T2DM).	*Diabetologie und Stoffwechsel* (2010b); 5.
Seck, T et al.	Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycemia and no body weight gain compared with glipizide.	*Diabetes Res Clin Pract* (2011); 93(1): e15-7.
NCT00701090 Goldstein, BJ et al.	Sitagliptin compared with glimepiride provides similar efficacy with weight loss and less hypoglycaemia when added to metformin therapy in patients with type 2 diabetes mellitus.	*Diabetologia* 53: S325. [abstract only]
NCT00701090 Arechavaleta, R et al.	Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: A randomized, double-blind, non-	*Diabetes, Obesity and Metabolism* (2011); 13(2): 160-168.

	inferiority trial.	
Kim et al	The comparative study of dipeptidyl peptidase-IV inhibitor and sulfonylurea on the effect of improving glucose variability and oxidative stress in type 2 diabetic patients with inadequate glycemic control on metformin.	*Diabetes* (2012); 61: A619. [abstract only]
Koren et al	The effect of sitagliptin versus glibenclamide on arterial stiffness, blood pressure, lipids, and inflammation in type 2 diabetes mellitus patients.	*Diabetes Technology and Therapeutics* (2012); 14(7): 561-567.
Srivastava et al	Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone.	*Journal of Association of Physicians of India* (2012); 60(3): 27-30.
Common reference using placebo (as an add-on to sulfonylurea)		
Dapagliflozin as an add-on to a sulfonylurea versus a sulfonylurea		
Trial CT-005		
Strojek, K et al.	Efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus and inadequate glycaemic control on glimepiride monotherapy.	*Diabetologia* (2010); 53: S347-S348. [abstract only]
Strojek, K et al.	Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: A randomized, 24-week, double-blind, placebo-controlled trial.	*Diabetes, Obesity and Metabolism* (2011); 13(10): 928-938.
Sitagliptin as an add-on to a sulfonylurea versus a sulfonylurea		
Hermansen et al	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.	*Diabetes, Obesity and Metabolism* (2007); 9(5): 733-745.
Tajima et al	Addition of sitagliptin to ongoing glimepiride therapy in Japanese patients with type 2 diabetes over 52 weeks leads to improved glycemic control.	*Diabetology International* (2011); 2(1): 32-44.

8. Results of Trials

Indirect comparison of dapagliflozin and sitagliptin via placebo as add-on therapy to metformin

There were no statistically significant differences between dapagliflozin and sitagliptin in the reduction of HbA1c in the indirect comparison, meeting the pre-specified criteria for non-inferiority of 0.40%.

The PBAC noted that, this baseline analysis was dependent on the exclusion of sitagliptin trials with high baseline HbA1c (Raz 2008 and Yang 2012) and the inclusion of sitagliptin trials of short duration (Rosenstock 2011 and Rosenstock 2012). The PBAC considered that as Rosenstock (2011) and Rosenstock (2012) were of short duration (12 weeks) and that the comparable therapeutic efficacy of sitagliptin may not be realised over the shorter period (particularly given the duration of the key dapagliflozin trial was 24 weeks), their inclusion was not appropriate.

The PBAC considered also that the inclusion of trials with high baseline HbA1c (Yang 2012 and Raz 2008), results in significant heterogeneity in the meta-analysis of included sitagliptin trials.

The PBAC noted that in a comparison that excludes the short duration trials (Rosenstock 2011 and Rosenstock 2012) and includes Yang (2012) and Raz (2008), dapagliflozin fails to show non-inferiority to sitagliptin, with the upper confidence interval exceeding the updated non-inferiority margin of 0.40%.

In considering the March 2012 submission the PBAC noted that for the indirect comparisons using metformin+sulfonylurea (glipizide) and sulfonylurea+placebo as common comparators, dapagliflozin generally met the pre-specified non-inferiority margin of 0.35-0.40%.

While more sitagliptin treated patients achieved HbA1c values of less than 7% in the clinical trials, the indirect analyses presented in the re-submission showed no statistically significant difference between dapagliflozin and sitagliptin treated patients. The statistically significant risk difference reported in the sulfonylurea+placebo common comparator analysis was considered most likely due to differences in the use of rescue medication, and imputation of data points following rescue.

The PBAC noted that the proximal diuresis, natriuresis and calorie leakage into urine with dapagliflozin may be associated with small reductions in blood pressure and body weight. The PBAC considered that these effects could be a factor in driving the clinical choice of dapagliflozin over other agents, should they be shown to occur in clinical practice.

Overall, the PBAC noted the challenges inherent in indirect comparisons, and considered that the analyses in the resubmission did not inform the assessment of comparative effectiveness any more than the previous submission. Notwithstanding this, the PBAC considered that it was reasonable to accept probable non-inferiority of dapagliflozin to sitagliptin.

With regards to comparative harms, additional safety data were presented for dapagliflozin (Trial CT-003) and sitagliptin (Bergenstal 2012, Rosenstock 2012 and Yang 2012). Post marketing data for dapagliflozin are not yet available. The impact of adverse events in practice is not predictable from the available evidence, particularly given the novel mechanism of action and the likely co-morbidities in an older diabetic population.

Similar to the analyses presented in the March 2012 submission the results show no statistically significant differences between dapagliflozin and sitagliptin in terms of patients with at least one adverse event, patients with at least one serious adverse event and adverse events leading to discontinuation.

Consistent with the dapagliflozin trials included in the March 2012 submission, patients treated with dapagliflozin in Trial CT-003 experienced more adverse events in general and more genital infections (exclusively in female patients) than patients treated with placebo. Genital and urinary tract infections were not identified as adverse events of interest in the sitagliptin trials.

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 viewed this claim as adequately supported in terms of comparative effectiveness based on HbA1c change only, but expressed concern and uncertainty in terms of comparative safety. The PBAC remained concerned over higher rates of genital mycotic infections and osmotic diuresis associated events compared with sitagliptin.

10. Economic Analysis

The re-submission presented a cost minimisation analysis. The equi-effective doses were estimated as dapagliflozin 10 mg daily and sitagliptin 100 mg daily. The PBAC considered that the equi-effective doses were appropriate.

The re-submission assumed substitution of all other agents will be at the price equivalent of sitagliptin 100 mg, and assumes no use of dapagliflozin outside the requested listing. The additional costs associated with treating genital and urinary tract infections were not included in the cost minimisation analysis, but were estimated to be small and to be offset by benefits associated with dapagliflozin that are not quantified (e.g. weight loss).

The PBAC considered dapagliflozin is non-inferior to sitagliptin (in dual oral therapy with metformin or a sulfonylurea) in terms of efficacy but considered that the price should take into account likely increased costs involved in managing and monitoring for infections resulting from dapagliflozin use. The costs presented in the submission did not adequately represent these costs. These offsets would include the cost of monitoring these events which would include additional visits to doctor (MBS item number 23), treatment with antibiotics and antifungals, and mid-stream urine testing.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be in the range 10,000 – 50,000 in Year 5.

Consistent with the March 2012 submission, this submission estimated a nil net cost per year to the PBS of listing dapagliflozin.

The submission estimated the listing of dapagliflozin to be cost neutral in that the cost of dapagliflozin was assumed to be offset by patients switching from other dual oral therapies of equal cost. The additional cost arising from the lower price of glitazones (particularly pioglitazone 30 mg) was estimated to be small by the submission, as the submission estimated that the listing of dapagliflozin was not expected to increase substitution rates away from pioglitazone beyond what was already occurring with the DPP4 inhibitors. The submission assumed that any costs would be offset by savings from substitution of fixed dose combinations of sitagliptin+metformin. The PBAC considered that this assumption was not reasonable given the underestimated number of pioglitazone scripts likely to be substituted by dapagliflozin and the uncertain proportion of patients switching from fixed dose combinations to dapagliflozin.

The PBAC noted the variation in usage estimates presented in this submission compared to the other sodium glucose transporter 2 inhibitor being considered for subsidy at this meeting, and requested the Department work with both sponsors to develop a single set of estimates.

12. Recommendation and Reasons

The PBAC recommended the listing of dapagliflozin on the PBS on a cost minimisation basis with sitagliptin. The equi-effective doses accepted for the purposes of cost-minimisation are dapagliflozin 10 mg being equivalent to sitagliptin 100 mg.

The PBAC recommended that cost-offsets be applied to dapagliflozin to account for an increased rate of adverse events such as genital mycotic infections and urinary tract infections compared with sitagliptin. These offsets would include the cost of monitoring these events which would include additional visits to doctor (MBS item number 23), treatment with antibiotics and antifungals, and mid-stream urine testing.

The PBAC noted the sponsor's assurance that the PBS listing of dapagliflozin would be cost neutral to the Commonwealth, and agreed that this was appropriate. In order to manage the risk of possible usage outside the third line setting proposed by the sponsor, the PBAC recommended that a risk share arrangement should be put in place. Any other sodium glucose transport 2 inhibitors listed on the PBS for use in the third line setting should be required to join the same risk share.

The PBAC accepted that dapagliflozin is non-inferior in regards to efficacy and safety with canagliflozin but noted variability in adverse events and differences in mode of action that may impact utilisation.

The PBAC recommended that dapagliflozin be listed as an Authority required benefit.

The PBAC noted the rapid evolution of diabetes management, as evidenced by current trends in utilisation of PBS listed medicine as highlighted in the DUSC analysis (October 2012 and February 2013). In particular, the PBAC noted utilisation patterns indicating prescribing of some agents outside PBS restrictions, and considered this to be a matter of concern. The availability of new classes of treatments, such as sodium-glucose cotransporter 2 (SGLT-2_ inhibitors, would be expected to further influence future treatment algorithms.

The PBAC noted that treatment choice may be influenced by patient reluctance to use injectable formulations. The PBAC noted that this was consistent with views expressed in correspondence the PBAC received from diabetes organisations.

The PBAC requested a DUSC review be undertaken twelve months after PBS listing.

The PBAC advised that dapagliflozin should be treated as interchangeable on an individual patient basis with canagliflozin.

The PBAC recommended dapagliflozin is suitable for nurse practitioner prescribing for continuing therapy only.

The PBAC noted with the listing of dapagliflozin, the NOTE for the currently listed gliptins, glitazones (including combination products) and glucagon-like peptide-1 agents will need to be updated to include sodium glucose transport 2 inhibitors.

Outcome:
Recommended

Recommended listing

Add the following new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
DAPAGLIFLOZIN Tablet 10 mg	28	5	Forxiga BM

Condition/Indication:	Diabetes mellitus type 2
Restriction:	Authority required *Restriction to be finalised*

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 is pleased with this recommendation and will continue to work with the PBAC to provide medicines to Australian patients.