Public Summary Document

Product: Canagliflozin, tablet, 100 mg and 300 mg, Invokana®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

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

2. Background

This drug had not been previously considered by the PBAC.

3. Registration Status

At the time of consideration in July 2013 the PBAC noted that the TGA regulatory application was still pending. Both the Clinical Evaluation Report and the TGA Delegate's Summary were available.

Canagliflozin was TGA registered on 12 September 2013 for treatment of adults with type 2 diabetes mellitus, as an adjunct to diet and exercise, to improve glycaemic control as:

- Monotherapy – When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- Add-on combination therapy - Combination therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control

4. Listing Requested and PBAC's View

Authority required
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 a dipeptidyl peptidase-IV (gliptin), thiazolidinedione (glitazone), glucagon-like peptide-1 or a sodium glucose co-transporter-2 inhibitor 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 of treatment with a sodium glucose co-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 co-transporter-2 inhibitor, 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 or a sodium glucose co-transporter-2 inhibitor, must be documented in the patient's medical records.

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

The PBAC agreed that the restriction proposed by the submission appropriately limits 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 canagliflozin 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 canagliflozin 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 submission proposed that the place in therapy of canagliflozin is as an alternative treatment option, with a different mechanism of action, to the currently available oral antidiabetic agents.

6. Comparator

Sitagliptin was the nominated comparator and the PBAC considered this was appropriate. The submission also included a supplementary comparison with dapagliflozin, a pharmacological analogue of canagliflozin.

7. Clinical Trials

The submission presented one head to head randomised trial (Study 3006, 52 weeks) comparing canagliflozin 100 mg (N=368) and 300 mg (N=367) with sitagliptin 100 mg (N=366), in combination with metformin. The PBAC considered that Study 3006 provided the highest quality evidence in the submission. The PBAC considered also that a comparison of canagliflozin 100 mg with sitagliptin 50 mg would also have been informative, but this was not provided by sponsor, as the submission stated there were no clinical data available for this comparison.

The submission also presented an indirect comparison of canagliflozin+sulfonylurea (N=72) with sitagliptin+sulfonylurea (N=106), with placebo+sulfonylurea as a common reference (3008 sulphonylurea (SU) sub-study, 18weeks; Hermansen 2007, 24 weeks). A supplementary head to head randomised trial (Study 3015, 52 weeks) was presented that compared canagliflozin 300 mg (N=377) with sitagliptin 100 mg (N=378), in combination with metformin and a sulfonylurea.

Supplementary indirect comparisons of canagliflozin 300 mg with dapagliflozin 10 mg were also presented:

- Canagliflozin+metformin (N=367) vs dapagliflozin+metformin (N=135), with placebo+metformin as a common reference (Study 3006, 26 weeks; Bailey 2010, 24 weeks);
- Canagliflozin+metformin (N=485) vs dapagliflozin+metformin (N=406), with sulfonylurea+metformin as a common reference (Study 3009, 52 weeks; Nauck 2011, 52 weeks);
- Canagliflozin+sulfonylurea vs dapagliflozin+sulfonylurea, with placebo+sulfonylurea as a common reference (3008 SU sub-study, 18 weeks; Strojek 2011, 24 weeks).

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

Hermansen, K 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, 733 – 745.

8. Results of Trials

The results for the efficacy outcome Least Square (LS) mean change in HbA1c (%) from baseline and proportion of responders in head to head trial (Study 3006) are shown in the following table:

Study 3006 (52 weeks, mITT)	**CANA 300 mg +MET N = 360**	**CANA 100 mg +MET N = 365**	**SITA 100 mg +MET N = 354**
Change in HbA1c from baseline			
LSM change HbA1c (SE)	**-0.88 (0.05)**	**-0.73 (0.05)**	**-0.73 (0.05)**
Difference in LSM change HbA1c [95% CI], vs sitagliptin	**-0.15 [-0.27, -0.03]**	0.00 [-0.12, 0.12]	-
Treatment responders (patients achieving HbA1c <7%)			

Study 3006 (52 weeks, mITT)	CANA 300 mg +MET N = 360	CANA 100 mg +MET N = 365	SITA 100 mg +MET N = 354
Proportion of patients achieving HbA1c <7% at endpoint (%)	(54.7)	(41.1)	(50.6)
Odds ratio [95% CI], vs sitagliptin	1.28 [0.92, 1.76]	**0.66 [0.48, 0.91]**	-

Note: **Bold** indicates that comparison met statistical significance (p <0.05).
Abbreviations: CANA, canagliflozin; MET, metformin; SITA, sitagliptin; HbA1c, glycosylated haemoglobin; mITT, modified intent to treat; SE, standard error; CI, confidence interval; LSM, least squares mean.

Studies 3006 and 3015 had a pre-specified non-inferiority margin of 0.3% change in HbA1c, which was met. The PBAC therefore considered that canagliflozin was non-inferior to sitagliptin with respect to efficacy. However, the PBAC recalled it had previously questioned the clinical significance of small changes in the surrogate outcome of HbA1c change from baseline (refer to Liraglutide Public Summary Document, November 2011) as noted in recent publications[1, 2].

The submission claimed that canagliflozin 300 mg treatment resulted in a statistically significant larger reduction in mean HbA1c from baseline compared with sitagliptin. The PBAC considered that the clinical importance of this difference was unclear, and noted that the proportions of patients achieving HbA1c less than 7% were similar between the canagliflozin 300 mg and sitagliptin 100 mg arms, and lower in the canagliflozin 100 mg arm.

The indirect comparison of mean change in HbA1c for canagliflozin 300 mg and sitagliptin 100 mg in combination with a sulfonylurea met the 0.4% non-inferiority margin specified in the submission. The PBAC considered that the results of the indirect analyses were difficult to interpret due to the small number of patients, reduced power of the indirect comparison and the resulting wide confidence intervals, and differences in the common comparator arms of the trials.

The PBAC considered overall that results for outcome Least Square (LS) mean change in glycosylated haemoglobin HbA1c (%) from baseline in indirect comparisons of canagliflozin and dapagliflozin (which were significant) indicated non-inferiority of canagliflozin 300 mg to dapagliflozin 10 mg in terms of efficacy, using the 0.3% non-inferiority margin specified in the submission.

The PBAC noted that the proximal diuresis, natriuresis and calorie leakage into urine with canagliflozin 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 canagliflozin over other agents, should they be shown to occur in clinical practice.

The submission claimed that canagliflozin 300 mg and dapagliflozin 10 mg have a comparable safety profile in terms of treatment emergent adverse events.

[1] Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Bergeonneau C, Kassai B, Erpeldinger S, Wright JM, Gueyffier F, Cornu C. Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised control trials. BMJ. 2011;343:1-12
[2] Kilpatrick ES, Bloomgarden ZT, Zimmet PZ. Is haemoglobin A_{1c} a step forward for diagnosing diabetes? BMJ 2009;339:1288-1290

With regard to the comparative harms, the PBAC noted differences in the incidence of adverse events between the common comparator arms of the included trials, complicating the indirect comparison.

The PBAC noted no statistically significant differences in the head to head trials and indirect comparisons between canagliflozin and sitagliptin in terms of patients with at least one adverse event, with at least one serious adverse event and with adverse events leading to discontinuation.

The PBAC noted a substantially higher incidence of both male and female genital mycotic infections and osmotic diuresis related adverse events in the canagliflozin arms compared to sitagliptin. The PBAC noted also a substantially higher proportion of patients experienced an event of mycotic vulvovaginitis at earlier time points compared with placebo.

The PBAC noted that post marketing and long term safety data for canagliflozin are not yet available, and considered that the toxicity profile may differ in clinical practice from that observed in the trials. The PBAC noted the small patient numbers in the Phase III studies with long term exposure to canagliflozin and considered that the long term safety is unclear. The following was noted from the Phase III trials:

- Osmotic diuresis events were reported more frequently in canagliflozin 300 mg patients than the non-canagliflozin group.
- Rates of volume depletion were higher with canagliflozin treated patients
- The incidence of patients with clinically significant decreases in eGFR was higher in the canagliflozin 300 mg arm compared to non-canagliflozin treatments.

The PBAC noted the concerns of the United States Food and Drug Administration (FDA) regarding the high number of cardiovascular (CV) events during the first 30 days post-dose with canagliflozin in CANVAS Study 3008. In CANVAS, during the first 30 days after randomisation, 13 CV events occurred on canagliflozin (0.45%) and 1 CV event occurred on placebo (0.07%). A possible cardiac safety signal, was biologically plausible and could relate to factors such as volume depletion. The PBAC also noted that, overall, CV events did not differ between the two groups during the entire period of follow up. Increases in LDL-cholesterol levels associated with canagliflozin were also noted. PBAC agreed that uncertainty persisted regarding the cardiovascular safety profile of canagliflozin and noted that additional post-marketing studies commenced following the FDA recommendation of canagliflozin in March 2013 which include:

- an additional CV outcomes trial (CANVAS 2);
- an enhanced pharmacovigilance program to monitor for malignancies, pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities and adverse pregnancy outcomes;
- a bone safety study;
- two paediatric studies, including a pharmacokinetic and pharmacodynamic study and a safety and efficacy study.

The PBAC noted the concerns of the Therapeutic Goods Administration (TGA) over the long term safety of this new class of drug, particularly regarding liver abnormalities.

Overall, the PBAC did not consider that the claim that canagliflozin has a comparable safety profile to sitagliptin was adequately supported.

9. Clinical Claim

The submission described canagliflozin 300 mg as non-inferior in terms of comparative effectiveness and quantitatively comparable but with a different safety profile, in terms of comparative safety over sitagliptin 100 mg, when both are used in combination with metformin or a sulfonylurea.

The PBAC considered that this claim was adequately supported in terms of comparative effectiveness based on HbA1c change only, but did not consider the claim of comparative safety to be adequately supported. The PBAC remained concerned over higher rates of genital mycotic infections and osmotic diuresis associated events compared with sitagliptin, and noted the limited long-term data regarding renal and cardiovascular effects.

The submission described canagliflozin 300 mg as non-inferior in terms of comparative efficacy and safety versus dapagliflozin 10 mg. The PBAC considered canagliflozin and dapagliflozin similar but noted they have different safety profiles.

The submission did not make a claim regarding the 100 mg dose of canagliflozin. The PBAC considered that a comparison of canagliflozin 100 mg with sitagliptin 50 mg would have been informative.

10. Economic Analysis

The submission presented a cost-minimisation analysis, based on non-inferiority claim of canagliflozin 300 mg to sitagliptin 100 mg for mean reduction in HbA1c from baseline. The submission did not include additional costs for adverse events.

The submission claimed that canagliflozin 300 mg is equi-effective to sitagliptin 100 mg, based on doses are derived from fixed dose head to head trials and consistent with the product information (PI) for both drugs. The submission also considered canagliflozin 100 mg equivalent to sitagliptin 50 mg. The PBAC noted that although the equi-effective doses of canagliflozin 300 mg and sitagliptin 100 mg were consistent with the evidence provided in the submission, no evidence is provided comparing canagliflozin 100 mg with sitagliptin 50 mg.

The submission did not anticipate any cost consequences with the PBS listing of canagliflozin, but did not account for any costs related to the management of adverse events. The PBAC noted that while the overall rates of adverse events associated with canagliflozin and sitagliptin treatment were similar, there was a higher rate of genital mycotic infections in canagliflozin treatment groups.

The sponsor claimed that most infections are self-diagnosed or diagnosed on clinical history, and therefore require no investigational diagnostic tests. The sponsor also claimed that such cases would be managed with over-the-counter treatments, and that therefore higher infection rates would not be associated with increased cost to government. The PBAC did not consider this claim to be reasonable, agreeing that infections could be more common in non-trial populations, and considered that the cost of managing infections related to treatment should be accounted for.

The submission did not include potential costs of renal function monitoring, as recommended in the FDA approved PI. The PBAC considered that as patients with diabetes will have regular monitoring of renal function as part of standard care, the omission of costs for such monitoring were appropriately excluded.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net R/PBS cost of less than $10 million in Year 5.

The submission assumed that canagliflozin would predominantly substitute for the growing gliptin market. The PBAC considered that canagliflozin could also substitute for sulfonylureas, glitazones and GLP-1 analogues.

The submission assumed that the PBS listing of canagliflozin will not increase the current market. The PBAC did not consider this assumption to be reasonable considering the novel mechanism of action of canagliflozin and the volatility of the current market. The PBAC considered also that prescribing of canagliflozin outside the proposed PBS restriction may be driven by its effects on weight loss, as well as the observed high utilisation of sitagliptin (the main comparator) outside its PBS listing.

The PBAC did not consider that the assumption of linear growth of the gliptin market was reasonable given the volatility of the diabetes market noted in the October 2012 and February 2013 DUSC reports. The PBAC considered that the submission's projected uptake rates may be unreliable and that the assumption of a constant uptake rate from gliptins and glitazones was not reasonable.

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 canagliflozin on the PBS on a cost minimisation basis with sitagliptin. The equi-effective doses are canagliflozin 300 mg to sitagliptin 100 mg.

The PBAC recommended that cost-offsets be applied to canagliflozin to account for an increased rate of adverse events such as genital mycotic 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 antifungals.

The PBAC considered that the PBS listing of canagliflozin in the third line setting should be cost neutral to the Commonwealth. 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 canagliflozin is non-inferior in regards to efficacy and safety with dapagliflozin but noted variability in adverse events and differences in mechanism of action that may impact utilisation.

The PBAC recommended that canagliflozin 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 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, and that this was consistent with views expressed in correspondence the PBAC received from diabetes organisations.

The PBAC requested a DUSC predicted versus actual review be undertaken twelve months post PBS listing.

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

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

The PBAC noted with the listing of canagliflozin, 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 co-transporter 2 inhibitors.

Outcome:
Recommended

Recommended listing

Add the following new items:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
CANAGLIFLOZIN			
Tablet 100 mg	30	5	Invokana JS
Tablet 300 mg	30	5	Invokana JS

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

Janssen is pleased that the PBAC has recommended canagliflozin and is in discussions with the Department of Health regarding a listing on the Pharmaceutical Benefits Scheme (PBS) as soon as possible.