Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Canagliflozin (as hemihydrate)

Proprietary Product Names: Invokana, Prominad

Sponsor: Janssen-Cilag Pty Ltd

March 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	6 September 2013
Active ingredient:	Canagliflozin (as hemihydrate)
Product names:	Invokana, Prominad
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
Dose form:	Film coated tablet
Strengths:	100 mg and 300 mg
Container:	Blister pack
Pack sizes:	10, 30 and 100
Approved therapeutic use:	Invokana/Prominad is indicated in 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 (see Pharmacology, Clinical Trials, and Precautions for available data on different add-on therapies).
Route of administration:	Oral
Dosage (abbreviated):	100 mg or 300 mg once daily
ARTG numbers:	200179, 200180, 200183, 200184

Product background

Canagliflozin is a member of a new drug class of sodium glucose co-transporter 2 (SGLT2) inhibitors. The low affinity/high capacity SGLT2 transporter in the proximal renal tubule reabsorbs most of the filtered glucose, and a relatively small amount of glucose is reabsorbed by the high affinity/low capacity sodium glucose co-transporter 1 (SGLT1)

isoform. Pharmacological inhibition of SGLT2 has been shown to decrease renal glucose re-absorption, and thereby increase urinary glucose excretion and lower plasma glucose.

This AusPAR describes the application by Janssen-Cilag Pty Ltd to register Invocana/Prominad tablets containing 100 mg and 300 mg canagliflozin (as hemihydrate) for the following indication:

> *Invocana/Prominad is indicated in adults with type 2 diabetes mellitus 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 therapy: Add on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Precautions, Interactions with other medicines and Pharmacology for available data on different add on therapies).*

The tradename 'Invocana' was proposed originally and subsequently was amended to 'Invokana' at the sponsor's request.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) 12 September 2013.

At the time this application was considered by the TGA a similar application had been approved in the US (March 2013) and was under consideration in the European Union (EU), Canada, New Zealand and Switzerland.

The indication approved in the US is: *Invokana (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus [see Clinical Studies]. Limitation of Use: Invokana is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.*

Product Information

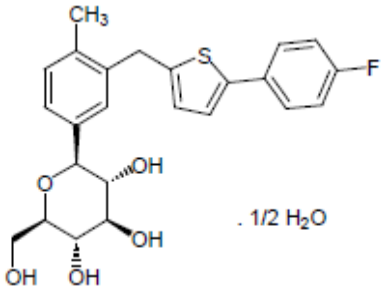
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The drug substance (structure shown below) is a SGLT2 inhibitor and is manufactured by chemical synthesis. It is a white to off-white powder, practically insoluble in aqueous media, and ranges from slightly soluble to freely solution in different organic solvents. It does not contain ionisable groups.

Figure 1. Structure of canagliflozin (as hemihydrate)



Several polymorphic forms are detected. Form I was found to be the most thermodynamically stable, and is consistently produced by the proposed synthetic process.

The drug substance specification includes appropriate tests and limits; in particular, particle size distribution was included in the specification.

Stability data show that the drug substance is stable and justify the proposed 24 month retest period when stored in the proposed packaging.

Drug product

The product is an unscored immediate release film-coated tablet containing 100 mg or 300 mg canagliflozin (as hemihydrate) as the active ingredient, and the tablets have been formulated with conventional excipients. Both strengths of the tablet are to be packaged in PVC/Al blister, in pack sizes of 10 (sample pack), 30 or 100 tablets.

The tablets specification includes controls for Identification (IR), Appearance, Assay, Chromatographic purity, Chromatographic purity, Uniformity of dosage, Dissolution and Microbial purity.

Stability data have been generated under accelerated, intermediate and long-term conditions. The results showed that the finished product is relatively stable. The stability data support a shelf-life assignment of 24 months stored below 25°C in the proposed PVC/Al blister packaging.

Biopharmaceutics

Seven biopharmaceutic studies were provided in support of this submission. Four of these studies used a formulation which was not proposed for registration and were not evaluated. Three studies, below, were relevant for this submission and were evaluated.

Table 1. Evaluated biopharmaceutic studies

Study Number	Comments	Study type	Action
28431754-DIA1021	To determine the absolute bioavailability of canagliflozin after a single 300 mg oral dose of canagliflozin (using FBG tablet, NPE API)	Absolute bioavailability	This study was summarised
28431754-DIA1017	To assess the relative bioavailability of FBG tablets (test, Phase III formulation) with respect to HSG tablets (reference, Phase II formulation) under fasted conditions; and safety and tolerability of canagliflozin.	Relative bioavailability study	This study was summarised

Study Number	Comments	Study type	Action
	Both tablets are manufactured using NPE API.		
28431754-DIA1043	To assess the effect of co-administration of a high fat meal on the oral bioavailability of 300 mg of canagliflozin as the to be marketed formulation (FGB tablets, PE API)	Food effect	This was evaluated in full

The results from the studies above indicate that:

- The mean absolute oral bioavailability after a single dose of canagliflozin 300 mg tablet was 64.9%.
- Canagliflozin 300 mg tablet Phase II formulation and Phase III formulation have been showed to be bioequivalent under fasted conditions in female and male volunteers.
- The high fat meal has no significant effect on the bioavailability of canagliflozin 300 mg tablet proposed for registration.

A formal justification was not provided for not conducting bioavailability studies on the lower strength (100 mg). However, given that:

1. the pharmacokinetics (PK) are linear,
2. both strengths are manufactured by the same process, from the same common blend, and
3. the dissolution of the two strengths are the same,

the biopharmaceutics results from the higher strength can be extended to the lower strength from a PCS perspective.

Advisory committee considerations

This submission was presented for advice to the Pharmaceutical Subcommittee (PCS) of the Advisory Committee on Prescription Medicines (ACPM) at its meeting in March 2013. The PSC endorsed all the questions raised by the TGA in relation to the chemistry and biopharmaceutic aspects of this submission. These issues have been adequately addressed during the evaluation phase.

Quality summary and conclusions

There are no outstanding issues from chemistry and quality control perspective, and approval can be recommended.

III. Nonclinical findings

Introduction

General comments

The overall quality of the nonclinical dossier was reasonably high. All pivotal safety-related studies were conducted under good laboratory practice (GLP) conditions with the exception of those on *in vitro* cardiovascular (CV) safety. The relevant EU guideline (*The*

nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals; CHMP/ICH/423/02, May 2005) specifies that such studies should be conducted according to GLP. However, the studies were well documented nevertheless and this is considered to be only a minor deficiency.

Pharmacology

Primary pharmacology

Sodium-glucose co-transporter 2 (SGLT2) is expressed in proximal renal tubules where it is responsible for resorption of the majority of glucose filtered by the renal glomerulus. Inhibition of SGLT2 results in increased urinary glucose excretion, leading to lowered plasma glucose.

Canagliflozin was shown to inhibit the recombinant human SGLT2 with a mean half maximal inhibitory concentration (IC_{50}) of 4.2 nM. Similar potency was demonstrated for canagliflozin against the rat form of SGLT2. The major circulating metabolites in humans, M5 and M7 (formed by *O*-glucuronidation), were shown to be poor inhibitors of SGLT2 (each about 800 times less potent than the parent drug).

In vivo, a single oral dose of canagliflozin increased urinary glucose excretion in a dose-dependent manner in laboratory animals (experiments in normal mice, rats and dogs; diabetic rodent models; obese dogs). Reductions in blood glucose area under the plasma concentration time curve (AUC) following oral glucose challenge and fed blood glucose levels were shown. Experiments in ZDF diabetic rats revealed significant urinary glucose excretion required a threshold blood glucose level, which was markedly reduced by the drug (from 415 to 94 mg/dL with canagliflozin at 1 mg/kg). With repeated oral dosing, canagliflozin decreased body weight gain in the absence of a concomitant reduction in food consumption in mice and rats. Plasma insulin was increased and fed blood glucose and glycosylated haemoglobin (HbA1c) decreased in ZDF diabetic rats treated with canagliflozin at ≥ 3 mg/kg/day for 4 weeks. An increase in fatty acid oxidation was suggested by a decrease in the respiratory exchange ratio.

Secondary pharmacodynamics and safety pharmacology

Canagliflozin inhibited human SGLT1 with an IC_{50} of 663 nM; >150-times more weakly than at SGLT2. Similar selectivity was evident for the drug at rat SGLT2 over SGLT1 (respective IC_{50} values of 3.7 and 555 nM). Canagliflozin showed no or only very weak activity against other related transporters (SGLT3, SGLT4, SGLT6, sodium myoinositol co-transporter 1 [SMIT1], glucose transporters [GLUT] GLUT1, GLUT2, GLUT4); the lowest IC_{50} observed (3.1 μM) being almost 20-times greater than the peak free plasma concentration of canagliflozin expected in patients.[1]

In screening assays against a panel of 50 rat, guinea pig or human receptors, transporters or ion channels, the most potent inhibition of ligand binding seen with canagliflozin was at the human A_1 adenosine receptor (62% inhibition at 10 μM), the human noradrenaline transporter (51% inhibition) and the human $5HT_{2A}$ receptor (56% inhibition). Given the peak level of canagliflozin expected in patients, these activities are not considered to be of clinical relevance.

Specialised safety pharmacology studies covered the central nervous system (CNS), CV and respiratory systems. No treatment-related CNS effects were observed in rats (≤ 1000 mg/kg PO; estimated relative exposure based on maximum concentration (C_{max}), 25).

[1] Based on a steady-state C_{max} of 4.12 μg/mL [= 9.27 μM] in patients treated at the maximum recommended human dose of 300 mg QD (pooled data from Clinical Studies DIA1007 & DIA1023), and plasma protein binding of 98.3%.

Canagliflozin produced no significant inhibition of the human ether-a-go-go gene related potassium ((hERG K^+) channel in transfected mammalian cells (≤ 3 μM). Shortening of the action potential duration at 60% repolarisation (APD_{60}) and increased coronary flow were observed *in vitro* in the Langendorff-perfused rabbit heart at ≥ 3 μM and at 10 μM, respectively; CV parameters were unaffected at 1 μM (>6-times the peak free plasma concentration of canagliflozin expected in patients). *In vivo*, canagliflozin had no significant effect on heart rate, blood pressure or ECG in guinea pigs (≤ 9.86 mg/kg as a cumulative intravenous (IV) dose; relative exposure based on C_{max}, 3.1) nor on CV or respiratory parameters in dogs (≤ 400 mg/kg PO; estimated relative exposure based on C_{max}, >14).

Pharmacokinetics

Peak plasma concentrations of canagliflozin following oral administration were reached within 1–2 h in mice, typically 3–7 h in rats (variable), 1–3 h in dogs, 3.5 h in monkeys and 1.5 h in humans. Oral bioavailability was complete in mice, high in dogs (65%), moderate in monkeys (50%) and lower in rats (35%). A micro-dose study indicated oral bioavailability of 65% in humans (at 300 mg). Plasma half life was rapid in mice (4 h), moderate in rats, dogs, monkeys (7–8 h) and somewhat longer in humans (10–13 h). Exposure was approximately dose-proportional in laboratory animal species and in humans, except at very high oral doses in rats. Exposure was generally higher in female mice and rats compared with males; no sex difference was evident in dogs.

Plasma protein binding by canagliflozin was high and similar in humans and laboratory animal species (mouse, rat, rabbit, dog and monkey; 98–99%). The drug showed high affinity for human serum albumin and lower affinity for α_1-acid glycoprotein. Distribution of radiolabelled (^{14}C)-canagliflozin-derived radioactivity from plasma into red blood cells was low (assessed in rat, dog and human). Volumes of distribution were higher than total body water in all species (mouse, rat, dog, monkey and human). Accordingly, wide tissue distribution of radioactivity was observed in rats following oral administration of ^{14}C-canagliflozin. Outside of the gastrointestinal (GI) tract, the greatest exposure was in the renal cortex (10 times the blood C_{max} and 12.5 times the blood AUC); penetration of the blood-brain barrier was low.

Metabolism of canagliflozin involved oxidation, alcohol oxidation (to carboxy), hydroxylation and glucuronidation. Unchanged drug was the predominant drug-related material in plasma in all laboratory animal species (mouse, rat and dog) as well as in humans. Oxidation was the prominent pathway in animals, while glucuronidation was the dominant pathway in humans. The two major metabolites in humans (M5 and M7, formed by direct *O*-glucuronidation) were also identified as plasma metabolites in mice, rats and dogs. A third, minor, *in vivo* metabolite identified in humans (M9; formed by hydroxylation), was also present in the three animal species (in urine and faeces in all, and additionally in plasma in mice). Cytochrome P450 subtype 3A (CYP3A4), and to a much lesser extent, CYP2D6, were found to contribute to the oxidative metabolism of canagliflozin. The uridine diphosphate glucuronosyl transferase UGT1A9 was identified as the main UGT isoform responsible for formation of M7, and UGT2B4 as the isoform responsible for formation of M5. These metabolites were shown to be convertible back to canagliflozin in the faeces of mice and humans via enzymatic reactions.

Excretion of canagliflozin and/or its metabolites was predominantly via the faeces in all species (mice, rats, dogs and humans). Renal excretion was much more prominent in humans (33%) *compared with* the laboratory animal species (2–6%), consistent with greater formation of glucuronide metabolites. Enterohepatic recirculation was demonstrated in mice, with 36% of ^{14}C-canagliflozin-derived radioactivity excreted via the bile seen to be reabsorbed from the intestinal tract.

Although the animal species tended to favour oxidative metabolism of canagliflozin over glucuronidation (the major metabolic pathway in humans), the PK profile of canagliflozin in the species used in the toxicity studies (mice, rats and dogs) is sufficiently similar to that in humans to allow them to serve as appropriate models for toxicity.

Pharmacokinetic drug interactions

Canagliflozin was shown to be able to inhibit CYP3A4, 2B6, 2C8 and 2C9. The IC_{50} values (27, 16, 75 and 80 μM, respectively) are 1.7–8.6-times the clinical C_{max} at the maximum recommended human dose. The drug did not inhibit CYPs 1A2, 2A6, 2C19, 2D6 or 2E1. The CYP inhibition potential of metabolites M5 and M7 was also examined, with M7 found to inhibit CYP2B6, 2C8 and 2C9 (respective IC_{50} values: 55, 64 and 100 μM; 11–20-times the clinical C_{max} for the metabolite); no significant inhibitory activity was seen with M5. Clinical *in vivo* interaction studies, described in the draft PI document, reportedly showed a low propensity for interactions with substrates of CYPs 3A4, 2C8 and 2C9. Canagliflozin did not induce CYP1A2, 2B6, 2C9, 2C19 or 3A4 (nor M5 and M7 induce CYPs 1A2, 2B6 or 3A4) in cultured human hepatocytes.

In vitro studies indicated that canagliflozin is a substrate of P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2), and a weak inhibitor of P-gp (IC_{50}, 19 μM). M5 and M7 were not substrates or inhibitors of P-gp. Canagliflozin, M5 and M7 were not substrates of human (h) sodium taurocholate cotransporting polypeptide (hNTCP), organic anion transporters hOAT1, hOAT3, hOATP2, and organic cation transporters hOCT1 or hOCT2. Weak inhibition of some of these transporters was seen with canagliflozin and M7 (IC_{50} values, ≥100 μM; >10-times the clinical C_{max}). Canagliflozin was not an inhibitor of urate transporter URAT1.

Canagliflozin increased exposure to metformin with co-administration in rats; canagliflozin exposure was unaffected by metformin. No clinically relevant PK interaction between the two drugs was reportedly found in humans.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted in mice and rats, using animals both sexes, the clinical (oral [PO]) and a parenteral route (intraperitoneal, IP), and an observation period of 14 days, in accordance with the EU guideline on single-dose toxicity (3BS1a). Maximum non-lethal doses by the oral route were 2000 mg/kg in mice and 1000 mg/kg in rats (and 500 and 125 mg/kg in the respective species with IP administration). Deaths (in rats only) occurred 3–11 days post-dose. Clinical signs, chiefly gastrointestinal (such as soft faeces, distended abdomen), were observed in both species and by both routes. Gross pathological examination revealed no notable effects apart from peritoneal adhesions in animals treated IP (consistent with a response to irritation).

Repeat-dose toxicity

Studies of up to 3 months duration were conducted in mice, 6 months in rats and 12 months in dogs. A 5-day study in rabbits (as a dose-range finding study for a subsequent embryofetal development study and without histopathological examination) was also submitted. All involved oral administration (the intended clinical route). The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with International Conference on Harmonisation (ICH) guidelines.

Relative exposure

Exposure ratios have been calculated in the table below based on animal:human plasma AUC from time of administration until 24 h post-dose ($AUC_{0-24\,h}$) values for canagliflozin. Human reference values are for the maximum recommended human dose (300 mg once daily), based on pooled data from Clinical Studies DIA1007 and DIA1023. High multiples of the maximum anticipated clinical systemic exposure to canagliflozin were obtained in animals at the high-dose levels used. Exposure ratios with respect to the lower proposed clinical dose (100 mg once daily) are 3.7-times higher than those shown. Exposure to metabolites M5 and M7 in animals in the pivotal repeat-dose toxicity studies and the carcinogenicity studies was below that of patients at the maximum recommended human dose (and below that at the lower proposed clinical dose too, except in high-dose female mice in the carcinogenicity study where the clinical AUC for M7 was marginally exceeded). However, given these metabolites have minimal primary pharmacological activity and glucuronidation can be considered a detoxification step, this is not of significant concern.

Table 2. Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)		Exposure ratio[#]	
			male	female	male	female
Mouse (CD-1)	3 months	30	65.9	102	2.5	3.9
		100	235	354	9	14
		300	651	736	25	28
	2 years [carcinogenicity]	10	11.3	36.4	0.4	1.4
		30	47.7	102	1.8	3.9
		100	194	353	7	14
Rat (Sprague Dawley)	6 months [pivotal]	4	14.1	21.6	0.5	0.8
		20	68.5	88.3	2.6	3.4
		100	321	379	12	15
	2 years [carcinogenicity]	10	38.35	61.96	1.5	2.4
		30	117.7	188.4	4.5	7
		100	316.0	559.9	12	21
Dog (Beagle)	12 months [pivotal]	4	59.6		2.3	
		30	263		10	
		100	516		20	
Human (type 2 diabetes mellitus patients)	steady state	[300 mg]	26.1		–	

[#] = animal:human plasma $AUC_{0-24\,h}$

Major toxicities

The major targets for canagliflozin toxicity were the bone and kidney, with gastrointestinal effects also seen.

Canagliflozin produced gastrointestinal clinical signs in the laboratory animal species, with faecal abnormalities (soft, unformed, decreased, watery and/or mucoid) observed in mice (≥ 250 mg/kg/day), rats (≥ 100 mg/kg/day) and dogs (≥ 4 mg/kg/day). Abdominal/caecal distension was seen in mice (300 mg/kg/day) and rats (≥ 10 mg/kg/day), and emesis in dogs (≥ 25 mg/kg/day). The only notable histopathological finding in the GI tract was gastric erosion, observed in rats, including at all dose levels in the pivotal 6 month study. A mechanistic study, together with the acute nature of the finding, supported this being largely related to overnight fasting of the animals prior to necropsy. No GI lesions were observed in dogs (≤ 100 mg/kg/day for 12 months; relative exposure, 20).

Canagliflozin caused bone hyperostosis in rats. This was characterised by an increase in trabecular bone in the metaphysis beneath the growth plate, and was shown to be reversible after an 8 week recover period in a 13-week study. Bone strength was reduced

at 100 mg/kg/day. The no observed adverse effect level (NOAEL) for hyperostosis in the rat is considered to be 4 mg/kg/day (relative exposure, 2.3). Bone was unaffected in mice (≤ 300 mg/kg/day for 3 months and ≤ 100 mg/kg/day for 2 years; relative exposure 25-28 and 7–14) and no significant effects were evident in dogs (≤ 100 mg/kg/day for 12 months; relative exposure, 20). Hyperostosis in rats was accompanied by a marked increase in urinary calcium excretion. A series of mechanistic studies support hyperostosis (and hypercalciuria) being related to increased calcium absorption, occurring secondary to carbohydrate malabsorption due to canagliflozin's inhibition of SGLT1. The plasma $AUC_{0-24\,h}$ for orally administered radioactive calcium was increased by about 40% in rats treated with canagliflozin (100 mg/kg). Despite the drug's substantial selectivity for SGLT2 over SGLT1, with prolonged oral absorption and modest oral bioavailability in rats, high intraluminal concentrations of canagliflozin sufficient to inhibit SGLT1 on the luminal surface of intestinal enterocytes are to be expected. The resulting inhibition of intestinal absorption of glucose and galactose will provide substrate for bacterial fermentation in the distal GI tract, lowering the luminal pH and thereby increasing the solubility (and absorption) of calcium. Consistent with this, canagliflozin-induced hyperostosis was prevented when rats were fed a glucose/galactose-free fructose diet (noting that fructose is absorbed by the [non-inhibited] GLUT5 transporter). The sponsor's Clinical Overview and draft PI report that carbohydrate malabsorption does not occur in humans.

In rats, treatment with canagliflozin caused renal tubular dilatation at all dose levels in the pivotal 6 month study (≥4 mg/kg/day; relative exposure, ≥0.5). Treatment was also associated with increased renal mineralisation, and at the high-dose level (100 mg/kg/day; relative exposure, 12–15), transitional cell hyperplasia was seen (without atypical changes that would suggest a pre-neoplastic effect). In dogs, the incidence/severity of renal tubular lesions (dilatation and regeneration/degeneration) was increased at the high-dose level in a 3-month study (involving dosing at 200 mg/kg/day for the first week, then subsequently 100 mg/kg/day), but no treatment-related kidney lesions were observed in the pivotal 12-month study (no observed effect level (NOEL), 100 mg/kg/day; relative exposure, 20). Mice treated with canagliflozin for 3 months also showed no treatment-related renal histopathological changes (≤ 300 mg/kg/day; relative exposure, ≤ 25–28). A mechanistic study in rats showed some aspects of the renal injury were prevented with feeding of a fructose diet. The renal findings observed in treated animals are considered likely to be secondary to the osmotic diuresis occurring as a consequence of the pharmacologically induced glucosuria, and additionally in rats, carbohydrate malabsorption (with associated increases in calcium absorption and excretion), rather than reflecting a direct toxic effect of the drug on the kidney.

The repeat-dose toxicity of canagliflozin in combination with metformin was assessed in rats. In studies of 1- and 3-months duration, co-administration of metformin (300 mg/kg/day) produced no relevant additional toxicological effects *cf.* that with canagliflozin administered alone (≤ 100 mg/kg/day). Hepatocyte hypereosinophilia was observed with combination treatment but not with either of the single agents in the 3 month study. The finding was graded minimal to slight, and is considered most likely to reflect pharmacologically-mediated changes in glucose handling (such as altered hepatocellular glycogen); no other liver histopathological findings or significant changes in serum chemistry that would indicate liver injury were seen.

Genotoxicity

The potential genotoxicity of canagliflozin was investigated in the standard battery of tests: a bacterial reverse mutation assay, an *in vitro* mouse lymphoma tyrosine kinase (tk) assay and a rat bone marrow micronucleus assay, and additionally in an *in vivo* rat liver Comet assay. The conduct of the studies was in accordance with ICH guidelines. Concentrations or doses used were appropriate (up to maximum recommended levels or

limited by cytotoxicity), a suitable set of *Salmonella typhimurium* and *Escherichia coli* strains was used in the bacterial gene mutation assay, and the assays were appropriately validated. Negative results were returned for canagliflozin in all assays except for the *in vitro* mouse lymphoma tk assay, where a positive result was observed in the presence of metabolic activation. The weight of evidence supports canagliflozin being non-genotoxic.

Carcinogenicity

The carcinogenic potential of canagliflozin by the oral route was investigated in 2 year studies in mice and rats. Group sizes were appropriate and suitable dose levels were selected, with the highest doses reducing survival in mice and producing significant suppression of body weight gain in rats. No treatment-related increase in tumour incidence was observed in mice (≤ 100 mg/kg/day; relative exposure, 7 for males and 14 for females). In rats, treatment with canagliflozin was associated with increases in benign adrenal phaeochromocytomas and renal tubular adenomas and carcinomas in both sexes at 100 mg/kg/day (relative exposure, 12 for males and 21 for females), and increased Leydig cell tumours at all dose levels in males (≥10 mg/kg/day; relative exposure, ≥ 1.5). Relative exposure at the NOEL for adrenal and renal carcinogenicity (30 mg/kg/day) is 4.5 in males and 7 for females.

The increase in phaeochromocytomas was accompanied by increased adrenal medullary hyperplasia, and occurred in the context of carbohydrate malabsorption and resultant altered calcium homeostasis in the species. The particular sensitivity of the rat to increases in the incidence of these adrenal proliferative lesions (common age-related spontaneous findings in the species) following disturbances in calcium homeostasis is well recognised. Analogous findings are seen with poorly absorbable sugars (such as lactose) and sugar alcohols in rats; lactose is not associated with increased tumours in humans. In a 6 month mechanistic study in rats, substitution of the standard diet for a glucose/galactose-free fructose diet was shown to prevent increased cell proliferation in the adrenal medulla (bromo-deoxyuridine labelling) induced by canagliflozin.

The majority of the renal tubular tumours in canagliflozin-treated rats appeared after 600 days. This stands in contrast to the rapid development of renal tumours seen in rats treated with agents that interact directly with DNA or indirectly through generation of oxidative free radicals or metabolic activation to a reactive species. Sustained compensatory cell proliferation in response to chronic renal damage is recognised to promote development of these tumours, and the finding of renal tumours in rats treated with acarbose (an α-glucosidase inhibitor; registered as Glucobay) also suggests the potential involvement of carbohydrate malabsorption in the observed tumourigenicity. In a 6 month mechanistic study in rats, substitution of the standard diet for a glucose/galactose-free fructose diet inhibited canagliflozin-induced increases in staining for Kidney Injury Molecule 1 (KIM-1, a marker of tubular injury) in the kidney, and prevented or reduced the incidence of microscopic findings of swollen or vacuolated tubules and exfoliated cells. While canagliflozin increased cell proliferation in the kidney (cortex and outer stripe of the outer medulla) of rats fed standard diet, it did not in animals fed a glucose/galactose-free fructose diet.

Leydig cell tumours in canagliflozin-treated rats occurred in conjunction with findings of atrophy of secondary sexual organs and decreased testosterone, which is associated with increased Leydig cell tumours in the species. A wide range of non-genotoxic agents produce Leydig cell tumours in rats, and the Leydig (interstitial) cells of the rat are recognised to be far more sensitive to proliferation in response to alterations in hormone status compared with humans. Acarbose also induces these tumours in rats, again suggesting the possible involvement of carbohydrate malabsorption. Luteinising hormone (LH), a Leydig cell mitogen, was found to be increased by canagliflozin in a 7 month mechanistic study in rats. The sponsor's Clinical Overview and draft PI note that

canagliflozin had no meaningful effect on testosterone or LH levels in male subjects in a 12-week study.

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal development, and pre- and postnatal development). Numbers of animals and the timing/duration of treatment were appropriate. All studies were conducted by the oral route.

Table 3. Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\ h}$* (µg·h/mL)	Exposure ratio#
Rat (Sprague Dawley)	Male fertility	4	14.1	0.5
		20	68.5	2.6
		100	321.0	12
	Female fertility	4	21.6	0.8
		20	88.3	3.4
		100	379.0	15
	Embryofetal development; Pre-/postnatal development	10	42.6	1.6
		30	154.9	6
		100	507.9	19
Rabbit (NZW)	Embryofetal development	10	9.84	0.4
		40	84.9	3.3
		160	486.6	19
Human (type 2 diabetes mellitus patients); steady state		[300 mg]	26.1	–

* = for male and female fertility, plasma AUC values from the 6-month rat repeat-dose toxicity study (TOX8574) are used; # = animal:human plasma $AUC_{0-24\ h}$;

Canagliflozin and/or its metabolites were shown to readily cross the placenta and be transferred into milk in rats.

Fertility was unaffected in male and female rats treated with canagliflozin at ≤ 100 mg/kg/day (relative exposure, 12 and 15 in the respective sexes). Canagliflozin was not teratogenic in either rats or rabbits. In rats, treatment at 100 mg/kg/day (relative exposure, 19) was associated with impaired ossification of the metatarsal bones and an increased incidence of rudimentary 14th ribs. An increased incidence of additional 13th ribs was observed in rabbits at all dose levels (≥10 mg/kg/day; relative exposure, ≥0.4). These doses were maternotoxic (producing significant suppression of body weight gain in rats and marked initial body weight loss in rabbits). The effects on embryofetal development observed here are considered most likely to be secondary to maternotoxicity, rather than to reflect a direct toxic effect on the fetus. Impaired ossification was also observed in the fetuses of rats treated with canagliflozin and metformin in combination (≥ 10 mg/kg/day canagliflozin + 300 mg/kg/day metformin); except at the lowest dose level, this occurred in conjunction with significantly reduced maternal body weight gain.

In a pre-/postnatal development study in rats, canagliflozin decreased pup birth weight at 100 mg/kg/day (relative exposure, 19) and reduced postnatal body weight gain at ≥ 30 mg/kg/day (relative exposure, ≥ 6). Some developmental delays (of air righting reflex and sexual maturation; attributed to decreased pup body weight) and impaired reproductive performance were observed at 100 mg/kg/day. Pup development was unaffected at 10 mg/kg/day (relative exposure, 1.6). Tissues of pups (most notably the kidney; see below) were not subjected to microscopic examination.

The developing kidney was identified as a target for irreversible changes in studies in rats conducted with the existing SGLT2 inhibitor, dapagliflozin (Forxiga). As described in the

AusPAR for the drug, an increased incidence of renal pelvic dilatation was observed in pups in a pre-/postnatal development study, and renal pelvic dilatation and tubular dilatation were observed in a study in juvenile animals. The findings may be associated with the reduced ability of the developing kidney to handle the increased urinary output induced by the drug. Kidney anatomical maturation occurs postnatally in rats, with nephrogenesis continuing to 11 days from birth (Kavlock and Gray, 1982[2]) and tubular differentiation continuing until the time of weaning (about 21 days of age); functional maturation occurs later still. Human anatomical renal maturation occurs *in utero* during the second and third trimesters and functional maturation continues for the first 2 years of life (Zoetis and Hurtt, 2003[3]). The sponsor reported that a rat toxicity study to evaluate renal effects in juvenile animals treated with canagliflozin from postnatal day 21 to 90 was ongoing at the time of submission. This study was subsequently submitted (see Addendum, below).

Pregnancy classification

The sponsor has proposed Pregnancy Category B1.[4] This category is for drugs in which studies in animals have not shown evidence of an increased occurrence of fetal damage. However, adverse effects on embryofetal development were observed in the submitted studies, albeit in the context of maternal toxicity (which would warrant placement in Category B3[5]). More significantly though, concerns regarding irreversible kidney changes, recognised for the class and applicable to the time of gestation in humans, remain outstanding. Accordingly, pregnancy category D[6] is considered to be appropriate. This category is for drugs which have caused, are suspected to have caused or may be expected to cause, and increased incidence of human fetal malformation or irreversible damage.

Phototoxicity

Canagliflozin absorbs light in the ultraviolet (UV) range (absorption peak, 291 nm). Phototoxicity was demonstrated for the drug *in vitro* (neutral red uptake assay in Balb/c 3T3 mouse fibroblasts). *In vivo*, skin reactions consistent with phototoxicity were observed in UV-exposed rats at ≥ 50 mg/kg PO (estimated relative exposure based on AUC, ≥ 7). Dermal phototoxicity was not evident at 5 mg/kg (yielding approximately the clinical AUC in females). Ocular phototoxicity was not seen (≤ 500 mg/kg PO). Canagliflozin was not photomutagenic in bacteria. No particular distribution to the skin and eyes, and no notable accumulation in melanin-containing tissues, was observed in a distribution study in rats. According to the Clinical Overview, no relevant phototoxicity occurs in patients.

[2] Kavlock, R.J and J.A. Gray. Evaluation of renal function in neonatal rats. *Biol. Neonate* 1982:41:279–288.
[3] Zoetis T. and Hurtt M.E. Species comparison of anatomical and functional renal development. *Birth Defects Res. (Pt B)* 2003:68**:**111–120.
[4] Use in pregnancy Category B 1 is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.*
[5] Use in pregnancy Category B3 is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have* shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[6] Use in pregnancy Category D is defined as: *Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

Local tolerance

Local tolerance tests were adequately conducted and revealed borderline non- to mild ocular irritation (*in vitro* bovine cornea assay), mild skin irritation (*in vivo* in mice) and no skin sensitisation potential (mouse local lymph node assay).

Paediatric use

Canagliflozin is not proposed for paediatric use and no specific studies in juvenile animals were submitted. A juvenile rat study became available at a later date (See Addendum, below). Concerns regarding potential toxicity to the developing kidney held for the pharmacological class extend to young children.

Impurities

Based on the toxicological argument presented by the sponsor, the proposed impurity specification is considered to be acceptable from a nonclinical perspective. Nevertheless, the impurity limits should be set with foremost consideration of reducing levels to as low as reasonably practicable (the 'as low as reasonably practicable' (ALARP) principle). This is a matter for the Quality evaluator.

Nonclinical summary

- The nonclinical dossier was of reasonably high quality. All pivotal safety-related studies, except those relating to the *in vitro* assessment of CV safety, were conducted according to GLP.
- Canagliflozin was shown to inhibit human SGLT2 with nanomolar potency. Consistent with the role of SGLT2 in renal glucose resorption, oral administration of the drug increased urinary glucose excretion, and reduced blood glucose and HbA1c in laboratory animals.
- The major human metabolites of canagliflozin, the *O*-glucuronides M5 and M7, are poor inhibitors of SGLT2, and will not contribute to pharmacological activity in patients.
- Canagliflozin has high selectivity for SGLT2 over SGLT1 (> 150-fold). No or only very weak inhibitory activity was found for the drug at other related transporters. Receptor screening assays revealed weak activity at the human A_1 adenosine receptor, noradrenaline transporter and serotonin 5-HT_{2A} receptor.
- Safety pharmacology studies covered the CNS, CV and respiratory systems. Canagliflozin produced no significant inhibition of the hERG K^+ channel, while shortening of action potential duration and increased coronary flow were observed in the Langendorff-perfused rabbit heart. No significant effects were observed on CV parameters *in vivo*, though, nor were there treatment-related effects on CNS or respiratory function.
- Oral absorption was rapid to moderate, and bioavailability moderate to high, in most of the laboratory animal species and in humans. More prolonged absorption and lower oral bioavailability was seen in the rat. Tissue distribution of radioactivity following oral administration of ^{14}C-canagliflozin was wide in the rat, with distribution to the target organ (kidney) particularly high; penetration of the blood-brain barrier was low. Plasma protein binding was high.
- Metabolism of canagliflozin involved oxidation, alcohol oxidation (to carboxy), hydroxylation and glucuronidation. Roles for CYP3A4, CYP2D6, UGT1A9 and UGT2B4 were shown. Glucuronidation was the major pathway in humans and oxidation the

major pathway in animals. Excretion was predominantly via the faeces in all species; renal excretion was a much more prominent route in humans *cf.* laboratory animals. Canagliflozin inhibited CYPs 3A4, 2B6, 2C8 and 2C9 at micromolar concentrations. The drug is a substrate and weak inhibitor of P-glycoprotein.

- Canagliflozin had a low order of acute oral toxicity in mice and rats.
- Pivotal repeat-dose toxicity studies were conducted by the oral route in rats (6 months) and dogs (12 months). The bone (hyperostosis) and kidney (renal tubular dilatation, tubular regeneration/degeneration, mineralisation, transitional cell hyperplasia) were identified as the major targets for toxicity. Gastrointestinal effects were also seen.
- A positive result was returned for canagliflozin in the mouse lymphoma tk assay (in the presence of metabolic activation); all other genotoxicity studies (bacterial mutagenicity, bone marrow micronucleus, rat liver Comet assay) were negative. Canagliflozin was not carcinogenic in a 2-year oral study in mice, while increases in Leydig cell tumours, adrenal phaeochromocytomas and renal tubular adenomas and carcinomas were observed in rats.
- No impairment of fertility was seen in rats. Treatment with canagliflozin during gestation was associated with reduced ossification and/or increased fetal skeletal variations in rats and rabbits, occurring in conjunction with maternal toxicity; no teratogenicity was observed in either species. Reductions in pup birth weight and postnatal bodyweight gain, and some developmental delays and impaired reproductive performance, were seen in a pre-/postnatal development study in rats.
- Phototoxicity was seen with canagliflozin *in vitro* and *in vivo* (dermal reactions in the rat). Local tolerance tests revealed at most mild ocular irritation, mild skin irritation and no skin sensitisation potential.

Conclusions

The nonclinical dossier contained no major deficiencies.

- Primary pharmacology studies, showing inhibition of SGLT2 *in vitro* and favourable changes in blood glucose parameters in animals *in vivo*, support the drug's use for the proposed indication.
- No clinically significant off-target activities are predicted from secondary pharmacodynamic studies.
- The bone and kidney were identified as targets for toxicity in repeat-dose studies in animals. The bone changes, and some of the kidney changes, are seen to be related to carbohydrate malabsorption in rats. The absence of treatment-related lesions in the pivotal 12-month dog study at a high multiple of the clinical exposure at the maximum recommended human dose (about 20) supports human safety and the findings being largely rat-specific.
- The weight of evidence indicates that canagliflozin is not genotoxic. This is supported by the absence of carcinogenicity in mice and the prolonged time for tumour development in rats.
- Being related to rat-specific carbohydrate malabsorption (with resultant disruption of calcium homeostasis) and hormonal changes, increases in Leydig cell tumours, phaeochromocytomas and renal tubular tumours in rats are not considered to indicate that canagliflozin poses a particular carcinogenic risk to patients. The claimed absence of carbohydrate malabsorption and effects on testosterone and luteinising hormone in humans requires verification by the clinical evaluator.

- Canagliflozin was not teratogenic in conventional studies in rats and rabbits. Adverse effects on fetal skeletal development observed with canagliflozin are consistent with being secondary to maternal toxicity, rather than to reflect a direct toxic effect of the drug on the fetus.
- The potential for irreversible changes in the developing kidney, found for dapagliflozin, the existing member of the pharmacological class, has not been addressed by the sponsor here. This requires histopathological examination of the renal tissue of the offspring or of treated juvenile animals. While this level of examination is not a standard requirement for a typical new chemical entity, it is warranted given the potential severity of the effect and the likelihood of applicability across the class. Until such time as these concerns are resolved, it is prudent that the drug be used with particular caution in pregnant women. As such, placement in Pregnancy Category D (rather than B1, as the sponsor proposes) is recommended.

Recommendation

There are no nonclinical objections to the registration of Invokana/Prominad for the proposed indication. A juvenile rat study to address renal toxicity (which will be applicable to fetal and paediatric exposure), identified by the sponsor as currently underway, should be submitted to the TGA for evaluation as soon as it becomes available.

Recommended revisions to nonclinical statements in the draft PI are beyond the scope of the AusPAR.

Addendum to nonclinical evaluation report

The sponsor submitted a juvenile rat study with canagliflozin in response to a request by the TGA. The study, initiated due to concerns over renal toxicity for the drug class, was ongoing at the time the submission was lodged but was subsequently completed.

Rats received oral doses of canagliflozin at 4, 20, 65 or 100 mg/kg/day for 10 weeks, beginning at 21 days of age. Resultant plasma exposure levels were comparable to those obtained in the pivotal 6 month general repeat-dose toxicity study in the species (in which animals were about 6 weeks old at the initiation of dosing).

Findings in the juvenile animal study were qualitatively similar to those in the 3 and 6 month repeat-dose toxicity studies in rats, with the kidney and bone the principal targets.

Conclusions

- The developing kidney is confirmed as a sensitive target for toxicity by canagliflozin. This is also recognised for dapagliflozin, the existing member of the pharmacological class.
- There remain no nonclinical objections to the registration of Invokana/Prominad for the proposed indication.
- The case for placement in Pregnancy Category D (rather than B1 as the sponsor has proposed) is strengthened.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The proposed indication is:

> *Invokana is indicated in adults with type 2 diabetes mellitus 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 therapy:*
>
> *Add-on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Precautions; Interactions with other medicines and Pharmacology for available data on different add-on therapies).*

Clinical rationale

The Sponsor's rationale for the development of canagliflozin is as follows:

> In Australia, diabetes is a national health priority area. It is the fastest growing chronic disease and is the sixth leading cause of death. The Australian Bureau of Statistics' 2007-08 National Health Survey estimated that 898,800 Australians have been diagnosed with diabetes and of these patients, the majority (approximately 787,500 Australians) were diagnosed with type 2 diabetes mellitus (T2DM). By 2023, T2DM diabetes is projected to be the leading specific cause of disease burden for males and second for females.
>
> There are currently agents from a number of different classes that are available for the treatment of T2DM. Most patients with T2DM are initially managed with single agent therapy, usually metformin. Despite initial monotherapy, many patients have progressive loss of glycaemic control, requiring combinations of agents, and often eventually insulin therapy. Underlying this progressive deterioration in glycaemic control is a gradual loss of beta-cell function. Thus, there remains a substantial unmet medical need for new medications to treat patients with T2DM that are well tolerated and efficacious, provide good durability, beneficially impact beta-cell function and insulin secretion.

Scope of the clinical dossier

The submission contained the following clinical information:

Module 5:

- 40 clinical pharmacology studies, including 25 that provided PK data and 15 that provided pharmacodynamic (PD) data.
- One population PK analyses and one population PK/PD analysis.
- Eight pivotal efficacy/safety studies.
- Two dose-finding studies.
- Two other efficacy/safety studies.
- Integrated Summary of Efficacy, and Integrated Summary of Safety.

Module 2:

Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All the submitted studies were stated to have been performed according to Good Clinical Practice. Good Clinical Practice appears to have been adhered to.

Pharmacokinetics

Studies providing pharmacokinetics data

The clinical data included the following PK/PD studies.

Table 4. Phase 1 Clinical studies of canagliflozin

Type of Study	Population/Number of Studies
Absolute bioavailability, relative bioavailability, and food effect	Healthy subjects, 4 studies
Mass-balance	Healthy subjects, 1 study
Single-dose PK and PK/PD	Healthy subjects, 3 studies
Multiple-dose, PK/PD	Healthy subjects, 3 studies Subjects with T2DM, 3 studies
Pharmacodynamic	Healthy subjects, 1 study Subjects with T2DM, 2 studies
Hepatic impairment	1 study
Renal impairment	1 study
Non-Caucasian subjects	Japanese/Indian subjects, 3 studies
Drug-drug interaction	Healthy subjects,12 studies
QT/QTc	Healthy subjects, 1 study
Photosensitivity	Healthy subjects, 4 studies

Key: PD=pharmacodynamic, PK=pharmacokinetic, T2DM=type 2 diabetes mellitus
Note: Studies were conducted in Caucasian subjects unless otherwise indicated.

Findings from the PK studies are detailed in the Extract from the clinical evaluation report (CER, at Attachment 2 of this AusPAR) and are summarised in the *Delegate's overview and recommendations* below (see *Overall conclusion and risk/benefit assessment* below).

Evaluator's overall conclusions on pharmacokinetics

The PK of canagliflozin are unlikely to pose any challenges in clinical practice. The PK of canagliflozin were linear at doses up to 800 mg. Excretion is a combination of biliary and renal excretion of the glucuronide metabolites. Renal clearance of parent canagliflozin was negligible. Less than 1% of the administered dose was recovered as unchanged drug in urine. Half-life was approximately 12-15 h. Digoxin will require additional monitoring when used in conjunction with canagliflozin. Other than for digoxin, there were no clinically significant interactions identified.

Pharmacodynamics

Studies providing pharmacodynamic data

See Table 4 above.

Findings from the PD studies are detailed in the Extract from the CER (Attachment 2 of this AusPAR) and are summarised in the Delegate's Overview for this application (see *Overall conclusion and risk/benefit assessment* below).

Evaluator's overall conclusions on pharmacodynamics

The PD data supported the choice of the 100 mg and 300 mg dose levels used in the Phase III studies. The data also support the sponsor's advice that canagliflozin has little effect in severe renal failure and should not be used in such patients. There was no demonstrated, clinically significant drug-drug interaction on PD.

Dosage selection for the pivotal studies

Two dose ranging studies were evaluated:

Study DIA2001: a randomised, double-blind, placebo-controlled, parallel-group, multicentre, dose-ranging study with seven treatment cohorts including an active reference arm. The study included men and women between 18 and 65 years of age, inclusive, with a diagnosis of T2DM, with HbA1c levels ≥7% and ≤10.5%, who were receiving a stable daily dose of metformin ≥ 1,500 mg/day, who had stable body weight and a body mass index (BMI) of 24 to 45 kg/m^2, with a serum creatinine concentration < 137 µmol/L for men and < 128 µmol/L for women.

The study treatments were canagliflozin 50-300 mg once daily, canagliflozin 300 mg twice daily, sitagliptin 100 mg once daily or placebo. The primary efficacy outcome measure was the change in HbA1c (%) from baseline through Week 12.

Study TA7284-04

Study TA7284-04 was a multicentre, randomised, placebo-controlled, double-blind, parallel-group comparative dose finding study. The study included subjects with T2DM, aged ≥ 20 years and ≤ 80 years, with HbA1c ≥ 6.5% and ≤ 9.5%, who had undergone diet and exercise therapy for T2DM; and who had not used diabetes drugs for at least 8 weeks.

The study treatments were canagliflozin 50-300 mg or placebo. The treatment duration was 12 weeks. The primary efficacy outcome measure was the change in HbA1c to Week 12.

Evaluator's conclusion with regard dose selection

The dose finding studies supported the selection of the canagliflozin 100 mg and 300 mg dose levels used in the Phase III studies. There was a plateau in effects at the 300 mg dose level and little difference between the 100 mg and 200 mg dose levels.

Efficacy

Studies providing efficacy data

Eight pivotal studies were provided:

- **Efficacy in combination with metformin and a sulphonylurea agent**
  - Study DIA3002: a multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm, study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily)

compared with placebo in subjects with T2DM who were inadequately controlled with metformin and a sulfonylurea agent

  - Study DIA3015: a multicentre, randomised, double-blind, active-controlled, two-arm, parallel-group, study of treatment with once daily canagliflozin 300 mg or sitagliptin 100 mg (1:1 randomisation ratio) over 52 weeks in subjects with T2DM

- **Efficacy as add-on therapy in moderate renal failure**
  - Study DIA3004: a multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm study to evaluate the efficacy, safety, and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM who were inadequately controlled on their current diabetes treatment regimen. The clinical study report (CSR) covers the first 26 weeks of a planned total duration of 52 weeks
- **Efficacy as monotherapy**
  - Study DIA3005: a multicentre, randomised, double-blind, placebo-controlled, three-arm, parallel-group study that evaluated the efficacy, safety and tolerability of canagliflozin monotherapy in subjects with T2DM who were inadequately controlled with diet and exercise
- **Efficacy in combination with metformin**
  - Study DIA3006: a multicentre, randomised, double-blind, four-arm, parallel-group, global multicentre study, conducted to evaluate the efficacy, safety, and tolerability of canagliflozin in subjects with T2DM who were inadequately controlled with metformin immediate release monotherapy. The study involved a stabilisation phase on metformin prior to randomisation
  - Study DIA3009: a multicentre, randomised, double-blind, three-arm, parallel-group, active-controlled study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) compared with glimepiride in subjects with T2DM with inadequate glycaemic control on a maximally effective dose of metformin
- **Efficacy in older subjects**
  - Study DIA3010: a multicentre, randomised, double-blind, placebo-controlled, parallel-group, three-arm study conducted to evaluate the efficacy, safety and tolerability of the addition of canagliflozin (100 mg daily and 300 mg daily) in older subjects with T2DM inadequately controlled on their current diabetes treatment regimen. The study was intended to be of 110 weeks duration and data for the first 26 weeks were presented
- **Efficacy in combination with metformin and pioglitazone**
  - Study DIA3012: a multicentre, Phase III, randomised, double-blind, placebo controlled, parallel group, three-arm study, of canagliflozin (100 mg daily and 300 mg daily) compared with placebo in subjects with T2DM who were inadequately controlled with metformin and pioglitazone. The intended study duration is 52 weeks and the results of the first 26 weeks were submitted.

In addition, a supportive long-term CV safety study (Study DIA3008) was provided. This was a Phase III, randomised, double-blind, placebo-controlled, three parallel-group study to evaluate the safety, tolerability, and CV risk with canagliflozin plus standard of care relative to placebo plus standard of care in subjects with T2DM, on a wide range of current anti-hyperglycaemic agents (AHAs), who had either a history or high risk of CV disease.

An Integrated Analysis of Efficacy was also provided, which examined the effects of demographic, anthropometric and baseline characteristics upon efficacy.

Evaluator's conclusions on clinical efficacy

For the primary efficacy outcome variable used in the pivotal studies (change from baseline in HbA1c):

Efficacy as monotherapy

- Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3005). The mean (standard deviation; SD) change from baseline in HbA1c was -0.79 (0.906) % for canagliflozin 100 mg, -1.03 (0.863) % for 300 mg and 0.14 (1.057) % for placebo. The least squares (LS) mean (95% confidence interval (CI)) difference (canagliflozin-placebo) was -0.91 (-1.088 to -0.729) % for 100 mg and -1.16 (-1.342 to -0.985) % for 300 mg. There was no subgroup effect on efficacy. Half of the subjects were "treatment naïve".

Efficacy in combination with metformin

- Over 26 weeks canagliflozin 300 mg and 100 mg were both superior to placebo but no formal comparison was performed with sitagliptin (Study DIA3006). The mean (SD) change from baseline in HbA1c was -0.81 (0.650) % for canagliflozin 100 mg, -0.98 (0.885) % for 300 mg, -0.84 (0.835) for sitagliptin and 0.20 (0.895) % for placebo. The LS mean (95% CI) difference (active-placebo) was -0.62 (-0.758 to -0.481) % for 100 mg and -0.77 (-0.914 to -0.636) % for 300 mg ($p < 0.001$) and -0.66 (-0.795 to -0.516) % for sitagliptin. There was no subgroup effect on efficacy.
- Canagliflozin 300 mg was superior to glimepiride, but canagliflozin 100 mg was not, over 52 weeks of treatment (Study DIA3009). The mean (SD) change from baseline in HbA1c to Week 52 was -0.78 (0.820) % for canagliflozin 100 mg, -0.89 (0.831) % for 300 mg and -0.79 (0.947) % for glimepiride. The LS mean (95% CI) difference (canagliflozin-glimepiride) was -0.01 (-0.109 to 0.085) % for 100 mg and -0.12 (-0.217 to -0.023) % for 300 mg. The treatment benefit of canagliflozin 300 mg is of doubtful clinical significance. There was no subgroup effect on efficacy.

Efficacy in combination with metformin and a sulfonylurea agent:

- Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3002). The mean (SD) change from baseline in HbA1c was -0.92 (0.985) % for canagliflozin 100 mg, -1.13 (0.936) % for 300 mg and -0.20 (0.915) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.71 (-0.904 to -0.524) % for 100 mg and -0.92 (-1.114 to -0.732) % for 300 mg. There was no subgroup effect on HbA1c.
- Canagliflozin 300 mg was superior to sitagliptin 100 mg over 52 weeks (Study DIA3015). The mean (SD) change from baseline in HbA1c was -1.0 (0.940) % for canagliflozin and -0.63 (1.022) % for sitagliptin. The LS mean (95% CI) difference (canagliflozin-sitagliptin) was -0.37 (-0.500 to -0.250) %. Effect was not demonstrated in the African American subgroup.

Efficacy in combination with metformin and pioglitazone

- Canagliflozin 300 mg and 100 mg were both superior to placebo (Study DIA3012). The mean (SD) change from baseline in HbA1c was -0.92 (0.802) % for canagliflozin 100 mg, -1.00 (0.806) % for 300 mg and -0.30 (0.860) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.62 (-0.811 to -0.437) % for 100 mg and -0.76 (-0.951 to -0.575) % for 300 mg. There was no subgroup effect on efficacy.

Efficacy as add-on therapy in moderate renal failure

- Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3004). The mean (SD) change from baseline in HbA1c was -0.37 (0.873) % for canagliflozin 100 mg, -0.52 (0.813) % for 300 mg and -0.13 (0.880) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.30 (-0.529 to -0.066) % (p = 0.012) for 100 mg and -0.40 (-0.635 to -0.174) % for 300 mg (p <0.001).

Efficacy in older subjects

- Canagliflozin 300 mg and 100 mg were both superior to placebo over 26 weeks (Study DIA3010). The mean (SD) change from baseline in HbA1c was -0.64 (0.747) % for canagliflozin 100 mg, -0.74 (0.753) % for 300 mg and -0.07 (0.922) % for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.57 (-0.708 to -0.436) % for 100 mg and -0.70 (-0.841 to -0.566) % for 300 mg. There was no subgroup effect on efficacy.

Efficacy in combination with insulin:

- Although efficacy was demonstrated for canagliflozin in comparison with placebo, this was in a selected population, in an 18 week substudy and where formal hypothesis testing had not been planned.

The glycaemic secondary efficacy outcome measures (HbA1c targets and fasting plasma glucose (FPG)) were all supportive of the primary outcome. There were consistent decreases in body weight, BMI and waist circumference that were clinically and statistically significant. However, it is not clear that these changes persisted once treatment was ceased. There were consistent increases in high density lipoprotein cholesterol (HDL-C) and in some studies total cholesterol and low density lipoprotein cholesterol (LDL-C) also increased.

The study population was typical of patients with T2DM. The outcome measures used in the studies were standard for studies in T2DM. The statistical analyses were appropriate. The non-inferiority margin used in the non-inferiority studies was clinically significant.

Safety

Studies providing evaluable safety data

Evaluable safety data were provided from all the clinical pharmacology, dose finding and efficacy studies.

Patient exposure

A total of 329 healthy subjects received canagliflozin in 14 completed single dose Phase I trials and 397 healthy subjects received canagliflozin in 16 completed multiple dose Phase I trials. In the four pooled Phase I trials in subjects with T2DM (Trials DIA1007, DIA1023, DIA1025, NAP1002), 154 subjects received canagliflozin (104 subjects received < 300 mg/day, 10 subjects received 300 mg/day, and 40 subjects received >300 mg/day). In one additional completed Phase I trial in subjects with T2DM (DIA1045), 37 subjects were dosed with canagliflozin.

Exposure in Phase II Studies: In Study DIA2001, there were 64 subjects exposed to canagliflozin 50 mg once daily, 64 to 100 mg once daily, 65 to 200 mg once daily, 64 to 300 mg once daily and 64 to 300 mg twice daily for up to 12 weeks. In Study TA7284-04, there were 82 subjects exposed to 50 mg daily, 74 to 100 mg, 77 to 200 mg and 75 to 300 mg for up to 12 weeks.

In Phase III studies, the safety of canagliflozin was evaluated in 10,285 subjects with T2DM, including 3,092 subjects treated with canagliflozin 100 mg and 3,462 subjects treated with canagliflozin 300 mg, randomised and dosed in nine double-blind, placebo- or active-controlled Phase III clinical trials. In all Phase III studies, there were 6645 subjects exposed to canagliflozin with 5936 exposed for 6 months, 4723 for 12 months, 1200 for 18 months and 144 for 24 months (Table 5).

Table 5. Overall exposure in canagliflozin Phase III program

	Exposure in Filing			
	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana
Total Number of Subject in Phase 3 Program	3,139	3,506	6,645	3,640
6-month Exposure	2,844	3,092	5,936	3,162
12-month Exposure	2,260	2,463	4,723	2,392
18-month Exposure	604	596	1,200	569
24-month Exposure	73	71	144	64

Note: The cutoff of Study DIA3015 is end of the study and the cutoff of the rest of the Phase 3 studies is 31 January. 2012. A subject is counted in the 6-month, 12-month, 18-month and 24-month exposure if his/her duration of treatment is greater or equal to 24 weeks, 50 weeks, 76 weeks, and 102 weeks.

A total of 703 subjects with moderate renal failure were exposed to canagliflozin: 338 to 100 mg daily and 365 to 300 mg daily (Table 6).

Table 6. Duration of exposure to study medication - regardless of use of rescue medication (ISS Phase III Moderate Renal Impairment Dataset: Safety Analysis Set)

	Placebo (N=382)	Cana 100 mg (N=338)	Cana 300 mg (N=365)	All Cana (N=703)
Total duration of exposure (weeks)				
N	382	338	365	703
Category, n (%)				
<2 weeks	4 (1.0)	5 (1.5)	1 (0.3)	6 (0.9)
2-<6 weeks	13 (3.4)	4 (1.2)	12 (3.3)	16 (2.3)
6-<12 weeks	9 (2.4)	11 (3.3)	14 (3.8)	25 (3.6)
12-<16 weeks	12 (3.1)	5 (1.5)	7 (1.9)	12 (1.7)
16-<24 weeks	14 (3.7)	14 (4.1)	13 (3.6)	27 (3.8)
24-<28 weeks	116 (30.4)	112 (33.1)	109 (29.9)	221 (31.4)
28-<50 weeks	139 (36.4)	109 (32.2)	122 (33.4)	231 (32.9)
≥50 weeks	75 (19.6)	78 (23.1)	87 (23.8)	165 (23.5)
≥76 weeks	12 (3.1)	13 (3.8)	8 (2.2)	21 (3.0)
Mean (SD)	35.57 (17.612)	37.41 (18.443)	37.31 (18.339)	37.36 (18.376)
Median	30.57	30.79	32.14	31.43
Range	(0.1;89.4)	(0.1;90.4)	(1.3;91.4)	(0.1;91.4)
Total Exposure (subject years)	260.4	242.3	261.0	503.3

Note: Total duration = Treatment duration = last dose date - first dose date + 1(in days).

Overall, there were 270 subjects aged 65 to < 75 years exposed to canagliflozin; 138 to 100 mg daily and 132 to 300 mg daily. There were 38 subjects aged ≥ 75 years exposed to canagliflozin: 21 to 100 mg daily and 17 to 300 mg daily.

Findings from the safety studies are detailed in the Extract from the CER (Attachment 2 of this AusPAR) and are summarised in the Delegates Overview for this application (see *Overall conclusion and risk/benefit assessment,* below).

Evaluator's overall summary and conclusions on clinical safety

- Overall the frequency and pattern of treatment emergent adverse events (TEAEs) was similar for canagliflozin and for placebo and comparator. The frequency of TEAEs did not appear to be dose related. However, the rates of vulvovaginal mycotic infection in females and superficial genital infection in males were increased with canagliflozin. Polyuria was also more common with canagliflozin.
- There were few deaths and none appeared to be related to treatment with canagliflozin.

- The rate and pattern of serious adverse events (SAEs) was similar to placebo and comparator. Renal SAEs were more common with canagliflozin.
- The rates and pattern of discontinuations due to adverse events (DAEs) was similar to placebo and comparator. DAEs due to a renal adverse event (AE) was more common in the canagliflozin groups.
- Although in individual studies there appeared to be more subjects in the canagliflozin groups with alanine aminotransferase (ALT) ≥ 3 x the upper limit of normal (ULN), overall in the development program the rates of ALT or aspartate aminotransferase (AST) ≥ 3 x ULN and bilirubin ≥ 2 x ULN were similar for canagliflozin and comparator. None of the episodes in the canagliflozin groups were considered to be definite or probable causality.
- Decreased renal function and renal failure were more common with canagliflozin than placebo or comparator. Overall in the placebo controlled studies there were 16 (2%) subjects in the canagliflozin 100 mg group, 33 (4.1%) in the 300 mg and 13 (2.1%) in the placebo with estimated glomerular filtration rate (eGFR) < 80 mL/min/1.73 m^2 and decrease > 30% from baseline. Acute renal failure was reported in two (0.2%) subjects in the canagliflozin 100 mg group, one (0.1%) in the 300 mg and none in the placebo.
- Hypoglycaemia was more common with canagliflozin than placebo, but less common than with glimepiride. The rate of hypoglycaemia with canagliflozin was increased with sulphonylurea comedication. Severe hypoglycaemia was uncommon with canagliflozin.
- An increase in an increase in QTc interval >30 ms and <60 ms was more common with canagliflozin than with comparator, but a thorough QT study did not indicate QTc increase of regulatory concern.
- Phototoxicity was demonstrated with canagliflozin but would not be expected to occur at normal sun exposures.
- Vulvovaginal AEs were reported in up to 25% of female subjects treated with canagliflozin. Male superficial genital infections were reported in up to 8.3% of male subjects treated with canagliflozin.
- In elderly subjects there was a decrease in bone mineralisation at the hip with canagliflozin relative to placebo. In Study DIA3010 there was a decrease in bone mineralization at the hip, relative to placebo, in the canagliflozin 300 mg group. The mean (SD) change from baseline in bone mineral density (BMD) at the hip was -0.5 (2.1) g/cm^2 for canagliflozin 100 mg, -0.6 (2.1) g/cm^2 for 300 mg and -0.1 (1.9) g/cm^2 for placebo. The LS mean (95% CI) difference (canagliflozin-placebo) was -0.4 (-0.8 to -0.0) g/cm^2 for 100 mg and -0.5 (-0.9 to -0.1) g/cm^2 for 300 mg.
- The AE profile is reflected in the proposed RMP.

First round benefit-risk assessment

First round assessment of benefits

The efficacy of canagliflozin has been demonstrated in:

- Monotherapy
- In combination with metformin
- In combination with metformin and a sulfonylurea agent

- In combination with metformin and pioglitazone
- As add-on therapy in moderate renal failure
- In older subjects

The effect size was clinically significant.

Efficacy in combination with insulin was not demonstrated in a pivotal study.

First round assessment of risks

- Canagliflozin was well tolerated with a similar rate of TEAEs to placebo or comparator. There were few deaths or SAEs.
- There is an increased rate of vulvovaginal AEs in females and superficial genital infections in males.
- There is an increased risk of renal impairment, but it is not clear whether there is an increased risk of irreversible renal impairment.
- There appears to be an effect on bone mineralisation.

First round assessment of benefit-risk balance

The benefit-risk balance of canagliflozin, given the proposed usage, is favourable.

First round recommendation regarding authorisation

The application for authorisation of canagliflozin for the following indication should be rejected:

> *Invokana/Prominad is indicated in adults with type 2 diabetes mellitus 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 therapy*
>
> *Add-on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Precautions; Interactions with other medicines; and Pharmacology for available data on different add-on therapies).*

The reasons for rejection are:

- Insufficient data demonstrating efficacy in combination with insulin. The data presented for this indication come from a substudy of Study DIA3008, were conducted in a selected population, over an 18 week duration of treatment and with no formal hypothesis testing intended in the study protocol.
- In its current wording the proposed indication does not refer to specific agents in combination, which may increase the likelihood of use with agents where there is no experience.

The TGA could consider approving the following alternative indication:

> *Invokana/Prominad is indicated in adults with type 2 diabetes mellitus 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 therapy

Add-on therapy with metformin alone or in combination with sulfonylureas or pioglitazone, when these, together with diet and exercise, do not provide adequate glycaemic control (see Precautions; Interactions with other medicines; and Pharmacology for available data on different add-on therapies).

Efficacy has not been demonstrated in combination with insulin.

List of questions

The clinical evaluator did not raise any questions regarding the clinical data submitted to support the application.

On receipt of the CER the sponsor submitted a response document that clarified which data were provided to support *"Efficacy in combination with SU"*; and provided an argument against the evaluator's conclusion that *"Insufficient data demonstrating efficacy in combination with insulin. The data presented for this indication come from a substudy of Study DIA3008, were conducted in a selected population, over an 18 week duration of treatment and with no formal hypothesis testing intended in the study protocol."*

The sponsor's response document was considered by the Delegate when preparing the Delegate's Overview for this application (see below under *Overall conclusion and risk/benefit assessment*).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Canagliflozin EU-RMP (version 2.0 date 15 February 2013, data lock point 31 December 2012) + Australian-specific Annex (ASA) (version 2)) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 7):

Table 7. Summary of the Ongoing Safety Concerns

Important identified risks	• Vulvovaginal candidiasis • Balanitis • Urinary tract infections • Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues • Reduced intravascular volume

Important potential risks	• Renal impairment/renal failure • Clinical consequences of increased haematocrit • Bone fractures • Hypoglycaemia in the absence of insulin or glucose-independent insulin secretagogues • Renal cancer • Off-label use for weight loss
Important missing information	• Long-term cardiovascular safety in patients • Use in patients with congestive heart failure defined as NYHA class IV • Use in paediatric patients between 10 and 18 years of age • Use in pregnancy • Use in nursing mothers • Use in very elderly patients (≥85 years) • Use in patients with severe hepatic impairment

OPR reviewer comment:

The list of ongoing safety concerns is considered acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities are summarised in Table 8.

Table 8. Proposed pharmacovigilance activities

Safety concern	Pharmacovigilance Activities
Important identified risks	
Vulvovaginal candidiasis	Routine pharmacovigilance
Balanitis or balanoposthitis	Routine pharmacovigilance
Urinary tract infections	Routine pharmacovigilance
Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues	Routine pharmacovigilance
Reduced intravascular volume	Routine pharmacovigilance

Safety concern	Pharmacovigilance Activities
Important potential risks	
Renal impairment/renal failure	Routine pharmacovigilance Long-term follow up in ongoing clinical trials (DIA3008, DIA 3010). Adjudication of renal events in clinical trials.
Clinical consequences of increased haematocrit	Routine pharmacovigilance Long-term follow up in ongoing clinical trials (DIA3008, DIA3010). Adjudication of potential venous thromboembolic events in clinical trials.
Bone fractures	Routine pharmacovigilance Long-term follow up in ongoing clinical trials (DIA3008, DIA3010). Adjudication of all bone fracture events in clinical trials.
Hypoglycaemia in the absence of insulin or glucose –independent insulin secretagogues	Routine pharmacovigilance
Renal cancer	Routine pharmacovigilance Long-term follow up in ongoing clinical trials (DIA3008, DIA3010).
Off-label use for weight loss	Routine pharmacovigilance
Important missing information	
Long-term cardiovascular safety in patients	Routine pharmacovigilance Meta-analyses of independently adjudicated MACE-plus events (cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, and unstable angina requiring hospitalisation) will be conducted in order to demonstrate the upper bound of the 2-sided 95% CI of the hazard ratio for canagliflozin versus combined active and placebo comparators is less than 1.3. Collection of additional cardiovascular events from ongoing clinical trials (DIA3008 and DIA3010) and future controlled clinical trials of 12 weeks in duration will continue, with subsequent meta-analyses planned when a total of approximately 500 and 700 cardiovascular events have occurred.

Safety concern	Pharmacovigilance Activities
Use in patients with congestive heart failure defined as NYHA class IV	Routine pharmacovigilance
Use in paediatric patients between 10 and 18 years of age	Routine pharmacovigilance Paediatric Investigational Plan
Use in pregnancy	Routine pharmacovigilance
Use in nursing mothers	Routine pharmacovigilance
Use in very elderly patients (≥85 years)	Routine pharmacovigilance
Use in patients with severe hepatic impairment	Routine pharmacovigilance

Risk minimisation activities

In the EU-RMP the sponsor has concluded that routine risk minimisation (product labelling) is sufficient to mitigate the safety concerns associated with canagliflozin. However the revised ASA proposes a "Quality Use of Medicines Educational Programme in Australia" as additional risk minimisation. According to the ASA this program will include education materials for prescribers, patients, educators, dispensers and allied healthcare professionals.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified:

- The evaluator is concerned that the study program is designed primarily to assess efficacy and is therefore uncertain of the program's power to appropriately monitor the safety concerns as specified in the pharmacovigilance plan. Advice sought from the Advisory Committee on Safety of Medicines (ACSOM) supported the evaluator's concerns. Therefore the sponsor should provide justification as to whether these studies are sufficiently powered to address the safety concerns that they are assigned to as part of the pharmacovigilance plan.
- The protocol for DIA3011 was provided with the original EU-RMP (version 1) submitted to the TGA. However references to this study appear to have been removed from the updated EU-RMP (version 2). The sponsor should confirm that this study is still proposed for Australia, as documented in the ASA.
- It is recommended to the Delegate that formulation of an education program acceptable to the TGA is imposed as a condition of registration for this product.

Recommendations above were addressed prior to a final decision regarding this application. In relation to the educational materials, the distribution plan and a plan to measure effectiveness of the educational materials, the OPR advised that it was acceptable for the sponsor to provide these to the TGA as per the commitment in the ASA, prior to launch, should canagliflozin be approved for registration.

The OPR recommendations regarding revisions to product literature (PI and Consumer Medicine Information (CMI)) are beyond the scope of the AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

This application seeks to register canagliflozin (as hemihydrate) 100 mg and 300 mg film coated tablets (proposed trade names Invokana and Prominad) for the following indications:

> *Invokana/Prominad is indicated in adults with type 2 diabetes mellitus 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 therapy: Add on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Precautions, Interactions with other medicines, and Pharmacology for available data on different add on therapies).*

Canagliflozin is a selective and reversible inhibitor of the SGLT2, which is selectively expressed in the kidney. Sodium-glucose co-transporter 2 is the major transporter for glucose reabsorption in the kidney. Inhibition of SGLT2 reduces the extent of reabsorption of filtered glucose in the proximal renal tubules leading to increased excretion of glucose in urine, thereby lowering plasma glucose levels.

The sodium-glucose transporter (SGLT) family is composed of seven members (SGLT1–7). SGLT1 is expressed in the small intestine and kidney of both rats and humans while SGLT2 is expressed almost exclusively in the kidneys. In normal healthy individuals, glucose in plasma is filtered by the kidneys, but nearly all is reabsorbed by SGLT2 with < 1% excreted in urine. The sponsor is also claiming additional benefits from the resulting glycosuria: the increased urinary glucose excretion that occurs with SGLT2 inhibition also results in an osmotic diuresis, with the diuretic effect offering the potential for reductions in systolic blood pressure; and that the increase in urinary glucose excretion results in a loss of calories and therefore could lead to a reduction in body weight. Because the renal threshold for glycosuria (RTG) remains above hypoglycemic levels in subjects with T2DM, and because very little urinary glucose excretion occurs when plasma glucose is less than the renal threshold, treatment with canagliflozin is not expected to induce hypoglycemia.

This is the second SGLT2 inhibitor to be considered by this committee. The first in this class, dapagliflozin, was registered in October 2012.

The proposed indications for canagliflozin differ from those of dapagliflozin in that the monotherapy indication is broader, allowing for use in patients in whom metformin is contraindicated and the add-on therapy indication does not specify the type or number of additional AHAs which may be combined with canagliflozin. Dapagliflozin may only be combined with metformin, a sulfonylurea or an insulin. Dapagliflozin is contraindicated in patients with eGFR <60 mL/min/1.73m^2 whereas the low dose of canagliflozin has been proposed for this group of patients.

Guidelines

The EMA adopted a revised *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* in May 2012 (CPMP/EWP/1080 Rev 1, 14 May 2012). The revised Guideline was undergoing review by TGA and was expected to be adopted, however the current guideline was the *Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus.* (CPMP/EWP/1080/00, 30 May 2002). Both the current and revised guideline were considered. The most notable amendments in the updated Guideline are to long term safety and CV risk assessment. The new Guideline provides more comprehensive advice on the requirements for long term safety and CV safety. Of particular note the Guideline recommends that drug development programs should include sufficient information supporting the lack of a drug-induced excess CV risk.

Quality

There are no outstanding pharmaceutical chemistry issues.

Nonclinical

There are no nonclinical objections to the registration. The nonclinical evaluator requested that a juvenile rat study to address renal toxicity should be submitted to the TGA for evaluation as soon as it becomes available. The evaluation of that study report is included as an attachment to the nonclinical evaluation report.

The nonclinical evaluator has noted that canagliflozin has high selectivity for SGLT2 over SGLT1 (> 150 fold). No or only very weak inhibitory activity was found for the drug at other related transporters. Receptor screening assays revealed weak activity at the human A_1 adenosine receptor, noradrenaline transporter and 5-HT_{2A} receptor. Canagliflozin inhibited CYPs 3A4, 2B6, 2C8 and 2C9 at micromolar concentrations and is a substrate and weak inhibitor of P-glycoprotein.

In repeat-dose toxicity studies in rats (6 months) and dogs (12 months) hyperostosis and kidney abnormalities (renal tubular dilatation, tubular regeneration/degeneration, mineralisation, transitional cell hyperplasia) were identified as the major targets for toxicity. Gastrointestinal effects and phototoxicity were also seen.

The sponsor had proposed a pregnancy classification of B1 however the nonclinical evaluator has noted that adverse fetal effects were observed in the animal studies, and concerns are held for potential irreversible kidney changes with the drug class. This was reinforced by the findings from the juvenile rat study. Pregnancy category D was recommended. This is consistent with the classification for dapagliflozin.

During the course clinical development program for canagliflozin nonclinical comment was requested on treatment-related increases in phaeochromocytoma, renal tubular tumours and Leydig cell tumours that were observed with canagliflozin in a 2 year oral carcinogenicity study in SD rats. The nonclinical evaluator accepted that the positive findings in the rat carcinogenicity study are unlikely to be of human relevance.

Clinical

Pharmacology

Pharmacokinetics:

The mean absolute oral bioavailability of canagliflozin was 65% for a single 300 mg dose. In subjects with T2DM the median (range) time to achieve the maximum concentration (T_{max}) was 4.00 h (1.5 to 6.0 h) for the 100 mg daily dose and 2.75 h (1.5 to 3.0 h) for 300 mg twice daily. The PK of canagliflozin and its major metabolites were linear in the dose range 50 mg to 300 mg. Food had no effect on the PK of the 300 mg tablet proposed for marketing. Steady state was reached after 4 to 5 days of once daily dosing with canagliflozin 100 to 300 mg. The mean volume of distribution at steady state (Vd_{ss}) after IV administration was 119 L. Canagliflozin is extensively bound to proteins in plasma (98.3% to 99.2%), mainly to albumin (97.3%), independent of plasma concentrations across the range of 200 to 20,000 ng/mL, which encompasses the therapeutic concentration range for canagliflozin. The mean terminal plasma elimination half-life of canagliflozin was 10.6 h and 13.1 h with canagliflozin doses of 100 and 300 mg, respectively, based on pooled data from healthy subjects.

The mean systemic clearance of canagliflozin after an IV infusion in healthy subjects was approximately 12.2 L/h, which is much lower (about 14%) than the hepatic blood flow in humans indicating that canagliflozin is a low-clearance drug. *O*-glucuronidation is the major metabolic elimination pathway for canagliflozin in humans and approximately 40% is excreted unchanged in faeces. Two non-pharmacologically active *O*-glucuronide conjugates canagliflozin, M5 and M7, accounted for 1.9% to 30% and 16% to 29% of total drug-related components in plasma. A minor oxidative metabolite (M9), formed predominantly by CYP3A4, represented < 4% of the total drug-related components in plasma. Unchanged canagliflozin accounted for about 57% of the plasma AUC of total drug-related material. The C_{max} and AUC of the M7 and M5 metabolites were dose proportional (linear) in the dose range 100 mg to 400 mg and there was no significant accumulation over 14 days of dosing.

Study NAP1006 showed that the predominant route of excretion following a single 192-mg oral dose of ^{14}C-canagliflozin was via faeces with about 60% of the administered radioactive dose recovered in faeces. It was estimated that excretion of canagliflozin in faeces was mainly as unchanged canagliflozin (41.5%), the hydroxylated metabolite M9 (7.0%), and the *O*-glucuronide M7 (3.2%). The *O*-glucuronide M5 was not detected in faeces.

Approximately 32.5% (13.3% as metabolite M5 and 17.2% as metabolite M7) of the administered dose was excreted in urine. Less than 1% of the administered dose was recovered as unchanged drug in urine.

Mild hepatic impairment has minimal impact on the AUC of canagliflozin. The effect of mild, moderate and severe impairment of renal function was examined in Study DIA1003. After a single 200 mg dose of canagliflozin the mean AUC of canagliflozin was increased by 15%, 29%, and 53% in subjects with mild, moderate, or severe renal impairment, respectively, relative to subjects with normal renal function. The mean AUC of the metabolites M5 and M7 increased in subjects with renal impairment (by 31% to 195% for M5, and by 3% to 127% for M7) relative to subjects with normal renal function. These results are consistent with the greater proportion of those metabolites excreted in urine compared with the parent compound. Haemodialysis was not effective in clearing canagliflozin or its metabolites.

Interaction studies were performed with oestradiol/levonorgestrel, hydrochlorothiazide, cyclosporin, metformin, rifampicin, glibenclamide, digoxin and simvastatin. There was a 20% increase in the AUC for digoxin when co-administered with canagliflozin and a 50%

reduction in the AUC of canagliflozin when co-administered with rifampicin. Other PK changes associated with co-administration were not clinically significant.

Pharmacodynamics:

The lowest concentration of plasma glucose at which appreciable amounts of glucose begin to appear in the urine is called the renal threshold for glucose excretion ($RT_{glucose}$). The rate of urinary glucose excretion depends on plasma glucose concentrations, GFR, and canagliflozin plasma concentrations. The $RT_{glucose}$ values provide a measure of the renal glucose reabsorptive capacity that is not dependent on the ambient glucose concentrations.

In healthy subjects given canagliflozin mean 24 h urinary glucose excretion (UGE24h) increased in a dose dependent manner with an apparent saturation of effect at doses of > 200 mg once daily providing UGE24h values of approximately 60-70 g. With the 100 mg once daily canagliflozin, UGE24h was about 70% of the amount seen with doses >200 mg. In subjects with T2DM, UGE24h also increased in a dose-dependent manner. The mean UGE24h was generally > 100 g in subjects with T2DM receiving ≥ 100 mg canagliflozin.

In subjects with T2DM, both FPG concentrations and 24 h mean plasma glucose (MPG24h) decreased in a dose-dependent manner. With canagliflozin doses ≥ 100 mg once daily, placebo-subtracted mean decreases of ≥ 40 mg/dL and ≥ 30 mg/dL were generally observed for FPG and MPG24h, respectively. Reductions in insulin concentrations were also observed.

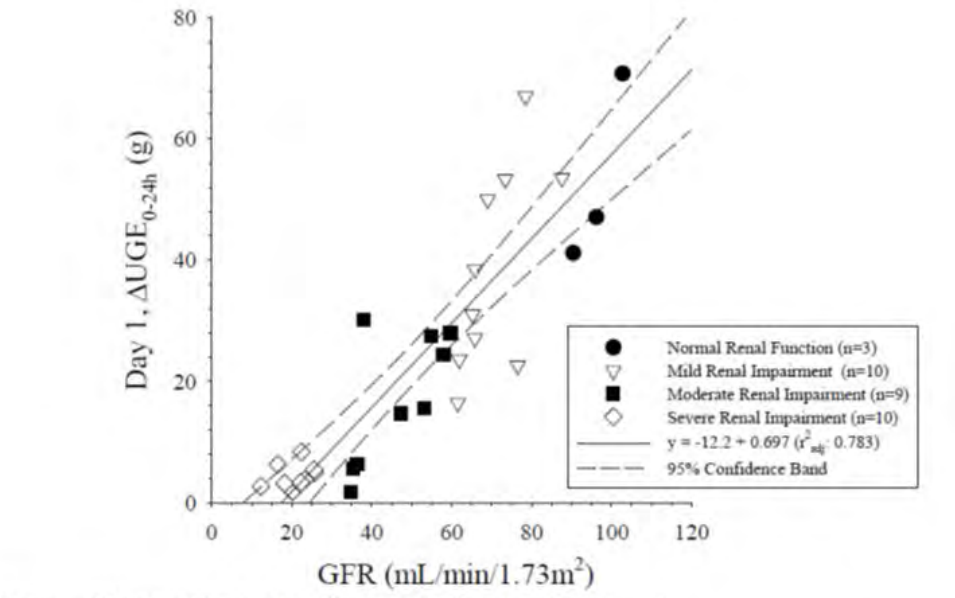
In Study DIA1003 the mean UGE24h was decreased in subjects with mild, moderate, or severe renal impairment however the extent of effect is seen most clearly in the difference in UGE24h from the day prior to dosing and the first day of dosing. There was a strong association between GFR and UGE in subjects with impaired renal function taking canagliflozin. Nevertheless canagliflozin treatment decreased 24 h mean $RT_{glucose}$ values in all groups relative to values reported in untreated healthy subjects (approximately 180 mg/dL), (Table 9). The association is presented graphically in Figure 2.

Table 9. Mean (SD) AUC_{0-4h} and C_{max} minus pre-meal serum insulin from subjects administered canagliflozin, (Parts 1, 2, and 3) (Study NAP1003)

Dose	Part 1 25 mg	Part 2 200 mg	Part 3 (Day-1) 400 mg	Part 3 Day 1 400 mg
Serum Insulin AUC_{0-4h} (uU.h/mL)				
Suspension, Fed	172 (84.4)	170 (104)	247 (123)	171 (90.5)
Tablet, Fed	159 (73.2)	167 (105)	255 (144)	155 (70.5
Tablet, Fasted	30.2 (10.6)	28.1 (12.3)	255 (141)[a]	154 (93.8)[a]
Serum Insulin C_{max} (uU/mL) minus Premeal Serum Insulin (uU/mL)				
Suspension, Fed	124 (75.3)	110 (72.3)	152 (92.2)	77.7 (44.6)
Tablet, Fed	106 (60.0)	90.6 (63.8)	147 (69.7)	54.1 (27.0)
Tablet, 30 min Prior to Meal	NA	NA	140 (82.2)	58.2 (38.7)

[a] Tablet, 30 min Prior to Meal
NA = Not Applicable

Figure 2. Individual UGE_{0-24h} changes from baseline (Day -1) versus eGFR in subjects with varying degrees of renal function (Study 28431754DIA1003 Addendum: Pharmacodynamics Data Analyses Set)



Note: ΔUGE_{0-24h} defined as the difference in UGE on Day 1 from Day -1.
Note: eGFR ranges for each renal function group are as follows: Normal = ≥ 90 mL/min/1.73m^2; Mild = 60-89 mL/min/1.73m^2; Moderate = 30-59 mL/min/1.73m^2; Severe = 15-29 mL/min/1.73m^2

A hydrogen breath test was used to explore carbohydrate malabsorption following canagliflozin in Study DIA1007. There was no significant increase in hydrogen breath content following canagliflozin administration. There was no clinically significant effect on postprandial glucagon-like peptide-1 (GLP-1) in the gut.

Excretion of N-acetyl-*β*-glucosamynidase (NAG) is increased in subjects exposed to substances toxic for renal tubular cells. 24 h urinary NAG excretion was increased in the 200 mg daily and greater dose groups, in a dose dependent manner. Excretion of NAG increased by 1949% over 4 days for the 400 mg twice daily dose of canagliflozin.

It was not clear if photosensitivity is an issue because there were inconsistent results across studies designed to assess the potential for photosensitivity however photosensitivity was apparent in the nonclinical studies. Canagliflozin was associated with a reduction from baseline of 20% in serum urate.

Efficacy

Two dose-finding studies were performed. The effect of canagliflozin doses between 50 mg once daily and 300 mg twice daily on measures of glycaemic control was examined. In the major dose-finding study the primary efficacy outcome measure was change in HbA1c from baseline to Week 12.

The mean (SD) change in HbA1c from baseline to Week 12 was -0.22 (0.702) % for placebo, -0.79 (0.749) % for 50 mg once daily, -0.76 (0.992) % for 100 mg, -0.70 (0.720) % for 200 mg, -0.92 (0.695) % for 300 mg, -0.95 (0.704) % for 300 mg twice daily and -0.74 (0.615) % for sitagliptin.

There were 9 Phase III studies. These are listed in Table 10. Seven of these studies were designed to show the superiority of canagliflozin 100 mg and/or 300 mg to placebo using the primary endpoint of HbA1c in various add-on scenarios, and the remaining 2 studies were designed to show noninferiority of canagliflozin to an active comparator (glimepiride in DIA3009 and sitagliptin in DIA3015).

Table 10. Phase III clinical studies of canagliflozin

Study ID/Type (No. Centers)	Study Design, Duration (Duration to primary endpoint/ Duration of extension phase)	HbA_{1c} Inclusion Criterion	Study Treatment Daily Dosing (qd)	No. Subjects per Treatment Arm (mITT)	Primary Efficacy Endpoint
MONOTHERAPY					
DIA3005 Main Study[a] Monotherapy (90 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.0%	Placebo CANA 100 mg CANA 300 mg	192 195 197	Δ BL to Wk 26 in HbA_{1c}
High Glycemic substudy Monotherapy (40 centers)	R, DB, PG 26 weeks double-blind (26 wks / no extension)	>10.0% to ≤12.0%	CANA 100 mg CANA 300 mg	47 44	Δ BL to Wk 26 in HbA_{1c}
ADD-ON TO AHA MONOTHERAPY					
DIA3006[a] Add-on to metformin monotherapy (169 centers)	R, DB, PC, AC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg Sitagliptin 100 mg	183 368 367 366	Δ BL to Wk 26 in HbA_{1c}
DIA3009 Add-on to metformin monotherapy (157 centers)	R, DB, AC, PG 104 weeks double-blind (52 wks / 52 wks)	≥7.0% to ≤9.5%	CANA 100 mg CANA 300 mg Glimepiride (titrated from 1 to 6 or 8 mg)	483 485 482	Δ BL to Wk 52 in HbA_{1c}
ADD-ON TO DUAL COMBINATION AHA THERAPY					
DIA3002 Add-on to metformin + sulfonylurea (85 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	156 157 156	Δ BL to Wk 26 in HbA_{1c}
DIA3012[a] Add-on to metformin + pioglitazone (74 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	115 113 114	Δ BL to Wk 26 in HbA_{1c}
DIA3015 Add-on to metformin + sulfonylurea (140 centers)	R, DB, AC, PG 52 weeks double-blind (52 wks / no extension)	≥7.0% to ≤10.5%	CANA 300 mg Sitagliptin 100 mg	377 378	Δ BL to Wk 52 in HbA_{1c}
SPECIAL POPULATION STUDIES					
DIA3010 Older adults (≥55 to ≤80 years of age) (90 centers)	R, DB, PC, PG 104 weeks double-blind (26 wks / 78 wks)	≥7.0% to ≤10.0%	Placebo CANA 100 mg CANA 300 mg	237 241 236	Δ BL to Wk 26 in HbA_{1c}

Table 10. continued. Phase III clinical studies of canagliflozin

Study ID/Type (No. Centers)	Study Design, Duration (Duration to primary endpoint/ Duration of extension phase)	HbA_{1c} Inclusion Criterion	Study Treatment Daily Dosing (qd)	No. Subjects per Treatment Arm (mITT)	Primary Efficacy Endpoint
SPECIAL POPULATION STUDIES					
DIA3004 Moderate renal impairment (eGFR ≥30 to <50 mL/min/1.73m^2) (89 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	90 90 89	Δ BL to Wk 26 in HbA_{1c}
CARDIOVASCULAR ASSESSMENT STUDY WITH EFFICACY SUBSTUDIES					
DIA3008 Cardiovascular study (369 centers)	R, DB, PC, PG Duration is event driven based on number of MACE events	≥7.0% to ≤10.5% (with history or high risk of CV disease)	Placebo CANA 100 mg CANA 300 mg	1441[b] 1445[b] 1441[b]	Assessment of hazard ratio for MACE events
Glycemic Efficacy Substudies					
Insulin substudy (316 centers)	R, DB, PC, PG 18 weeks double-blind (18 wks / no extension)	≥7.0% to ≤10.5% while receiving insulin as monotherapy or in combination with other AHAs[c]	Placebo CANA 100 mg CANA 300 mg	565 566 587	Δ BL to Wk 18 in HbA_{1c}
Sulfonylurea substudy (80 centers)	R, DB, PC, PG 18 weeks double-blind (18 wks / no extension)	≥7.0% to ≤10.5% while SU monotherapy[d]	Placebo CANA 100 mg CANA 300 mg	45 42 40	Δ BL to Wk 18 in HbA_{1c}

[a] Subjects assigned to placebo were switched to sitagliptin during the double-blind extension period.

[b] Randomized and treated subjects (ie, safety analysis set).

[c] The primary analysis population discussed in this ISE for the DIA3008 Insulin substudy was defined as subjects randomized to any of the 3 insulin strata who were receiving insulin ≥30 IU/day at study entry (Population 2).

[d] The primary analysis population discussed in this ISE for the DIA3008 SU substudy was defined as subjects on protocol-specified doses of SU monotherapy regardless of the stratification used for randomization (Population 1).

Key: Δ = change from, AC = active-controlled, AHA = anti-hyperglycemic agent, BL = baseline, CANA = canagliflozin, CV = cardiovascular, DB = double-blind, eGFR = estimated glomerular filtration rate, MACE = major adverse cardiovascular events, mITT = modified intent-to-treat population, No = number, PC = placebo-controlled, PG = parallel group, qd = once daily, R = randomized, SU = sulfonylurea; wks = weeks.

There was one placebo-controlled monotherapy study (Study 3005). The add-on studies were to metformin only, metformin + sulphonylurea, and metformin + pioglitazone. Additionally 18 week substudies of Study 3008, a long term safety and efficacy study, assessed canagliflozin as add-on therapy to a sulphonylurea only and to insulin either as monotherapy or in combination with metformin or any other oral AHA(s). Study 3010, conducted in adults aged ≥ 55 years and Study 3004, conducted in subjects with moderate renal impairment added canagliflozin to "treatment as usual" which could include insulin and or any approved oral AHA being used in accordance with local prescribing information.

The major inclusion criteria across the studies related to glycaemic control. Subjects were required to have sufficiently controlled T2DM at screening and at the start of the placebo run-in period such that they could reasonably receive placebo treatment. The requirements for glycaemic control varied somewhat across the studies but generally an HbA1c level of ≥ 7.0% and ≤ 10.5% at screening and a FPG of ≤ 15 mmol/L was required. The major exception was Study 3005 which included a "high glycaemic" substudy in which subjects had an HbA1c of >10% and ≤12%f and fasting plasma glucose of ≤19.44 mmol/L. Only adults were enrolled with a maximum age of up to 80 years. Subjects with complications of diabetes were included in the program, including those with moderate renal impairment in one study (Study 3009). The long term safety and efficacy study, Study 3008 enrolled subjects with either a history of symptomatic atherosclerotic CV disease or , if aged ≥50 years, with 2 or more risk factors for CV disease but no formal diagnosis of CV disease.

In the superiority studies the primary analysis was of the modified intent to treat (mITT) population with the last observation carried forward (LOCF) for missing data. In the non-inferiority studies the per-protocol analysis was the primary analysis. In those studies the non-inferiority margin for HbA1c was 0.3%. The primary efficacy endpoint in each of the Phase III studies was the change from baseline in HbA1c at the primary assessment timepoint (Week 18, Week 26, or Week 52, depending on the study). Results for the primary efficacy endpoint for the Phase III studies are shown in Table 11.

Table 11. HbA1c (%) change from baseline to primary assessment time-point – LOCF: study-by-study comparison (ISE Phase III studies: Modified Intent-to-Treat Analysis set)

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Monotherapy					
DIA3005					
N	189	191	194		
Baseline, mean (SD)	7.97(0.955)	8.06(0.959)	8.01(0.988)		
Change from baseline, LS mean (SE)	0.14(0.065)	-0.77(0.065)	-1.03(0.064)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.91(0.091)	-1.16(0.091)		
95% CI[a]		(-1.088;-0.729)	(-1.342;-0.985)		
Dual therapy					
DIA3006 - Add-on to metformin					
N	181	365	360	354	
Baseline, mean (SD)	7.96(0.896)	7.94(0.879)	7.95(0.931)	7.92(0.875)	
Change from baseline, LS mean (SE)	-0.17(0.060)	-0.79(0.044)	-0.94(0.044)	-0.82(0.044)	
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.62(0.071)	-0.77(0.071)	-0.66(0.071)	
95% CI[a]		(-0.758;-0.481)	(-0.914;-0.636)	(-0.795;-0.516)	
DIA3009 - Add-on to metformin					
N		478	474		473
Baseline, mean (SD)		7.78(0.787)	7.79(0.779)		7.83(0.795)
Change from baseline, LS mean (SE)		-0.82(0.039)	-0.93(0.039)		-0.81(0.039)
Diff of LS mean (SE) (minus glimepiride)		-0.01(0.050)	-0.12(0.050)		
95% CI[a]		(-0.109;0.085)	(-0.217;-0.023)		
DIA3008 substudy - Add-on to SU					
N	40	40	39		
Baseline, mean (SD)	8.49(1.130)	8.29(0.831)	8.28(1.005)		
Change from baseline, LS mean (SE)	0.04(0.146)	-0.70(0.145)	-0.79(0.147)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.74(0.206)	-0.83(0.207)		
95% CI[a]		(-1.145;-0.329)	(-1.237;-0.415)		

Table 11 continued. HbA1c (%) change from baseline to primary assessment time-point – LOCF: study-by-study comparison (ISE Phase III studies: Modified Intent-to-Treat Analysis set)

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Triple therapy					
DIA3002 - Add-on to metformin and SU					
N	150	155	152		
Baseline, mean (SD)	8.12(0.896)	8.13(0.926)	8.13(0.942)		
Change from baseline, LS mean (SE)	-0.13(0.075)	-0.85(0.075)	-1.06(0.076)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.71(0.097)	-0.92(0.097)		
95% CI[a]		(-0.904;-0.524)	(-1.114;-0.732)		
DIA3012 - Add-on to metformin and pioglitazone					
N	114	113	112		
Baseline, mean (SD)	8.00(1.010)	7.99(0.940)	7.84(0.911)		
Change from baseline, LS mean (SE)	-0.26(0.069)	-0.89(0.069)	-1.03(0.070)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.62(0.095)	-0.76(0.096)		
95% CI[a]		(-0.811;-0.437)	(-0.951;-0.575)		
DIA3015 – Add-on to metformin and SU					
N			374	365	
Baseline, mean (SD)			8.12 (0.910)	8.13 (0.916)	
Change from baseline, LS mean (SE)			-1.03 (0.048)	-0.66 (0.049)	
Diff of LS mean (SE) (minus sitagliptin)			-0.37 (0.064)		
95% CI[a]			(-0.500;-0.250)		
Add-on to insulin					
DIA3008 substudy					
N	517	540	562		
Baseline, mean (SD)	8.20(0.837)	8.33(0.905)	8.27(0.894)		
Change from baseline, LS mean (SE)	0.01(0.032)	-0.63(0.031)	-0.72(0.030)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.65(0.044)	-0.73(0.043)		
95% CI[a]		(-0.731;-0.559)	(-0.815;-0.645)		

Table 11 continued. HbA1c (%) change from baseline to primary assessment time-point – LOCF: study-by-study comparison (ISE Phase III studies: Modified Intent-to-Treat Analysis set)

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Special populations					
DIA3004 - Moderate renal impairment					
N	87	88	89		
Baseline, mean (SD)	8.02(0.917)	7.89(0.898)	7.97(0.805)		
Change from baseline, LS mean (SE)	-0.03(0.090)	-0.33(0.090)	-0.44(0.089)		
P value (minus placebo)[a]		0.012	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.30(0.117)	-0.40(0.117)		
95% CI[a]		(-0.529;-0.066)	(-0.635;-0.174)		
DIA3010 - Older adults					
N	232	239	229		
Baseline, mean (SD)	7.76(0.785)	7.77(0.773)	7.69(0.779)		
Change from baseline, LS mean (SE)	-0.03(0.063)	-0.60(0.063)	-0.73(0.064)		
P value (minus placebo)[a]		<0.001	<0.001		
Diff of LS mean (SE) (minus placebo)		-0.57(0.069)	-0.70(0.070)		
95% CI[a]		(-0.708;-0.436)	(-0.841;-0.566)		

[a] Pairwise comparison: p values and CIs are based on the ANCOVA model with treatment, study specific stratification factors and baseline HbA_{1c}.

Key: CANA=canagliflozin, CI = confidence interval, ISE = Integrated Summary of Efficacy, LOCF = last observation carried forward, LS = least squares, N = number, SD = standard deviation, SE = standard error, SU=sulfonylurea.

Note: Predefined timepoint of primary endpoint: Week 18 LOCF (DIA3008 SU and Insulin substudies), Week 26 LOCF (DIA3002, DIA3004, DIA3005 [excluding High Glycemic substudy], DIA3006, DIA3010, DIA3012) and Week 52 LOCF (DIA3009, DIA3015).

Note: Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification), while data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 IU/day).

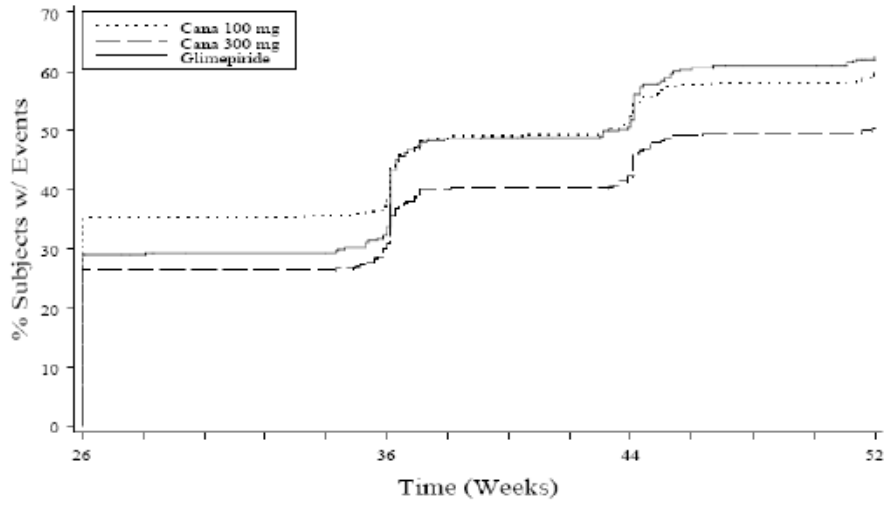
Reductions in mean Hb1Ac were in region of 0.7 to 0.8 for the 100 mg canagliflozin dose and 0.93 to 1.03 for the 300 mg dose for the majority of canagliflozin combinations. The effect was reduced in older subjects (mean reduction of 0.6 and 0.73 for the 100 mg and 300 mg doses respectively), subjects also taking insulin (mean reduction of 0.63 and 0.73 for the 100 mg and 300 mg dose respectively) and in subjects with moderate renal impairment (mean reduction 0.3 and 0.4 for the 100 mg and 300 mg dose respectively). In all comparisons with placebo canagliflozin, either as monotherapy or as add-on therapy was superior to the comparator for the primary efficacy measure.

Secondary efficacy assessments included changes from baseline in FPG and 2-hour post-prandial glucose (PPG), the proportion achieving a HbA1c target of < 7.0%), along with endpoints associated with diabetic comorbidities, such as changes from baseline in body weight, systolic blood pressure (SBP), and lipid parameters of HDL-C and triglyceride (TG). The glycaemic secondary efficacy outcome measures (HbA1c targets and FPG) were all supportive of the primary outcome.

There were consistent decreases in body weight, BMI and waist circumference that were clinically and statistically significant. There were consistent increases in HDL-C and in some studies total cholesterol and LDL-C also increased. The extent of weight loss was in the region of 2 to 4% baseline body weight and occurred within the first 26 weeks of treatment. Continuing weight loss did not occur in the 52 week studies however weight stabilised at the reduced level in those studies. The lipid changes were generally small and of uncertain clinical significance. Reductions in mean systolic blood pressure (at time of primary efficacy assessment) ranged from -4.27 to -6.87 mmHg for the canagliflozin 300 mg dose and from -3.27 to -6.05 mmHg for the canagliflozin 100 mg dose (compared to +1.52 to -3.38 mmHg for placebo groups).

Persistence of effect was assessed by comparing the change in HbA1c from baseline to Week 52 in Studies 3009 and 3015. Figure 3 shows the time to develop an increase in HbA1c of at least 0.3% from Week 26 through Week 52 among subjects who had a decrease from baseline in HbA1c of at least 0.4% at Week 26 (mITT). While HbA1c increased in all groups the increases were less in subjects given canagliflozin than glimepiride.

Figure 3. Time to develop an increase in HbA1c of at least 0.3% from Week 26 through Week 52 among subjects who had a decrease from baseline in HbA1c of at least 0.4% at Week 26 (mITT) (Study DIA3009)



Assessment of the use of canagliflozin with oral AHA other than metformin and sulphonylureas is quite limited. Combinations with dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 analogues and insulin were studied only in studies which included

treatment as usual with an add-on of canagliflozin (Studies 3008 and 3010). The combination with pioglitazone was assessed only as an add-on to dual combination with metformin (Study 3012) and the combination with insulin only in an 18-week sub-study of study 3008.

Safety

The clinical trial program was comprehensive with 52 completed clinical studies which included 10,285 subjects in 9 Phase III studies, 1,210 subjects in 3 Phase II studies, and 1,300 subjects in 40 Phase I studies. The primary group for analysis of pooled safety data was the patients enrolled in the 26 week placebo-controlled studies, excluding the high risk patient studies (Study 3008 high risk CV patients; 3010 patients aged ≥ 55 years and 3004 moderate renal impairment). This group is useful for identifying short-term AEs associated with canagliflozin.

In the placebo-controlled combined analysis group the median age of subjects was 57 years with 79% of subjects aged between 35 to 64 years, 17% between 65 and 74 years, and 2% older than 75 years. The median duration of diabetes was 6.0 years. The median eGFR ranged from 85.1 to 87.0 mL/min/1.73 m^2 across the studies. Approximately 60% of subjects in the placebo and canagliflozin 100 mg and 300 mg groups experienced an adverse event during study. The incidence of events occurring in ≥2% of patients is shown in Table 12.

Table 12. Adverse Events in at least 2% of subjects in any treatment group by body system and Preferred Term (PT) - Prior to use of rescue medication (ISS Phase III placebo-controlled studies dataset: Safety Analysis Set) (Integrated Summary of Safety)

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=646) n (%)	Cana 100 mg (N=833) n (%)	Cana 300 mg (N=834) n (%)	All Cana (N=1667) n (%)
Total no. subjects with the AEs	371 (57.4)	500 (60.0)	494 (59.2)	994 (59.6)
Gastrointestinal Disorders	88 (13.6)	124 (14.9)	128 (15.3)	252 (15.1)
Constipation	6 (0.9)	15 (1.8)	19 (2.3)	34 (2.0)
Diarrhoea	28 (4.3)	26 (3.1)	37 (4.4)	63 (3.8)
Nausea	9 (1.4)	18 (2.2)	18 (2.2)	36 (2.2)
Infections and Infestations	180 (27.9)	247 (29.7)	241 (28.9)	488 (29.3)
Influenza	20 (3.1)	19 (2.3)	16 (1.9)	35 (2.1)
Nasopharyngitis	30 (4.6)	37 (4.4)	44 (5.3)	81 (4.9)
Sinusitis	11 (1.7)	17 (2.0)	8 (1.0)	25 (1.5)
Upper Respiratory Tract Infection	31 (4.8)	38 (4.6)	38 (4.6)	76 (4.6)
Urinary Tract Infection	23 (3.6)	45 (5.4)	33 (4.0)	78 (4.7)
Vulvovaginal Mycotic Infection	4 (0.6)	25 (3.0)	23 (2.8)	48 (2.9)
Metabolism and Nutrition Disorders	41 (6.3)	51 (6.1)	41 (4.9)	92 (5.5)
Hyperglycaemia	16 (2.5)	6 (0.7)	1 (0.1)	7 (0.4)
Hypoglycaemia	13 (2.0)	21 (2.5)	19 (2.3)	40 (2.4)
Musculoskeletal and Connective Tissue Disorders	83 (12.8)	93 (11.2)	104 (12.5)	197 (11.8)
Arthralgia	23 (3.6)	23 (2.8)	19 (2.3)	42 (2.5)
Back Pain	16 (2.5)	23 (2.8)	34 (4.1)	57 (3.4)
Nervous System Disorders	47 (7.3)	74 (8.9)	65 (7.8)	139 (8.3)
Headache	27 (4.2)	34 (4.1)	29 (3.5)	63 (3.8)
Renal and Urinary Disorders	13 (2.0)	61 (7.3)	52 (6.2)	113 (6.8)
Pollakiuria	4 (0.6)	35 (4.2)	26 (3.1)	61 (3.7)
Respiratory, Thoracic and Mediastinal Disorders	41 (6.3)	42 (5.0)	42 (5.0)	84 (5.0)
Cough	15 (2.3)	12 (1.4)	13 (1.6)	25 (1.5)

There were 16 AEs with a higher incidence in one of the canagliflozin groups or the combined canagliflozin group. Seven of these were related to male or female genital mycotic infections and 5 (dry mouth, thirst, polydipsia, pollakiuria, and polyuria) are consistent with the osmotic diuretic effect of canagliflozin.

In the 26 week report for patients with or at high risk of CV disease (from Study 3008) the pattern of AEs was similar to the main safety analysis group with the addition of events related to volume depletion. Volume depletion related AEs (reduced blood pressure, dehydration, dizziness, syncope, presyncope) were reported in 1.9%, 2.8% and 4.6% of patients given placebo, canagliflozin 100 mg and 300 mg respectively. Renal AEs (renal failure, renal impairment, decreased GFR, renal function test (RFT) abnormal, increased blood creatinine) were reported in 1.3%, 2.6% and 3.7% of patients given placebo, canagliflozin 100 mg and 300 mg respectively.

A similar pattern of increases in renal AEs was reported in Study 3004 (subjects with moderate renal impairment) with renal events reported in 4.4%, 3.3% and 8% of patients given placebo, canagliflozin 100 mg and 300 mg respectively. That study also showed a reduction in GFR for patients taking canagliflozin. The mean (SD) change in GFR was -3.44 (6.693) mL/min/1.73 m^2 in the canagliflozin 100 mg group, -3.56 (7.458) mL/min/1.73 m^2 in the 300 mg and -1.14 (4.875) mL/min/1.73 m^2 in the placebo group. There were also some reductions in serum calcium and magnesium and increases in phosphate in the canagliflozin group which were dose-related.

Further information on the effect of canagliflozin in patients at high risk of CV disease was available from the interim safety report. A meta-analysis of Phase II and III canagliflozin studies in subjects with T2DM and was performed to evaluate CV. It allows examination of whether canagliflozin is associated with an unacceptable increase in CV risk. This analysis included data from 9 studies and 6305 canagliflozin-treated subjects who contributed 6715 person-years of exposure to study medication (Integrated Summary of Safety). That analysis showed no trend towards increased CV events in patients given canagliflozin.

The effect of canagliflozin on bone mineralisation was examined in Study 3010. This 26 week study showed decreased bone mineralisation at the hip for the 300 mg dose compared to placebo. Serum collagen type 1 carboxy-telopeptide (CTx) a marker of bone resorption was increased in a dose-dependent manner.

Clinical evaluator's recommendation

The clinical evaluator has recommended that there are insufficient data demonstrating efficacy in combination with insulin. The evaluator noted the data presented for this indication come from a substudy of Study DIA3008, were conducted in a selected population, over an 18 week duration of treatment and with no formal hypothesis testing intended in the study protocol. Following receipt of the CER, the sponsor responded to this statement by re-presenting the hypothesis testing for that substudy. Efficacy results of that sub-study have been previously noted. Efficacy results for the major efficacy studies are summarised above in Table 10.

Risk management plan

The advice of ACSOM was requested for the RMP. The RMP evaluator has noted that the sponsor proposes routine pharmacovigilance and long term follow up of patients enrolled in Studies 3008 (high risk CV study) and 3010 (patients aged ≥ 55 years) to assess the risks of reductions in renal function, effects of increased haematocrit, of bone fractures and of renal cancer.

The RMP evaluator recommended that an education program acceptable to the TGA be imposed as a condition of registration for this product. It was further recommended that the sponsor should provide the TGA with the following details for agreement:

- All draft education materials
- A clear distribution plan

- A clear plan to measure the effectiveness of the education program as additional risk minimisation.

The education program should include (but not be limited to) information on the common and progressive AEs such as urinary tract infections (UTIs), renal effects, the volume depletion effect and effects on bone loss. Specific focus should also be made on the precautions regarding using canagliflozin in the setting of renal impairment. The education program should also include a consideration of specific issues relevant to use in the Australian Indigenous population.[7]

Amendments to the PI to better describe and manage the known risks from use of canagliflozin were also recommended.

Risk-benefit analysis

Delegate considerations

The PD studies demonstrated the extent of effect of canagliflozin on urinary excretion of glucose in subjects who do not have T2DM as well as those who do. The effectiveness of canagliflozin in increasing urinary excretion of glucose reduces with reduced renal function and canagliflozin is not effective in subjects with severe renal impairment. Given this lack of effectiveness in addition to the increased urinary excretion of NAG, canagliflozin should not be given to individuals with moderate or severe renal impairment. Baseline and regular monitoring of renal function in individuals taking canagliflozin long term is required. Some of the effect on renal function would be due to the reduced blood volume due to the osmotic diuretic effect of canagliflozin but a direct renal toxicity effect has not been excluded and it is not known if long term exposure to canagliflozin will be associated with more rapid deterioration in renal function than would occur in patients with T2DM who received alternative treatments. This will be examined in one of the agreed long term studies that have been included in the post-market authorisation requirements in Europe.

The dose-finding study suggests that the minimum effective dose has not been established. There was a clear increase in efficacy between the 100 mg and 300 mg daily doses and no further increase with increasing doses beyond 300 mg daily.

Canagliflozin has shown clinically useful reductions in measures of hyperglycaemia. Efficacy is dependent on renal function, therefore it will be less effective in older patients and those on multi-AHA therapy including insulin (suggesting more severe and/ or a longer duration of T2DM) due to the generally reduced renal function in these patient groups. The response in patients with moderate renal impairment was quite small. In the USA canagliflozin is contraindicated in patients with severe renal impairment and those with moderate impairment (eGFR between 45-60 mL/min/1.73 m^2) are recommended to take a maximum of 100 mg daily. All patients are to have baseline assessment of renal function and treatment is to be ceased if eGRF falls below 45 mL/min/1.73 m^2, however no frequency of monitoring is recommended.

The sponsor has examined a wide range of patients with T2DM. The initial efficacy results from patients either with CV disease or at high risk for CV disease show it is effective in reducing hyperglycaemia in that population. Long term safety data are expected from that study.

[7] In relation to the educational materials, the distribution plan and a plan to measure effectiveness of the educational materials, the OPR considered it was acceptable for the sponsor to provide these to the TGA as per the commitment in the ASA, prior to launch, should canagliflozin be approved for registration.

A major benefit from canagliflozin is that it is not associated with weight gain. There was a small reduction in weight occurring within months of commencing treatment and weight stabilised. There were small and inconsistent changes in blood lipid parameters with a slight trend towards improvement but the clinical significance of these changes is unclear.

The major established risks for canagliflozin are: events associated with volume depletion including increases in serum creatinine and hypotension; mycotic infections in the genital area, UTIs, and hypoglycaemia when used in combination with insulin or medicines that induce insulin secretion. Initial reporting of major adverse CV event rates does not suggest that canagliflozin will worsen CV outcomes however long term data are required to assess the long term effect.

The effect of canagliflozin on renal function and bone density is unknown but initial data suggest these may be safety issues with long term use. Numerical imbalances of bladder cancer identified in the clinical program of another SLT2-inhibitor, dapagliflozin, were not observed with canagliflozin. Bladder tumours were observed in the rat carcinogenicity study in the high dose groups in both males and females except for one female rat receiving low-dose treatment. None of the findings were statistically significant.

Proposed action

Given the evidence submitted to date, the Delegate was inclined to approve canagliflozin 100 mg and 300 mg film coated tablets, pending advice from the ACPM.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request comment on the following specific issues:

1. The proposed monotherapy indication (*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*) is appropriate. The monotherapy indication for the approved product in this class is: *dapagliflozin is as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.*

   Should these indications be aligned?

2. The Delegate does not propose to specify groups of AHAs that may be used in combination with canagliflozin in the indication. The efficacy and safety of combinations with medicines other than metformin, sulphonylureas and pioglitazone have been examined only is studies where canagliflozin was added to treatment as usual. Does the committee have safety concerns with this proposal?

3. It is not clear whether canagliflozin should be contraindicated in patients with moderate renal impairment, defined as eGFR ≥ 45 and < 60 mL/min/1.73 m^2. Given that efficacy declines with declining GFR, the reduced capacity for adaptation to any osmotic diuresis in those patients, and that it is not clear whether long term use will be associated with reductions in renal function the benefit/risk in those patients appears to favour alternative treatments. The Delegate notes that dapagliflozin is contraindicated in patients with eGFR < 60mL/min/1.73 m^2 and proposes the same contraindication for canagliflozin. Does the committee consider this is appropriate?

Response from sponsor

Introduction

The sponsor agrees with the Delegate's recommendation to approve canagliflozin 100 mg and 300 mg film-coated tablets. The proposed indication remains as follows:

> *Invokana is indicated in adults with type 2 diabetes mellitus 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 therapy:*
>
> *Add on therapy with other anti hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Precautions; Interactions with other medicines and Pharmacology for available data on different add on therapies).*

The sponsor provided comments on the issues for which the Delegate proposed to seek advice from the ACPM.

Indications

Monotherapy wording (Delegate's question 1 to ACPM)

The Delegate has noted differences in the proposed wording of the monotherapy indication for canagliflozin (listed above) compared with the approved wording for dapagliflozin (*as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated*). The sponsor suggests that the difference in wording derives from the fact that dapagliflozin is not indicated for use in patients with eGFR < 60 mL/min/1.73 m^2. Metformin is also contraindicated in patients with eGFR < 60 mL/min/1.73 m^2. Therefore dapagliflozin is not recommended for patients who have a contraindication to metformin use. Since the data support the use of canagliflozin in patients with eGFR > 45 mL/min/1.73 m^2, the sponsor proposes that existing canagliflozin wording appropriately allows access to patients in whom metformin use is contraindicated due to renal impairment.

Therefore the sponsor proposes to retain the current proposed indication for canagliflozin. This proposed indication also aligns with the proposed indications for canagliflozin in other countries such as the EU and reflects the data for canagliflozin, rather than dapagliflozin.

Add-on therapy (Delegate's question 2 to ACPM)

The sponsor agrees with the Delegate's proposal not to specify groups of AHAs that may be used in combination with canagliflozin in the indication. A clinically meaningful improvement in glycaemia control was seen when canagliflozin was given as monotherapy and when given in dual combinations (add-on to metformin [DIA3006 and DIA3009] or to sulphonylurea agents [DIA3008 sulphonylurea substudy]), in triple oral AHA combinations (add-on to metformin plus a sulphonylurea agent [DIA3002 and DIA3015] or metformin plus pioglitazone [DIA3012]), in combination with insulin (alone or in combination with other agents [DIA3008 Insulin substudy]), or as an add-on to existing diabetes therapy (for example, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitor, GLP-1 analogue, DPP-4 inhibitor, or insulin [DIA3004, DIA3008, and DIA3010]). The similar degree of placebo-subtracted HbA1c lowering seen in response to treatment with canagliflozin across these studies suggests that the response to canagliflozin does not vary in a clinically meaningfully fashion when used in combination with different AHAs.

Given the unique mechanism of action (increasing urinary glucose excretion), it is predicted that HbA1c lowering in response to canagliflozin would not vary based on the concomitant use of other AHAs.

The safety profile of canagliflozin has been extensively studied in a comprehensive clinical development program. While specific patient populations may be at increased risk for at least some of the mechanistically plausible AEs, the safety profile was not meaningfully different across different background AHA therapies, except for the risk of hypoglycemia. There is a low risk of hypoglycemia in subjects treated with canagliflozin alone or in combination with other therapies not associated with hypoglycemia. An increased incidence of hypoglycemia was observed when canagliflozin was used in combination with insulin or non-glucose- dependent insulin secretagogues, which is consistent with the expected increase in hypoglycemia when an agent not associated with hypoglycemia is added to insulin or a non-glucose dependent insulin secretagogue. A similar increase in hypoglycemia when used in combination with agents causing hypoglycemia is seen with classes of agents with low intrinsic hypoglycemic risk such as DPP4 inhibitors, peroxisome proliferator-activated receptor gamma (PPARγ) agonists and GLP-1 agonists.

Based on the similar safety and efficacy profile when used with different classes of AHAs, the sponsor believes a broad indication statement for use in patients with type 2 diabetes as monotherapy or as add-on therapy (including insulin) is warranted and that there are no safety concerns with the Delegate's proposal.

Use in renal impairment (Delegate's question 3 to ACPM)

As noted by the reviewer, glycaemic response to SGLT2 inhibitors attenuates in patients with lower baseline eGFRs. Below are summarised data from an analysis of 721 subjects with baseline eGFR 45 to < 60 mL/min/1.73 m^2 from the pooled Phase III renal impairment dataset (including studies DIA3004, DIA3005, DIA3008, and DIA3010), demonstrating clinically meaningful improvement in glycemic control, similar in extent to that reported with other oral AHAs available for use in these patients and greater than that seen in dapagliflozin trials.

The placebo-subtracted reduction in HbA1c in subjects with baseline eGFR 45 to < 60 mL/min/1.73 m^2 for canagliflozin 100 mg (n = 216) was 0.47%. In a similar population, dapagliflozin 10 mg (n = 33) reduced HbA1c by 0.33%.[8] Clinically important reductions in fasting plasma glucose (-1.21 mmol/L, placebo-subtracted) and body weight (-1.8%, placebo-subtracted) were seen with the canagliflozin 100 mg dose in this patient population. In contrast to other AHAs used in patients with moderate renal impairment (that is, sulphonylureas and insulin), the improvement in glycaemic control was not associated with an increased risk of hypoglycemia when not used in combination with agents which themselves induce hypoglycemia and was not associated with weight gain.

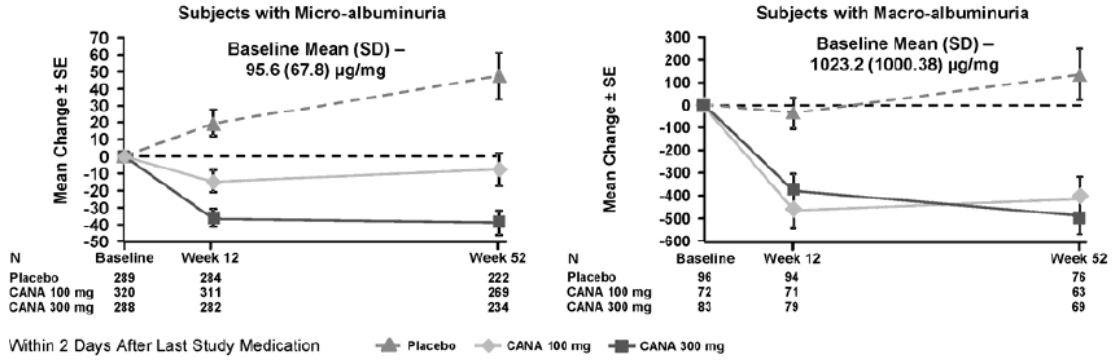
In subjects with baseline eGFR 45 to < 60 mL/min/1.73 m^2, the overall incidence of AEs (69.0% versus 66.9%) and of AEs leading to discontinuation (5.1% versus 6.0%) was not notably different in the canagliflozin 100 mg and placebo groups, respectively. The incidence of SAEs and death was lower with canagliflozin 100 mg compared with placebo. Incidence of volume depletion-related AEs in these subjects was higher in the canagliflozin 100 mg group (4.2%) compared with the placebo group (3.0%). None of the volume depletion-related AEs were considered serious in the canagliflozin 100 mg group compared with an incidence of 1.5% in the placebo group. The incidence of renal AEs was higher in the canagliflozin 100 mg group (7.9%) compared with placebo (2.6%); this imbalance was predominantly due to the increase in the canagliflozin groups of

[8] Table 7 on page 11 of the FDA briefing document for dapagliflozin tablets, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM262994.pdf>

non-serious AEs of serum creatinine increased and GFR decreased, likely related to the osmotic diuretic effects of the drug that occurred early after canagliflozin initiation and that tended to attenuate with continued use. There were no subjects with serious renal AEs compared with 1.1% of subjects in the placebo group experiencing a serious renal AE. The incidence of AEs leading to discontinuation was similar in the canagliflozin 100 mg and placebo groups.

Fifty-two week data from Study DIA3009 and recently updated 52 week data now available from Study DIA3008 (CANVAS) did not show an adverse effect of canagliflozin on renal function or evidence for glomerular or tubule injury. Decreases in eGFR were seen at the earliest post-randomisation visit, tended to attenuate over time, and reversed with discontinuation of canagliflozin treatment. These effects on eGFR are consistent with an acute, reversible hemodynamic effect and are not indicative of an adverse effect on renal function. Canagliflozin was associated with a reduction in albuminuria, relative to placebo (Figure 4), which is not consistent with glomerular or tubule injury and may reflect a reduction in glomerular and tubule damage. Thus, the renal findings after a 52-week treatment period are reassuring in terms of not demonstrating evidence for renal injury. The effect of longer term canagliflozin treatment on renal function is currently being collected in the 104 week DIA3009 and DIA3010 studies as well as in the long term study in subjects at high risk for CV disease (DIA3008/CANVAS) which will end in 2017. An independent data safety monitoring board examines unblinded data from DIA3008/CANVAS on a semi-annual basis and will continue to do so until the study ends in 2017. The output from the data safety monitoring board is being made available to health agencies upon request.

Figure 4. Change from baseline in albumin/creatinine ratio in CANVAS (DIA3008) through 01 July 2012



In summary, the sponsor's assessment is that the efficacy and safety profile of canagliflozin 100 mg in subjects with eGFR 45 to <60 mL/min/1.73 m^2 is sufficiently well characterised and has a positive benefit/risk profile. The data suggest that the HbA1c lowering with canagliflozin is clinically meaningful and statistically significant. The safety profile of canagliflozin 100 mg is generally similar to that seen in subjects in the placebo group in terms of overall AEs and clinically meaningful volume and renal-related AEs. The decreases in eGFR seen with canagliflozin treatment were generally reversible and were likely secondary to reductions in intravascular volume and not due to renal injury. Given the limited anti-hyperglycemic treatment options for patients with moderate renal impairment, with metformin and GLP-1 agonists not being indicated for use in this population, and the side effects associated with other AHAs (such as hypoglycemia with insulin and sulfonylureas; fluid retention with PPARγ agonists and insulin), patients with moderate renal impairment and physicians are in need of more anti-hyperglycemic treatment options. The sponsor deems that canagliflozin at the 100 mg dose has a favourable benefit risk profile and would provide physicians and patients with another option for use in achieving glycemic control.

Therefore, the sponsor considers that a contraindication for eGFR < 60 mL/min/1.73 m^2 for canagliflozin, the same as dapagliflozin, is not appropriate. However, the sponsor proposes changes to the dosage for patients with renal impairment which are consistent with the US product information, and precautionary statements in the Australian PI.[9]

Response to RMP evaluation report

A response to the RMP evaluation report submitted to the TGA included discussion of proposed PI changes requested by the RMP evaluator.

Pregnancy category

The nonclinical valuator has requested a change in pregnancy category from B1 to D. However the sponsor considers that category C appropriately reflects the current data. In the toxicity study in juvenile rats dosed for 10 weeks (Day 21 to 90 postnatal) with canagliflozin, renal and bone findings were consistent with those in repeat-dose toxicity studies in adult rats, and there were no new or unexpected effects. These effects are considered to be pharmacological effects that show reversibility and may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. Therefore, pregnancy category C (*defined as drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible*) is proposed for the Australian PI.

Other PI changes requested by Delegate

Details of these and other revisions to product literature are beyond the scope of the AusPAR.

Conclusion

Results from an extensive clinical development program for canagliflozin have shown sustained reductions in HbA1c in addition to secondary endpoints assessed. The evaluations of safety and tolerability have concluded a positive benefit-risk profile and canagliflozin has the potential to be an important addition to the currently available AHAs, as both a monotherapy and add-on therapy.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Invokana/Prominad film coated tablets containing 100 mg and 300 mg of canagliflozin (as hemihydrate) to have an overall positive benefit–risk profile for the indication;

> *Invokana/Prominad is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:*
>
> *Monotherapy: Invokana/Prominad is indicated as an adjunct to diet and exercise in adults with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.*
>
> *Add on combination therapy: Invokana/Prominad is indicated for use in combination therapy with other anti-hyperglycaemic agents including insulin, as an adjunct to diet and exercise in adults with type 2 diabetes mellitus when these, together with*

[9] Details of these and other revisions to product literature are beyond the scope of the AusPAR.

diet and exercise, do not provide adequate glycaemic control (see Precautions; Interactions with other medicines; and Pharmacology for available data on different add-on therapies).

The ACPM agreed with the Delegate's proposal not to specify groups of AHAs that may be used in combination with canagliflozin in the indication.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory negotiation of the Risk Management Plan most recently approved by the TGA,
  - This particularly includes the risk of UTIs in the educational material
- Negotiation of PI and CMI to the satisfaction of the TGA.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the *Contraindications* section of the PI and relevant sections of the CMI to ensure canagliflozin is not used in patients with eGFR < 60 mL/min/1.73 m^2.

The ACPM agreed that risk in low eGFR outweighs the benefit given that the benefit is modest.

- Recommendations on the monitoring of renal function should be included in the PI and CMI
- A statement in the *Precautions* section of the PI and relevant sections of the CMI on use in reduced eGFR patients for volume-depletion and reduced efficacy.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI on UTI risk which should be commensurate with vulvovaginitis and balanitis.
- The terminology for Chronic Kidney Disease stages should be included in the PI when referring to degrees of renal impairment.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Invokana and Prominad film coated tablets containing 100 and 300 mg canagliflozin (as hemihydrate), indicated for:

Invokana/Prominad is indicated in 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

(see Precautions; Interactions with other medicines and Pharmacology for available data on different add-on therapies[10]).

Specific conditions applying to these therapeutic goods

- The Invokana/Prominad canagliflozin EU Risk Management Plan (RMP), version 2.0, dated 15 February 2013 [data lock point 31 December 2012] + Australian specific Annex (version 2), included with submission PM-2012-02302-3-5, and any subsequent revisions, as agreed with the TGA must be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

[10] The text in brackets was subsequently amended to: *(see Pharmacology, Clinical Trials, and Precautions for available data on different add-on therapies)*.

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