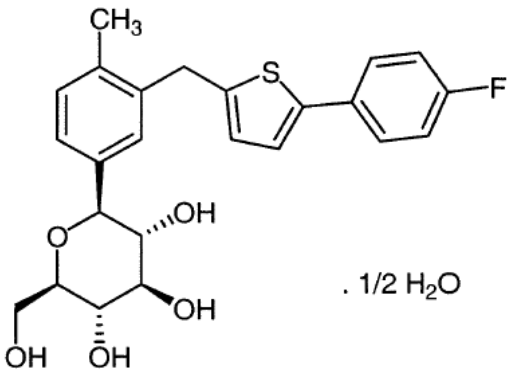
INVOKANA®

PRODUCT INFORMATION

NAME OF THE MEDICINE

Canagliflozin

The chemical name is (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol present in the tablets as the hemihydrate.



Molecular Formula: $C_{24}H_{25}FO_5S.½\ H_2O$
CAS: 928672-86-0(hemihydrate) and 842133-18-0(anhydrous)
MW: 453.53

DESCRIPTION

Canagliflozin hemihydrate drug substance is a white to off white powder, soluble in many organic solvents (ethanol, methanol, tetrahydrofuran, acetone) but insoluble in aqueous media. The log P of the drug substance is 3.44 at 20°C and pH=7. There is no pKa in the physiological pH range.

INVOKANA is available as film-coated tablets containing 100 and 300 mg of canagliflozin present as 102 mg and 306 mg of canagliflozin hemihydrate in each tablet strength, respectively. Both strengths contain the inactive ingredients microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol 3350 and talc-purified. In addition, the 100 mg strength contains iron oxide yellow.

PHARMACOLOGY

Mechanism of Action

INVOKANA is an inhibitor of sodium-glucose co-transporter 2 (SGLT2). SGLT2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Patients with diabetes have been shown to have elevated renal glucose reabsorption which may contribute

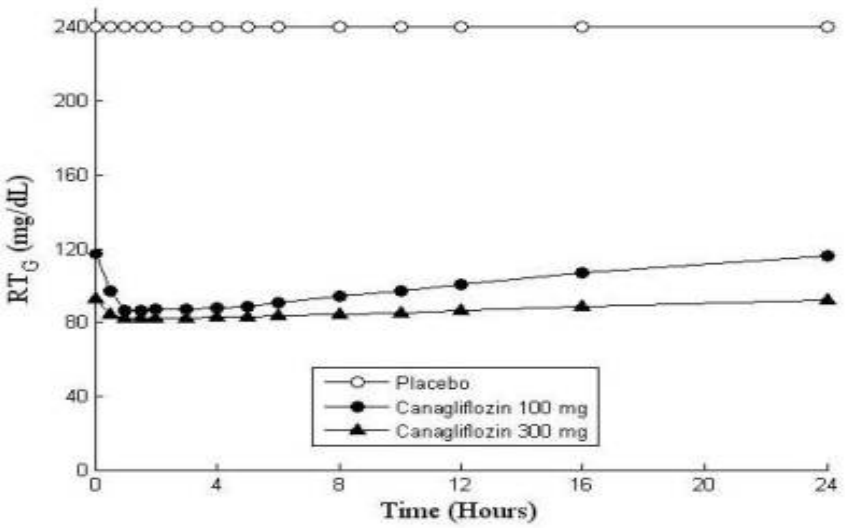
to persistent elevated blood glucose concentrations. Canagliflozin is an orally-active inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion (UGE), lowering elevated plasma glucose concentrations by an insulin-independent mechanism in patients with type 2 diabetes. Urinary glucose excretion induced by canagliflozin leads to an osmotic diuresis, which can be associated with caloric loss and reduction in weight (see PHARMACOLOGY - Clinical Studies).

In Phase 3 studies in which a mixed meal tolerance test was performed, canagliflozin 300 mg provided a greater reduction in postprandial glucose excursion than observed at 100 mg. Clinical studies have shown no glucose malabsorption with canagliflozin.

Pharmacodynamics

Following single and multiple oral doses of canagliflozin in patients with type 2 diabetes, dose-dependent decreases in the renal threshold for glucose (RT_G) and increases in UGE were observed. From a starting value of RT_G of approximately 13 mmol/L, maximal suppression of 24-hour mean RT_G was seen with the 300 mg daily dose to approximately 4 to 5 mmol/L in patients with type 2 diabetes in Phase 1 studies (see Figure 1), suggesting a low risk for treatment-induced hypoglycaemia. In patients with type 2 diabetes given 100 to 300 mg once daily over a 16-day dosing period, reductions in RT_G and increases in UGE were sustained over the dosing period. In this study, plasma glucose declined in a dose-dependent fashion within the first day of dosing with subsequent sustained fasting and postprandial glucose lowering.

Figure 1: Predicted (PK/PD Modelled) 24-Hour Profile for RT_G in Subjects with Type 2 Diabetes Treated with Canagliflozin 100 mg and 300 mg



In single-dose studies in patients with type 2 diabetes, treatment with 300 mg before a mixed meal delayed intestinal glucose absorption and reduced postprandial glucose through a nonrenal mechanism.

Cardiac Electrophysiology

In a randomised, double-blind, placebo-controlled, active-comparator, 4-way crossover study, 60 healthy subjects were administered a single oral dose of canagliflozin 300 mg, canagliflozin 1,200 mg (4 times the maximum recommended dose), moxifloxacin, and placebo. No meaningful changes in QTc interval were observed with either the recommended dose of 300 mg or the 1,200 mg dose. At the 1,200 mg dose, peak canagliflozin plasma concentrations were approximately 1.4 times the steady-state peak concentrations following a 300 mg once-daily dose.

Blood pressure

In an analysis of four 26-week, placebo-controlled studies (N=2,313), mean reductions in systolic blood pressure relative to placebo were observed with canagliflozin 100 mg (-3.9 mmHg), canagliflozin 300 mg (-5.3 mmHg), and placebo (-0.1 mmHg). In this same population, there was a smaller effect on diastolic

blood pressure with mean changes of -2.1 mmHg with canagliflozin 100 mg, -2.5 mmHg with canagliflozin 300 mg, and -0.3 mmHg with placebo. There was no discernible change in heart rate.

Lipid effects

In an integrated analysis of four placebo-controlled studies of 26 weeks, patients with type 2 diabetes treated with both doses of canagliflozin had increased serum concentrations of total cholesterol, LDL-C, and HDL-C (high-density lipoprotein cholesterol) compared to small changes in placebo, while serum concentrations of triglycerides decreased compared to placebo. At week 26, the LDL-C/HDL-C ratio minimally changed compared to baseline in all three treatment groups. Similar to changes observed in non-HDL-C, concentrations of ApoB and LD particle number (measured in two studies) increased to a smaller extent than LDL-C changes in the monotherapy and 26-week metformin add-on therapy study (see ADVERSE EFFECTS).

Pharmacokinetics

The pharmacokinetics of canagliflozin are essentially similar in healthy subjects and patients with type 2 diabetes. After single-dose oral administration of 100 mg and 300 mg in healthy subjects, canagliflozin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 2 hours post-dose. Plasma C_{max} and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life ($t_{1/2}$) was 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 to 5 days of once-daily dosing with canagliflozin 100 mg to 300 mg. Canagliflozin does not exhibit time-dependent pharmacokinetics, and accumulated in plasma up to 36% following multiple doses of 100 mg and 300 mg.

Absorption:

The mean absolute oral bioavailability of canagliflozin is approximately 65%. Co-administration of a high-fat meal with canagliflozin had no effect on the pharmacokinetics of canagliflozin; therefore, canagliflozin may be taken with or without food. However, based on the potential to reduce postprandial plasma glucose excursions due to delayed intestinal glucose absorption, it is recommended that canagliflozin be taken before the first meal of the day (see DOSAGE AND ADMINISTRATION; PHARMACOLOGY – Pharmacodynamics).

Distribution:

The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 119 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (98%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metabolism:

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites. CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

Excretion:

Following administration of a single oral [^{14}C]canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in faeces as canagliflozin, a hydroxylated metabolite, and an *O*-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible.

Approximately 33% of the administered radioactive dose was excreted in urine, mainly as *O*-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance for the 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min.

Canagliflozin is a low-clearance medicinal product, with a mean systemic clearance of approximately 192 mL/min in healthy subjects following intravenous administration.

Special Populations:

Renal Impairment:

A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects. The study included 3 subjects with normal renal function (CKD Stage 1; eGFR ≥ 90 mL/min/1.73 m^2), 10 subjects with mild renal impairment (CKD stage 2; eGFR 60 to < 90 mL/min/1.73 m^2), 9 subjects with moderate renal impairment (CKD stage 3; eGFR 30 to < 60 mL/min/1.73 m^2), and 10 subjects with severe renal impairment (CKD stage 4; eGFR 15 to < 30 mL/min/1.73 m^2) as well as 8 subjects with end-stage renal disease on haemodialysis (CKD stage 5).

Renal impairment did not affect the C_{max} of canagliflozin. Compared to healthy subjects, plasma AUC of canagliflozin was increased by approximately 15%, 29%, and 53% in subjects with mild, moderate, and severe renal impairment, respectively, but was similar for end stage renal disease subjects and healthy subjects. Increases in canagliflozin AUC of this magnitude are not considered clinically relevant (see DOSAGE AND ADMINISTRATION; PRECAUTIONS; ADVERSE EFFECTS).

Canagliflozin was negligibly removed by haemodialysis.

Hepatic Impairment:

Relative to subjects with normal hepatic function, the C_{max} and AUC_{∞} of canagliflozin increased by 7% and 10%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and decreased by 4% and increased by 11%, respectively, in subjects with Child-Pugh class B (moderate hepatic impairment) following administration of a single 300 mg dose of canagliflozin.

These differences are not considered to be clinically meaningful. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment and, therefore, INVOKANA is not recommended for use in this patient population.

Elderly:

Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis (see DOSAGE AND ADMINISTRATION; PRECAUTIONS; ADVERSE EFFECTS).

Paediatric:

Studies characterising the pharmacokinetics of canagliflozin in paediatric patients have not been performed.

Characteristics of other special populations:

No dose adjustment is necessary based on gender, race/ethnicity, or body mass index. These characteristics had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis.

CLINICAL TRIALS

INVOKANA has been studied as monotherapy (DIA3005), in combination with metformin (DIA3006 and DIA3009), sulfonylurea (DIA3008), metformin and sulfonylurea (DIA3002 and DIA3015), metformin and a thiazolidinedione (i.e. pioglitazone; DIA3012), and in combination with insulin (with or without other antihyperglycemic agents; DIA3008).

INVOKANA has also been studied in patients 55 to 80 years of age (DIA3010) and in patients with moderate renal impairment (DIA3004). In these studies, INVOKANA was added to patients' existing diabetic therapy (eg, metformin, sulfonylurea, pioglitazone, alpha-glucosidase inhibitor, DPP4 inhibitors, or GLP1 agonists).

A total of 10,285 patients with type 2 diabetes who received medicinal product participated in nine double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of INVOKANA on glycaemic control. Approximately 58% of patients were male. Patients had an overall mean age of 59.5 years (range 21 to 96 years), with 3,082 patients 65 years of age and older and 510 patients ≥ 75 years of age. One study was conducted in patients with renal impairment with an eGFR 30 to < 50 mL/min/1.73 m^2 (N=269) and three other studies included patients with renal impairment with an eGFR 30 to < 60 mL/min/1.73 m^2 (N=816).

INVOKANA produced clinically and statistically significant improvements relative to placebo in glycaemic control, including HbA_{1c}, percentage of patients achieving HbA_{1c} < 7%, change from baseline fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG), and clinically relevant improvement in percent change in body weight. The reductions in HbA_{1c} were similar across different subgroups including age, gender, race, body mass index (BMI), and baseline beta-cell function. Greater reductions in HbA_{1c} relative to placebo were observed in patients with higher baseline HbA_{1c} or higher eGFR values.

For patients treated with canagliflozin there are no clinical data regarding substitution of canagliflozin with another SGLT2 inhibitor.

Efficacy of canagliflozin is dependent on renal function. Reductions in mean HbA_{1c} relative to placebo ranged from 0.62 to 0.91 for the 100 mg canagliflozin dose and 0.76 to 1.16 for the 300 mg dose. The effect was reduced in older subjects (mean reduction of 0.57 and 0.70 for the 100 mg and 300 mg doses respectively), subjects taking insulin (mean reduction of 0.65 and 0.73 for the 100 mg and 300 mg doses respectively) and in subjects with moderate renal impairment (mean reductions of 0.3 and 0.4 for the 100 mg and 300 mg doses respectively).

Table 1: HbA1c (%) Change from Baseline to Primary Assessment Timepoint - LOCF: Study-by-Study Comparison (ISE Phase 3 Studies: Modified Intent-to-Treat Analysis Set)

	Placebo	CANA 100 mg	CANA 300 mg	Sitagliptin	Glimepiride
Monotherapy					
DIA3005					
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)		
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					
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)	
Diff of LS mean (SE) (minus placebo)		-0.62(0.071)	-0.77(0.071)		
95% CI[a]		(-0.758;-0.481)	(-0.914;-0.636)		
DIA3009					
Add-on to metformin					
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					
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)		
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)		
Triple therapy					
DIA3002					
Add-on to metformin and SU					
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)		
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					
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)		
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				
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				
With or without other antihyperglycaemic agent				
DIA3008 substudy				
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)	
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)	
Special populations				
DIA3004				
Moderate renal impairment				
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)	
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 (≥ 55 years)				
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)	
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: CIs are based on the ANCOVA model with treatment, study specific stratification factors and baseline HbA1c.
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).

Monotherapy study (INVOKANA as monotherapy in patients ineligible for metformin)

Study DIA3005

INVOKANA as monotherapy produced statistically significant (p<0.001) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, statistically significant improvements relative to placebo were observed for the percent change in body weight. Patients with more severe hyperglycaemia (HbA_{1c} > 10 and ≤ 12%) participated in a separate active-treatment substudy; canagliflozin produced significant reductions in HbA_{1c} and body weight.

Table 2: Results from 26-week placebo-controlled clinical study with INVOKANA as monotherapy[1]

Efficacy parameter	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**	**Placebo (N=192)**
HbA_{1c} (%)			
Baseline (mean)	8.06	8.01	7.97
Change from baseline (adjusted mean)	-0.77[2]	-1.03[2]	0.14
Difference from placebo (adjusted mean) (95% CI)	-0.91[2] (-1.09; -0.73)	-1.16[2] (-1.34; -0.99)	N/A
Patients (%) achieving HbA_{1c} < 7%	44.5[2]	62.4[2]	20.6
Body weight			
Baseline (mean) in kg	85.9	86.9	87.5
% change from baseline (adjusted mean)	-2.8[2]	-3.9[2]	-0.6
Difference from placebo (adjusted mean) (95% CI)	-2.2[2] (-2.9; -1.6)	-3.3[2] (-4.0; -2.6)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	126.7	128.5	127.7
Change from baseline (adjusted mean)	-3.3	-5.0	0.4
Difference from placebo (adjusted mean) (95% CI)	-3.7[2] (-5.9; -1.6)	-5.4[2] (-7.6; -3.3)	N/A
	Active-treatment substudy of patients with high baseline HbA_{1c} concentrations (> 10 to ≤ 12%)		
Efficacy parameter	**INVOKANA 100 mg (N=47)**	**INVOKANA 300 mg (N=44)**	
HbA_{1c} (%)			
Baseline (mean)	10.59	10.62	
Change from baseline (adjusted mean)	-2.13	-2.56	
Patients (%) achieving HbA_{1c} < 7%	17.4	11.6	
Body weight			
Baseline (mean) in kg	83.2	81.6	
% Change from baseline (adjusted mean)	-3.0	-3.8	
Systolic Blood Pressure (mmHg)			
Baseline (mean)	125.0	126.6	
Change from baseline (adjusted mean)	-4.5	-5.0	

[1] Intent-to-treat population using last observation in study prior to metformin rescue.

[2] p<0.001 compared to placebo.

N/A = Not applicable.

Dual therapy studies (INVOKANA with metformin or sulphonylurea)

Study DIA3006

INVOKANA as dual therapy with metformin produced statistically significant (p<0.001) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, significant and sustained improvements relative to placebo were observed for the percent change in body weight.

Table 3: Results from 26-week placebo-controlled clinical study of INVOKANA as dual therapy with metformin[1]

Efficacy parameter	INVOKANA + metformin 100 mg (N=368)	INVOKANA + metformin 300 mg (N=367)	Placebo + metformin (N=183)
HbA_{1c} (%)			
Baseline (mean)	7.94	7.95	7.96
Change from baseline (adjusted mean)	-0.79	-0.94	-0.17
Difference from placebo (adjusted mean) (95% CI)	-0.62[2] (-0.76; -0.48)	-0.77[2] (-0.91; -0.64)	N/A
Patients (%) achieving HbA_{1c} < 7%	45.5[2]	57.8[2]	29.8
Body weight			
Baseline (mean) in kg	88.7	85.4	86.7
% change from baseline (adjusted mean)	-3.7[2]	-4.2[2]	-1.2
Difference from placebo (adjusted mean) (95% CI)	-2.5[2] (-3.1; -1.9)	-2.9[2] (-3.5; -2.3)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	128.0	128.7	128.0
Change from baseline (adjusted mean)	-3.8	-5.1	1.5
Difference from placebo (adjusted mean) (95% CI)	-5.4[2] (-7.3; -3.4)	-6.6[2] (-8.5; -4.6)	N/A

[1] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

[2] p<0.001 compared to placebo.

N/A = Not applicable

Study DIA3009

INVOKANA as dual therapy with metformin produced similar reductions in HbA_{1c} with INVOKANA 100 mg from baseline compared to glimepiride and superior (p<0.05) reductions in HbA_{1c} with INVOKANA 300 mg compared to glimepiride. These reductions were sustained over the course of the 52-week period. In the glimepiride arm of the study, glimepiride was titrated to optimise glycaemic control throughout the 52-week study. In addition, significant improvements relative to glimepiride were observed for the percent change in body weight.

A subset of patients (N=208) who underwent DXA and abdominal CT scans for evaluation of body composition demonstrated that approximately two-thirds of the weight loss with canagliflozin was due to loss of fat mass with similar amounts of visceral and abdominal subcutaneous fat being lost.

Table 4: Results from 52-week clinical study comparing INVOKANA to glimepiride as dual therapy with metformin[1]

Efficacy parameter	INVOKANA + metformin		Glimepiride (titrated) + metformin (N=482)
	100 mg (N=483)	300 mg (N=485)	
HbA_{1c} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82[2]	-0.93[2]	-0.81
Difference from glimepiride (adjusted mean) (95% CI)	-0.01[2] (−0.11; 0.09)	-0.12[2] (−0.22; −0.02)	N/A
Patients (%) achieving HbA_{1c} < 7%	53.6	60.1	55.8
Body weight			
Baseline (mean) in kg	86.8	86.6	86.6
% change from baseline (adjusted mean)	-4.2	-4.7	1.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.2[4] (−5.7; −4.7)	-5.7[4] (−6.2; −5.1)	N/A
Systolic Blood Pressure (mmHg[5])			
Baseline (mean)	130.0	130.0	129.5
Change from baseline (adjusted mean)	-3.3	-4.6	-0.2
Difference from glimepiride (adjusted mean) (95% CI)	-3.5 (−4.9; −2.1)	-4.8 (−6.2; −3.4)	N/A

[1] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

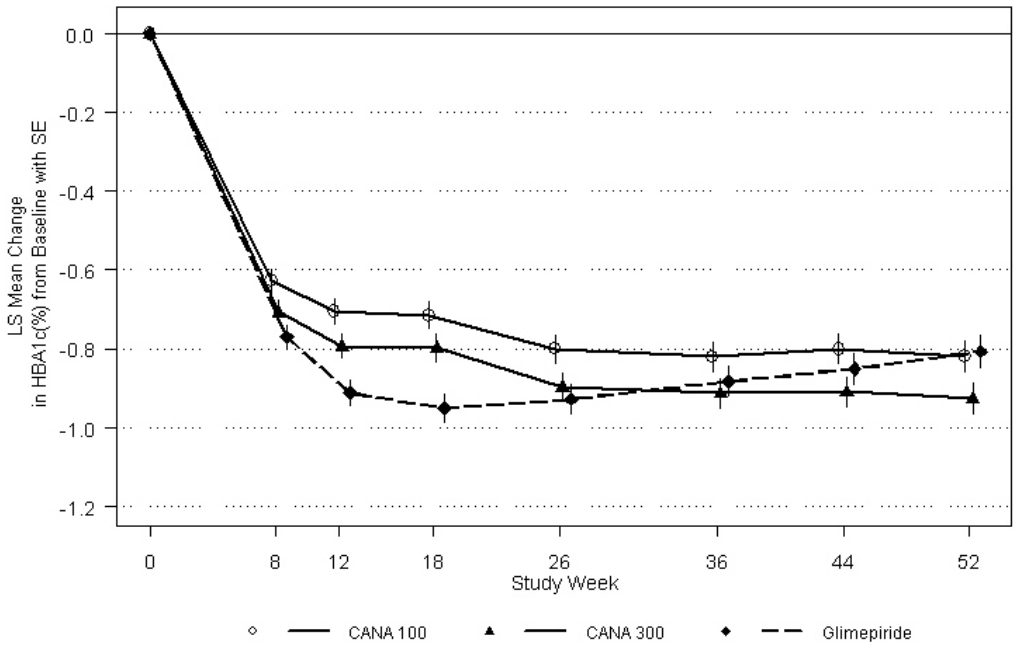
[2] 95% confidence intervals - 100 mg (−0.11;0.09), 300 mg (−0.22;−0.02). Met pre-specified criteria for non-inferiority to glimepiride (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of < 0.3%). In a pre-specified assessment, the upper bound of the 95% CI for INVOKANA 300 mg, but not for INVOKANA 100 mg was < 0, indicating greater reduction in A1C for INVOKANA 300 mg relative to glimepiride.

[3] p<0.001.

N/A = Not applicable

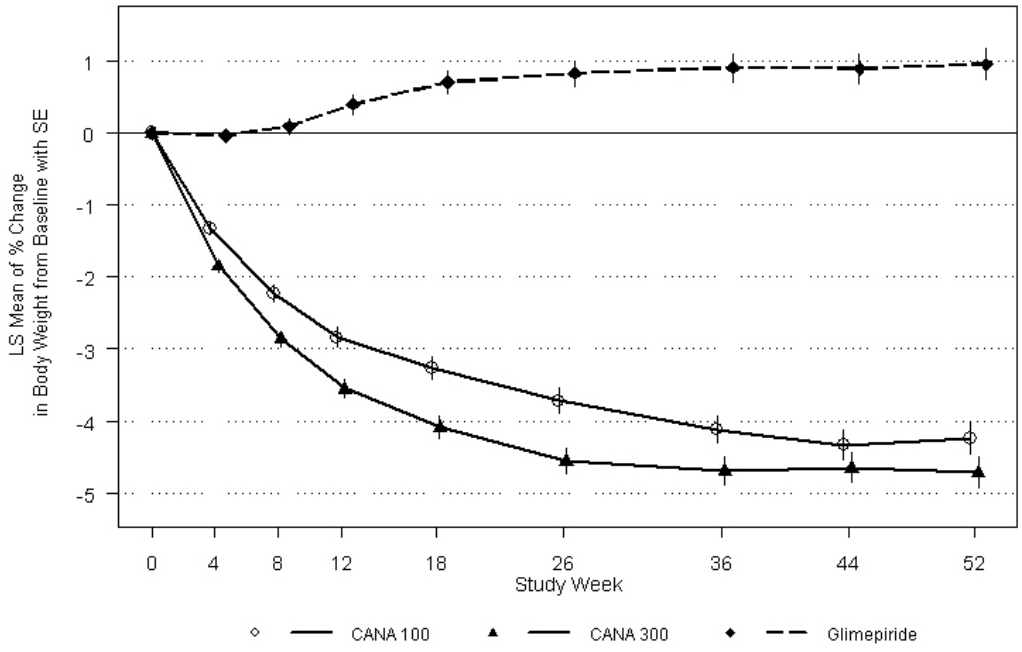
[4] Includes only patients who had both baseline and post-baseline values

Figure 2. Mean Changes from Baseline for HbA_{1C} (%) Over 52 Weeks in a Study Comparing INVOKANA to Glimepiride in Combination with Metformin



Note: LS Mean and SE in each post baseline visit are based on data with LOCF.

Figure 3. **Mean Changes from Baseline for Body Weight Over 52 Weeks in a Study Comparing INVOKANA to Glimepiride in Combination with Metformin**



Note: LS Mean and SE in each post baseline visit are based on data with LOCF.

Study DIA3008 – Sulphonylurea Substudy

INVOKANA as dual therapy with sulphonylurea produced statistically significant (p<0.001) improvements in HbA_{1c} over 18 weeks. In addition, INVOKANA as dual therapy with sulphonylurea resulted in a reduction in the percent change in body weight relative to placebo.

Table 5: Results from 18-week placebo-controlled clinical study of INVOKANA as dual therapy with sulphonylurea[1]

Efficacy parameter	INVOKANA + sulphonylurea 100 mg (N=42)	INVOKANA + sulphonylurea 300 mg (N=40)	Placebo + sulphonylurea (N=45)
HbA_{1c} (%)			
Baseline (mean)	8.29	8.28	8.49
Change from baseline (adjusted mean)	-0.70[2]	-0.79[2]	0.04
Difference from placebo (adjusted mean) (95% CI)	-0.74[2] (-1.15; -0.33)	-0.83[2] (-1.24; -0.41)	N/A
Patients (%) achieving HbA_{1c} < 7%	25.0[3]	33.3[3]	5.0
Body weight			
Baseline (mean) in kg	85.1	80.4	85.5
% change from baseline (adjusted mean)	-0.6	-2.0	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.4 (-1.8; 1.0)	-1.8 (-3.2; -0.4)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	138	133.5	137.3
Change from baseline (adjusted mean)	-3.5	-5.1	-3.4
Difference from placebo (adjusted mean) (95% CI)	-0.1 (-6.5; 6.2)	-1.8 (-8.2; 4.7)	N/A

[1] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

[2] p<0.001 compared to placebo

[3] p<0.01

N/A = Not applicable

Triple therapy studies (INVOKANA with metformin and sulphonylurea or metformin and pioglitazone)

Study DIA3002

INVOKANA as triple therapy with metformin and sulphonylurea produced statistically significant (p<0.001) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, statistically significant improvements in the percent change in body weight were observed.

Table 6: Results from 26-week placebo-controlled clinical study of INVOKANA as triple therapy with metformin and sulphonylurea[1]

Efficacy parameter	INVOKANA + metformin and sulphonylurea		Placebo + metformin and sulphonylurea (N=156)
	100 mg (N=157)	300 mg (N=156)	
HbA_{1c} (%)			
Baseline (mean)	8.13	8.13	8.12
Change from baseline (adjusted mean)	-0.85[2]	-1.06[2]	-0.13
Difference from placebo (adjusted mean) (95% CI)	-0.71[2] (-0.90; -0.52)	-0.92[2] (-1.11; -0.73)	N/A
Patients (%) achieving HbA_{1c} < 7%	43.2[2]	56.6[2]	18.0
Body weight			
Baseline (mean) in kg	93.5	93.5	90.8
% change from baseline (adjusted mean)	-2.1[2]	-2.6[2]	-0.7
Difference from placebo (adjusted mean) (95% CI)	-1.4[2] (-2.1; -0.7)	-2.0[2] (-2.7; -1.3)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	130.4	130.8	130.1
Change from baseline (adjusted mean)	-4.9	-4.3	-2.6
Difference from placebo (adjusted mean) (95% CI)	-2.2 (-4.7; 0.2)	-1.6 (-4.1; 0.9)	N/A

[1] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

[2] p<0.001 compared to placebo.

N/A = Not applicable or not measured in this study

Study DIA3015

INVOKANA as triple therapy with metformin and sulphonylurea provided superior (p<0.05) reductions in HbA_{1c} compared with sitagliptin over 52 weeks. Significant improvements in percent change in body weight compared with sitagliptin were also observed.

Table 7: Results from 52-week clinical study comparing INVOKANA to sitagliptin as triple therapy with metformin and sulphonylurea[1]

Efficacy parameter	INVOKANA 300 mg + metformin and sulphonylurea (N=377)	Sitagliptin 100 mg + metformin and sulphonylurea (N=378)
HbA_{1c} (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)	-0.37[2] (-0.50; -0.25)	N/A
Patients (%) achieving HbA_{1c} < 7%	47.6	35.3
Body weight		
Baseline (mean) in kg	87.6	89.6
Change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI)	-2.8[3] (-3.3; -2.2)	N/A
Systolic Blood Pressure (mmHg)[1]		
Baseline (mean)	131.2	130.1
Change from baseline (adjusted mean)	-5.1	-0.9
Difference from sitagliptin (adjusted mean) (95% CI)	-5.9[3] (-7.6; -4.2)	N/A

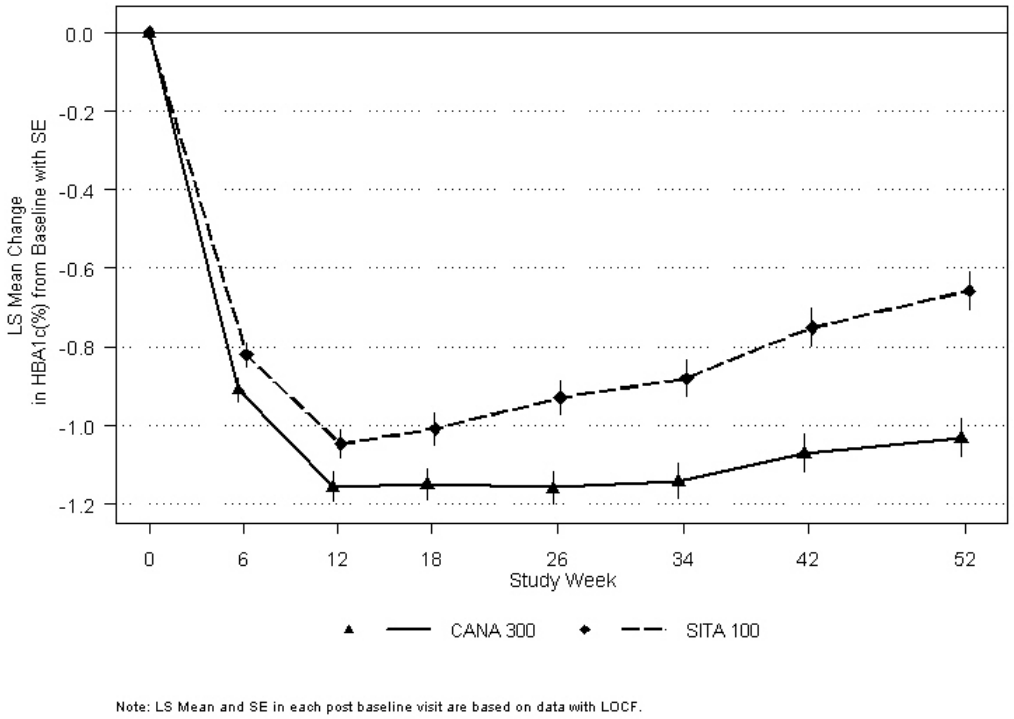
[1] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

[2] 95% confidence intervals for 300 mg - (-0.50; -0.25). Met pre-specified criteria for non-inferiority to sitagliptin (with the upper bound of the 95% CI around the between-group difference less than the pre-specified non-inferiority margin of < 0.3%); in a pre-specified assessment, the upper bound of the 95% CI for INVOKANA 300 mg was < 0, indicating greater reduction in A1C with INVOKANA 300 mg relative to sitagliptin.

[3] p<0.001.

N/A = Not applicable

Figure 4. Mean Change from Baseline for HbA_{1C} (%) Over 52 Weeks in a Study Comparing INVOKANA to Sitagliptin in Combination with Metformin and Sulfonylurea



Note: LS Mean and SE in each post baseline visit are based on data with LOCF.

Study DIA3012

INVOKANA as triple therapy with metformin and pioglitazone produced statistically significant (p<0.001) and sustained reductions in HbA_{1c} relative to placebo over 26 weeks. In addition, statistically significant improvements relative to placebo in the percent change in body weight were observed.

Table 8: Results from 26-week placebo-controlled clinical study of INVOKANA as triple therapy with metformin and pioglitazone[1]

Efficacy parameter	INVOKANA + metformin and pioglitazone 26 weeks		Placebo + metformin and pioglitazone (N=115)
	100 mg (N=113)	300 mg (N=114)	
HbA_{1c} (%)			
Baseline (mean)	7.99	7.84	8.00
Change from baseline (adjusted mean)	-0.89	-1.03	-0.26
Difference from placebo (adjusted mean) (95% CI)	-0.62[2] (-0.81; -0.44)	-0.76[2] (-0.95; -0.58)	N/A
Patients (%) achieving HbA_{1c} < 7%	46.9[2]	64.3[2]	32.5
Mean body weight (kg)			
Baseline	94.2	94.4	94.0
% change from baseline (adjusted mean)	-2.8	-3.8	-0.1
Difference from placebo (adjusted mean) (95% CI)	-2.7[2] (-3.6; -1.8)	-3.7[2] (-4.6; -2.8)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	126.4	126.7	128.2
Change from baseline (adjusted mean)	-5.3	-4.7	-1.2
Difference from placebo (adjusted mean) (95% CI)	-4.1 (-6.9; -1.3)	-3.5 (-6.3; -0.6)	N/A

[1] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.
[2] p<0.001 compared to placebo.
N/A = Not applicable or not measured in this study

Studies as add-on therapy with insulin

Study DIA3008 – Insulin Substudy

INVOKANA as add-on therapy with insulin (with or without other anti-hyperglycaemic agents) produced statistically significant (p<0.001) improvements in HbA_{1c} and percent change in body weight relative to placebo over 18 weeks. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups. The majority of patients were on basal/bolus insulin regimen.

Table 9: Results from 18-week placebo-controlled clinical study of INVOKANA as add-on therapy with insulin ≥ 30 units/day (with or without other oral anti-hyperglycaemic agents)[1]

Efficacy parameter	INVOKANA + insulin 18 weeks		Placebo + insulin (N=565)
	100 mg (N=566)	300 mg (N=587)	
HbA_{1c} (%)			
Baseline (mean)	8.33	8.27	8.20
Change from baseline (adjusted mean)	-0.63	-0.72	0.01
Difference from placebo (adjusted mean) (95% CI)	-0.65[2] (-0.73; -0.56)	-0.73[2] (-0.82; -0.65)	N/A
Patients (%) achieving HbA_{1c} < 7%	19.8	24.7[2]	7.7[2]
Body weight			
Baseline (mean) in kg	96.9	96.7	97.7
% change from baseline (adjusted mean)	-1.8	-2.3	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-1.9[2] (-2.2; -1.6)	-2.4[2] (-2.7; -2.1)	N/A
Systolic Blood Pressure (mmHg)[1]			
Baseline (mean)	137.0	138.2	138.2
Change from baseline (adjusted mean)	-5.1	-6.9	-2.5
Difference from placebo (adjusted mean) (95% CI)	-2.6[2] (-4.1; -1.1)	-4.4[2] (-5.8; -2.9)	N/A

[1] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.
[2] p<0.001 compared to placebo.
N/A = Not applicable or not measured in this study

Special populations

Older patients

Study DIA3010

A total of 714 patients ≥ 55 to ≤ 80 years of age with inadequate glycaemic control on current diabetes treatment (anti-hyperglycaemic agents and/or diet and exercise) participated in a double-blind, placebo-controlled study over 26 weeks. Statistically significant ($p<0.001$) changes from baseline HbA_{1c} relative to placebo of -0.60% and -0.73% were observed for 100 mg and 300 mg, respectively. Statistically significant improvements relative to placebo were seen with INVOKANA treatment in FPG lowering and the percentage of patients achieving HbA_{1c} < 7%. Patients treated with INVOKANA100 mg and INVOKANA 300 mg exhibited a statistically significant improvement in percent change in body weight relative to placebo of -2.4% and -3.1%, respectively (see DOSAGE AND ADMINISTRATION; ADVERSE EFFECTS).

A subset of patients (N=211) participated in the body composition substudy using DXA body composition analysis. This demonstrated that approximately two-thirds of the weight loss with INVOKANA was due to loss of fat mass relative to placebo.

CKD Stage 3A moderate renal impairment (eGFR 45 mL/min/1.73 m^2 *to < 60 mL/min/1.73 m^2)*

In a pooled analysis of patients (N=721) with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2, canagliflozin provided clinically meaningful reduction in HbA_{1c} compared to placebo, with -0.47% for canagliflozin 100 mg and -0.52% for canagliflozin 300 mg. Patients with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 treated with canagliflozin 100 mg and 300 mg exhibited mean improvements in percent change in body weight relative to placebo of -1.8% and -2.0%, respectively.

The majority of patients with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 were on insulin and/or a sulphonylurea (85% [N = 614]). Consistent with the expected increase of hypoglycaemia when a medicinal product not associated with hypoglycaemia is added to insulin and/or sulphonylurea, an increase in hypoglycaemia episodes/events was seen when canagliflozin was added to insulin and/or a sulphonylurea (see ADVERSE EFFECTS).

Fasting plasma glucose

In four placebo-controlled studies, treatment with INVOKANA as monotherapy or add-on therapy with one or two oral anti-hyperglycaemic agents resulted in mean changes from baseline relative to placebo in FPG of -1.2 mmol/L to -1.9 mmol/L for INVOKANA 100 mg and -1.9 mmol/L to -2.4 mmol/L for INVOKANA 300 mg, respectively. These reductions were sustained over the treatment period and near maximal after the first day of treatment.

Postprandial glucose

Using a standardised mixed meal tolerance test, post-prandial glucose was measured in three placebo-controlled clinical studies as monotherapy or add-on therapy with one or two oral anti-hyperglycaemic agents. INVOKANA resulted in mean change reductions from baseline relative to placebo in postprandial glucose of -1.5 mmol/L to -2.7 mmol/L for INVOKANA 100 mg and -2.1 mmol/L to -3.5 mmol/L for INVOKANA 300 mg, respectively due to reductions in the pre-meal glucose concentration and reduced postprandial glucose excursions.

Cardiovascular risk

Preliminary results from a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from Phase 2 and 3 clinical studies (including a long-term study in patients with established cardiovascular disease or who are at high risk of cardiovascular disease) has not shown evidence of an increase in cardiovascular risk with canagliflozin relative to comparators.

Body weight

In general, clinically relevant, statistically significant, and dose-related weight loss, compared to placebo, was observed with canagliflozin across the placebo-controlled studies; the only exception was the lack of meaningful weight loss in the DIA3008 SU substudy at the 100 mg canagliflozin dose. Across the placebo-controlled Phase 3 studies (excluding the results from the 100 mg dose in the DIA3008 SU substudy), the

placebo-subtracted LS mean percent changes from baseline in body weight (at time of primary efficacy assessment) ranged from approximately -1.8% to -3.7% with the canagliflozin 300 mg dose and from approximately -1.4% to -2.7% with the canagliflozin 100 mg dose.

In the pooled population of 5 placebo-controlled studies, treatment with canagliflozin lowered body weight in a dose-related manner at the primary assessment time point. The LS mean percent change from baseline in body weight relative to placebo, was -2.0% (-1.4% to -2.7%) for the 100 mg dose and -2.7% (-2.0% to 3.7%) for the 300 mg dose. The lowest weight loss seen was in the metformin and sulphonylurea add-on study. A subset of patients (N=208) from the active controlled dual therapy study with metformin who underwent dual energy X ray densitometry (DXA) and abdominal computed tomography (CT) scans for evaluation of body composition demonstrated that approximately two thirds of the weight loss with canagliflozin was due to loss of fat mass with similar amounts of visceral and abdominal subcutaneous fat being lost. Similar findings on the relative contribution of fat to lean mass loss with canagliflozin were seen in the Phase 3 study in older subjects.

INDICATIONS

INVOKANA 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).

CONTRAINDICATIONS

Hypersensitivity to INVOKANA or to any of the excipients.

Patients with CKD stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30 mL/min/1.73 m^2 or CrCl < 30 mL/min) or eGFR persistently < 45 mL/min/1.73m^2 or CrCl persistently < 45 mL/min (CKD stage 3B). The efficacy of INVOKANA is dependent on renal function (see PRECAUTIONS).

PRECAUTIONS

INVOKANA has not been studied in patients with type 1 diabetes and is therefore not recommended for use.

INVOKANA should not be used for the treatment of diabetic ketoacidosis as it would not be effective in these settings.

Hyperkalaemia

Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalaemia (see ADVERSE EFFECTS).

Serum potassium levels should be monitored periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalaemia due to medications or other medical conditions.

Hypoglycaemia in add-on therapy with other anti-hyperglycaemic agents

When used alone or as add-on therapy with anti-hyperglycaemic agents not associated with hypoglycaemia, INVOKANA showed a low incidence of hypoglycaemia. Insulin and insulin secretagogues (e.g., sulphonylurea) are known to cause hypoglycaemia. When INVOKANA was used as add-on therapy with insulin or an insulin secretagogue (e.g., sulphonylurea) the incidence of hypoglycaemia was increased over that of placebo.

Therefore, to lower the risk of hypoglycaemia, a dose reduction of insulin or an insulin secretagogue may be considered (see DOSAGE AND ADMINISTRATION; ADVERSE EFFECTS).

Reduced intravascular volume

INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA (see ADVERSE EFFECTS) particularly in patients with impaired renal function (CKD stages 3, 4 or 5; eGFR < 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Patients should be advised to report symptoms of reduced intravascular volume. Before initiating INVOKANA, assess volume status and correct hypovolaemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or if on diuretics, ACEi, or ARB. Monitor for signs and symptoms of reduced intravascular volume after initiating therapy.

Genital mycotic infections

In 26-week clinical studies, vulvovaginal candidiasis (including vulvovaginitis and vulvovaginal mycotic infection) was reported in 10.4% and 11.4% of female patients treated with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 3.2% in placebo-treated female patients. Patients with a history of vulvovaginal candidiasis were more likely to develop this infection. Among female patients taking INVOKANA, 2.3% experienced more than one infection. Most reports of vulvovaginal candidiasis occurred during the first four months after initiation of INVOKANA. Overall, 0.7% of all female patients discontinued INVOKANA due to vulvovaginal candidiasis (see ADVERSE EFFECTS). The diagnosis of vulvovaginal candidiasis was usually made based on symptoms only. In clinical studies, female patients responded to topical or oral antifungal treatment either prescribed by a healthcare professional or self-treated while continuing therapy with INVOKANA.

In 26-week clinical studies, candidal balanitis or balanoposthitis was reported in 4.2% and 3.7% of male patients treated with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 0.6% in placebo-treated male patients. Balanitis or balanoposthitis occurred primarily in uncircumcised male patients and was more common in male patients with a prior history of balanitis or balanoposthitis. Among male patients taking INVOKANA, 0.9% had more than one infection. Overall, 0.5% of male patients discontinued INVOKANA due to candidial balanitis or balanoposthitis (see ADVERSE EFFECTS). In clinical studies, the majority of infections were treated with topical antifungal treatments either prescribed by a healthcare professional or self-treated while continuing therapy with INVOKANA. In rare instances, phimosis was reported and sometimes circumcision was performed.

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in patients with renal impairment

The efficacy of INVOKANA is dependent on renal function. Patients with CKD stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30 mL/min/1.73 m^2 or CrCl < 30 mL/min) or eGFR persistently < 45 mL/min/1.73m^2 or CrCl persistently < 45 mL/min (CKD stage 3B) should not receive INVOKANA (see CONTRAINDICATIONS).

Monitoring of renal function is recommended as follows:

- prior to initiation of INVOKANA and at least yearly thereafter;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;
- for renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function consistently falls below Stage 3A CKD (eGFR < 45 mL/min/1.73 m^2 or CrCl < 45 mL/min) treatment with INVOKANA should be discontinued.

Effects on fertility

The effect of canagliflozin on fertility in humans has not been studied. In fertility studies in male and female rats, canagliflozin had no adverse effects on early embryonic development, mating, and fertility up to the highest dose of 100 mg/kg/day (12 and 15 times the clinical dose of 300 mg in the respective sexes based on AUC exposure).

Use in pregnancy - Category C

There are no adequate and well-controlled studies in pregnant women. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Placental transfer of canagliflozin and/or its metabolites was demonstrated in the rat.

In conventional studies in animals, canagliflozin was not teratogenic and did not affect embryofetal viability or fetal weight when administered during the period of organogenesis at oral doses up to 100 mg/kg/day (rats) or 160 mg/kg/day (rabbits), yielding 19 times the human exposure to canagliflozin at the maximum recommended human dose (MRHD) of 300 mg once daily. In rats, slight increases in the number of fetuses with reduced ossification, indicative of a slight developmental delay and an increased incidence in rudimentary 14th ribs, were observed at 100 mg/kg (relative exposure, 19x). In rabbits, an increased incidence of additional 13th ribs (a minor skeletal abnormality) was seen at all doses tested (≥ 10 mg/kg/day; relative exposure, ≥ 0.4x).

Canagliflozin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring at maternally toxic doses only (≥ 30 mg/kg/day; exposures ≥ 5.9 times the human exposure to canagliflozin at the MRHD). Some developmental delays (attributed to decreased pup body weight) and impaired reproductive performance were observed in the offspring of rats treated at 100 mg/kg/day. No adverse effects on postnatal development were noted at 10 mg/kg/day (relative exposure, 1.6x).

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. These effects are considered to be pharmacological effects that show reversibility and may be suspected of causing harmful effects on the human fetus or neonate without causing malformations.

Use in lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin in milk. It is not known if canagliflozin is excreted in human milk. Data in juvenile rats directly exposed to canagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur,

there may be risk to the developing human kidney. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from INVOKANA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Genotoxicity

Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was genotoxic in the *in vitro* mouse lymphoma tk assay with but not without metabolic activation. Canagliflozin was not mutagenic or clastogenic in an *in vivo* oral micronucleus assay in rats and an *in vivo* oral Comet assay in rats. The overall weight of evidence indicates that canagliflozin is not genotoxic.

Carcinogenicity

Two-year oral carcinogenicity studies were conducted in mice and rats. Canagliflozin did not increase the incidence of tumours in mice at doses of up to 100 mg/kg/day. This dose was provided up to 7 (males) or 14 times (females) the exposure (plasma AUC) at the clinical dose of 300 mg. Canagliflozin increased the incidence of testicular Leydig cell tumours in male rats at all doses tested; the lowest dose of 10 mg/kg/day is approximately 1.5 times the clinical dose of 300 mg based on AUC exposure. Higher doses of canagliflozin (100 mg/kg/day) increased the incidence of pheochromocytomas and renal tubular adenomas and carcinomas in male and female rats; based on AUC exposure, this dose is approximately 12 (males) or 21 times (females) at the clinical dose of 300 mg. Based on preclinical and clinical mechanistic studies, the Leydig and renal tubule tumours and pheochromocytomas are seen to be due to mechanisms not considered to be of human relevance. Canagliflozin-induced renal tubule tumours and pheochromocytomas in rats appear to be caused by carbohydrate malabsorption; mechanistic clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the maximum recommended human dose. The Leydig cell tumours are associated with an increase in luteinizing hormone (LH), which is a known mechanism of Leydig cell tumour formation in rats. In a 12-week clinical study, LH did not increase in male patients treated with canagliflozin.

Effect on ability to drive or operate machinery

Canagliflozin has no known influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia, especially when INVOKANA is used as add-on therapy with insulin or an insulin secretagogue, and to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness (see DOSAGE AND ADMINISTRATION; PRECAUTIONS; ADVERSE EFFECTS).

INTERACTIONS WITH OTHER MEDICINES

In vitro assessment of interactions

Canagliflozin did not induce CYP450 enzyme expression (3A4, 2C9, 2C19, 2B6, and 1A2) in cultured human hepatocytes. Canagliflozin did not inhibit the CYP450 isoenzymes (1A2, 2A6, 2C19, 2D6, or 2E1) and weakly inhibited CYP2B6, CYP2C8, CYP2C9, and CYP3A4 based on *in vitro* studies with human hepatic microsomes. *In vitro* investigations indicate that canagliflozin is a substrate for the metabolising enzymes UGT1A9 and UGT2B4, and the transporters P-glycoprotein (P-gp) and MRP2. Canagliflozin is a weak inhibitor of P-gp.

Canagliflozin undergoes minimal oxidative metabolism (see PHARMACOLOGY – Pharmacokinetics) and thus clinically relevant effects of other medicinal products on canagliflozin pharmacokinetics via the cytochrome P450 system are unlikely to occur.

In vivo assessment of interactions

Effects of other medicinal products on canagliflozin

In clinical studies, the effects of other drugs on canagliflozin were assessed. Cyclosporin, hydrochlorothiazide, oral contraceptives (ethinyl oestradiol and levonorgestrel), metformin, and probenecid had no clinically relevant effect on the pharmacokinetics of canagliflozin.

Medicinal products that induce UDP-glucuronosyl transferase (UGT) enzymes and transport proteins

Co-administration with rifampicin, a nonselective inducer of several UGT enzymes and medicinal product transporters including UGT1A9, UGT2B4, P-gp, and MRP2, decreased canagliflozin exposure. These decreases in exposure to canagliflozin may decrease efficacy. If a combined inducer of these UGTs and transport proteins (e.g., rifampicin, phenytoin, barbituates, phenobarbitol, ritonavir, carbamazepine, efavirenz, St John's wort [Hypericum perforatum]) must be co-administered with INVOKANA, monitor HbA_{1c} in patients receiving INVOKANA 100 mg once daily with consideration to increasing the dose to 300 mg once daily if additional glycaemic control is needed. In patients with CKD stage 3A (eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 or CrCl 45 mL/min to < 60 mL/min) taking canagliflozin 100 mg who are receiving concurrent therapy with a UGT enzyme inducer and who require additional glycaemic control, other antihyperglycemic therapies should be considered (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Medicinal products that inhibit UGT enzymes and transport proteins

Probenecid: Co-administration of canagliflozin with probenecid, a nonselective inhibitor of several UGT enzymes and transporters including UGT1A9 and MRP2, had no clinically relevant effect on the pharmacokinetics of canagliflozin. Because canagliflozin undergoes glucuronidation by two different UGT enzymes and glucuronidation is a high-capacity/low-affinity system, clinically relevant interactions of other medicinal products on canagliflozin pharmacokinetics via glucuronidation are unlikely to occur.

Cyclosporin: No clinically meaningful pharmacokinetic interaction was observed after co-administration of cyclosporin, an inhibitor of P-gp, CYP3A, and several transporters, including MRP2, with canagliflozin. Mild, transient flushing was observed when cyclosporin and canagliflozin were co-administered. No dose adjustment of INVOKANA is recommended. No meaningful interactions with other P-gp inhibitors would be expected.

Table 10: Effect of co-administered medicinal products on systemic exposure of canagliflozin

Co-administered medicinal product	Dose of co-administered medicinal product[1]	Dose of canagliflozin[1]	Geometric mean ratio (ratio with/without co-administered medicinal product) No effect=1.0	
			AUC[2] (90% CI)	C_{max} (90% CI)
No dose adjustments of INVOKANA required for the following:				
Cyclosporin	400 mg	300 mg once daily for 8 days	1.23 (1.19; 1.27)	1.01 (0.91; 1.11)
Ethinyl oestradiol and levonorgestrel	0.03 mg ethinyl oestradiol and 0.15 mg levonorgestrel	200 mg once daily for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)
Hydrochlorothiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
Metformin	2,000 mg	300 mg once daily for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)
Probenecid	500 mg twice daily for 3 days	300 mg once daily for 17 days	1.21 (1.16; 1.25)	1.13 (1.00; 1.28)
Rifampicin	600 mg once daily for 8 days	300 mg	0.49 (0.44; 0.54)	0.72 (0.61; 0.84)

[1] Single dose unless otherwise noted.

[2] AUC_{inf} for medicinal products given as a single dose and AUC_{24h} for medicinal products given as multiple doses.

Effects of canagliflozin on other medicinal products

In clinical studies, as described below, canagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, oral contraceptives (ethinyl oestradiol and levonorgestrel), glyburide, simvastatin, paracetamol or warfarin providing *in vivo* evidence of a low propensity for causing medicinal product interactions with substrates of CYP3A4, CYP2C9, CYP2C8, and organic cationic transporter (OCT).

Digoxin: Canagliflozin had a small effect on plasma digoxin concentrations. Patients taking digoxin should be monitored appropriately.

Table 11: Effect of canagliflozin on systemic exposure of co-administered medicinal products

Co-administered medicinal product	Dose of Co-administered medicinal product[1]	Dose of canagliflozin[1]	Geometric mean ratio (ratio with/without co-administered medicinal product) No effect=1.0		
				AUC[2] (90% CI)	C_{max} (90% CI)
No dose adjustments of co-administered medicinal product required for the following:					
Digoxin	0.5 mg once daily first day followed by 0.25 mg once daily for 6 days	300 mg once daily for 7 days	digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)
Ethinyl oestradiol and levonorgestrel	0.03 mg ethinyl oestradiol and 0.15 mg levonorgestrel	200 mg once daily for 6 days	ethinyl oestradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)
			levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)
Glyburide	1.25 mg	200 mg once daily for 6 days	glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)
Hydrochloro-thiazide	25 mg once daily for 35 days	300 mg once daily for 7 days	hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2,000 mg	300 mg once daily for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Paracetamol	1,000 mg	300 mg twice daily for 25 days	paracetamol	1.06[3] (0.98; 1.14)	1.00 (0.92; 1.09)
Simvastatin	40 mg	300 mg once daily for 7 days	simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)
			simvastatin acid	1.18 (1.03; 1.35)	1.26 (1.10; 1.45)
Warfarin	30 mg	300 mg once daily for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (0.98; 1.03)	1.05 (0.99; 1.12)

[1] Single dose unless otherwise noted.
[2] AUC_{inf} for medicinal products given as a single dose and AUC_{24h} for medicinal products given as multiple doses.
[3] AUC_{0-12h}
INR = International Normalised Ratio.

ADVERSE EFFECTS

Clinical Trial Data

The safety of INVOKANA was evaluated in 10,285 patients with type 2 diabetes, including 3,092 patients treated with INVOKANA 100 mg and 3,462 patients treated with INVOKANA 300 mg, who received medicinal product in nine double-blind, controlled Phase 3 clinical studies.

The primary assessment of safety and tolerability was conducted in a pooled analysis (n=2,313) of four 26-week placebo-controlled clinical studies (monotherapy and add-on therapy with metformin, metformin and a sulphonylurea, and metformin and pioglitazone). The most commonly reported adverse reactions during treatment were hypoglycaemia in combination with insulin or a sulphonylurea, vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (i.e., urinary frequency). Adverse reactions leading to discontinuation of ≥ 0.5% of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of female patients) and balanitis or balanoposthitis (0.5% of male patients). Additional safety analyses (including long-term data) from data across the entire canagliflozin programme (placebo- and active-controlled studies) were conducted to assess reported adverse reactions in order to identify adverse reactions (see Table 1) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Tabulated list of adverse reactions

Table 12 lists adverse reactions reported in ≥ 2% of INVOKANA-treated patients in the four pooled, 26-week, placebo-controlled clinical studies (N=2313). The safety profiles of the individual placebo-controlled studies in the pooled analysis were similar in adverse reactions and frequencies.

Table 12: Adverse Reactions From Four Pooled 26-Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients

	INVOKANA 100 mg N=833 %	**INVOKANA 300 mg N=834 %**	**Placebo N=646 %**
System Organ Class Adverse Reaction			
Gastrointestinal Disorders			
Constipation	15 (1.8)	19 (2.3)	6 (0.9)
Nausea	18 (2.2)	19 (2.3)	10 (1.5)
Thirst	23 (2.8)	19 (2.3)	1 (0.2)
Renal and Urinary Disorders			
Polyuria or Pollakiuria	44 (5.3)	38 (4.6)	5 (0.8)
Urinary tract infection	49 (5.9)	36 (4.3)	26 (4.0)
Reproductive System and Breast Disorders			
Balanitis or Balanoposthitis	17 (4.2)	15 (3.7)	2 (0.6)
Vulvovaginal candidiasis	44 (10.4)	49 (11.4)	10 (3.2)

Other adverse reactions in clinical studies of INVOKANA that occurred at a rate < 2% in placebo-controlled studies were adverse reactions related to reduced intravascular volume (postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope) (see below), skin rash, and urticaria.

Description of selected adverse reactions

Cardiovascular events
A prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from Phase 2 and 3 clinical studies in 9,632 patients with type 2 diabetes, including 4,327 patients who are participating in an ongoing cardiovascular study (patients with cardiovascular disease or at high risk for cardiovascular disease) was conducted.[1] The hazard ratio for the primary endpoint (time to event in composite of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and unstable angina requiring hospitalisation) for (both doses pooled) versus combined active and placebo comparators was 0.91 (95% CI: 0.68; 1.22). The hazard ratios for the 100 mg and 300 mg doses were 0.92 (95% CI: 0.65,1.28) and 0.91 (95%CI: 0.65, 1.28) respectivley. Therefore, there was no evidence of an increase in cardiovascular risk with either 100 mg or 300 mg relative to comparators.

Adverse reactions related to reduced intravascular volume
In the pooled analysis of the four 26-week, placebo-controlled studies, the incidence of all adverse reactions related to reduced intravascular volume (postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope) was 1.2% for INVOKANA 100 mg, 1.3% INVOKANA 300 mg and 1.1% for placebo.

In the dedicated cardiovascular study, the incidences of adverse reactions related to reduced intravascular volume were 2.8% with INVOKANA 100 mg, 4.6% with INVOKANA 300 mg, and 1.9% with placebo.

To assess risk factors for these adverse reactions, a larger pooled analysis (N=9,439) of patients from eight controlled Phase 3 studies including both doses of INVOKANA was conducted. In this pooled analysis, patients on loop diuretics, patients with moderate renal impairment, and patients ≥ 75 years of age had generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidences were 3.2% on INVOKANA 100 mg and 8.8% on INVOKANA 300 mg compared to 4.7% in the control group. For patients with moderate renal impairment, the incidences were 4.7% on INVOKANA 100 mg and 8.1% on INVOKANA 300 mg compared to 2.5% in the control group. In patients ≥ 75 years of age, the incidences were 4.9% on INVOKANA 100 mg and 8.7% on INVOKANA 300 mg compared to 2.6% in the control group (see DOSAGE AND ADMINISTRATION; PRECAUTIONS).

In the dedicated cardiovascular study and the larger pooled analysis, serious adverse reactions related to reduced intravascular volume were not increased with INVOKANA and discontinuations due to these adverse reactions were infrequent.

Hypoglycaemia in add-on therapy with insulin or insulin secretagogues
When INVOKANA was used as add-on therapy with insulin or sulphonylurea (with or without metformin), hypoglycaemia was reported more frequently, which is consistent with the expected increase of hypoglycaemia when an agent not associated with hypoglycaemia is added to insulin or an insulin secretagogue (e.g., sulphonylurea). In the 18-week substudy with insulin, episodes of biochemically documented hypoglycaemia were observed in 49.3%, 48.2%, and 36.8% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively. Severe hypoglycaemia occurred in 1.8%, 2.7%, and 2.5% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively. In the 18-week substudy with sulphonylurea, biochemically documented hypoglycaemia was observed in 4.1%, 12.5%, and 5.8% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively, with no reports of severe hypoglycaemia in any treatment group (see DOSAGE AND ADMINISTRATION; PRECAUTIONS).

Urinary tract infections
Urinary tract infections were more frequently reported for INVOKANA 100 mg and 300 mg (5.9% versus 4.3%, respectively) compared to 4.0% with placebo. Most infections were mild to moderate with no increase in the occurrence of serious adverse events. Subjects responded to standard treatments while continuing canagliflozin treatment. The incidence of recurrent infections was not increased with canagliflozin.

Bone fractures
In a pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, with the fracture imbalance occurring in women and within the first 26 weeks of therapy, more commonly in the upper extremity, and not progressing thereafter. Over 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Laboratory tests
The below incidence rates of abnormal laboratory values are derived from the pooled analysis of 26-week, placebo-controlled clinical studies unless otherwise noted.

Increases in serum potassium
Episodes of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were seen in 4.4% of patients treated with INVOKANA 100 mg, 7.0% of patients treated with INVOKANA 300 mg, and 4.8% of patients treated with placebo. In a pooled analysis of patients with moderate renal impairment (N=1,085), overall incidences of elevated serum potassium were observed with INVOKANA 100 mg (7.5%), INVOKANA 300 mg (12.3%), and placebo (8.1%). The majority of patients with elevated values had potassium levels that were only mildly elevated (< 6 mEq/L). Rare, more severe elevations were seen in patients with moderate renal impairment who had elevated potassium concentrations prior to treatment with INVOKANA and/or who were on multiple medications that reduce potassium excretion, such as potassium-sparing diuretics and angiotensin-converting-enzyme (ACE) inhibitors. In general, elevations were transient and did not require specific treatment (see PRECAUTIONS, Hyperkalaemia).

Increases in serum creatinine and urea
Mean percent changes from baseline in creatinine, with commensurate decreases in eGFR, were 2.8% and 4.0% for INVOKANA 100 mg and 300 mg, respectively, compared to 1.5% for placebo. Mean percent changes from baseline in urea were 17.1% and 18.0% for INVOKANA 100 mg and 300 mg, respectively, compared to 0.0% for placebo. These changes were generally observed within six weeks of treatment initiation. Subsequently, serum creatinine concentrations gradually trended toward baseline and urea levels remained stable.
The proportion of patients with larger decreases in eGFR (> 30%) from baseline, occurring at any time during treatment, was 2.0% with INVOKANA 100 mg and 4.1% with INVOKANA 300 mg relative to 2.1% with placebo. These decreases in eGFR were often transient with fewer patients having this level of decrease at study endpoint, occurring in 0.7% of patients with INVOKANA 100 mg, 1.4% of patients with INVOKANA 300 mg, and 0.5% of placebo-treated patients). (see PRECAUTIONS).

After discontinuation of INVOKANA therapy, these changes in laboratory values improved or returned to baseline.

Lipid changes
The mean percent changes from baseline relative to placebo for low density lipoprotein cholesterol (LDL-C) were 0.11 mmol/L (4.5%) and 0.21 mmol/L (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. Smaller increases in total cholesterol of 4.3% and 6.1% relative to placebo for INVOKANA 100 mg and INVOKANA 300 mg, respectively, were seen. Increases in high density lipoprotein cholesterol (HDL-C) were 5.4%, and 6.3% relative to placebo for INVOKANA 100 mg and INVOKANA 300 mg, respectively. Increases in non-HDL-C relative to placebo were 0.05 mmol/L (1.5%) and 0.13 mmol/L (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The LDL-C/HDL-C ratios did not change with either INVOKANA dose compared to placebo. Concentrations of ApoB and LDL-C particle number (measured in two studies) and non-HDL-C increased to a smaller extent compared to LDL-C changes.

Increases in haemoglobin
Mean changes (percent changes) from baseline in hemoglobin concentrations were 4.7 g/L (3.5%) with INVOKANA 100 mg, 5.1 g/L (3.8%) with INVOKANA 300 mg, and 1.8 g/L (1.1%) with placebo. Small increases in the mean percent change from baseline in hemoglobin concentration were observed in the INVOKANA 100 mg and 300 mg groups (3.5% and 3.8%, respectively) compared to a slight decrease in placebo (1.1%). Commensurate small increases in the mean percent change from baseline in blood erythrocytes and hematocrit were observed. At the end of treatment, 4.0%, 2.7%, and 0.8% of patients treated with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively, had hemoglobin levels above the upper limit of normal. A higher proportion of patients had increases in hemoglobin (> 20 g/L), occurring in 6.0% of patients treated with INVOKANA 100 mg, 5.5% in patients treated with INVOKANA 300 mg, and 1.0% in placebo-treated patients. Most values remained within the normal range.

Increases in serum phosphate
Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo-controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. Episodes of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were seen in 0.6% and 1.6% of patients treated with INVOKANA 100 mg and 300 mg, respectively, compared to 1.3% of patients treated with placebo.

Decreases in serum urate
Moderate decreases in the mean percent change from baseline in serum urate were observed in the INVOKANA 100 mg and 300 mg groups (-10.1% and -10.6%, respectively) compared with placebo, where a slight increase from baseline (1.9%) was observed. Decreases in serum urate in the INVOKANA groups were maximal or near maximal by week 6 and maintained with dosing. A transient increase in urinary uric acid excretion was seen, which was not persistent. In a pooled analysis (N=9,439) of patients from eight controlled Phase 3 studies including both doses of INVOKANA, events of nephrolithiasis were not increased.

<u>Adverse reactions in specific populations</u>

Renal impairment
In an analysis of patients with a baseline eGFR 45 to < 60 mL/min/1.73 m^2 or CrCl 45 to < 60 mL/min (CKD stage 3A), the incidences of adverse reactions related to reduced intravascular volume were 4.6% with INVOKANA 100 mg and 7.1% with INVOKANA 300 mg relative to 3.4% with placebo (see DOSAGE AND ADMINISTRATION and PRECAUTIONS). Serum creatinine levels increased by 4.9% and 7.3% for INVOKANA 100 mg and 300 mg, respectively, relative to 0.2% with placebo. Blood urea nitrogen levels increased by 13.2% and 13.6% for INVOKANA 100 mg and 300 mg, respectively, relative to 0.7% with placebo. The proportion of patients with larger decreases in eGFR (> 30%) at any time during treatment was 6.1%, 10.4%, and 4.3% with INVOKANA 100 mg, INVOKANA 300 mg, and placebo, respectively. At study endpoint, 2.3% of patients treated with INVOKANA 100 mg, 4.3% with INVOKANA 300 mg, and 3.5% with placebo had such decreases (see PRECAUTIONS).

The incidences of elevated serum potassium (> 5.4 mEq/L and 15% above baseline) were 5.2% with INVOKANA 100 mg, 9.1% with INVOKANA 300 mg and 5.2% with placebo (see PRECAUTIONS). Rare, more severe elevations were seen in patients with moderate renal impairment who had prior elevated potassium concentrations and/or who were on multiple medications that reduce potassium excretion, such as potassium-sparing diuretics and angiotensin-converting-enzyme (ACE) inhibitors. In general, elevations were transient and did not require specific treatment.

Serum phosphate levels increased by 3.3% and 4.2% for INVOKANA 100 mg and 300 mg, respectively, compared to 1.1% for placebo. The incidences of elevated serum phosphate (> 1.65 mmol/L and 25% above baseline) were 1.4% with INVOKANA 100 mg, 1.3% with INVOKANA 300 mg and 0.4% with placebo. In general, elevations were transient and did not require specific treatment.

Due to the reduced benefit and increased risks from use of INVOKANA in patients with an eGFR persistently < 45 mL/min/1.73 m^2 or CrCl persistently < 45 mL/min (CKD stage 3B), 4, and 5, INVOKANA is contraindicated in these patients (see CONTRAINDICATIONS).

DOSAGE AND ADMINISTRATION

INVOKANA should be taken orally once a day, preferably taken before the first meal of the day. Tablets are to be swallowed whole. If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken to make up for the missed one.

The management of therapy should be individualised.

The recommended dose of INVOKANA is 100 mg or 300 mg once daily. The 300 mg dose may be considered for patients with CKD stages 1 or 2 (eGFR ≥ 60 mL/min/1.73 m^2 or a creatinine clearance (CrCl) ≥ 60 mL/min), who need tighter glycemic control and who have a low risk of adverse reactions associated with reduced intravascular volume with INVOKANA treatment (see below and PRECAUTIONS).

A starting dose of 100 mg once daily should be used in patients on loop diuretics and patients ≥ 75 years of age. In patients with evidence of reduced intravascular volume, correcting this condition prior to initiation of INVOKANA is recommended. For those patients who are tolerating INVOKANA 100 mg and who need tighter glycemic control, the dose can be increased to INVOKANA 300 mg (see PRECAUTIONS).

When INVOKANA is used as add-on therapy with anti-hyperglycaemic agents other than insulin or an insulin secretagogue, the dose(s) of the anti-hyperglycaemic agents can be maintained and INVOKANA administered concomitantly.

When INVOKANA is used as add-on therapy with insulin or an insulin secretagogue (e.g., sulphonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see PRECAUTIONS; ADVERSE EFFECTS).

Elderly
In patients ≥ 75 years of age, the starting dose of INVOKANA is 100 mg once daily. Renal function and risk of volume depletion should be taken into account (see PRECAUTIONS; ADVERSE EFFECTS and PHARMACOLOGY- Pharmacodynamics, Pharmcokinetics).

Renal impairment
Assessment of renal function is recommended prior to initiation of INVOKANA therapy and periodically thereafter (see PRECAUTIONS).

For patients with mild renal impairment (CKD stage 2; eGFR 60 to < 90 mL/min/1.73m^2 or CrCl 60 to < 90 mL/min), no dose adjustment is required.

In patients with CKD stage 3A (eGFR 45 to < 60 mL/min/1.73m^2 or CrCl 45 to < 60 mL/min), the dose of INVOKANA is limited to 100 mg once daily. INVOKANA should not be initiated in patients with an eGFR < 45 mL/min/1.73 m^2 or a CrCl < 45 mL/min. INVOKANA should be discontinued when eGFR is persistently < 45 mL/min/1.73 m^2 or CrCl is persistently < 45 mL/min (see PRECAUTIONS and ADVERSE EFFECTS).

INVOKANA should not be used in patients with an eGFR < 45 mL/min/1.73 m^2 as it would not be effective in these patient populations (see CONTRAINDICATIONS).

Hepatic impairment
For patients with mild or moderate hepatic impairment, no dose adjustment is required.

INVOKANA has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients (see PHARMACOLOGY- Pharmcokinetics).

Paediatric population
The safety and efficacy of INVOKANA in children under 18 years of age have not been established. No data are available.

OVERDOSAGE

During controlled clinical studies in healthy subjects, single doses up to 1600 mg (equivalent to 5.3 times the recommended dose) and 300 mg twice daily for 12 days were generally well tolerated. There is no experience with single doses above 1600 mg or 300 mg twice daily for 12 days in humans.

Management of Overdosage

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute clinical measures if required. Canagliflozin was negligibly removed during a 4-hour haemodialysis session. It is not known whether canagliflozin is dialyzable by peritoneal dialysis.

Contact the Poisons Information Centre (telephone no. 13 11 26) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

100 mg: Yellow, capsule-shaped, approximately 11 mm in length, film-coated tablet, with “CFZ” on one side and “100” on the other side.
Pack size^: Blister packs of 10, 30 or 100 tablets.

300 mg: White, capsule-shaped, approximately 17 mm in length, film-coated tablet, with “CFZ” on one side and “300” on the other side.
Pack size^: Blister packs of 10, 30 or 100 tablets.

^Not all presentations may be marketed.

Store below 25^{o}C.

NAME AND ADDRESS OF THE SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Road,
Macquarie Park, NSW, 2113, AUSTRALIA

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

12 Sep 2013

DATE OF MOST RECENT AMENDMENT:

19 Feb 2014