Metformin

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin hydrochloride 500 to 1,500 mg, and 850 to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution

Canagliflozin

The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 83.5 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), 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.

Metformin

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride 850 mg tablets averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally less than 1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Canagliflozin

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.

Metformin

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Excretion

Canagliflozin

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 feces 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 of canagliflozin 100 mg and 300 mg doses ranged from 1.30 to 1.55 mL/min.

Mean systemic clearance of canagliflozin was approximately 192 mL/min in healthy subjects following intravenous administration.

Metformin

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of INVOKAMET were not conducted in patients with renal and hepatic impairment. Descriptions of the individual components in this patient population are described below.

Renal Impairment

Canagliflozin

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.

Renal impairment did not affect the C_{max} of canagliflozin. Compared to healthy subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m^2), plasma AUC of canagliflozin was increased by approximately 15%, 29%, and 53% in subjects with mild (N=10), moderate (N=9), and severe (N=10) renal impairment, respectively, (eGFR 60 to less than 90, 30 to less than 60, and 15 to less than 30 mL/min/1.73 m^2, respectively) but was similar for ESRD (N=8) subjects and healthy subjects. Increases in canagliflozin AUC of this magnitude are not considered clinically relevant. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Canagliflozin was negligibly removed by hemodialysis.

Metformin

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Hepatic Impairment

Canagliflozin

Relative to subjects with normal hepatic function, the geometric mean ratios for C_{max} and AUC_{∞} of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and 96% and 111%, 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. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment *[see Warnings and Precautions (5.1)]*.

Metformin

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency *[see Warnings and Precautions (5.1)]*.

Pharmacokinetic Effects of Age, Body Mass Index (BMI)/Weight, Gender and Race

Canagliflozin

Based on the population PK analysis with data collected from 1526 subjects, age, body mass index (BMI)/weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of canagliflozin *[see Use in Specific Populations (8.5)]*.

Metformin

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender.

No studies of metformin pharmacokinetic parameters according to race have been performed.

Geriatric

INVOKAMET

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of INVOKAMET in geriatric patients have not been performed *[see Warnings and Precautions (5.1, 5.5) and Use in Specific Populations (8.5)]*.

Canagliflozin

Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis *[see Adverse Reactions (6.1) and Use in Specific Populations (8.5)]*.

Metformin

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the

change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of canagliflozin and metformin after administration of INVOKAMET in pediatric patients have not been performed.

Drug-Drug Interactions

INVOKAMET

Pharmacokinetic drug interaction studies with INVOKAMET have not been performed; however, such studies have been conducted with the individual components canagliflozin and metformin hydrochloride.

Co-administration of multiple doses of canagliflozin (300 mg) and metformin (2,000 mg) given once daily did not meaningfully alter the pharmacokinetics of either canagliflozin or metformin in healthy subjects.

Canagliflozin

In Vitro Assessment of Drug 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. Canagliflozin is a weak inhibitor of P-gp.

Canagliflozin is also a substrate of drug transporters P-glycoprotein (P-gp) and MRP2.

In Vivo Assessment of Drug Interactions

Table 7: Effect of Co−Administered Drugs on Systemic Exposures of Canagliflozin

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Canagliflozin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0**	
			AUC[†] (90% CI)	**C_{max} (90% CI)**
***See Drug Interactions (7.2)* for the clinical relevance of the following:**				
Rifampin	600 mg QD for 8 days	300 mg	0.49 (0.44; 0.54)	0.72 (0.61; 0.84)
No dose adjustments of canagliflozin required for the following:				
Cyclosporine	400 mg	300 mg QD for 8 days	1.23 (1.19; 1.27)	1.01 (0.91; 1.11)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg	200 mg QD for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)

	levonorgestrel			
Hydrochlorothiazide	25 mg QD for 35 days	300 mg QD for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
Metformin	2,000 mg	300 mg QD for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)
Probenecid	500 mg BID for 3 days	300 mg QD for 17 days	1.21 (1.16; 1.25)	1.13 (1.00; 1.28)

* Single dose unless otherwise noted

† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses

QD = once daily; BID = twice daily

Table 8: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Canagliflozin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0**		
				AUC† (90% CI)	**C_{max} (90% CI)**
***See Drug Interactions (7.2)* for the clinical relevance of the following:**					
Digoxin	0.5 mg QD first day followed by 0.25 mg QD for 6 days	300 mg QD for 7 days	digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)
No dose adjustments of co-administered drug required for the following:					
Acetaminophen	1,000 mg	300 mg BID for 25 days	acetaminophen	1.06‡ (0.98; 1.14)	1.00 (0.92; 1.09)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	ethinyl estradiol	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 QD 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)
Hydrochlorothiazide	25 mg QD for 35 days	300 mg QD for 7 days	Hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2,000 mg	300 mg QD for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Simvastatin	40 mg	300 mg QD 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 QD 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	1.05

				(0.98; 1.03)	(0.99; 1.12)

* Single dose unless otherwise noted
† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
‡ AUC_{0-12h}
QD = once daily; BID = twice daily; INR = International Normalized Ratio

Metformin

Table 9: Effect of Co−Administered Drugs on Plasma Metformin Systemic Exposures

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Metformin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.00**	
			AUC†	**C_{max}**
No dose adjustments required for the following:				
Glyburide	5 mg	500 mg‡	0.98§	0.99§
Furosemide	40 mg	850 mg	1.09§	1.22§
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05§	1.07§
Drugs that are eliminated by renal tubular secretion increase the accumulation of metformin *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Warnings and Precautions (5) and Drug Interactions (7)]*				
Topiramate¶	100 mg	500 mg	1.25#	1.18

* Single dose unless otherwise noted
† AUC = $AUC_{0-\infty}$
‡ Metformin hydrochloride extended-release tablets 500 mg
§ Ratio of arithmetic means
¶ Healthy volunteer study at steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours for 7 days. Study conducted to assess pharmacokinetics only
# Steady state AUC_{0-12h}.

Table 10: Effect of Metformin on Co−Administered Drug Systemic Exposures

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Metformin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.00**	
			AUC†	**C_{max}**
No dose adjustments required for the following:				
Glyburide	5 mg	500 mg‡	0.78§	0.63§
Furosemide	40 mg	850 mg	0.87§	0.69§
Nifedipine	10 mg	850 mg	1.10‡	1.08
Propranolol	40 mg	850 mg	1.01‡	0.94
Ibuprofen	400 mg	850 mg	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	0.95‡	1.01

Table 10: Effect of Metformin on Co−Administered Drug Systemic Exposures

* Single dose unless otherwise noted
† AUC = $AUC_{0-\infty}$
‡ $AUC_{0-24\ hr}$ reported
§ Ratio of arithmetic means, p-value of difference <0.05
¶ Ratio of arithmetic means.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

INVOKAMET

No animal studies have been conducted with the combined products in INVOKAMET to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on findings in studies with canagliflozin and metformin individually.

Canagliflozin

Carcinogenesis

Carcinogenicity was evaluated in 2-year studies conducted in CD1 mice and Sprague-Dawley rats. Canagliflozin did not increase the incidence of tumors in mice dosed at 10, 30, or 100 mg/kg (less than or equal to 14 times exposure from a 300 mg clinical dose).

Testicular Leydig cell tumors, considered secondary to increased luteinizing hormone (LH), increased significantly in male rats at all doses tested (10, 30, and 100 mg/kg). In a 12-week clinical study, LH did not increase in males treated with canagliflozin.

Renal tubular adenoma and carcinoma increased significantly in male and female rats dosed at 100 mg/kg, or approximately 12-times exposure from a 300 mg clinical dose. Also, adrenal pheochromocytoma increased significantly in males and numerically in females dosed at 100 mg/kg. Carbohydrate malabsorption associated with high doses of canagliflozin was considered a necessary proximal event in the emergence of renal and adrenal tumors in rats. Clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the recommended clinical dose of 300 mg.

Mutagenesis

Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was mutagenic in the *in vitro* mouse lymphoma 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.

Metformin

Carcinogenesis

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility

Canagliflozin had no effects on the ability of rats to mate and sire or maintain a litter up to the high dose of 100 mg/kg (approximately 14 times and 18 times the 300 mg clinical dose in males and females, respectively), although there were minor alterations in a number of reproductive parameters (decreased sperm velocity, increased number of abnormal sperm, slightly fewer corpora lutea, fewer implantation sites, and smaller litter sizes) at the highest dosage administered.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

14 CLINICAL STUDIES

Canagliflozin has been studied in combination with metformin alone, metformin and sulfonylurea, metformin and sitagliptin, metformin and a thiazolidinedione (i.e. pioglitazone), and metformin and insulin (with or without other anti-hyperglycemic agents). The efficacy of canagliflozin was compared to a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin), both as add-on combination therapy with metformin and sulfonylurea, and a sulfonylurea (glimepiride), both as add-on combination therapy with metformin.

There have been no clinical efficacy studies conducted with INVOKAMET; however, bioequivalence of INVOKAMET to canagliflozin and metformin co-administered as individual tablets was demonstrated in healthy subjects.

In patients with type 2 diabetes, treatment with canagliflozin and metformin produced clinically and statistically significant improvements in HbA_{1C} compared to placebo. Reductions in HbA_{1C}

were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

14.1 Canagliflozin as Initial Combination Therapy with Metformin

A total of 1186 patients with type 2 diabetes inadequately controlled with diet and exercise participated in a 26-week double-blind, active-controlled, parallel-group, 5-arm, multicenter study to evaluate the efficacy and safety of initial therapy with canagliflozin in combination with metformin XR. The median age was 56 years, 48% of patients were men, and the mean baseline eGFR was 87.6 mL/min/1.73 m^2. The median duration of diabetes was 1.6 years, and 72% of patients were treatment naïve. After completing a 2-week single-blind placebo run-in period, patients were randomly assigned for a double-blind treatment period of 26 weeks to 1 of 5 treatment groups (Table 11). The metformin XR dose was initiated at 500 mg/day for the first week of treatment and then increased to 1000 mg/day. Metformin XR or matching placebo was up-titrated every 2-3 weeks during the next 8 weeks of treatment to a maximum daily dose of 1500 to 2000 mg/day, as tolerated; about 90% of patients reached 2000 mg/day.

At the end of treatment, canagliflozin 100 mg and canagliflozin 300 mg in combination with metformin XR resulted in a statistically significant greater improvement in HbA_{1C} compared to their respective canagliflozin doses (100 mg and 300 mg) alone or metformin XR alone.

Table 11: Results from 26-Week Active-Controlled Clinical Study of Canagliflozin Alone or Canagliflozin as Initial Combination Therapy with Metformin*

Efficacy Parameter	**Metformin XR (N=237)**	**Canagliflozin 100 mg (N=237)**	**Canagliflozin 300 mg (N=238)**	**Canagliflozin 100 mg + Metformin XR (N=237)**	**Canagliflozin 300 mg + Metformin XR (N=237)**
HbA_{1C} (%)					
Baseline (mean)	8.81	8.78	8.77	8.83	8.90
Change from baseline (adjusted mean)¶	-1.30	-1.37	-1.42	-1.77	-1.78
Difference from canagliflozin 100 mg (adjusted mean) (95% CI) †				-0.40‡ (-0.59, -0.21)	
Difference from canagliflozin 300 mg (adjusted mean) (95% CI) †					-0.36‡ (-0.56, -0.17)
Difference from metformin XR (adjusted mean) (95% CI) †				-0.46‡ (-0.66, -0.27)	-0.48‡ (-0.67, -0.28)
Percent of patients achieving HbA_{1C} < 7%	38	34	39	47§§	51§§

* Intent-to-treat population
† Least squares mean adjusted for covariates including baseline value and stratification factor
‡ Adjusted p=0.001
§§ Adjusted p<0.05
¶ There were 121 patients without week 26 efficacy data. Analyses addressing missing data gave consistent results with the results provided in

this table.

14.2 Canagliflozin as Add-on Combination Therapy with Metformin

A total of 1284 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 26-week, double-blind, placebo- and active-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin. The mean age was 55 years, 47% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the required metformin dose (N=1009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin dose or patients on metformin in combination with another antihyperglycemic agent (N=275) were switched to metformin monotherapy (at doses described above) for at least 8 weeks before entering the 2-week, single-blind, placebo run-in. After the placebo run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo, administered once daily as add-on therapy to metformin.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo when added to metformin. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin (see Table 12). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -5.4 mmHg and -6.6 mmHg with canagliflozin 100 mg and 300 mg, respectively.

Table 12: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin[*]

Efficacy Parameter	Placebo + Metformin (N=183)	Canagliflozin 100 mg + Metformin (N=368)	Canagliflozin 300 mg + Metformin (N=367)
HbA_{1C} (%)			
Baseline (mean)	7.96	7.94	7.95
Change from baseline (adjusted mean)	-0.17	-0.79	-0.94
Difference from placebo (adjusted mean) (95% CI)[†]		-0.62[‡] (-0.76, -0.48)	-0.77[‡] (-0.91, -0.64)
Percent of patients achieving HbA_{1C} < 7%	30	46[‡]	58[‡]
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	173
Change from baseline (adjusted mean)	2	-27	-38
Difference from placebo (adjusted mean) (95% CI)[†]		-30[‡] (-36, -24)	-40[‡] (-46, -34)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	249	258	262
Change from baseline (adjusted mean)	-10	-48	-57
Difference from placebo (adjusted mean) (95% CI)[†]		-38[‡] (-49, -27)	-47[‡] (-58, -36)

Table 12: Results from 26-Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin*

Efficacy Parameter	Placebo + Metformin (N=183)	Canagliflozin 100 mg + Metformin (N=368)	Canagliflozin 300 mg + Metformin (N=367)
Body Weight			
Baseline (mean) in kg	86.7	88.7	85.4
% change from baseline (adjusted mean)	-1.2	-3.7	-4.2
Difference from placebo (adjusted mean) (95% CI)†		-2.5‡ (-3.1, -1.9)	-2.9‡ (-3.5, -2.3)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

14.3 Canagliflozin Compared to Glimepiride, Both as Add-on Combination Therapy with Metformin

A total of 1450 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) participated in a 52-week, double-blind, active-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin.

The mean age was 56 years, 52% of patients were men, and the mean baseline eGFR was 90 mL/min/1.73 m^2. Patients tolerating maximally required metformin dose (N=928) were randomized after completing a 2-week, single-blind, placebo run-in period. Other patients (N=522) were switched to metformin monotherapy (at doses described above) for at least 10 weeks, then completed a 2-week single-blind run-in period. After the 2-week run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride (titration allowed throughout the 52-week study to 6 or 8 mg), administered once daily as add-on therapy to metformin.

As shown in Table 13 and Figure 1, at the end of treatment, canagliflozin 100 mg provided similar reductions in HbA_{1C} from baseline compared to glimepiride when added to metformin therapy. Canagliflozin 300 mg provided a greater reduction from baseline in HbA_{1C} compared to glimepiride, and the relative treatment difference was -0.12% (95% CI: −0.22; −0.02). As shown in Table 13, treatment with canagliflozin 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

Table 13: Results from 52−Week Clinical Study Comparing Canagliflozin to Glimepiride in Combination with Metformin*

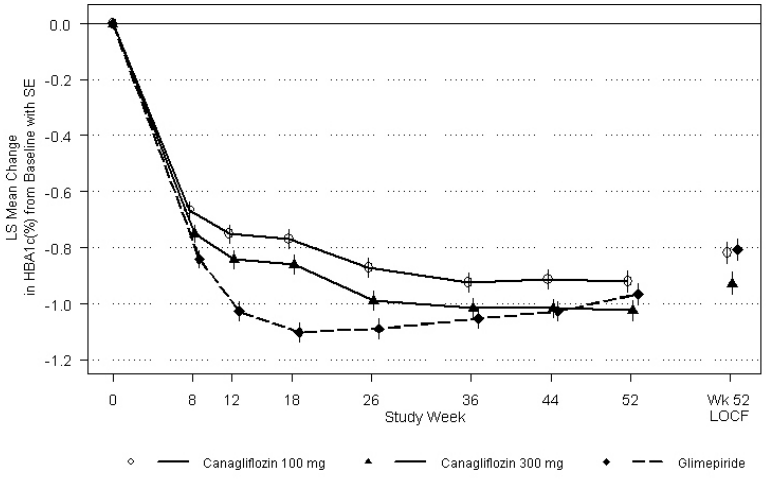
Efficacy Parameter	Canagliflozin 100 mg + Metformin (N=483)	Canagliflozin 300 mg + Metformin (N=485)	Glimepiride (titrated) + Metformin (N=482)
HbA_{1C} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81

Table 13: Results from 52−Week Clinical Study Comparing Canagliflozin to Glimepiride in Combination with Metformin*

Efficacy Parameter	Canagliflozin 100 mg + Metformin (N=483)	Canagliflozin 300 mg + Metformin (N=485)	Glimepiride (titrated) + Metformin (N=482)
Difference from glimepiride (adjusted mean) (95% CI)†	-0.01‡ (-0.11, 0.09)	-0.12‡ (-0.22, -0.02)	
Percent of patients achieving HbA_{1C} < 7%	54	60	56
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	165	164	166
Change from baseline (adjusted mean)	-24	-28	-18
Difference from glimepiride (adjusted mean) (95% CI)†	-6 (-10, -2)	-9 (-13, -5)	
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§ (-5.7, -4.7)	-5.7§ (-6.2, -5.1)	

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ Canagliflozin + metformin is considered non-inferior to glimepiride + metformin because the upper limit of this confidence interval is less than the pre-specified non-inferiority margin of < 0.3%.
§ p<0.001

Figure 1: Mean HbA_{1C} Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



14.4 Canagliflozin as Add-on Combination Therapy with Metformin and Sitagliptin

A total of 217 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 1,500 mg/day) and sitagliptin 100 mg/day (or equivalent fixed-dose combination) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and sitagliptin. The mean age was 57 years, 58% of patients were men, 73% of patients were Caucasian, 15%

were Asian, and 12% were Black or African-American. The mean baseline eGFR was 90 mL/min/1.73 m^2 and the mean baseline BMI was 32 kg/m^2. The mean duration of diabetes was 10 years. Eligible patients entered a 2-week, single-blind, placebo run-in period and were subsequently randomized to canagliflozin 100 mg or placebo, administered once daily as add-on to metformin and sitagliptin. Patients with a baseline eGFR of 70 mL/min/1.73 m^2 or greater who were tolerating canagliflozin 100 mg and who required additional glycemic control (fasting finger stick 100 mg/dL or greater at least twice within 2 weeks) were up-titrated to canagliflozin 300 mg. While up-titration occurred as early as Week 4, most (90%) patients randomized to canagliflozin were up-titrated to canagliflozin 300 mg by 6 to 8 weeks.

At the end of 26 weeks, canagliflozin once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$) compared to placebo when added to metformin and sitagliptin.

Table 14: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sitagliptin

Efficacy Parameter	**Placebo + Metformin and Sitagliptin (N=108*)**	**Canagliflozin + Metformin and Sitagliptin (N=109*)**
HbA_{1C} (%)		
Baseline (mean)	8.40	8.50
Change from baseline (adjusted mean)	-0.03	-0.83
Difference from placebo (adjusted mean) (95% CI)[†§]		-0.81[#] (-1.11; -0.51)
Percent of patients achieving HbA_{1C} < 7%[‡]	9	28
Fasting Plasma Glucose (mg/dL)[¶]		
Baseline (mean)	180	185
Change from baseline (adjusted mean)	-3	-28
Difference from placebo (adjusted mean) (95% CI)		-25[#] (-39; -11)

* To preserve the integrity of randomization, all randomized patients were included in the analysis. The patient who was randomized once to each arm was analyzed on canagliflozin.

† Early treatment discontinuation before week 26, occurred in 11.0% and 24.1% of canagliflozin and placebo patients, respectively.

‡ Patients without week 26 efficacy data were considered as non-responders when estimating the proportion achieving HbA_{1c} < 7%.

§ Estimated using a multiple imputation method modeling a "wash-out" of the treatment effect for patients having missing data who discontinued treatment. Missing data was imputed only at week 26 and analyzed using ANCOVA.

¶ Estimated using a multiple imputation method modeling a "wash-out" of the treatment effect for patients having missing data who discontinued treatment. A mixed model for repeated measures was used to analyze the imputed data.

# $p<0.001$

14.5 Canagliflozin as Add-on Combination Therapy with Metformin and Sulfonylurea

A total of 469 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (maximal or near-maximal effective dose) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and sulfonylurea. The mean age was 57 years, 51% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the protocol-specified doses of metformin and sulfonylurea (N=372) entered a 2-week, single-blind, placebo run-in period. Other patients (N=97) were required to be on a stable protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo administered once daily as add-on to metformin and sulfonylurea.

At the end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo when added to metformin and sulfonylurea. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7.0%, in a significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin and sulfonylurea (see Table 15).

Table 15: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	Placebo + Metformin and Sulfonylurea (N=156)	Canagliflozin 100 mg + Metformin and Sulfonylurea (N=157)	Canagliflozin 300 mg + Metformin and Sulfonylurea (N=156)
HbA_{1C} (%)			
Baseline (mean)	8.12	8.13	8.13
Change from baseline (adjusted mean)	-0.13	-0.85	-1.06
Difference from placebo (adjusted mean) (95% CI)†		-0.71‡ (-0.90, -0.52)	-0.92‡ (-1.11, -0.73)
Percent of patients achieving HbA_{1C} < 7%	18	43‡	57‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	170	173	168
Change from baseline (adjusted mean)	4	-18	-31
Difference from placebo (adjusted mean) (95% CI)†		-22‡ (-31, -13)	-35‡ (-44, -25)
Body Weight			
Baseline (mean) in kg	90.8	93.5	93.5
% change from baseline (adjusted mean)	-0.7	-2.1	-2.6
Difference from placebo (adjusted mean) (95% CI)†		-1.4‡ (-2.1, -0.7)	-2.0‡ (-2.7, -1.3)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

14.6 Canagliflozin Compared to Sitagliptin, Both as Add-on Combination Therapy with Metformin and Sulfonylurea

A total of 755 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (near-maximal or maximal effective dose) participated in a 52 week, double-blind, active-controlled study to compare the efficacy and safety of canagliflozin 300 mg versus sitagliptin 100 mg in combination with metformin and sulfonylurea. The mean age was 57 years, 56% of patients were men, and the mean baseline eGFR was 88 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin and sulfonylurea (N=716) entered a 2-week single-blind, placebo run-in period. Other patients (N=39) were required to be on a stable protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 300 mg or sitagliptin 100 mg as add-on to metformin and sulfonylurea.

As shown in Table 16 and Figure 2, at the end of treatment, canagliflozin 300 mg provided greater HbA_{1C} reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea ($p<0.05$). Canagliflozin 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg. A mean change in systolic blood pressure from baseline of -5.06 mmHg was observed with canagliflozin 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

Table 16: Results from 52−Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	**Canagliflozin 300 mg + Metformin and Sulfonylurea (N=377)**	**Sitagliptin 100 mg + Metformin and Sulfonylurea (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‡ (-0.50, -0.25)	
Percent of patients achieving HbA_{1C} < 7%	48	35
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	170	164
Change from baseline (adjusted mean)	-30	-6
Difference from sitagliptin (adjusted mean) (95% CI)†	-24 (-30, -18)	
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, -2.2)	

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy

† Least squares mean adjusted for baseline value and stratification factors

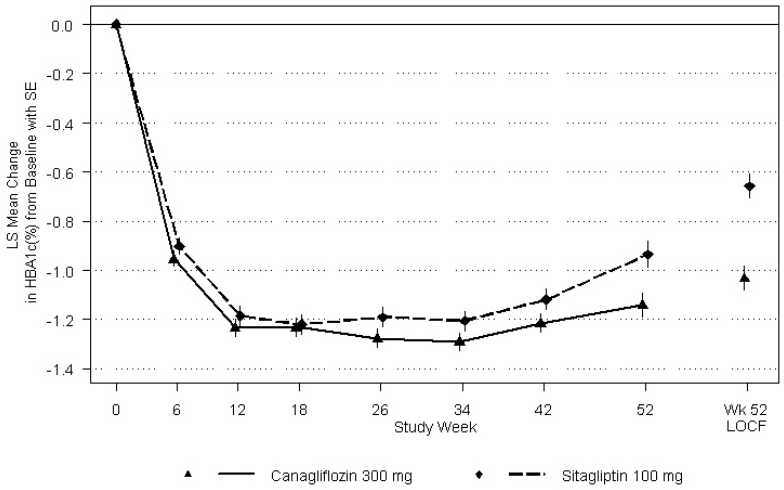
‡ Canagliflozin + metformin+ sulfonylurea is considered non-inferior to sitagliptin + metformin+ sulfonylurea because the upper limit of this confidence interval is less than the pre-specified non-inferiority margin of < 0.3%.

Table 16: Results from 52−Week Clinical Study Comparing Canagliflozin to Sitagliptin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	Canagliflozin 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)

§ p<0.001

Figure 2: Mean HbA_{1C} Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



14.7 Canagliflozin as Add-on Combination Therapy with Metformin and Pioglitazone

A total of 342 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 2,000 mg/day or at least 1,500 mg/day if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of canagliflozin in combination with metformin and pioglitazone. The mean age was 57 years, 63% of patients were men, and the mean baseline eGFR was 86 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin and pioglitazone (N=163) entered a 2-week, single-blind, placebo run-in period. Other patients (N=181) were required to be on stable protocol-specified doses of metformin and pioglitazone for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo, administered once daily as add-on to metformin and pioglitazone.

At the of end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo when added to metformin and pioglitazone. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when

added to metformin and pioglitazone (see Table 17). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -4.1 mmHg and -3.5 mmHg with canagliflozin 100 mg and 300 mg, respectively.

Table 17: Results from 26−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Pioglitazone*

Efficacy Parameter	Placebo + Metformin and Pioglitazone (N=115)	Canagliflozin 100 mg + Metformin and Pioglitazone (N=113)	Canagliflozin 300 mg + Metformin and Pioglitazone (N=114)
HbA_{1C} (%)			
Baseline (mean)	8.00	7.99	7.84
Change from baseline (adjusted mean)	-0.26	-0.89	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.81, -0.44)	-0.76‡ (-0.95, -0.58)
Percent of patients achieving HbA_{1C} < 7%	33	47‡	64‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	164
Change from baseline (adjusted mean)	3	-27	-33
Difference from placebo (adjusted mean) (95% CI)†		-29‡ (-37, -22)	-36‡ (-43, -28)
Body Weight			
Baseline (mean) in kg	94.0	94.2	94.4
% change from baseline (adjusted mean)	-0.1	-2.8	-3.8
Difference from placebo (adjusted mean) (95% CI)†		-2.7‡ (-3.6, -1.8)	-3.7‡ (-4.6, -2.8)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p<0.001$

14.8 Canagliflozin as Add-on Combination Therapy with Insulin (With or Without Other Anti-Hyperglycemic Agents, Including Metformin)

A total of 1718 patients with type 2 diabetes inadequately controlled on insulin greater than or equal to 30 units/day or insulin in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled substudy of a cardiovascular study to evaluate the efficacy and safety of canagliflozin in combination with insulin. Of these patients, a subgroup of 432 patients with inadequate glycemic control received canagliflozin or placebo plus metformin and ≥ 30 units/day of insulin over 18 weeks.

In this subgroup, the mean age was 61 years, 67% of patients were men, and the mean baseline eGFR was 81 mL/min/1.73 m^2. Patients on metformin in combination with basal, bolus, or basal/bolus insulin for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. Approximately 74% of these patients were on a background of metformin and basal/bolus insulin regimen. After the run-in period, patients were randomized to canagliflozin 100 mg, canagliflozin 300 mg, or placebo, administered once daily as add-on to metformin and insulin. The mean daily insulin dose at baseline was 93 units, which was similar across treatment groups.

At the of end of treatment, canagliflozin 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} ($p<0.001$ for both doses) compared to placebo when added to metformin and insulin. Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reductions in fasting plasma glucose (FPG), and in percent body weight reductions compared to placebo (see Table 18). Statistically significant ($p=0.023$ for the 100 mg and $p<0.001$ for the 300 mg dose) mean change from baseline in systolic blood pressure relative to placebo was –3.5 mmHg and –6 mmHg with canagliflozin 100 mg and 300 mg, respectively. Fewer patients on canagliflozin in combination with metformin and insulin required glycemic rescue therapy: 3.6% of patients receiving canagliflozin 100 mg, 2.7% of patients receiving canagliflozin 300 mg, and 6.2% of patients receiving placebo. An increased incidence of hypoglycemia was observed in this study, which is consistent with the expected increase of hypoglycemia when an agent not associated with hypoglycemia is added to insulin *[see Warnings and Precautions (5.8) and Adverse Reactions (6.1)]*.

Table 18: Results from 18−Week Placebo-Controlled Clinical Study of Canagliflozin in Combination with Metformin and Insulin ≥ 30 Units/Day*

Efficacy Parameter	**Placebo + Metformin + Insulin (N=145)**	**Canagliflozin 100 mg + Metformin + Insulin (N=139)**	**Canagliflozin 300 mg + Metformin + Insulin (N=148)**
HbA_{1C} (%)			
Baseline (mean)	8.15	8.20	8.22
Change from baseline (adjusted mean)	0.03	-0.64	-0.79
Difference from placebo (adjusted mean) (95% CI)†		-0.66‡ (-0.81, -0.51)	-0.82‡ (-0.96, -0.67)
Percent of patients achieving HbA_{1C} < 7%	9	19§	29‡
Fasting Plasma Glucose (mg/dL)			
Baseline	163	168	167
Change from baseline (adjusted mean)	1	-16	-24
Difference from placebo (adjusted mean) (97.5% CI)†		-16‡ (-28, -5)	-25‡ (-36, -14)
Body Weight			
Baseline (mean) in kg	102.3	99.7	101.1
% change from baseline (adjusted mean)	0.0	-1.7	-2.7
Difference from placebo (adjusted mean) (97.5% CI)†		-1.7‡ (-2.4, -1.0)	-2.7‡ (-3.4, -2.0)

* Intent-to-treat population using last observation in study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ $p\leq0.001$
§ $p\leq0.01$

16 HOW SUPPLIED/STORAGE AND HANDLING

INVOKAMET (canagliflozin and metformin hydrochloride) tablets are available in the strengths and packages listed below:

Canagliflozin 50 mg and metformin hydrochloride 500 mg tablets are immediate-release, capsule-shaped, white film-coated tablets with “CM” on one side and “155” on the other side.

- NDC 50458-540-60 Bottle of 60

Canagliflozin 50 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, beige film-coated tablets with “CM” on one side and “551” on the other side.

- NDC 50458-541-60 Bottle of 60

Canagliflozin 150 mg and metformin hydrochloride 500 mg tablets are immediate-release, capsule-shaped, yellow film-coated tablets with “CM” on one side and “215” on the other side.

- NDC 50458-542-60 Bottle of 60

Canagliflozin 150 mg and metformin hydrochloride 1,000 mg tablets are immediate-release, capsule-shaped, purple film-coated tablets with “CM” on one side and “611” on the other side.

- NDC 50458-543-60 Bottle of 60

Storage and Handling

Keep out of reach of children.

Store at 68-77°F (20-25°C); excursions permitted between 59°F and 86°F (15°C and 30°C) [see USP Controlled Room Temperature]. Store and dispense in the original container. Storage in a pill box or pill organizer is allowed for up to 30 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Medication Guide).

- Lactic Acidosis: Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in *Warnings and Precautions (5.1)*. Advise patients to discontinue INVOKAMET immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on INVOKAMET, gastrointestinal symptoms, which are common during initiation of metformin, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

- Instruct patients to keep INVOKAMET in the original bottle to protect from moisture. Advise patients that storage in a pill box or pill organizer is allowed for up to 30 days.

- Counsel patients against excessive alcohol intake while receiving INVOKAMET.

- Inform patients about importance of regular testing of renal function and hematological parameters while receiving INVOKAMET.

- Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

- Instruct patients to take INVOKAMET only as prescribed twice daily with food. If a dose is missed, advise patients not to take two doses of INVOKAMET at the same time.

- Lower Limb Amputation: Inform patients that INVOKAMET is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Boxed Warning and Warnings and Precautions (5.2)]*.

- Hypotension: Inform patients that symptomatic hypotension may occur with INVOKAMET and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.3)]*. Inform patients that dehydration may increase the risk for hypotension and to have adequate fluid intake.

- Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of canagliflozin. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKAMET and seek medical advice immediately *[see Warnings and Precautions (5.4)]*.

- Acute Kidney Injury: Inform patients that acute kidney injury has been reported during use of canagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting), or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue INVOKAMET use in those settings *[see Warnings and Precautions (5.5)]*.

- Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.7)]*.

- Genital Mycotic Infections in Females: Inform female patients that vaginal yeast infection (e.g., vulvovaginitis) may occur and provide them with information on the signs and symptoms of a vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.9)]*.

- Genital Mycotic Infections in Males: Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.9)]*.

- Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with canagliflozin. Advise patients to report immediately any signs or symptoms suggesting allergic reaction and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions (5.10)]*.

- Bone Fracture: Inform patients that bone fractures have been reported in patients taking canagliflozin. Provide them with information on factors that may contribute to fracture risk.

- Laboratory Tests: Inform patients that they will test positive for glucose in their urine while on INVOKAMET *[see Drug Interactions (7.2)]*.

- Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKAMET *[see Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

- Lactation: Advise women that breastfeeding is not recommended during treatment with INVOKAMET *[see Use in Specific Populations (8.2)]*.

- Inform females that treatment with INVOKAMET may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy *[see Use in Specific Populations (8.3)]*.

- Inform patients that the most common adverse reactions associated with canagliflozin are genital mycotic infection, urinary tract infection, and increased urination. Most common adverse reactions associated with metformin are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

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Titusville, NJ 08560

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Medication Guide
INVOKAMET® (in vok' a met)
(canagliflozin and metformin hydrochloride)
Tablets

What is the most important information I should know about INVOKAMET?
INVOKAMET can cause serious side effects, including:

- **Lactic Acidosis.** Metformin, one of the medicines in INVOKAMET, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

  Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:
  - you feel cold in your hands or feet
  - you feel very weak or tired
  - you have trouble breathing
  - you have stomach pains, nausea, or vomiting
  - you have a slow or irregular heartbeat
  - you have unusual (not normal) muscle pain
  - you have unusual sleepiness or sleep longer than usual
  - you feel dizzy or lightheaded

Most people who have had lactic acidosis had other conditions that, in combination with metformin use, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with INVOKAMET if you:
- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
- have liver problems.
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking.
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery.
- have a heart attack, severe infection, or stroke.

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor will decide to stop your INVOKAMET for a while if you have any of these things.

- **Amputations. INVOKANA may increase your risk of lower limb amputations. Amputations mainly involve removal of the toe or part of the foot, however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body.**

  You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - have heart disease or are at risk for heart disease
  - have had blocked or narrowed blood vessels, usually in your leg
  - have damage to the nerves (neuropathy) in your leg
  - have had diabetic foot ulcers or sores

Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot.
Your doctor may decide to stop your INVOKAMET for a while if you have any of these signs or symptoms.
Talk to your doctor about proper foot care.
INVOKAMET can have other serious side effects. See **"What are the possible side effects of INVOKAMET?"**

What is INVOKAMET?
- INVOKAMET contains 2 prescription medicines called canagliflozin (INVOKANA) and metformin hydrochloride (GLUCOPHAGE). INVOKAMET can be used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes when treatment with both canagliflozin and metformin is appropriate.
- INVOKAMET is not for people with diabetic ketoacidosis (increased ketones in blood or urine).
- It is not known if INVOKAMET is safe and effective in children under 18 years of age.

Who should not take INVOKAMET?
Do not take INVOKAMET if you:
- have moderate to severe kidney problems or are on dialysis.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to canagliflozin, metformin, or any of the ingredients in INVOKAMET. See the end of this Medication Guide for a list of ingredients in INVOKAMET. Symptoms of allergic reaction to INVOKAMET may include:
  - rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, mouth, tongue, and throat that may cause difficulty in breathing or swallowing

What should I tell my doctor before taking INVOKAMET?

Before you take INVOKAMET, tell your doctor if you:

- have a history of amputation.
- have heart disease or are at risk for heart disease.
- have had blocked or narrowed blood vessels, usually in your leg.
- have damage to the nerves (neuropathy) in your leg.
- have had diabetic foot ulcers or sores.
- have moderate to severe kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems with urination.
- are on a low sodium (salt) diet. Your doctor may change your diet or your dose of INVOKAMET.
- have ever had an allergic reaction to INVOKAMET.
- are going to get an injection of dye or contrast agents for an x-ray procedure. INVOKAMET may need to be stopped for a short time. Talk to your doctor about when you should stop INVOKAMET and when you should start INVOKAMET again. See "**What is the most important information I should know about INVOKAMET?**"
- have heart problems, including congestive heart failure.
- are going to have surgery.
- are eating less due to illness, surgery, or a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short-term ("binge" drinking).
- have other medical conditions.
- are pregnant or plan to become pregnant. INVOKAMET may harm your unborn baby. If you become pregnant while taking INVOKAMET, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are a premenopausal woman (before the “change of life”), who does not have periods regularly or at all. INVOKAMET may increase your chance of becoming pregnant. Talk to your doctor about birth control choices while taking INVOKAMET, if you are not planning to become pregnant. Tell your doctor right away if you become pregnant while taking INVOKAMET.
- are breastfeeding or plan to breastfeed. INVOKAMET may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking INVOKAMET. Do not breastfeed while taking INVOKAMET.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

INVOKAMET may affect the way other medicines work and other medicines may affect how INVOKAMET works. Especially tell your doctor if you take:

- diuretics (water pills)
- phenytoin or phenobarbital (used to control seizures)
- digoxin (Lanoxin®)* (used to treat heart problems)
- rifampin (used to treat or prevent tuberculosis)
- ritonavir (Norvir®, Kaletra®)* (used to treat HIV infection)

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take INVOKAMET?

- Take INVOKAMET by mouth 2 times each day with meals exactly as your doctor tells you to take it. Taking INVOKAMET with meals may lower your chance of having an upset stomach.
- Your doctor will tell you how much INVOKAMET to take and when to take it. Your doctor may change your dose if needed.
- Your doctor may tell you to take INVOKAMET along with other diabetes medicines. Low blood sugar can happen more often when INVOKAMET is taken with certain other diabetes medicines. See “**What are the possible side effects of INVOKAMET?**”
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take 2 doses of INVOKAMET at the same time. Talk to your doctor if you have questions about a missed dose.
- If you take too much INVOKAMET, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery,

the amount of diabetes medicine you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.

- Stay on your prescribed diet and exercise program while taking INVOKAMET.
- Check your blood sugar as your doctor tells you to.
- INVOKAMET will cause your urine to test positive for glucose.
- Your doctor may do certain blood tests before you start INVOKAMET and during treatment as needed. Your doctor may change your dose of INVOKAMET based on the results of your blood tests.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A_{1C}.

What should I avoid while taking INVOKAMET?

- Avoid drinking alcohol very often, or drinking a lot of alcohol in a short period of time ("binge" drinking). It can increase your chances of getting serious side effects.

What are the possible side effects of INVOKAMET?

INVOKAMET may cause serious side effects including:

- See "What is the most important information I should know about INVOKAMET?"
- **dehydration**. INVOKAMET can cause some people to become dehydrated (the loss of too much body water). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).

You may be at higher risk of dehydration if you:

- have low blood pressure
- take medicines to lower your blood pressure, including diuretics (water pill)
- are on a low sodium (salt) diet
- have kidney problems
- are 65 years of age or older

Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

- **ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes**, during treatment with canagliflozin, one of the medicines in INVOKAMET. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with INVOKAMET, even if your blood sugar is less than 250 mg/dL. Stop taking INVOKAMET and call your doctor right away if you get any of the following symptoms:**
  - nausea
  - vomiting
  - stomach area (abdominal) pain
  - tiredness
  - trouble breathing

  If you get any of these symptoms during treatment with INVOKAMET, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- **kidney problems**. Sudden kidney injury has happened to people taking INVOKAMET. Talk to your doctor right away if you:
  - reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
  - you start to lose liquids from your body for example, from vomiting, diarrhea or being in the sun too long.
- a high amount of potassium in your blood.
- **serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking canagliflozin, one of the medicines in INVOKAMET. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people may also have a fever, back pain, nausea, or vomiting.
- **low blood sugar (hypoglycemia).** If you take INVOKAMET with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take INVOKAMET. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - confusion
  - dizziness
  - irritability
  - hunger
  - fast heartbeat
  - sweating
  - shaking or feeling jittery
- **vaginal yeast infection.** Women who take INVOKAMET may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:

- vaginal odor
- white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
- vaginal itching

- **yeast infection of the penis (balanitis or balanoposthitis).** Men who take INVOKAMET may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around the penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

- **serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking INVOKAMET and call your doctor right away or go to the nearest hospital emergency room. See "**Who should not take INVOKAMET?**". Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
- **broken bones (fractures).** Bone fractures have been seen in patients taking canagliflozin. Talk to your doctor about factors that may increase your risk of bone fracture.
- **low vitamin B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} blood levels before. Your doctor may do blood tests to check your vitamin B_{12} levels.

Other common side effects of INVOKAMET include:

- nausea and vomiting
- diarrhea
- weakness
- gas
- upset stomach
- indigestion
- headache
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of INVOKAMET. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Janssen Pharmaceuticals, Inc. at 1-800-526-7736.

How should I store INVOKAMET?

- Store INVOKAMET at room temperature between 68°F to 77°F (20°C to 25°C).
- Store in the original container to protect from moisture. Storage in a pill box or pill organizer is allowed for up to 30 days.

Keep INVOKAMET and all medicines out of the reach of children.

General information about the safe and effective use of INVOKAMET.

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use INVOKAMET for a condition for which it was not prescribed. Do not give INVOKAMET to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about INVOKAMET. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about INVOKAMET that is written for healthcare professionals.

For more information about INVOKAMET, call 1-800-526-7736 or visit our website at www.invokamet.com.

What are the ingredients of INVOKAMET?

Active ingredients: canagliflozin and metformin hydrochloride

Inactive ingredients: The tablet core contains croscarmellose sodium, hypromellose, magnesium stearate, and microcrystalline cellulose. The magnesium stearate is vegetable-sourced. In addition, the tablet coating contains Macrogol/PEG, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, iron oxide yellow (50 mg/1,000 mg and 150 mg/500 mg tablets only), iron oxide red (50 mg/1,000 mg, 150 mg/500 mg and 150 mg/1,000 mg tablets only), and iron oxide black (150 mg/1,000 mg tablets only).

Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560. Manufactured by: Janssen Ortho LLC, Gurabo, PR 00778. Licensed from Mitsubishi Tanabe Pharma Corporation.

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