HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVOKANA safely and effectively. See full prescribing information for INVOKANA.

INVOKANA® (canagliflozin) tablets, for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.6)	06/2026
Warnings and Precautions (5.4)	06/2026

----------INDICATIONS AND USAGE----------

INVOKANA is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus (1).
- To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).
- To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (1).

Limitations of Use:

- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus (1).
- Not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2 (1).

----------DOSAGE AND ADMINISTRATION----------

- Assess renal function before initiating and as clinically indicated. Assess volume status and correct volume depletion before initiating (2.1).
- The recommended starting dosage in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus is 100 mg orally once daily, taken before the first meal of the day to improve glycemic control. The dosage can be increased to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control (2.2).
- For all other indications in adults, the recommended dosage of INVOKANA is 100 mg orally once daily (2.2).
- Dosage adjustments for patients with renal impairment may be required (2.3).
- See full prescribing information for INVOKANA dosage modifications due to drug interactions (2.4).
- Withhold INVOKANA at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg, 300 mg (3)

----------CONTRAINDICATIONS----------

- Serious hypersensitivity reaction to INVOKANA (4)

INVOKANA® (canagliflozin) tablets

----------WARNINGS AND PRECAUTIONS----------

- Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis: Consider ketone monitoring in patients at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue INVOKANA if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting (5.1).
- Lower Limb Amputation: Monitor patients for infections or ulcers of lower limb and institute appropriate treatment (5.2).
- Volume Depletion: May result in acute kidney injury. Before initiating INVOKANA, assess and correct volume status in patients with renal impairment, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy (5.3).
- Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections: Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated. Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis and if suspected, discontinue INVOKANA, and promptly institute appropriate medical and/or surgical intervention (5.4).
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKANA (5.5).
- Hypersensitivity Reactions: Discontinue INVOKANA and monitor until signs and symptoms resolve (5.6).
- Bone Fracture: Consider factors that contribute to fracture risk before initiating INVOKANA (5.7).

----------ADVERSE REACTIONS----------

Most common adverse reactions (5% or greater incidence): female genital mycotic infections, urinary tract infection, and increased urination (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

See full prescribing information for information on drug interactions and interference of INVOKANA with laboratory tests (7).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1).
- Lactation: Not recommended when breastfeeding (8.2).
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume (8.5).
- Renal Impairment: Higher incidence of adverse reactions related to hypotension and renal function (8.6).
- Hepatic Impairment: Not recommended in patients with severe hepatic impairment (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Prior to Initiation of INVOKANA
2.2 Recommended Dosage and Administration
2.3 Recommended Dosage in Adults and Pediatric Patients Aged 10 Years and Older with Renal Impairment
2.4 Concomitant Use with UDP-Glucuronosyl transferase (UGT) Enzyme Inducers
2.5 Temporary Interruption for Surgery
2.6 Recommendations Regarding Missed Dose
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis
5.2 Lower Limb Amputation
5.3 Volume Depletion
5.4 Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections
5.5 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
5.6 Hypersensitivity Reactions
5.7 Bone Fracture
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus
14.2 Glycemic Control Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus
14.3 Cardiovascular Outcomes in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease
14.4 Renal and Cardiovascular Outcomes in Adults with Diabetic Nephropathy and Albuminuria
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INVOKANA (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

Limitations of Use

INVOKANA is not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.

INVOKANA is not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is likely to be ineffective in this setting based upon its mechanism of action.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of INVOKANA

Assess renal function before initiating INVOKANA and as clinically indicated *[see Dosage and Administration (2.3) and Warnings and Precautions (5.3)]*.

In patients with volume depletion, correct this condition before initiating INVOKANA *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage and Administration

Recommended Dosage for Glycemic Control in Adults and Pediatric Patients Aged 10 Years and Older

- The recommended starting dosage of INVOKANA is 100 mg orally once daily to improve glycemic control, taken before the first meal of the day.
- For additional glycemic control, the dosage of INVOKANA may be increased to the maximum recommended dosage of 300 mg once daily.

Recommended Dosage for Other Indications in Adults

The recommended dosage of INVOKANA is 100 mg orally once daily for the following indications in adults:

- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

2.3 Recommended Dosage in Adults and Pediatric Patients Aged 10 Years and Older with Renal Impairment

Table 1 provides dosage recommendations for adults and pediatric patients aged 10 years and older with renal impairment, based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage in Adults and Pediatric Patients Aged 10 Years and Older with Renal Impairment

Estimated Glomerular Filtration Rate [eGFR (mL/min/1.73 m^2)]	Recommended Dosage
eGFR 30 to less than 60	The maximum recommended dosage is 100 mg orally once daily.
eGFR less than 30	• Initiation is not recommended • Adult patients taking INVOKANA with albuminuria greater than 300 mg/day may continue INVOKANA 100 mg once daily to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure *[see Indications and Usage (1) and Use in Specific Populations (8.6)]*.

2.4 Concomitant Use with UDP-Glucuronosyl transferase (UGT) Enzyme Inducers

When co-administering INVOKANA with an inducer of UGT (e.g., rifampin, phenytoin, phenobarbital, ritonavir), increase the dosage of INVOKANA based on renal function *[see Drug Interactions (7)]:*

- In patients with eGFR 60 mL/min/1.73 m^2 or greater, increase the dosage to 200 mg orally once daily in patients currently tolerating INVOKANA 100 mg once daily. The maximum recommended dosage of INVOKANA is 300 mg once daily.
- In patients with eGFR less than 60 mL/min/1.73 m^2, increase to a maximum recommended dosage of 200 mg orally once daily in patients currently tolerating INVOKANA 100 mg once daily.

2.5 Temporary Interruption for Surgery

Withhold INVOKANA at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. Resume INVOKANA when the patient is clinically stable and has resumed oral intake *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*.

INVOKANA® (canagliflozin) tablets

2.6 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible.
- Advise patients not to double up the next dose.

3 DOSAGE FORMS AND STRENGTHS

- INVOKANA 100 mg tablets are yellow, capsule-shaped, tablets with "CFZ" on one side and "100" on the other side.
- INVOKANA 300 mg tablets are white, capsule-shaped, tablets with "CFZ" on one side and "300" on the other side.

4 CONTRAINDICATIONS

INVOKANA is contraindicated in patients with a serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1, 6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, INVOKANA significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose transporter 2 (SGLT2) inhibitors compared to patients who received placebo; this risk may be greater with higher doses of INVOKANA. INVOKANA is not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including INVOKANA.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing INVOKANA *[see Clinical Pharmacology (12.2)];* however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue INVOKANA, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting INVOKANA.

Withhold INVOKANA, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume INVOKANA when the patient is clinically stable and has resumed oral intake *[see Dosage and Administration (2.5)]*.

Educate all patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA and seek medical attention immediately if signs and symptoms occur.

5.2 Lower Limb Amputation

An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1,000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1,000 patient-years), two randomized, placebo-controlled trials evaluating adult patients with type 2 diabetes mellitus who had either established cardiovascular disease or were at risk for cardiovascular disease *[see Adverse Reactions (6.1) and Clinical Studies (14.3)]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

5.3 Volume Depletion

INVOKANA can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions (6.1)]*. There have been post-marketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.

5.4 Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

INVOKANA increases urinary glucose excretion *[see Clinical Pharmacology (12.2)]* and increases the risk of genitourinary infections including urinary tract infections and genital mycotic infections in both male and female patients *[see Adverse Reactions (6.1)]*.

Serious genitourinary infections, including urosepsis, pyelonephritis, and necrotizing fasciitis of the perineum (Fournier's gangrene, a rare life-threatening infection requiring urgent surgical intervention), have occurred in patients receiving SGLT2 inhibitors, including INVOKANA *[see Adverse Reactions (6.2)]*. Cases have required hospitalization. In patients with Fournier's gangrene, serious outcomes have included multiple surgeries and death.

Patients with a history of genitourinary infections are more likely to develop genitourinary infections when using INVOKANA. Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated.

Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis. If suspected, discontinue INVOKANA and promptly institute appropriate medical and/or surgical intervention.

5.5 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]*. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve [*see Contraindications (4) and Adverse Reactions (6.1, 6.2)]*.

5.7 Bone Fracture

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in adult patients using INVOKANA in the CANVAS trial *[see Clinical Studies (14.3)]*. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Diabetic Ketoacidosis in Patients with Type 1 Diabetes and Other Ketoacidosis *[see Warnings and Precautions (5.1)]*
- Lower Limb Amputation *[see Warnings and Precautions (5.2)]*
- Volume Depletion *[see Warnings and Precautions (5.3)]*
- Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Bone Fracture *[see Warnings and Precautions (5.7)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

INVOKANA has been evaluated in clinical trials in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. Additionally, INVOKANA has been studied in clinical trials in adult patients with type 2 diabetes mellitus who also have heart failure or chronic kidney disease. The overall safety profile of INVOKANA was consistent across the studied indications.

Clinical Trials in Adult Patients with Type 2 Diabetes Mellitus

Pool of Placebo-Controlled Trials for Glycemic Control

The data in Table 2 are derived from four 26-week placebo-controlled trials where INVOKANA was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,667 adult patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were White, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 2 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

INVOKANA® (canagliflozin) tablets

Table 2: Adverse Reactions from Pool of Four 26–Week Placebo-Controlled Trials Reported in ≥ 2% of INVOKANA-Treated Adult Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin HCl, metformin HCl and sulfonylurea, or metformin HCl and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Trial weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Placebo-Controlled Trial in Diabetic Nephropathy

The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in CREDENCE, a trial in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day *[see Clinical Studies (14.4)]*. These data reflect exposure of 2,201 adult patients to INVOKANA and a mean duration of exposure to INVOKANA of 137 weeks.

- The rate of lower limb amputations associated with the use of INVOKANA 100 mg relative to placebo was 12.3 vs 11.2 events per 1,000 patient-years, respectively, with 2.6 years mean duration of follow-up.
- The incidence of hypotension was 2.8% and 1.5% on INVOKANA 100 mg and placebo, respectively.

Pool of Placebo- and Active-Controlled Trials for Glycemic Control and Cardiovascular Outcomes in Adult Patients

The occurrence of adverse reactions for INVOKANA was evaluated in adult patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials, CANVAS and CANVAS-R.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 adult patients to INVOKANA) were consistent with those listed in Table 2. Percentages were weighted by trials. Trial weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively) and loss of strength or energy (i.e., asthenia) (0.6%, 0.7%, and 1.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of adult patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Lower Limb Amputation

An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1,000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1,000 patient-years), two randomized, placebo-

controlled trials evaluating adult patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.3)]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 3 and 4, respectively.

Table 3: Amputations in the CANVAS Trial in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

	Placebo N=1,441	INVOKANA 100 mg N=1,445	INVOKANA 300 mg N=1,441	INVOKANA (Pooled) N=2,886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1,000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 4: Amputations in the CANVAS-R Trial in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

	Placebo N=2,903	INVOKANA 100 mg (with up-titration to 300 mg) N=2,904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1,000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Renal Cell Carcinoma

In the CANVAS trial in adults (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.3)]*, the incidence of renal cell carcinoma was 0.15% (2/1,331) and 0.29% (8/2,716) for placebo and INVOKANA, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to INVOKANA could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions

INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in adult patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions in these trials were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 5) *[see Use in Specific Populations (8.5 and 8.6)]*.

Table 5: Proportion of Adult Patients with at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups

† Patients could have more than 1 of the listed risk factors

Falls

In a pool of nine clinical trials in adults with mean duration of exposure to INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Genital Mycotic Infections

In the pool of four placebo-controlled clinical trials in adults for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

INVOKANA® (canagliflozin) tablets

Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively.

In the pool of four placebo-controlled clinical trials in adults, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo) and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively.

In the pooled analysis of 8 randomized trials in adults evaluating glycemic control, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis.

Hypoglycemia

In all glycemic control trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials of glycemic control in adults *[see Clinical Studies (14.1)]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 6).

Table 6: Incidence of Hypoglycemia* in Randomized Clinical Trials of Glycemic Control in Adults

Monotherapy (26 weeks)	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin HCl (26 weeks)	**Placebo + Metformin HCl (N=183)**	**INVOKANA 100 mg + Metformin HCl (N=368)**	**INVOKANA 300 mg + Metformin HCl (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin HCl (52 weeks)	**Glimepiride + Metformin HCl (N=482)**	**INVOKANA 100 mg + Metformin HCl (N=483)**	**INVOKANA 300 mg + Metformin HCl (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin HCl + Sulfonylurea (26 weeks)	**Placebo + Metformin HCl + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin HCl + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin HCl + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin HCl + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin HCl + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin HCl + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin HCl + Pioglitazone (26 weeks)	**Placebo + Metformin HCl + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin HCl + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin HCl + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture

In the CANVAS trial in adults *[see Clinical Studies (14.3)]*, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through the end of the trial. Fractures were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities.

Laboratory and Imaging Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of INVOKANA causes an increase in serum creatinine and decrease in estimated GFR. In adult patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dL, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Clinical Pharmacology (12.1)]*. The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA.

Increases in Serum Potassium

In a pooled population of adult patients (N=723) in glycemic control trials with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Use in Specific Populations (8.6)]*.

In CREDENCE, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no increase in absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed in adults treated with INVOKANA 100 mg relative to placebo.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C)

In the pool of four glycemic control placebo-controlled trials in adults, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups.

Dose-related increases in non-HDL-C with INVOKANA were observed in adults. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin

In the pool of four placebo-controlled trials of glycemic control in adults, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.1)]*. At 2 years, adult patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

Clinical Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

INVOKANA was administered to 84 pediatric patients in a double-blind, placebo-controlled trial of 171 pediatric patients aged 10 to 17 years with a mean exposure to INVOKANA of 48.3 weeks *[see Clinical Studies (14.2)]*. At baseline, background therapies included metformin monotherapy (46%), metformin and insulin (29%), diet and exercise only (14%), and insulin monotherapy (11%). Approximately 42% were Asian, 42% were White, 11% were Black or African American, 5% were American Indian/Alaska Native, and 36% identified as Hispanic or Latino ethnicity. The mean baseline eGFR was 157.3 mL/min/1.73 m^2, and approximately 16% (24/151) of the trial population with measurements had microalbuminuria or macroalbuminuria. The safety profile of pediatric patients treated with INVOKANA was similar to that observed in adults with type 2 diabetes mellitus.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of INVOKANA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

INVOKANA® (canagliflozin) tablets

Metabolism and Nutrition

Ketoacidosis

Renal and Urinary

Acute Kidney Injury

Immune System

Anaphylaxis

Skin and Subcutaneous Tissue

Angioedema

Infections

Urosepsis and Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's gangrene)

7 DRUG INTERACTIONS

Table 7: Clinically Significant Drug Interactions with INVOKANA

UGT Enzyme Inducers	
Clinical Impact:	UGT enzyme inducers decrease canagliflozin exposure which may reduce the effectiveness of INVOKANA.
Intervention:	For patients with eGFR 60 mL/min/1.73 m^2 or greater, if an inducer of UGTs is administered with INVOKANA, increase the dosage to 200 mg daily in patients currently tolerating INVOKANA 100 mg daily. The total daily dosage may be increased to 300 mg daily in patients currently tolerating INVOKANA 200 mg daily who require additional glycemic control. For patients with eGFR less than 60 mL/min/1.73 m^2, if an inducer of UGTs is administered with INVOKANA, increase the dosage to 200 mg daily in patients currently tolerating INVOKANA 100 mg daily. Consider adding another antihyperglycemic agent in patients who require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.
Examples:	Rifampin, phenytoin, phenobarbital, ritonavir
Insulin or Insulin Secretagogues	
Clinical Impact:	The risk of hypoglycemia is increased when INVOKANA is used concomitantly with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention:	Concomitant use may require a lower dosage of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Digoxin	
Clinical Impact:	Canagliflozin increases digoxin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor patients taking INVOKANA with concomitant digoxin for a need to adjust the dosage of digoxin.
Lithium	
Clinical Impact:	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention:	Monitor serum lithium concentration more frequently during INVOKANA initiation and dosage changes.
Drug/Laboratory Test Interference	
Positive Urine Glucose Test	
Clinical Impact:	SGLT2 inhibitors increase urinary glucose excretion which will lead to positive urine glucose tests.
Intervention:	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact:	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention:	Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on juvenile animal data showing adverse renal effects, INVOKANA is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKANA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In juvenile animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data

Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. 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.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKANA is not recommended while breastfeeding.

Data

Animal Data

Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.4 Pediatric Use

The safety and effectiveness of INVOKANA as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older.

Use of INVOKANA for this indication is supported by evidence from a 52-week double-blind, placebo-controlled trial in 171 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus and in a pediatric pharmacokinetic study *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*. The safety profile of pediatric patients treated with INVOKANA was similar to that observed in adults with type 2 diabetes mellitus.

The safety and effectiveness of INVOKANA for glycemic control in patients with type 2 diabetes have not been established in pediatric patients under 10 years of age.

The safety and effectiveness of INVOKANA have not been established in pediatric patients to reduce the risk of:

- major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in patients with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

8.5 Geriatric Use

In 13 clinical trials of INVOKANA, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to INVOKANA *[see Clinical Studies (14.1)]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) and Adverse Reactions (6.1)]*. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

8.6 Renal Impairment

The efficacy and safety of INVOKANA for glycemic control were evaluated in a trial that included adult patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.1)]*. These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of the trial. Patients with renal impairment using INVOKANA for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury *[see Warnings and Precautions (5.3)]*.

INVOKANA® (canagliflozin) tablets

Efficacy and safety trials with INVOKANA did not enroll adult patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

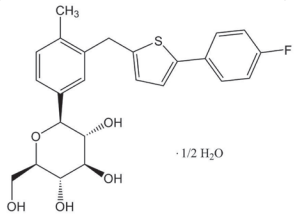
No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of an overdose, contact the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

11 DESCRIPTION

INVOKANA® (canagliflozin) contains canagliflozin, an inhibitor of SGLT2, the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. Canagliflozin, the active ingredient of INVOKANA, is chemically known as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate and its molecular formula and weight are $C_{24}H_{25}FO_5S \cdot 1/2\ H_2O$ and 453.53, respectively. The structural formula for canagliflozin is:



Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9.

INVOKANA is supplied as film-coated tablets for oral administration, containing 102 and 306 mg of canagliflozin in each tablet strength, corresponding to 100 mg and 300 mg of canagliflozin (anhydrous), respectively.

Inactive ingredients of the core tablet are croscarmellose sodium (E468), hydroxypropyl cellulose (E463), lactose anhydrous, magnesium stearate (E572), and microcrystalline cellulose (E460[i]). The magnesium stearate is vegetable-sourced. The tablets are finished with a commercially available film-coating consisting of the following excipients: iron oxide yellow (E172) (100 mg tablet only), macrogol/PEG3350 (E1521), polyvinyl alcohol (E1203) (partially hydrolyzed), talc (E553b), and titanium dioxide (E171).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SGLT2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an 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).

Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption. This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure.

12.2 Pharmacodynamics

Following single and multiple oral doses of canagliflozin in adult patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in urinary glucose excretion were observed. From a starting RT_G value of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RT_G throughout the 24-hour period. Data from single oral doses of canagliflozin in healthy volunteers indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for doses up to 300 mg once daily. Maximal suppression of mean RT_G over the 24-hour period was seen with the 300 mg daily dose to approximately 70 to 90 mg/dL in patients with type 2 diabetes in Phase 1 trials. The reductions in RT_G led to increases in mean UGE of approximately 100 g/day in patients with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin. 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 urinary glucose excretion were observed over the dosing period. In this trial, plasma glucose declined in a dose-dependent fashion within the first day of dosing. In single-dose trials in healthy and type 2 diabetic patients, treatment with canagliflozin 300 mg before a mixed-meal delayed intestinal glucose absorption and reduced postprandial glucose.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, active-comparator, 4-way crossover trial, 60 healthy adult 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.

12.3 Pharmacokinetics

The pharmacokinetics of canagliflozin is similar in healthy subjects and patients with type 2 diabetes. Following single-dose oral administration of 100 mg and 300 mg of INVOKANA, peak plasma concentrations (median T_{max}) of canagliflozin occurs within 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, INVOKANA 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 INVOKANA be taken before the first meal of the day *[see Dosage and Administration (2.2)]*.

Distribution

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.

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 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.

Specific Populations

Pediatric Patients

The pharmacokinetics and pharmacodynamics of canagliflozin were investigated in pediatric patients aged 10 years and older with type 2 diabetes mellitus. Oral administration of canagliflozin at 100 mg and 300 mg resulted in exposures and responses consistent with those found in adult patients.

Patients with Renal Impairment

A single-dose, open-label trial evaluated the pharmacokinetics of canagliflozin 200 mg in adult 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 adult 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 ESKD (N=8) subjects and healthy subjects.

Increases in canagliflozin AUC of this magnitude are not considered clinically relevant. The glucose lowering pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Canagliflozin was negligibly removed by hemodialysis.

Patients with Hepatic Impairment

Relative to adult 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 adult patients with Child-Pugh class C (severe) hepatic impairment *[see Use in Specific Populations (8.7)]*.

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

Based on the population PK analysis with data collected from 1,526 adult 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)]*.

Drug Interaction Studies

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.

INVOKANA® (canagliflozin) tablets

In Vivo Assessment of Drug Interactions

Table 8: 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)* 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 INVOKANA 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 levonorgestrel	200 mg QD for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)
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 HCl	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 9: 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)* 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 HCl	2,000 mg	300 mg QD for 8 days	Metformin HCl	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 (0.98; 1.03)	1.05 (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

‡ $AUC_{0\text{-}12h}$

QD = once daily; BID = twice daily; INR = International Normalized Ratio

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 trial, 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 trials 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.

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.

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

INVOKANA (canagliflozin) has been studied as monotherapy, in combination with metformin HCl, sulfonylurea, metformin HCl and sulfonylurea, metformin HCl and sitagliptin, metformin HCl and a thiazolidinedione (i.e., pioglitazone), and in combination with insulin (with or without other anti-hyperglycemic agents). The efficacy of INVOKANA was compared to a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin), both as add-on combination therapy with metformin HCl and sulfonylurea, and a sulfonylurea (glimepiride), both as add-on combination therapy with metformin HCl. INVOKANA was also evaluated in adults 55 to 80 years of age and patients with moderate renal impairment.

Monotherapy

A total of 584 adult patients with type 2 diabetes inadequately controlled on diet and exercise participated in a 26-week double-blind, placebo-controlled trial to evaluate the efficacy and safety of INVOKANA. The mean age was 55 years, 44% of patients were male, and the mean baseline eGFR was 87 mL/min/1.73 m^2. Patients taking other antihyperglycemic agents (N=281) discontinued the agent and underwent an 8-week washout followed by a 2-week, single-blind, placebo run-in period. Patients not taking oral antihyperglycemic agents (N=303) entered the 2-week, single-blind, placebo run-in period directly. After the placebo run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily for 26 weeks.

At the end of treatment, INVOKANA 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. INVOKANA 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 (see Table 10). Statistically significant (p<0.001 for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -3.7 mmHg and -5.4 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 10: Results from 26-Week Placebo-Controlled Clinical Trial with INVOKANA as Monotherapy in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
HbA_{1C} (%)			
Baseline (mean)	7.97	8.06	8.01
Change from baseline (adjusted mean)	0.14	-0.77	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.91‡ (-1.09; -0.73)	-1.16‡ (-1.34; -0.99)
Percent of Patients Achieving HbA_{1C} < 7%	21	45‡	62‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	166	172	173
Change from baseline (adjusted mean)	8	-27	-35
Difference from placebo (adjusted mean) (95% CI)†		-36‡ (-42; -29)	-43‡ (-50; -37)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	229	250	254
Change from baseline (adjusted mean)	5	-43	-59
Difference from placebo (adjusted mean) (95% CI)†		-48‡ (-59.1; -37.0)	-64‡ (-75.0; -52.9)

Table 10: Results from 26-Week Placebo-Controlled Clinical Trial with INVOKANA as Monotherapy in Adults with Type 2 Diabetes Mellitus* (continued)

Efficacy Parameter	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
Body Weight			
Baseline (mean) in kg	87.5	85.9	86.9
% change from baseline (adjusted mean)	-0.6	-2.8	-3.9
Difference from placebo (adjusted mean) (95% CI)†		-2.2‡ (-2.9; -1.6)	-3.3‡ (-4.0; -2.6)

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

Add-on Combination Therapy with Metformin HCl

A total of 1,284 adult patients with type 2 diabetes inadequately controlled on metformin HCl 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 trial to evaluate the efficacy and safety of INVOKANA in combination with metformin HCl. The mean age was 55 years, 47% of patients were male, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the required metformin HCl dose (N=1,009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin HCl dose or patients on metformin HCl in combination with another antihyperglycemic agent (N=275) were switched to metformin HCl 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 INVOKANA 100 mg, INVOKANA 300 mg, sitagliptin 100 mg, or placebo, administered once daily as add-on therapy to metformin HCl.

At the end of treatment, INVOKANA 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 HCl. INVOKANA 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 HCl (see Table 11). 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 INVOKANA 100 mg and 300 mg, respectively.

Table 11: Results from 26-Week Placebo-Controlled Clinical Trial of INVOKANA in Combination with Metformin HCl in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo + Metformin HCl (N=183)	INVOKANA 100 mg + Metformin HCl (N=368)	INVOKANA 300 mg + Metformin HCl (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)
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 the trial prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p<0.001

Initial Combination Therapy with Metformin HCl Extended-Release

A total of 1,186 adult 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 trial to evaluate the efficacy and safety of initial therapy with INVOKANA in combination with metformin HCl extended-release. The median age was 56 years, 48% of patients were male, 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 12). The metformin HCl extended-release dose was initiated at 500 mg/day for the first week of treatment and then increased to 1,000 mg/day. Metformin HCl extended-release or matching placebo was up-titrated every 2-3 weeks during the next 8 weeks of treatment to a maximum daily dose of 1,500 to 2,000 mg/day, as tolerated; about 90% of patients reached 2,000 mg/day.

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

Table 12: Results from 26-Week Active-Controlled Clinical Trial of INVOKANA Alone or INVOKANA as Initial Combination Therapy with Metformin HCl Extended-Release in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Metformin HCl extended-release (N=237)	INVOKANA 100 mg (N=237)	INVOKANA 300 mg (N=238)	INVOKANA 100 mg + Metformin HCl extended-release (N=237)	INVOKANA 300 mg + Metformin HCl extended-release (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 HCl extended-release (adjusted mean) (95% CI)†		-0.06‡‡ (-0.26, 0.13)	-0.11‡‡ (-0.31, 0.08)	-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 for superiority
‡‡ Adjusted p=0.001 for non-inferiority
§§ 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.

INVOKANA Compared to Glimepiride, Both as Add-on Combination With Metformin HCl

A total of 1,450 adult patients with type 2 diabetes inadequately controlled on metformin HCl 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 trial to evaluate the efficacy and safety of INVOKANA in combination with metformin HCl.

The mean age was 56 years, 52% of patients were male, and the mean baseline eGFR was 90 mL/min/1.73 m^2. Patients tolerating maximally required metformin HCl dose (N=928) were randomized after completing a 2-week, single-blind, placebo run-in period. Other patients (N=522) were switched to metformin HCl 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 INVOKANA 100 mg, INVOKANA 300 mg, or glimepiride (titration allowed throughout the 52-week trial to 6 or 8 mg), administered once daily as add-on therapy to metformin HCl.

As shown in Table 13 and Figure 1, at the end of treatment, INVOKANA 100 mg provided similar reductions in HbA_{1C} from baseline compared to glimepiride when added to metformin HCl therapy. INVOKANA 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 INVOKANA 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

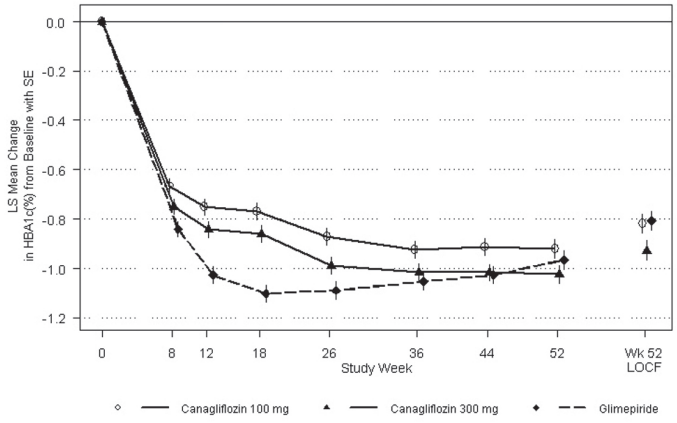
INVOKANA® (canagliflozin) tablets

Table 13: Results from 52–Week Clinical Trial Comparing INVOKANA to Glimepiride in Combination with Metformin HCl in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	INVOKANA 100 mg + Metformin HCl (N=483)	INVOKANA 300 mg + Metformin HCl (N=485)	Glimepiride (titrated) + Metformin HCl (N=482)
HbA_{1C} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
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 the trial prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ INVOKANA + metformin HCl is considered non-inferior to glimepiride + metformin HCl 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 in Adults with Type 2 Diabetes Mellitus Treated with INVOKANA or Glimepiride in Combination with Metformin HCl at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



Add-on Combination Therapy with Sulfonylurea

A total of 127 adult patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy participated in an 18-week, double-blind, placebo-controlled sub-trial to evaluate the efficacy and safety of INVOKANA in combination with sulfonylurea. The mean age was 65 years, 57% of patients were male, and the mean baseline eGFR was 69 mL/min/1.73 m^2. Patients treated with sulfonylurea monotherapy on a stable protocol-specified dose (greater than or equal to 50% maximal dose) for at least 10 weeks completed a 2-week, single-blind, placebo run-in period. After the run-in period, patients with inadequate glycemic control were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to sulfonylurea.

As shown in Table 14, at the end of treatment, INVOKANA 100 mg and 300 mg daily provided statistically significant (p<0.001 for both doses) improvements in HbA_{1C} relative to placebo when added to sulfonylurea. INVOKANA 300 mg once daily compared to placebo resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, (33% vs 5%), greater reductions in fasting plasma glucose (-36 mg/dL vs +12 mg/dL), and greater percent body weight reduction (-2.0% vs -0.2%).

Table 14: Results from 18-Week Placebo–Controlled Clinical Trial of INVOKANA in Combination with Sulfonylurea in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo + Sulfonylurea (N=45)	INVOKANA 100 mg + Sulfonylurea (N=42)	INVOKANA 300 mg + Sulfonylurea (N=40)
HbA_{1C} (%)			
Baseline (mean)	8.49	8.29	8.28
Change from baseline (adjusted mean)	0.04	-0.70	-0.79
Difference from placebo (adjusted mean) (95% CI)†		-0.74‡ (-1.15; -0.33)	-0.83‡ (-1.24; -0.41)

* Intent-to-treat population using last observation in the trial prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value
‡ p<0.001

Add-on Combination Therapy with Metformin HCl and Sulfonylurea

A total of 469 adult patients with type 2 diabetes inadequately controlled on the combination of metformin HCl (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 trial to evaluate the efficacy and safety of INVOKANA in combination with metformin HCl and sulfonylurea. The mean age was 57 years, 51% of patients were male, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the protocol-specified doses of metformin HCl 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 HCl and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to metformin HCl and sulfonylurea.

At the end of treatment, INVOKANA 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 HCl and sulfonylurea. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in a significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin HCl and sulfonylurea (see Table 15).

Table 15: Results from 26-Week Placebo-Controlled Clinical Trial of INVOKANA in Combination with Metformin HCl and Sulfonylurea in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo + Metformin HCl and Sulfonylurea (N=156)	INVOKANA 100 mg + Metformin HCl and Sulfonylurea (N=157)	INVOKANA 300 mg + Metformin HCl 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 A_{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 the trial prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p<0.001

INVOKANA® (canagliflozin) tablets

Add-on Combination Therapy with Metformin HCl and Sitagliptin

A total of 217 adult patients with type 2 diabetes inadequately controlled on the combination of metformin HCl (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 trial to evaluate the efficacy and safety of INVOKANA in combination with metformin HCl and sitagliptin. The mean age was 57 years, 58% of patients were male, 73% of patients were White, 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 INVOKANA 100 mg or placebo, administered once daily as add-on to metformin HCl and sitagliptin. Patients with a baseline eGFR of 70 mL/min/1.73 m^2 or greater who were tolerating INVOKANA 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 INVOKANA 300 mg. While up-titration occurred as early as Week 4, most (90%) patients randomized to INVOKANA were up-titrated to INVOKANA 300 mg by 6 to 8 weeks.

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

Table 16: Results from 26–Week Placebo-Controlled Clinical Trial of INVOKANA in Combination with Metformin HCl and Sitagliptin in Adults with Type 2 Diabetes Mellitus

Efficacy Parameter	Placebo + Metformin HCl and Sitagliptin (N=108*)	INVOKANA + Metformin HCl 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 INVOKANA.
† Early treatment discontinuation before week 26, occurred in 11.0% and 24.1% of INVOKANA 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

INVOKANA Compared to Sitagliptin, Both as Add-on Combination Therapy with Metformin HCl and Sulfonylurea

A total of 755 adult patients with type 2 diabetes inadequately controlled on the combination of metformin HCl (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 trial to compare the efficacy and safety of INVOKANA 300 mg versus sitagliptin 100 mg in combination with metformin HCl and sulfonylurea. The mean age was 57 years, 56% of patients were male, and the mean baseline eGFR was 88 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin HCl 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 HCl and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to INVOKANA 300 mg or sitagliptin 100 mg as add-on to metformin HCl and sulfonylurea.

As shown in Table 17 and Figure 2, at the end of treatment, INVOKANA 300 mg provided greater HbA_{1C} reduction compared to sitagliptin 100 mg when added to metformin HCl and sulfonylurea (p<0.05). INVOKANA 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 INVOKANA 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

Table 17: Results from 52-Week Clinical Trial Comparing INVOKANA to Sitagliptin in Combination with Metformin HCl and Sulfonylurea in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	INVOKANA 300 mg + Metformin HCl and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin HCl 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)	

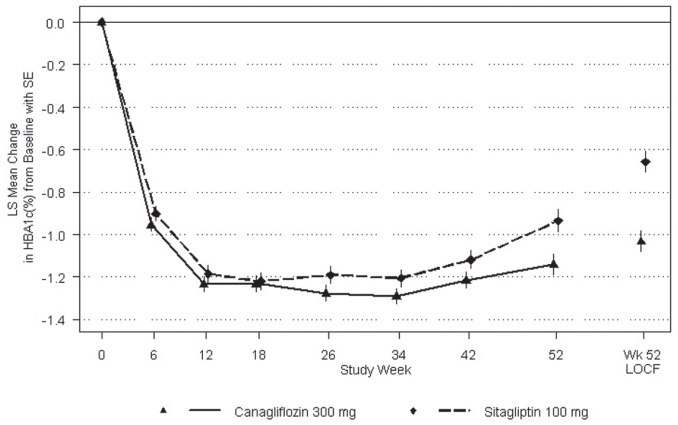
* Intent-to-treat population using last observation in the trial prior to glycemic rescue therapy

† Least squares mean adjusted for baseline value and stratification factors

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

§ p<0.001

Figure 2: Mean HbA_{1C} Change in Adults with Type 2 Diabetes Mellitus Treated with INVOKANA or Sitagliptin in Combination with Metformin HCl and Sulfonylurea at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



Add-on Combination Therapy with Metformin HCl and Pioglitazone

A total of 342 adult patients with type 2 diabetes inadequately controlled on the combination of metformin HCl (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 trial to evaluate the efficacy and safety of INVOKANA in combination with metformin HCl and pioglitazone. The mean age was 57 years, 63% of patients were male, and the mean baseline eGFR was 86 mL/min/1.73 m^2. Patients already on protocol-specified doses of metformin HCl 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 HCl and pioglitazone for at least 8 weeks before entering the 2-week run-in period. Following the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to metformin HCl and pioglitazone.

At the end of treatment, INVOKANA 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 HCl and pioglitazone. INVOKANA 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 HCl and pioglitazone (see Table 18). 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 INVOKANA 100 mg and 300 mg, respectively.

Table 18: Results from 26-Week Placebo-Controlled Clinical Trial of INVOKANA in Combination with Metformin HCl and Pioglitazone in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo + Metformin HCl and Pioglitazone (N=115)	INVOKANA 100 mg + Metformin HCl and Pioglitazone (N=113)	INVOKANA 300 mg + Metformin HCl 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 the trial prior to glycemic rescue therapy

† Least squares mean adjusted for baseline value and stratification factors

‡ p<0.001

Add-On Combination Therapy with Insulin (With or Without Other Antihyperglycemic Agents)

A total of 1,718 adult 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 subtrial of a cardiovascular trial to evaluate the efficacy and safety of INVOKANA in combination with insulin. The mean age was 63 years, 66% of patients were male, and the mean baseline eGFR was 75 mL/min/1.73 m^2. Patients on basal, bolus, or basal/bolus insulin for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. Approximately 70% of patients were on a background basal/bolus insulin regimen. After the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to insulin. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups.

At the end of treatment, INVOKANA 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 insulin. INVOKANA 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 19). Statistically significant (p<0.001 for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -2.6 mmHg and -4.4 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 19: Results from 18-Week Placebo-Controlled Clinical Trial of INVOKANA in Combination with Insulin ≥ 30 Units/Day (With or Without Other Oral Antihyperglycemic Agents) in Adults with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo + Insulin (N=565)	INVOKANA 100 mg + Insulin (N=566)	INVOKANA 300 mg + Insulin (N=587)
HbA_{1C} (%)			
Baseline (mean)	8.20	8.33	8.27
Change from baseline (adjusted mean)	0.01	-0.63	-0.72
Difference from placebo (adjusted mean) (95% CI)†		-0.65‡ (-0.73; -0.56)	-0.73‡ (-0.82; -0.65)
Percent of patients achieving HbA_{1C} < 7%	8	20‡	25‡
Fasting Plasma Glucose (mg/dL)			
Baseline	169	170	168
Change from baseline (adjusted mean)	4	-19	-25
Difference from placebo (adjusted mean) (97.5% CI)†		-23‡ (-29; -16)	-29‡ (-35; -23)
Body Weight			
Baseline (mean) in kg	97.7	96.9	96.7
% change from baseline (adjusted mean)	0.1	-1.8	-2.3
Difference from placebo (adjusted mean) (97.5% CI)†		-1.9‡ (-2.2; -1.6)	-2.4‡ (-2.7; -2.1)

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

† Least squares mean adjusted for baseline value and stratification factors

‡ p<0.001

Trial in Patients Ages 55 to 80

A total of 714 type 2 diabetes patients ages 55 to 80 years and inadequately controlled on current diabetes therapy (either diet and exercise alone or in combination with oral or parenteral agents) participated in a 26-week, double-blind, placebo-controlled trial to evaluate the efficacy and safety of INVOKANA in combination with current diabetes treatment. The mean age was 64 years, 55% of patients were male, and the mean baseline eGFR was 77 mL/min/1.73 m^2. Patients were randomized in a 1:1:1 ratio to the addition of INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily. At the end of treatment, INVOKANA provided statistically significant improvements from baseline relative to placebo in HbA_{1C} (p<0.001 for both doses) of -0.57% (95% CI: -0.71%; -0.44%) for INVOKANA 100 mg and -0.70% (95% CI: -0.84%; -0.57%) for INVOKANA 300 mg *[see Use in Specific Populations (8.5)]*.

Glycemic Control in Patients with Moderate Renal Impairment

A total of 269 adult patients with type 2 diabetes and a baseline eGFR of 30 mL/min/1.73 m^2 to less than 50 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy participated in a 26-week, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of INVOKANA in combination with current diabetes treatment (diet or antihyperglycemic agent therapy, with 95% of patients on insulin and/or sulfonylurea). The mean age was 68 years, 61% of patients were male, and the mean baseline eGFR was 39 mL/min/1.73 m^2. Patients were randomized in a 1:1:1 ratio to the addition of INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily.

At the end of treatment, INVOKANA 100 mg and INVOKANA 300 mg daily provided greater reductions in HbA_{1C} relative to placebo (-0.30% [95% CI: -0.53%; -0.07%] and -0.40%, [95% CI: -0.64%; -0.17%], respectively) *[see Warnings and Precautions (5.3), Adverse Reactions (6.1), Use in Specific Populations (8.6), and Clinical Studies (14.4)]*.

14.2 Glycemic Control Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

In a double-blind, placebo-controlled, parallel-group pediatric trial (NCT03170518), 171 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (HbA_{1C} ≥6.5% and ≤11.0%) were randomized to INVOKANA (84 patients) or placebo (87 patients) as add-on to diet and exercise, metformin HCl (≥1,000 mg per day or maximally tolerated dosage), insulin, or a combination of metformin HCl and insulin, for a total of 52-weeks. At Week 13, patients in the INVOKANA arm whose HbA_{1C} was ≥7.0% and eGFR ≥60 mL/min/1.73 m^2 were re-randomized to either continue on INVOKANA 100 mg orally once daily (n=16) or to up-titrate to INVOKANA 300 mg orally once daily (n=17).

At baseline, background therapies included diet and exercise only (14%), insulin monotherapy (11%), metformin HCl and insulin (29%), and metformin HCl monotherapy (46%). The mean HbA_{1C} at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2 years. The mean eGFR at baseline was 157.3 mL/min/1.73 m^2, and approximately 16% (24/151) of the trial population with measurements had microalbuminuria or macroalbuminuria. Patients with an eGFR less than 60 mL/min/1.73 m^2 were not enrolled in the trial; no patients in the trial reached an eGFR < 60 mL/min/1.73 m^2. The mean age was 14.3 years, 47% were under 15 years of age, and 68% were female. Approximately 42% were Asian, 42% were White, 11% were Black or African American, 5% were American Indian/Alaska Native, and 36% were of Hispanic or Latino ethnicity. The mean BMI was 30.8 kg/m^2 (range 18-57 kg/m^2) and the mean BMI Z-score was 1.84.

At Week 26, treatment with canagliflozin provided statistically significant improvement in HbA_{1C} from baseline, compared with placebo (see Table 20).

Table 20: Results at Week 26 in a Placebo-Controlled Trial of INVOKANA in Combination with Metformin HCl and/or Insulin or as Monotherapy in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus*

Efficacy Parameter	Placebo (N=87)	INVOKANA (N=84)
HbA_{1C} (%)		
Baseline (mean)	8.3	7.8
Change from baseline †‡	0.34	-0.38
Difference from placebo 95% CI †‡		-0.73 (-1.26, -0.19) §
FPG (mg/dL)		
Baseline (mean)	156.5	154.8
Change from baseline †‡	17.29	-8.22
Difference from placebo 95% CI †‡		-25.51 (-49.55, -1.47) ¶

* Modified intent-to-treat set (All randomized and treated patients with baseline HbA_{1C} measurement).

† Multiple imputation using retrieved dropout approach with 1000 iterations for missing data (canagliflozin N=7 (8.3%), placebo N=7 (8.1%) for HbA_{1C} and canagliflozin N=9 (10.7%), placebo N=7 (8.1%) for FPG).

‡ Least-Square Mean from Analysis of Covariance (ANCOVA) adjusted for baseline value, baseline age stratum (< 15 years vs 15 to < 18 years) and baseline antihyperglycemic agent (AHA) background (i.e, diet and exercise only, metformin monotherapy, insulin monotherapy, or combination of insulin and metformin).

§ P-value=0.008 (two-sided)

¶ Not evaluated for statistical significance, not part of sequential testing procedure.

14.3 Cardiovascular Outcomes in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The CANVAS and CANVAS-R trials were multicenter, multi-national, randomized, double-blind parallel group, with similar inclusion and exclusion criteria. Patients eligible for enrollment in both CANVAS and CANVAS-R trials were: 30 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease (66% of the enrolled population) or were 50 years of age or older and had two or more other specified risk factors for cardiovascular disease (34% of the enrolled population).

The integrated analysis of the CANVAS and CANVAS-R trials compared the risk of Major Adverse Cardiovascular Event (MACE) between canagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

In CANVAS, patients were randomly assigned 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. In CANVAS-R, patients were randomly assigned 1:1 to canagliflozin 100 mg or matching placebo, and titration to 300 mg was permitted at the investigator's discretion (based on tolerability and glycemic needs) after Week 13. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 10,134 adult patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin) for a mean exposure duration of 149 weeks (223 weeks [4.3 years] in CANVAS and 94 weeks [1.8 years] in CANVAS-R). Approximately 78% of the trial population was White, 13% was Asian, and 3% was Black or African American. The mean age was 63 years and approximately 64% were male.

The mean HbA_{1C} at baseline was 8.2% and mean duration of diabetes was 13.5 years with 70% of patients having had diabetes for 10 years or more. Approximately 31%, 21% and 17% reported a past history of neuropathy, retinopathy and nephropathy, respectively, and the mean eGFR 76 mL/min/1.73 m^2. At baseline, patients were treated with one (19%) or more (80%) antidiabetic medications including metformin HCl (77%), insulin (50%), and sulfonylurea (43%).

At baseline, the mean systolic blood pressure was 137 mmHg, the mean diastolic blood pressure was 78 mmHg, the mean LDL was 89 mg/dL, the mean HDL was 46 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 115 mg/g. At baseline, approximately 80% of patients were treated with renin angiotensin system inhibitors, 53% with beta-blockers, 13% with loop diuretics, 36% with non-loop diuretics, 75% with statins, and 74% with antiplatelet agents (mostly aspirin). During the trial, investigators could modify anti-diabetic and cardiovascular therapies to achieve local standard of care treatment targets with respect to blood glucose, lipid, and blood pressure. More patients receiving canagliflozin compared to placebo initiated anti-thrombotics (5.2% vs 4.2%) and statins (5.8% vs 4.8%) during the trial.

For the primary analysis, a stratified Cox proportional hazards model was used to test for non-inferiority against a pre-specified risk margin of 1.3 for the hazard ratio of MACE.

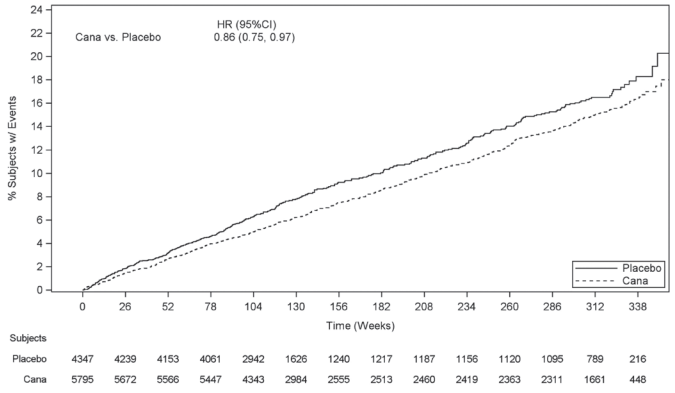
In the integrated analysis of CANVAS and CANVAS-R trials, canagliflozin reduced the risk of first occurrence of MACE. The estimated hazard ratio (95% CI) for time to first MACE was 0.86 (0.75, 0.97). Refer to Table 21. Vital status was obtained for 99.6% of patients across the trials. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 3.

Table 21: Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the Integrated Analysis of CANVAS and CANVAS-R Trials in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease*

	Placebo N=4,347(%)	Canagliflozin N=5,795 (%)	Hazard ratio (95% C.I.)¶
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)†, ‡, §	426 (10.4)	585 (9.2)	0.86 (0.75, 0.97)
Non-fatal myocardial infarction‡, §	159 (3.9)	215 (3.4)	0.85 (0.69, 1.05)
Non-fatal Stroke‡, §	116 (2.8)	158 (2.5)	0.90 (0.71, 1.15)
Cardiovascular Death‡, §	185 (4.6)	268 (4.1)	0.87 (0.72, 1.06)

* Intent-To-Treat Analysis Set
† P-value for superiority (2-sided) = 0.0158
‡ Number and percentage of first events
§ Due to pooling of unequal randomization ratios, Cochran-Mantel-Haenszel weights were applied to calculate percentages
¶ Stratified Cox-proportional hazards model with treatment as a factor and stratified by the trial and by prior CV disease

Figure 3: Time to First Occurrence of MACE in Adults with Type 2 Diabetes Mellitus



14.4 Renal and Cardiovascular Outcomes in Adults with Diabetic Nephropathy and Albuminuria

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) was a multinational, randomized, double-blind, placebo-controlled trial comparing canagliflozin with placebo in adult patients with type 2 diabetes mellitus, an eGFR ≥ 30 to < 90 mL/min/1.73 m^2 and albuminuria (urine albumin/creatinine > 300 to ≤ 5,000 mg/g) who were receiving standard of care including a maximum-tolerated, labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

The primary objective of CREDENCE was to assess the efficacy of canagliflozin relative to placebo in reducing the composite endpoint of end stage kidney disease (ESKD), doubling of serum creatinine, and renal or CV death.

Patients were randomized to receive canagliflozin 100 mg (N=2,202) or placebo (N=2,199) and treatment was continued until the initiation of dialysis or renal transplantation.

The median follow-up duration for the 4,401 randomized subjects was 137 weeks. Vital status was obtained for 99.9% of subjects.

The population was 67% White, 20% Asian, and 5% Black or African American; 32% were of Hispanic or Latino ethnicity. The mean age was 63 years and 66% were male.

At randomization, the mean HbA_{1C} was 8.3%, the median urine albumin/creatinine was 927 mg/g, the mean eGFR was 56.2 mL/min/1.73 m^2, 50% had prior CV disease, and 15% reported a history of heart failure. The most frequent antihyperglycemic agents (AHA) medications used at baseline were insulin (66%), biguanides (58%), and sulfonylureas (29%). Nearly all subjects (99.9%) were on ACEi or ARB at randomization, approximately 60% were taking an anti-thrombotic agent (including aspirin), and 69% were on a statin.

The primary composite endpoint in the CREDENCE trial was the time to first occurrence of ESKD (defined as an eGFR < 15 mL/min/1.73 m^2, initiation of chronic dialysis or renal transplant), doubling of serum creatinine, and renal or CV death. Canagliflozin 100 mg significantly reduced the risk of the primary composite endpoint based on a time-to-event analysis [HR: 0.70; 95% CI: 0.59, 0.82; p<0.0001] (see Figure 4). The treatment effect reflected a reduction in progression to ESKD, doubling of serum creatinine and cardiovascular death as shown in Table 22 and Figure 4. There were few renal deaths during the trial. Canagliflozin 100 mg also significantly reduced the risk of hospitalization for heart failure [HR: 0.61; 95% CI: 0.47 to 0.80; p<0.001].

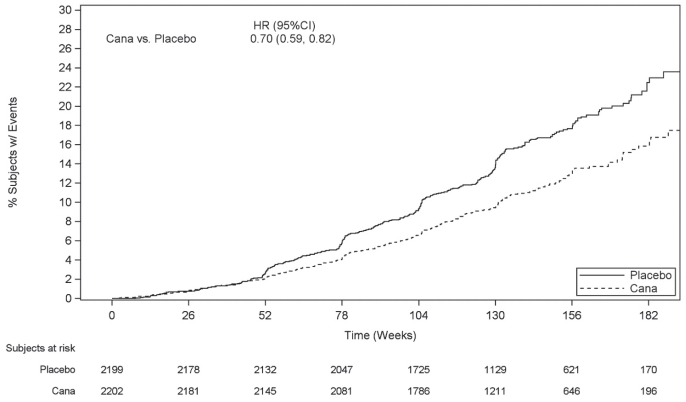
Table 22: Analysis of Primary Endpoint (including the Individual Components) and Secondary Endpoints from the CREDENCE Trial in Adults with Diabetic Nephropathy and Albuminuria

	Placebo		canagliflozin		
Endpoint	**N=2,199 (%)**	**Event Rate***	**N=2,202 (%)**	**Event Rate***	**HR† (95% CI)**
Primary Composite Endpoint (ESKD, doubling of serum creatinine, renal death, or CV death)	340 (15.5)	6.1	245 (11.1)	4.3	0.70 (0.59, 0.82) ‡
ESKD	165 (7.5)	2.9	116 (5.3)	2.0	0.68 (0.54, 0.86)
Doubling of serum creatinine	188 (8.5)	3.4	118 (5.4)	2.1	0.60 (0.48, 0.76)
Renal death	5 (0.2)	0.1	2 (0.1)	0.0	
CV death	140 (6.4)	2.4	110 (5.0)	1.9	0.78 (0.61, 1.00)
CV death or hospitalization for heart failure	253 (11.5)	4.5	179 (8.1)	3.1	0.69 (0.57, 0.83) §
CV death, non-fatal myocardial infarction or non-fatal stroke	269 (12.2)	4.9	217 (9.9)	3.9	0.80 (0.67, 0.95) ¶
Non-fatal myocardial infarction	87 (4.0)	1.6	71 (3.2)	1.3	0.81 (0.59, 1.10)
Non-fatal stroke	66 (3.0)	1.2	53 (2.4)	0.9	0.80 (0.56, 1.15)
Hospitalization for heart failure	141 (6.4)	2.5	89 (4.0)	1.6	0.61 (0.47, 0.80) §
ESKD, doubling of serum creatinine or renal death	224 (10.2)	4.0	153 (6.9)	2.7	0.66 (0.53, 0.81) ‡

Intent-To-Treat Analysis Set (time to first occurrence)
The individual components do not represent a breakdown of the composite outcomes, but rather the total number of subjects experiencing an event during the course of the trial.
* Event rate per 100 patient-years.
† Hazard ratio (canagliflozin compared to placebo), 95% CI and p-value are estimated using a stratified Cox proportional hazards model including treatment as the explanatory variable and stratified by screening eGFR (≥ 30 to < 45, ≥ 45 to < 60, ≥ 60 to < 90 mL/min/1.73 m^2). HR is not presented for renal death due to the small number of events in each group.
‡ P-value <0.0001
§ P-value <0.001
¶ P-value <0.02

The Kaplan-Meier curve (Figure 4) shows time to first occurrence of the primary composite endpoint of ESKD, doubling of serum creatinine, renal death, or CV death. The curves begin to separate by Week 52 and continue to diverge thereafter.

Figure 4: CREDENCE: Time to First Occurrence of the Primary Composite Endpoint



16 HOW SUPPLIED/STORAGE AND HANDLING

INVOKANA® (canagliflozin) tablets are available in the strengths and packages listed below:

100 mg tablets are yellow, capsule-shaped, film-coated tablets with "CFZ" on one side and "100" on the other side.

NDC 50458-140-30	Bottle of 30
NDC 50458-140-90	Bottle of 90
NDC 50458-140-50	Bottle of 500

300 mg tablets are white, capsule-shaped, film-coated tablets with "CFZ" on one side and "300" on the other side.

NDC 50458-141-30	Bottle of 30
NDC 50458-141-90	Bottle of 90
NDC 50458-141-50	Bottle of 500

Storage and Handling

Keep out of reach of children.

Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C to 30 °C (59 °F to 86 °F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

Inform patients that INVOKANA can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.

Educate all patients on precipitating factors (such as insulin dose reduction or missed doses, infection, reduced caloric intake, ketogenic diet, surgery, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue INVOKANA and seek medical attention immediately *[see Warnings and Precautions (5.1)]*.

Lower Limb Amputation

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 Warnings and Precautions (5.2)]*.

Volume Depletion

Inform patients that symptomatic hypotension may occur with INVOKANA 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.

Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

Counsel patients that genitourinary infections may occur when taking INVOKANA and may become serious. Educate patients on the symptoms and advise them to seek medical advice if symptoms occur. Specifically, advise patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4 °F or malaise *[see Warnings and Precautions (5.4)]*.

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

Inform patients that hypoglycemia has been reported when INVOKANA is used with insulin or insulin secretagogues. Educate patients or caregivers on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.5)]*.

INVOKANA® (canagliflozin) tablets

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. 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 (5.6)]*.

Bone Fracture

Inform patients that bone fractures have been reported in adult patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions (5.7)]*.

Pregnancy

Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[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 INVOKANA *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

Inform patients that due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine *[see Drug Interactions (7)]*.

Missed Dose

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, it should be taken as soon as possible. Advise patients not to double their next dose *[see Dosage and Administration (2.6)]*.

Active ingredient made in Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560, USA

Licensed from Tanabe Pharma Corporation

For patent information: www.janssenpatents.com

© Johnson & Johnson and its affiliates 2013 – 2024

Medication Guide
INVOKANA® (in-vo-KAHN-uh)
(canagliflozin)
tablets, for oral use

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

- **Diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 and other ketoacidosis.** INVOKANA can cause ketoacidosis that can be life-threatening and may lead to death. Ketoacidosis is a serious condition which needs to be treated in a hospital. People with type 1 diabetes have a high risk of getting ketoacidosis. People with type 2 diabetes or pancreas problems also have an increased risk of getting ketoacidosis. Ketoacidosis can also happen in people who: are sick, cannot eat or drink as usual, skip meals, are on a diet high in fat and low in carbohydrates (ketogenic diet), take less than the usual amount of insulin or miss insulin doses, drink too much alcohol, have a loss of too much fluid from the body (volume depletion), or who have surgery or a procedure that requires not having food for a long time (prolonged fasting). Ketoacidosis can happen even if your blood sugar is less than 250 mg/dL. Your healthcare provider may ask you to periodically check ketones in your urine or blood.
- **Stop taking INVOKANA and call your healthcare provider or get medical help right away if you get any of the following. If possible, check for ketones in your urine or blood, even if your blood sugar is less than 250 mg/dL:**
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
  - tiredness
  - trouble breathing
  - ketones in your urine or blood
- **Amputations. INVOKANA may increase your risk of lower limb amputations.**
  You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - 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 healthcare provider right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Talk to your healthcare provider about proper foot care.

- **Dehydration. INVOKANA 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). There have been reports of sudden worsening of kidney function in people with type 2 diabetes who are taking INVOKANA.**
  You may be at higher risk of dehydration if you:
  - 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 healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Call your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you cannot eat or you start to lose liquids from your body, for example from vomiting, diarrhea, or being in the sun too long.

- **Genital and urinary tract infections.** INVOKANA can cause serious infections in your genital area or urinary tract that could require hospitalization. **A rare but serious bacterial infection called necrotizing fasciitis can cause damage to the tissue under the skin in the area between and around the anus and genitals (perineum).** This infection may require hospitalization, multiple surgeries, and could lead to death. **Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:**
  - pain or tenderness
  - swelling
  - redness of skin (erythema)

Also tell your healthcare provider if you have any of these signs or symptoms of urinary tract infections or yeast infections:

- **Urinary tract infection:**
  - burning feeling when you urinate
  - need to urinate often or right away
  - pain in the lower part of your stomach (pelvis)
  - blood in your urine

You may also have a fever, back pain, nausea, or vomiting.

- **Vaginal yeast infection:**
  - vaginal odor
  - white or yellowish vaginal discharge (may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the skin around the penis (balanitis or balanoposthitis):** If you are uncircumcised, swelling may make it difficult to pull back the skin around the tip of your penis. Other symptoms include:
  - redness, itching, or swelling of the penis
  - rash on the penis
  - bad smelling discharge from the penis
  - pain in the skin around the penis

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection. They may suggest you use an over-the-counter antifungal medicine. Contact your healthcare provider right away if your symptoms do not improve after using an over-the-counter antifungal medicine.

What is INVOKANA?

- INVOKANA is a prescription medicine used:
  - along with diet and exercise to lower blood sugar (glucose) in adults and children aged 10 years and older with type 2 diabetes.
  - to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes who have known cardiovascular disease.
  - to reduce the risk of end stage kidney disease (ESKD), worsening of kidney function, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic kidney disease (nephropathy) with a certain amount of protein in the urine.
- INVOKANA is not recommended to decrease blood sugar (glucose) in people with type 1 diabetes.
- INVOKANA is not recommended to decrease blood sugar (glucose) in people with type 2 diabetes with severe kidney problems.
- It is not known if INVOKANA is safe and effective in children under 10 years of age.

Do not take INVOKANA if you:

- are allergic to canagliflozin or any of the ingredients in INVOKANA. See the end of this Medication Guide for a list of ingredients in INVOKANA. Symptoms of allergic reaction to INVOKANA 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

Before taking INVOKANA, tell your healthcare provider about all of your medical conditions, including if you:

- have type 1 diabetes or have had diabetic ketoacidosis.
- have a decrease in your insulin dose.
- have a serious infection.
- have a history of infection of the vagina or penis.
- have a history of amputation.
- 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 kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems with urination.
- are on a low sodium (salt) diet. Your healthcare provider may change your diet or your dose of INVOKANA.
- are going to have surgery or a procedure that requires not having food for a long time (prolonged fasting). Your healthcare provider may stop your INVOKANA before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking INVOKANA and when to start it again.
- are eating less or there is a change in your diet.
- are dehydrated.
- 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 ever had an allergic reaction to INVOKANA.
- are pregnant or plan to become pregnant. INVOKANA may harm your unborn baby. If you become pregnant while taking INVOKANA, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. INVOKANA may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking INVOKANA. Do not breastfeed while taking INVOKANA.

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

INVOKANA may affect the way other medicines work, and other medicines may affect how INVOKANA works. Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take INVOKANA?

- Take INVOKANA by mouth 1 time each day exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much INVOKANA to take and when to take it. Your healthcare provider may change your dose if needed.
- It is best to take INVOKANA before the first meal of the day.
- Your healthcare provider may tell you to take INVOKANA along with other diabetes medicines. Low blood sugar can happen more often when INVOKANA is taken with certain other diabetes medicines. See "**What are the possible side effects of INVOKANA?**"
- Your healthcare provider may tell you to stop taking INVOKANA at least 3 days before any surgery or procedure that requires not having food or water for a long time (prolonged fasting).
- 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 two doses of INVOKANA at the same time. Talk to your healthcare provider if you have questions about a missed dose.
- If you take too much INVOKANA, call your healthcare provider or Poison Help line at 1-800-222-1222 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 healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.
- INVOKANA will cause your urine to test positive for glucose.
- Your healthcare provider may do certain blood tests before you start INVOKANA and during treatment as needed. Your healthcare provider may change your dose of INVOKANA based on the results of your blood tests.

What are the possible side effects of INVOKANA?
INVOKANA may cause serious side effects including:

See "**What is the most important information I should know about INVOKANA?**"

- **low blood sugar (hypoglycemia).** If you take INVOKANA 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 INVOKANA.

  Signs and symptoms of low blood sugar may include:
  - headache
  - confusion
  - hunger
  - shaking or feeling jittery
  - drowsiness
  - dizziness
  - fast heartbeat
  - weakness
  - irritability
  - sweating
- **serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking INVOKANA and call your healthcare provider right away or go to the nearest hospital emergency room. See **"Do not take INVOKANA if you:"**. Your healthcare provider 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 INVOKANA. Talk to your healthcare provider about factors that may increase your risk of bone fracture.

The most common side effects of INVOKANA include:

- vaginal yeast infections and yeast infections of the penis (See "**What is the most important information I should know about INVOKANA?**")
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night

These are not all the possible side effects of INVOKANA.

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 INVOKANA?

- Store INVOKANA at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- **Keep INVOKANA and all medicines out of the reach of children.**

General information about the safe and effective use of INVOKANA.

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

You can ask your pharmacist or healthcare provider for information about INVOKANA that is written for health professionals.

What are the ingredients in INVOKANA?

Active ingredient: canagliflozin

Inactive ingredients: croscarmellose sodium (E468), hydroxypropyl cellulose (E463), lactose anhydrous, magnesium stearate (E572), and microcrystalline cellulose (E460[i]). In addition, the tablet coating contains iron oxide yellow (E172) (100 mg tablet only), macrogol/PEG3350 (E1521), polyvinyl alcohol (E1203) (partially hydrolyzed), talc (E553b), and titanium dioxide (E171).

Active ingredient made in Belgium. Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560, USA.
Licensed from Tanabe Pharma Corporation. For patent information: www.janssenpatents.com
© Johnson & Johnson and its affiliates 2013 - 2024
For more information about INVOKANA, call 1-800-526-7736 or visit our website at www.invokana.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 06/2026

cp-33540v17