About Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM), which accounts for 90% to 95% of all cases of diabetes in adults, is a disorder that is characterized by hyperglycemia. Insulin resistance and impaired insulin secretion by beta cells in the pancreas are 2 abnormalities that contribute to hyperglycemia. Insulin resistance is defined as the inability of the muscles, fat, and liver cells to respond appropriately to insulin. The causes of insulin resistance have not been fully elucidated, but obesity, physical inactivity, and other factors such as age, sleep problems, and ethnicity are thought to play a role.

In the presence of insulin resistance, additional insulin is required to maintain blood glucose levels within the normal range. Initially, the production of insulin by beta cells in the pancreas is increased in response to the additional need for insulin, and normoglycemia is maintained. As T2DM progresses, however, beta cells are unable to keep up with the increased demand for insulin, resulting in a relative insulin deficiency and hyperglycemia. Over time, the deterioration of beta-cell mass and function may necessitate the initiation of insulin.

The Importance of Achieving and Maintaining Glycemic Control

Controlling blood glucose levels can reduce the risk of complications due to T2DM. The glycated hemoglobin (A1C) test is commonly used to assess glycemic control over the longer term. A1C reflects glucose levels over the past 2 to 3 months. The American Diabetes Association recommends a goal A1C of less than 7% for nonpregnant adults, while the American Association of Clinical Endocrinologists recommends a goal A1C of 6.5% or less for healthy patients without concurrent illness and at low hypoglycemic risk.

Additional Insights into the Pathophysiology of T2DM

In addition to insulin resistance and beta cell dysfunction, research has revealed the role of other organs and tissues in the pathophysiology of T2DM. Perturbations in the brain, adipose tissue, and kidneys contribute to the hyperglycemia characteristic of T2DM. The kidney plays a key role in glucose homeostasis by regulating the reabsorption of glucose following plasma filtration. Sodium-glucose co-transporters (SGLTs: SGLT1 and SGLT2) are responsible for glucose reabsorption in the kidney.

This article was sponsored by Janssen Pharmaceuticals, Inc.

Please read Important Safety Information and the Brief Summary of full Prescribing Information on the following pages.
About INVOKANA™
INVOKANA™ (canagliflozin) has been developed to inhibit SGLT2; this novel mechanism of action adds to existing treatment modalities for T2DM and provides an alternate treatment target.

INVOKANA™ is an SGLT2 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. INVOKANA™ is not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.10

Clinical Efficacy: INVOKANA™ Monotherapy vs Placebo
INVOKANA™ has been studied as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and a thiazolidinedione (ie, pioglitazone), and in combination with insulin (with or without other antihyperglycemic agents). The efficacy of INVOKANA™ was compared with the efficacy of a dipeptidyl peptidase-4 inhibitor (sitagliptin) and a sulfonylurea (glimepiride). INVOKANA™ was also evaluated in adults 55 to 80 years of age and patients with moderate renal impairment.10

To evaluate the efficacy and safety of INVOKANA™ monotherapy versus placebo, a total of 584 patients with T2DM inadequately controlled on diet and exercise participated in a 26-week, double-blind, placebo-controlled study. The mean age was 55 years, 44% of patients were men, and the mean baseline estimated glomerular filtration rate (GFR) was 87 mL/min/1.73 m². 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.10,11

The primary end point was the change in A1C from baseline to week 26. Secondary end points included the proportion of patients achieving A1C less than 7%, change from baseline in fasting plasma glucose (FPG) and systolic blood pressure, and percent change from baseline in body weight and plasma lipids. At the end of treatment, INVOKANA™ 100 mg and INVOKANA™ 300 mg once daily resulted in a statistically significant improvement in A1C (P <.001 for both doses) compared with placebo. INVOKANA™ 100 mg and INVOKANA™ 300 mg once daily also resulted in a greater proportion of patients achieving an A1C less than 7%, significant reduction in FPG, improved postprandial glucose, and percent body weight reduction compared with placebo (Table 1).11 Statistically significant (P <.001 for both doses) mean changes from baseline in systolic blood pressure relative to placebo were –3.7 mm Hg and –5.4 mm Hg with INVOKANA™ 100 mg and INVOKANA™ 300 mg, respectively. Increases from baseline in low-

VOLUME STATUS SHOULD BE ASSESSED AND CORRECTED. MONITOR FOR SIGNS AND SYMPTOMS AFTER INITIATING THERAPY.

CONSEQUENCES OF RENAL FUNCTION: INVOKANA™ INCREASES SERUM CREATININE AND DECREASES GFR. PATIENTS WITH HYPERTENSION MAY BE MORE SUSCEPTIBLE TO THESE CHANGES. RENAL FUNCTION ABNORMALITIES CAN OCCUR AFTER INITIATING INVOKANA™. MORE FREQUENT RENAL FUNCTION MONITORING IS RECOMMENDED IN PATIENTS WITH AN eGFR BELOW 60 mL/min/1.73 m².

HYPERKALEMIA: INVOKANA™ CAN LEAD TO HYPERKALEMIA. PATIENTS WITH MODERATE RENAL IMPAIRMENT WHO ARE TAKING MEDICATIONS THAT INTERFERE WITH POTASSIUM EXCRETION, SUCH AS POTASSIUM-SPARING DIURETICS, OR MEDICATIONS THAT INTERFERE WITH THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM ARE MORE LIKELY TO DEVELOP HYPERKALEMIA. MONITOR SERUM POTASSIUM LEVELS PERIODICALLY AFTER INITIATING INVOKANA™ IN PATIENTS WITH IMPAIRED RENAL FUNCTION AND IN PATIENTS PREDISPOSED TO HYPERKALEMIA DUE TO MEDICATIONS OR OTHER MEDICAL CONDITIONS.

HYPGLYCEMIA WITH CONCOMITANT USE WITH INSULIN AND INSULIN SECRETAGOGUES: INSULIN AND INSULIN SECRETAGOGUES ARE KNOWN TO CAUSE HYPGLYCEMIA. INVOKANA™ CAN INCREASE THE RISK OF HYPGLYCEMIA WHEN COMBINED WITH INSULIN OR AN INSULIN SECRETAGOGUE. THEREFORE, A LOWER DOSE OF INSULIN OR INSULIN SECRETAGOGUE MAY BE REQUIRED TO MINIMIZE THE RISK OF HYPGLYCEMIA WHEN USED IN COMBINATION WITH INVOKANA™.

GENITAL MYCOTIC INFECTIONS: INVOKANA™ INCREASES THE RISK OF GENITAL MYCOTIC INFECTIONS. PATIENTS WITH A HISTORY OF GENITAL MYCOTIC INFECTIONS AND UNCIRCUMCISED MALES WERE MORE LIKELY TO DEVELOP GENITAL MYCOTIC INFECTIONS. MONITOR AND TREAT APPROPRIATELY.

HYPERSENSITIVITY REACTIONS: HYPERSENSITIVITY REACTIONS (EG, GENERALIZED URTICARIA), SOME SERIOUS, WERE REPORTED WITH INVOKANA™ TREATMENT; THESE REACTIONS GENERALLY OCCURRED WITHIN HOURS TO DAYS AFTER INITIATING INVOKANA™.
INVOKANA™ (canagliflozin). If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.

• Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.

• Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

DRUG INTERACTIONS

• UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m², and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.

• Digoxin: There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

Table 1: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA™ as Monotherapy¹,¹⁰,¹¹

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo (N = 192)</th>
<th>INVOKANA™ 100 mg (N = 195)</th>
<th>INVOKANA™ 300 mg (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.97</td>
<td>8.06</td>
<td>8.01</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>0.14</td>
<td>-0.77</td>
<td>-1.03</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>Not Applicable</td>
<td>-0.91 (1.09, -0.73)</td>
<td>-1.16 (1.34, -0.99)</td>
</tr>
<tr>
<td>Percent of Patients Achieving A1C &lt; 7%</td>
<td>21</td>
<td>45c</td>
<td>62c</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>166</td>
<td>172</td>
<td>173</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>8</td>
<td>-27</td>
<td>-35</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>Not Applicable</td>
<td>-36c (42, -29)</td>
<td>-43c (-50, -37)</td>
</tr>
<tr>
<td>2-Hour Postprandial Glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>229</td>
<td>250</td>
<td>254</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>5</td>
<td>-43</td>
<td>-59</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>Not Applicable</td>
<td>-48c (59.1, -37.0)</td>
<td>-64c (-75.0, -52.9)</td>
</tr>
<tr>
<td>Body Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean) in kg</td>
<td>87.5</td>
<td>85.9</td>
<td>86.9</td>
</tr>
<tr>
<td>% change from baseline (adjusted mean)</td>
<td>-0.6</td>
<td>-2.8</td>
<td>-3.9</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>Not Applicable</td>
<td>-2.2c (-2.9, -1.6)</td>
<td>-3.3c (-4.0, -2.6)</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; CI = confidence interval.
¹intent-to-treat population using last observation in study prior to glycemic rescue therapy.
¹Least squares mean adjusted for baseline value and stratification factors.
¹P < .001.

IMPORTANT SAFETY INFORMATION (cont)

Please read additional Important Safety Information and the Brief Summary of full Prescribing Information on the following pages.

USE IN SPECIFIC POPULATIONS

• Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used dur-
TABLE 2: SUMMARY OF OVERALL SAFETY AND SELECTED ADVERSE EVENTS IN THE INVOKANA™ MONOTHERAPY STUDY

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 192)</th>
<th>INVOKANA™ 100 mg (n = 195)</th>
<th>INVOKANA™ 300 mg (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>101 (52.6)</td>
<td>119 (61.0)</td>
<td>118 (59.9)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>2 (1.0)</td>
<td>6 (3.1)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>AEs related to study drug a</td>
<td>18 (9.4)</td>
<td>34 (17.4)</td>
<td>50 (25.4)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>4 (2.1)</td>
<td>8 (4.1)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Deaths b</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Selected AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>8 (4.2)</td>
<td>14 (7.2)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Genital mycotic infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male a</td>
<td>0</td>
<td>2 (2.5)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Female b</td>
<td>4 (3.8)</td>
<td>10 (8.8)</td>
<td>8 (7.4)</td>
</tr>
<tr>
<td>Osmotic diuresis-related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollakiuria a</td>
<td>1 (0.5)</td>
<td>5 (2.6)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Polyuria a</td>
<td>0</td>
<td>0</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Volume-related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural dizziness</td>
<td>0</td>
<td>1 (0.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
</tbody>
</table>

AE = adverse event; UTI = urinary tract infection.
aAll AEs are reported for regardless of rescue medication except for osmotic diuresis- and volume-related AEs, which are reported for prior to initiation of rescue therapy.
bPossibly, probably, or very likely related to study drug, as assessed by investigators.
cDeath in the placebo group due to intracranial hemorrhage and brain hernia reported as serious AEs, and death in the INVOKANA™ 100 mg group due to pneumonia, septic shock, acute renal failure, and ischemic hepatitis reported as serious AEs; neither death was considered by the reporting investigator to be drug-related.
dPlacebo, n = 88; INVOKANA™ 100 mg, n = 81; INVOKANA™ 300 mg, n = 89.
eIncluding balanitis, balanitis candida, balanoposthitis, and genital infection fungal.
fIncluding vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
gIncreased urine frequency.
hIncreased urine volume.

IMPORTANT SAFETY INFORMATION (cont)

...ing pregnancy only if the potential benefit justifies the potential risk to the fetus.

- **Nursing Mothers**: It is not known if INVOKANA™ (canagliflozin) is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.

- **Pediatric Use**: Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.

- **Geriatric Use**: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. 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; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C 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).

- **Renal Impairment**: The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m²). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m²); patients treated with INVOKANA™...
density lipoprotein were seen with INVOKANA™ (canagliflozin) 100 mg (2.0%) and INVOKANA™ 300 mg (6.1%) compared with placebo (1.0%).10,11

Hypoglycemia and Other Adverse Events

The incidence of hypoglycemia was similar between placebo (2.6%) and the INVOKANA™ 100-mg (3.6%) and 300-mg (3.0%) treatment groups, and there were no reports of severe hypoglycemia.11 In the treatment groups, 10 patients discontinued treatment due to an adverse event compared with 2 patients in the placebo group. Overall, adverse events were more common in the treatment groups (Table 2).11 Serious adverse event rates were low across groups. The most common adverse events were genital mycotic infections and urinary tract infections; urinary tract infection adverse events were generally mild to moderate in severity and did not lead to study discontinuation.11

Role of the Pharmacist

In the setting of treatment with a first-in-class therapy such as INVOKANA™, pharmacists can play an important role in educating patients and health care professionals. As such, it is especially important for the pharmacist to understand the mechanism of action and safety and efficacy profile of INVOKANA™. Pharmacists should advise patients to report any signs of urinary tract infection or genital mycotic infections, as these events were more common in patients treated with INVOKANA™ during clinical trials. Physicians should be counseled to monitor patients for the signs and symptoms of hypotension, especially elderly patients, patients with renal impairment, and patients who are receiving concomitant treatment with a diuretic.10

The recommended starting dose of INVOKANA™ is 100 mg once daily, taken before the first meal of the day. The dose can be increased to 300 mg once daily in patients tolerating INVOKANA™ 100 mg once daily who have an estimated GFR of 60 mL/min/1.73 m² or greater and require additional glycemic control. The dose of INVOKANA™ should be limited to 100 mg once daily in patients who have an estimated GFR of 45 to less than 60 mL/min/1.73 m². Physicians should be advised to monitor renal function, especially in patients with an estimated GFR less than 60 mL/min/1.73 m². INVOKANA™ should not be used in those with severe renal impairment, end-stage renal disease, or patients on dialysis.10

References


IMPORTANT SAFETY INFORMATION (cont)

300 mg were more likely to experience increases in potassium.

The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

• 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 it is therefore not recommended.

OVERDOSAGE

• There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, 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.

ADVERSE REACTIONS

The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

Please read the Brief Summary of full Prescribing Information on the following pages.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.
INVOKANA™ (canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information:

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus [see Clinical Studies (14) in full Prescribing Information].

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

• History of a serious hypersensitivity reaction to INVOKANA [see Warnings and Precautions].
• Severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease or patients on dialysis [see Warnings and Precautions and Use in Specific Populations].

WARNINGS AND PRECAUTIONS

Hypoglycemia: INVOKANA causes intravascular volume contraction. Symptomatic hypoglycemia can occur after initiating INVOKANA [see Adverse Reactions] particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA [see Adverse Reactions]. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m².

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with the renin-angiotensin-aldosterone system or potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia [see Adverse Reactions]. Monitor serum potassium levels periodically after initiating INVOKANA in patients with one or more of these characteristics and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue [see Adverse Reactions]. There is a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncurcumcised males were more likely to develop genital mycotic infections [see Adverse Reactions]. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria, angioedema, anaphylaxis) were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If a hypersensitivity reaction occurs, discontinue use of INVOKANA and treat per standard of care and monitor until signs and symptoms resolve [see Warnings and Precautions and Adverse Reactions].

Increases in Low-Density Lipoprotein (LDL-C): Increases in low-density lipoprotein (LDL-C) occur with INVOKANA; treat per standard of care and monitor until signs and symptoms resolve [see Contraindications and Adverse Reactions].

Hyperkalemia: Hyperkalemia due to medications or other medical conditions.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (3.3%) and 17.6 per 1000 patient-years of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients receiving INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 56% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m²).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (7.7% with comparator), 2.2% with INVOKANA 100 mg, 2.0% with INVOKANA 300 mg and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (88 weeks), the incidence rate of bone fracture was 14.2, 16.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA
100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator. In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.7%, and 4.2% of 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, photocutaneous 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:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, 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 patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²) and age 75 years and older (Table 2) [see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations].

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Comparator Group*</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Overall population</td>
<td>1.5%</td>
<td>2.3%</td>
<td>3.4%</td>
</tr>
<tr>
<td>75 years of age and older†</td>
<td>2.6%</td>
<td>4.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>eGFR less than 60 mL/min/1.73 m²</td>
<td>2.5%</td>
<td>4.7%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Use of loop diuretic†</td>
<td>4.7%</td>
<td>3.2%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

* Includes placebo and active-comparator groups
† Patients could have more than 1 of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

<table>
<thead>
<tr>
<th>Pool of Four Placebo-Controlled Trials</th>
<th>Placebo (N=466)</th>
<th>INVOKANA 100 mg (N=833)</th>
<th>INVOKANA 300 mg (N=834)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CREATININE (mg/dL)</td>
<td>0.84</td>
<td>0.82</td>
<td>0.82</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>87.0</td>
<td>88.3</td>
<td>88.8</td>
</tr>
<tr>
<td>Week 6 Change CREATININE (mg/dL)</td>
<td>0.01</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>-1.6</td>
<td>-3.8</td>
<td>-5.0</td>
</tr>
<tr>
<td>End of Treatment Change eGFR (mL/min/1.73 m²)</td>
<td>-1.6</td>
<td>-2.3</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

Overall [N (%)] 5 (2.6) 7 (3.2) 6 (3.0)

In Combination with Metformin (N=162) Placebo + Metformin (N=163) Placebo + Metformin (N=164) Placebo + Metformin (N=165)
Overall [N (%)] 3 (1.6) 16 (4.3) 17 (4.6)
Severe [N (%)] 0 (0.0) 1 (0.3) 0 (0.0)

Overall [N (%)] 165 (33.4) 27 (5.6) 24 (4.9)
Severe [N (%)] 15 (3.1) 2 (0.4) 3 (0.6)

Overall [N (%)] 4 (5.8) 3 (4.1) 9 (12.5)
Overall [N (%)] 24 (15.4) 42 (27.4) 47 (38.1)
Severe [N (%)] 0 (0.0) 1 (0.6) 0 (0.0)

* Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 60 mL/min/1.73 m² and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.
INVOGLI cation tablets

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies (continued)

<table>
<thead>
<tr>
<th>In Combination with Metformin + Metformin + Sulfonlurea (52 weeks)</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>154 (47)</td>
<td>163 (43)</td>
<td>165 (48)</td>
</tr>
<tr>
<td>Severe [N (%)]</td>
<td>12 (3.4)</td>
<td>15 (4.1)</td>
<td>15 (4.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Combination with Metformin + Pioglitazone (26 weeks)</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>3 (0.8)</td>
<td>5 (1.3)</td>
<td>5 (1.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Combination with Insulin (26 weeks)</th>
<th>Placebo</th>
<th>INVOKANA 100 mg</th>
<th>INVOKANA 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [N (%)]</td>
<td>9 (2.7)</td>
<td>9 (2.7)</td>
<td>9 (2.7)</td>
</tr>
</tbody>
</table>

| Severe [N (%)]                     | 1 (0.3) | 1 (0.3)        | 1 (0.3)        |

* 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 biochemically documented)

Laboratory Tests: Increases in Serum Potassium: Dose-related, transient mean increases in serum potassium was observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment [see Clinical Studies (14.3) in full Prescribing Information]. In this trial, increases in serum potassium were greater than 5.4 meq/L and a baseline potassium level occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 meq/L occurred in 1.1%, 1.1%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers [see Warnings and Precautions].

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -6.8% with placebo. In a trial of patients with moderate renal impairment [see Clinical Studies (14.3) in full Prescribing Information], serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increase in serum phosphate levels were observed in a trial of patients with moderate renal impairment [see Clinical Studies (14.3) in full Prescribing Information], serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, 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 [see Warnings and Precautions]. Dose-related increases in non-HDL-C with INVOKANA were observed. 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.

In Hemoglobin: In the pool of four placebo-controlled trials, mean change (percent changes) from baseline were -0.14 g/dL (-0.1%) with placebo, -0.47 g/dL (2.5%) 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, 0.5% and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

**Urine Enzyme Indicators:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A1, UGT2B7, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If co-administration of these UGT inhibitors, (e.g., rifampin, phenobarbital, etc.) is required, INVOKANA must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m², and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer and require additional glycemic control [see Dosage and Administration (2.3) and Warnings and Precautions (5.2) in full prescribing information].

**Diogoxin:** There was an increase in the area AUC and mean peak drug concentration (Cmax) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg [see Clinical Pharmacology (12.3) in full Prescribing Information]. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect fetal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose [see Nonclinical Toxicology (13.2) in full Prescribing Information].

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother [see Nonclinical Toxicology (13.2) in full Prescribing Information].

**Geriatic Use:** Two thousand thirty-four (2304) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA [see Clinical Studies (14.3) in full Prescribing Information].

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 300 mg daily dose, compared to younger patients. More prominent increase in the incidence of adverse reactions who were 75 years and older [see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]. Smaller reductions in HbA1C 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).

**Renal Impairment:** The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²) [see Clinical Studies (14.3) in full Prescribing Information]. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m²); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium [see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions].

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations [see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information].

**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) in full Prescribing Information].
OVERDOSAGE
There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).
In the event of an overdose, contact the Poison Control Center. 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.

PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide).
Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.
Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.
Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.
Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.
Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.
Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.
Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.
Hypotension: 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). Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.
Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice (see Warnings and Precautions).
Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice (see Warnings and Precautions).
Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.
Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.
Active ingredient made in Belgium
Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Licensed from Mitsubishi Tanabe Pharma Corporation
© 2013 Janssen Pharmaceuticals, Inc.
Introducing a NEW approach in type 2 diabetes treatment...
INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

» History of a serious hypersensitivity reaction to INVOKANA™

» Severe renal impairment (eGFR <30 mL/min/1.73 m²), end-stage renal disease, or patients on dialysis.

WARNINGS and PRECAUTIONS

» Hypotension: INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m²), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on adjacent pages.
ENVISION NEW POSSIBILITIES

Introducing INVOKANA™—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter 2 (SGLT2) inhibition.

A1C Reductions as Monotherapy
INVOKANA™ monotherapy provided statistically significant A1C reductions vs placebo at 26 weeks.

A1C Reductions vs Sitagliptin
INVOKANA™ 300 mg demonstrated greater A1C reductions vs sitagliptin 100 mg, in combination with metformin + a sulfonylurea, at 52 weeks (P<0.05).

Incidence of Hypoglycemia
With metformin and a sulfonylurea over 52 weeks:
INVOKANA™ 300 mg: 43.2%; sitagliptin 100 mg: 40.7%

Convenient Once-Daily Dosing
Recommended starting dose: INVOKANA™ 100 mg
Dose can be increased to 300 mg in patients tolerating 100 mg, who have an eGFR of ≥60 mL/min/1.73 m² and require additional glycemic control.

The most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.


Learn more at INVOKANAhcp.com/journal

INVOKANA™ is not indicated for weight loss or as antihypertensive treatment.
WARNINGS and PRECAUTIONS (cont’d)

- Impairment in Renal Function: INVOKANA™ (canagliflozin) increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m².

- Hyperkalemia: INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

- Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.

- Genital Mycotic Infections: INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.

- Hypersensitivity Reactions: Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.

- Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.

- Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

DRUG INTERACTIONS

- UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m², and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.

- Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥20.5 times clinical exposure from a 300-mg dose. These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- Nursing Mothers: It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing...
WARNINGS and PRECAUTIONS

IMPORTANT SAFETY INFORMATION

Impairment in Renal Function:

Macrovascular Outcomes:

Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues

Genital Mycotic Infections:

Hyperkalemia:

Hepatic Impairment:

OVERDOSAGE

ADVERSE REACTIONS

The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

Please see Brief Summary of full Prescribing Information on adjacent pages.