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

----------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 with type 2 diabetes mellitus (1)

Limitation of Use:
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1)

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

- The recommended starting dose is 100 mg once daily, taken before the first meal of the day (2.1)
- Dose can be increased to 300 mg once daily in patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control (2.1)
- INVOKANA is limited to 100 mg once daily in patients who have an eGFR of 45 to less than 60 mL/min/1.73 m^2 (2.2)
- Assess renal function before initiating INVOKANA. Do not initiate INVOKANA if eGFR is below 45 mL/min/1.73 m^2 (2.2)
- Discontinue INVOKANA if eGFR falls below 45 mL/min/1.73 m^2 (2.2)

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

Tablets: 100 mg, 300 mg (3)

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

- History of serious hypersensitivity reaction to INVOKANA (4)
- Severe renal impairment, ESRD, or on dialysis (4)

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

- Hypotension: Before initiating INVOKANA, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or if on diuretics, ACEi, or ARB. Monitor for signs and symptoms during therapy (5.1)
- Impairment in Renal Function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR below 60 mL/min/1.73 m^2 (5.2)
- Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia (5.3)
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKANA (5.4)
- Genital mycotic infections: Monitor and treat if indicated (5.5)
- Hypersensitivity reactions: Discontinue INVOKANA and monitor until signs and symptoms resolve (5.6)
- Increased LDL-C: Monitor LDL-C and treat per standard of care (5.7)

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

- Most common adverse reactions associated with INVOKANA (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----------

- UGT inducers (e.g., rifampin): Canagliflozin exposure is reduced. Consider increasing dose from 100 mg to 300 mg (2.3, 7.1)
- Digoxin: Monitor digoxin levels (7.2)

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

- Pregnancy: No adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Nursing mothers: Discontinue drug or nursing (8.3)
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume (5.1, 8.5)
- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.2, 5.2, 8.6)
- Hepatic impairment: Not recommended with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INVOKANA® (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14)]*.

Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dose of INVOKANA (canagliflozin) is 100 mg once daily, taken before the first meal of the day. In patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control, the dose can be increased to 300 mg once daily *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.2), and Patient Counseling Information (17)]*.

In patients with volume depletion, correcting this condition prior to initiation of INVOKANA is recommended *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5 and 8.6), and Patient Counseling Information (17)]*.

2.2 Patients with Renal Impairment

No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater).

The dose of INVOKANA is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m^2.

INVOKANA should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

Assessment of renal function is recommended prior to initiation of INVOKANA therapy and periodically thereafter. INVOKANA should be discontinued when eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

2.3 Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers

If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, consider increasing the dosage to 300 mg once daily in patients currently tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control *[see Drug Interactions (7.1)]*.

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Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions (5.6)]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions (6.1)]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

5.2 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 (6.1)]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

5.3 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 *[see Adverse Reactions (6.1)]*.

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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.

5.4 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 (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

5.5 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 *[see Adverse Reactions (6.1)]*. Monitor and treat appropriately.

5.6 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., 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 *[see Contraindications (4) and Adverse Reactions (6.1)]*.

5.7 Increases in Low-Density Lipoprotein (LDL-C)

Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions (6.1)]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

5.8 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

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

- Hypotension *[see Warnings and Precautions (5.1)]*
- Impairment in Renal Function *[see Warnings and Precautions (5.2)]*
- Hyperkalemia *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.5)]*

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- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Increases in Low-Density Lipoprotein (LDL-C) *[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.

Pool of Placebo-Controlled Trials

The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14)]*. These data reflect exposure of 1667 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 Caucasian, 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 HbA1C 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 1 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.

Table 1: Adverse Reactions From Pool of Four 26−Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	**Placebo N=646**	**INVOKANA 100 mg N=833**	**INVOKANA 300 mg N=834**
Female genital mycotic infections[†]	3.2%	10.4%	11.4%
Urinary tract infections[‡]	4.0%	5.9%	4.3%
Increased urination[§]	0.8%	5.3%	4.6%
Male genital mycotic infections[¶]	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst[#]	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

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* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.
† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).
‡ 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. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).
# Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

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%).

Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14)]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received 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 5% 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 81 mL/min/1.73 m^2).

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 (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 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.

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In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. 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%, 3.8%, 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, 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:

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 m^2), and age 75 years and older (Table 2) *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), and Use in Specific Populations (8.5 and 8.6)]*.

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

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

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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

			Placebo N=646	**INVOKANA 100 mg N=833**	**INVOKANA 300 mg N=834**
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

* 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 80 mL/min/1.73 m^2 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.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3)]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall

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incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions (5.2)]*.

Genital Mycotic Infections

In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. 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 *[see Warnings and Precautions (5.5)]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% 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 the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions (5.5)]*.

Hypoglycemia

In all clinical 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

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(regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14)]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions (5.4)]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

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 (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (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 (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (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 + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + 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 + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + 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)

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Laboratory Tests

Increases in Serum Potassium

Dose-related, transient mean increases in serum potassium were 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 this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline 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%, 2.2%, 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 (5.2 and 5.3)]*.

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 -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3)]*, 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 increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3)]*, the mean 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 (5.7)]*.

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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.

Increases in Hemoglobin

In the pool of four placebo-controlled trials, 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.

7 DRUG INTERACTIONS

7.1 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 (e.g., 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 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.2 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 *[see Clinical Pharmacology (12.3)]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

7.3 Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

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7.4 Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 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 renal 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)]*.

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.

8.3 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 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 *[see Nonclinical Toxicology (13.2)]*.

8.4 Pediatric Use

Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

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8.5 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 *[see Clinical Studies (14.3)]*.

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 and older *[see Dosage and Administration (2.1) and Adverse Reactions (6.1)]*. 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).

8.6 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 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3)]*. 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 m^2)*;* patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, and 5.3), and Adverse Reactions (6.1)]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications (4) and 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

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

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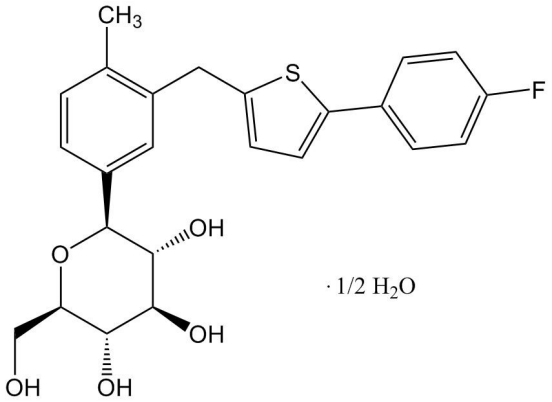
In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

11 DESCRIPTION

INVOKANA (canagliflozin) contains canagliflozin, an inhibitor of sodium-glucose co-transporter 2 (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 $C_{24}H_{25}FO_5S \bullet 1/2\ H_2O$ 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, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. The magnesium stearate is vegetable-sourced. The tablets are finished with a commercially available film-coating consisting of the following excipients: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, macrogol/PEG, talc, and iron oxide yellow, E172 (100 mg tablet only).

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium-glucose co-transporter 2 (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.

12.2 Pharmacodynamics

Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in the renal threshold for glucose (RT_G) and increases in urinary glucose excretion were observed. From a starting value of RT_G of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RT_G throughout the 24-hour period. 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 studies. In patients with type 2 diabetes given 100 mg 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 study, plasma glucose declined in a dose-dependent fashion within the first day of dosing. In single-dose studies in healthy and type 2 diabetic subjects, 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 study, 60 healthy subjects were administered a single oral dose of canagliflozin 300 mg, canagliflozin 1,200 mg (4 times the maximum recommended dose), moxifloxacin, and placebo. No meaningful changes in QTc interval were observed with either the recommended dose of 300 mg or the 1,200 mg dose.

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.

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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 (2.1)]*.

Distribution

The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 119 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (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.

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Specific Populations

Renal Impairment

A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using the MDRD-eGFR formula) compared to healthy subjects.

Renal impairment did not affect the C_{max} of canagliflozin. Compared to healthy subjects (N=3; eGFR greater than or equal to 90 mL/min/1.73 m^2), plasma AUC of canagliflozin was increased by approximately 15%, 29%, and 53% in subjects with mild (N=10), moderate (N=9), and severe (N=10) renal impairment, respectively, (eGFR 60 to less than 90, 30 to less than 60 and 15 to less than 30 mL/min/1.73 m^2, respectively), but was similar for ESRD (N=8) subjects and healthy subjects.

Increases in canagliflozin AUC of this magnitude are not considered clinically relevant. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

Canagliflozin was negligibly removed by hemodialysis.

Hepatic Impairment

Relative to subjects with normal hepatic function, the geometric mean ratios for C_{max} and AUC_{∞} of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and 96% and 111%, respectively, in subjects with Child-Pugh class B (moderate hepatic impairment) following administration of a single 300 mg dose of canagliflozin.

These differences are not considered to be clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment *[see Use in Specific Populations (8.7)]*.

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

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

Pediatric

Studies characterizing the pharmacokinetics of canagliflozin in pediatric patients have not been conducted.

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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.

In Vivo Assessment of Drug Interactions

Table 5: 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 (7.1)* 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	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 6: 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)

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Table 6: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	Dose of Co-Administered Drug*	Dose of Canagliflozin*	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0		
				AUC† (90% CI)	C_{max} (90% CI)
See *Drug Interactions (7.2)* for the clinical relevance of the following:					
Digoxin	0.5 mg QD first day followed by 0.25 mg QD for 6 days	300 mg QD for 7 days	digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)
No dose adjustments of co-administered drug required for the following:					
Acetaminophen	1,000 mg	300 mg BID for 25 days	acetaminophen	1.06‡ (0.98; 1.14)	1.00 (0.92; 1.09)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	ethinyl estradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)
			levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)
Glyburide	1.25 mg	200 mg QD for 6 days	glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)
Hydrochloro-thiazide	25 mg QD for 35 days	300 mg QD for 7 days	hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2,000 mg	300 mg QD for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Simvastatin	40 mg	300 mg QD for 7 days	simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)
			simvastatin acid	1.18 (1.03; 1.35)	1.26 (1.10; 1.45)
Warfarin	30 mg	300 mg QD for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (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_{0-12h}
QD = once daily; BID = twice daily; INR = International Normalized Ratio

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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 study, LH did not increase in males treated with canagliflozin.

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

Mutagenesis

Canagliflozin was not mutagenic with or without metabolic activation in the Ames assay. Canagliflozin was mutagenic in the *in vitro* mouse lymphoma assay with but not without metabolic activation. Canagliflozin was not mutagenic or clastogenic in an *in vivo* oral micronucleus assay in rats and an *in vivo* oral Comet assay in rats.

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.

13.2 Animal Toxicology and/or Pharmacology

In a juvenile toxicity study in which canagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg, increased kidney weights and a dose-related increase in the incidence and severity renal pelvic and renal tubular dilatation were reported at all dose levels. Exposure at the lowest dose tested was greater than or equal to 0.5 times the maximum clinical dose of 300 mg. The renal pelvic dilatations observed in

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juvenile animals did not fully reverse within the 1-month recovery period. Similar effects on the developing kidney were not seen when canagliflozin was administered to pregnant rats or rabbits during the period of organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21 and pups were indirectly exposed *in utero* and throughout lactation.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of non-renal organogenesis in humans.

No developmental toxicities were observed at any dose tested other than a slight increase in the number of fetuses with reduced ossification at a dose that was associated with maternal toxicity and that is approximately 19 times the human exposure to canagliflozin at the 300 mg clinical dose.

14 CLINICAL STUDIES

INVOKANA (canagliflozin) has been studied as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and a thiazolidinedione (i.e., pioglitazone), and in combination with insulin (with or without other antihyperglycemic agents). The efficacy of INVOKANA was compared to a dipeptidyl peptidase-4 (DPP-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.

In patients with type 2 diabetes, treatment with INVOKANA produced clinically and statistically significant improvements in HbA1C compared to placebo. Reductions in HbA1C were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

14.1 Monotherapy

A total of 584 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of INVOKANA. The mean age was 55 years, 44% of patients were men, 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 HbA1C ($p<0.001$ for both doses) compared to placebo. INVOKANA

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100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C 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 7). 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 7: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA as Monotherapy*

Efficacy Parameter	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
HbA1C (%)			
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 HbA1C < 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)
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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p<0.001

14.2 Combination Therapy

Add-on Combination Therapy With Metformin

A total of 1284 patients with type 2 diabetes inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day if higher dose not tolerated) participated in a 26-week, double-blind, placebo- and active-controlled study to evaluate the efficacy and safety of INVOKANA in combination with metformin. The mean age was 55 years, 47% of patients were men, and the mean baseline eGFR was 89 mL/min/1.73 m^2. Patients already on the required metformin dose (N=1009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin dose or

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patients on metformin in combination with another antihyperglycemic agent (N=275) were switched to metformin monotherapy (at doses described above) for at least 8 weeks before entering the 2-week, single-blind, placebo run-in. After the placebo run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, sitagliptin 100 mg, or placebo, administered once daily as add-on therapy to metformin.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C (p<0.001 for both doses) compared to placebo when added to metformin. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin (see Table 8). 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 8: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin*

Efficacy Parameter	Placebo + Metformin (N=183)	INVOKANA 100 mg + Metformin (N=368)	INVOKANA 300 mg + Metformin (N=367)
HbA1C (%)			
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 HbA1C < 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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value and stratification factors
‡ p<0.001

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

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

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

As shown in Table 9 and Figure 1, at the end of treatment, INVOKANA 100 mg provided similar reductions in HbA1C from baseline compared to glimepiride when added to metformin therapy. INVOKANA 300 mg provided a greater reduction from baseline in HbA1C compared to glimepiride, and the relative treatment difference was -0.12% (95% CI: −0.22; −0.02). As shown in Table 9, treatment with INVOKANA 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

Table 9: Results from 52−Week Clinical Study Comparing INVOKANA to Glimepiride in Combination with Metformin*

Efficacy Parameter	INVOKANA 100 mg + Metformin (N=483)	INVOKANA 300 mg + Metformin (N=485)	Glimepiride (titrated) + Metformin (N=482)
HbA1C (%)			
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 HbA1C < 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)	

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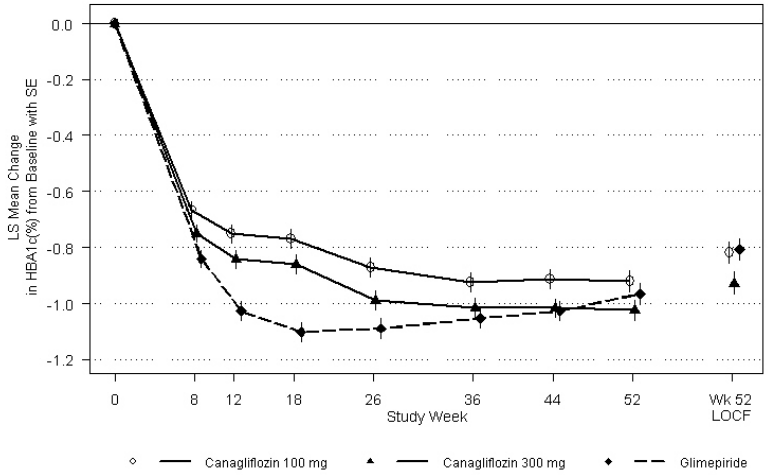
Table 9: Results from 52−Week Clinical Study Comparing INVOKANA to Glimepiride in Combination with Metformin*

Efficacy Parameter	INVOKANA 100 mg + Metformin (N=483)	INVOKANA 300 mg + Metformin (N=485)	Glimepiride (titrated) + Metformin (N=482)

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

Figure 1: Mean HbA1C Change 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 patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy participated in an 18-week, double-blind, placebo-controlled sub-study to evaluate the efficacy and safety of INVOKANA in combination with sulfonylurea. The mean age was 65 years, 57% of patients were men, 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 10, at the end of treatment, INVOKANA 100 mg and 300 mg daily provided statistically significant (p<0.001 for both doses) improvements in HbA1C relative to placebo when added to sulfonylurea. INVOKANA 300 mg once daily compared to placebo resulted in a

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greater proportion of patients achieving an HbA1C 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 10: Results from 18-Week Placebo−Controlled Clinical Study of INVOKANA in Combination with Sulfonylurea*

Efficacy Parameter	Placebo + Sulfonylurea (N=45)	INVOKANA 100 mg + Sulfonylurea (N=42)	INVOKANA 300 mg + Sulfonylurea (N=40)
HbA1C (%)			
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 study prior to glycemic rescue therapy
† Least squares mean adjusted for baseline value
‡ p<0.001

Add-on Combination Therapy With Metformin and Sulfonylurea

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

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C (p<0.001 for both doses) compared to placebo when added to metformin and sulfonylurea. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C 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 and sulfonylurea (see Table 11).

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Table 11: Results from 26−Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	Placebo + Metformin and Sulfonylurea (N=156)	INVOKANA 100 mg + Metformin and Sulfonylurea (N=157)	INVOKANA 300 mg + Metformin and Sulfonylurea (N=156)
HbA1C (%)			
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 A1C < 7%	18	43‡	57‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	170	173	168
Change from baseline (adjusted mean)	4	-18	-31
Difference from placebo (adjusted mean) (95% CI)†		-22‡ (-31 , -13)	-35‡ (-44,- 25)
Body Weight			
Baseline (mean) in kg	90.8	93.5	93.5
% change from baseline (adjusted mean)	-0.7	-2.1	-2.6
Difference from placebo (adjusted mean) (95% CI)†		-1.4‡ (-2.1;- 0.7)	-2.0‡ (-2.7;- 1.3)

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

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

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

As shown in Table 12 and Figure 2, at the end of treatment, INVOKANA 300 mg provided greater HbA1C reduction compared to sitagliptin 100 mg when added to metformin 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

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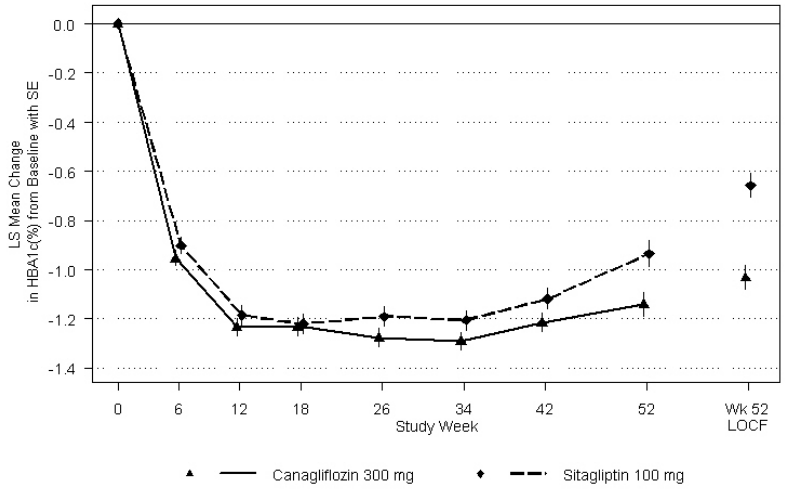
blood pressure from baseline of -5.06 mmHg was observed with INVOKANA 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

Table 12: Results from 52−Week Clinical Study Comparing INVOKANA to Sitagliptin in Combination with Metformin and Sulfonylurea*

Efficacy Parameter	INVOKANA 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
HbA1C (%)		
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 HbA1C < 7%	48	35
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	170	164
Change from baseline (adjusted mean)	-30	-6
Difference from sitagliptin (adjusted mean) (95% CI) †	-24 (-30; -18)	
Body Weight		
Baseline (mean) in kg	87.6	89.6
% change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI) †	-2.8§ (-3.3; -2.2)	

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

Figure 2: Mean HbA1C Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



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Add-on Combination Therapy With Metformin and Pioglitazone

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

At the of end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin and pioglitazone. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG) and in percent body weight reduction compared to placebo when added to metformin and pioglitazone (see Table 13). 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 13: Results from 26−Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin and Pioglitazone*

Efficacy Parameter	Placebo + Metformin and Pioglitazone (N=115)	INVOKANA 100 mg + Metformin and Pioglitazone (N=113)	INVOKANA 300 mg + Metformin and Pioglitazone (N=114)
HbA1C (%)			
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 HbA1C < 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

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Table 13: Results from 26−Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin and Pioglitazone*

Efficacy Parameter	Placebo + Metformin and Pioglitazone (N=115)	INVOKANA 100 mg + Metformin and Pioglitazone (N=113)	INVOKANA 300 mg + Metformin and Pioglitazone (N=114)
Difference from placebo (adjusted mean) (95% CI)[†]		-2.7[‡] (-3.6; -1.8)	-3.7[‡] (-4.6; -2.8)

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

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

A total of 1718 patients with type 2 diabetes inadequately controlled on insulin greater than or equal to 30 units/day or insulin in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled substudy of a cardiovascular study to evaluate the efficacy and safety of INVOKANA in combination with insulin. The mean age was 63 years, 66% of patients were men, 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 of end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C (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 HbA1C less than 7%, in significant reductions in fasting plasma glucose (FPG), and in percent body weight reductions compared to placebo (see Table 14). 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 14: Results from 18−Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Insulin ≥ 30 Units/Day (With or Without Other Oral Antihyperglycemic Agents)*

Efficacy Parameter	Placebo + Insulin (N=565)	INVOKANA 100 mg + Insulin (N=566)	INVOKANA 300 mg + Insulin (N=587)
HbA1C (%)			
Baseline (mean)	8.20	8.33	8.27
Change from baseline (adjusted mean)	0.01	-0.63	-0.72

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Table 14: Results from 18−Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Insulin ≥ 30 Units/Day (With or Without Other Oral Antihyperglycemic Agents)*

Efficacy Parameter	Placebo + Insulin (N=565)	INVOKANA 100 mg + Insulin (N=566)	INVOKANA 300 mg + Insulin (N=587)
Difference from placebo (adjusted mean) (95% CI) †		-0.65‡ (-0.73, -0.56)	-0.73‡ (-0.82, -0.65)
Percent of patients achieving HbA1C < 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, -1.5)	-2.4‡ (-2.8, -2.0)

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

14.3 Studies in Special Populations

Adults 55 to 80 Years of Age

A total of 714 older patients with type 2 diabetes 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 study to evaluate the efficacy and safety of INVOKANA in combination with current diabetes treatment. The mean age was 64 years, 55% of patients were men, and the mean baseline eGFR was 77 mL/min/1.73 m^2. Patients were randomized 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 HbA1C (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. Statistically significant (p<0.001 for both doses) reductions from baseline in fasting plasma glucose (FPG) and body weight were also observed in this study relative to placebo *[see Use in Specific Populations (8.5)]*.

Moderate Renal Impairment

A total of 269 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 study to evaluate the efficacy and safety of INVOKANA in combination with current diabetes treatment (diet or antihyperglycemic agent

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therapy, with 95% of patients on insulin and/or sulfonylurea). The mean age was 68 years, 61% of patients were men, and the mean baseline eGFR was 39 mL/min/1.73 m^2. Patients were randomized 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 HbA1C 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 (5.2), Adverse Reactions (6.1), and Use in Specific Populations (8.6)]*.

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
NDC 50458-140-10	Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

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
NDC 50458-141-10	Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

17 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

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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 (5.1)]*. 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 (5.5)]*.

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

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foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.5)]*.

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

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

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Licensed from Mitsubishi Tanabe Pharma Corporation

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MEDICATION GUIDE
INVOKANA™ (in-vo-KAHN-uh)
(canagliflozin)
Tablets

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

INVOKANA can cause important side effects, including:

- **Dehydration. INVOKANA can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).**

  You may be at higher risk of dehydration if you:

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

- **Vaginal yeast infection.** Women who take INVOKANA may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:

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

- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take INVOKANA may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:

  - redness, itching, or swelling of the penis
  - rash of the penis

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- foul smelling discharge from the penis
- pain in the skin around penis

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

What is INVOKANA?

- INVOKANA is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- INVOKANA is not for people with type 1 diabetes.
- INVOKANA is not for people with diabetic ketoacidosis (increased ketones in blood or urine).
- It is not known if INVOKANA is safe and effective in children under 18 years of age.

Who should not take INVOKANA?

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, tongue, and throat that may cause difficulty in breathing or swallowing
- have severe kidney problems or are on dialysis.

What should I tell my doctor before taking INVOKANA?

Before you take INVOKANA, tell your doctor if you:

- have kidney problems
- have liver problems

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- are on a low sodium (salt) diet. Your doctor may change your diet or your dose of INVOKANA.
- have ever had an allergic reaction to INVOKANA
- have other medical conditions
- are pregnant or plan to become pregnant. It is not known if INVOKANA will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if INVOKANA passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking INVOKANA.

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

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

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

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

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

How should I take INVOKANA?

- Take INVOKANA by mouth 1 time each day exactly as your doctor tells you to take it.
- Your doctor will tell you how much INVOKANA to take and when to take it. Your doctor may change your dose if needed.
- It is best to take INVOKANA before the first meal of the day.

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- Your doctor 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?**"
- 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 doctor if you have questions about a missed dose.
- If you take too much INVOKANA, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Stay on your prescribed diet and exercise program while taking INVOKANA.
- Check your blood sugar as your doctor tells you to.
- INVOKANA will cause your urine to test positive for glucose.
- Your doctor may do certain blood tests before you start INVOKANA and during treatment as needed. Your doctor may change your dose of INVOKANA based on the results of your blood tests.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

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?"**

- **kidney problems**
- **a high amount of potassium in your blood (hyperkalemia)**

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- **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
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heart-beat
  - sweating
  - shaking or feeling jittery

- **serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking INVOKANA and call your doctor right away or go to the nearest hospital emergency room. See **"Who should not take INVOKANA?".** Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.

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?**")
- urinary tract infection
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Pharmaceuticals, Inc. at 1-800-526-7736.

How should I store 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.**

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General information about the safe and effective use of INVOKANA.

Medicines are sometimes prescribed for purposes other than those listed in the 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 you have. It may harm them.

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

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

What are the ingredients of INVOKANA?

Active ingredient: canagliflozin

Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, and microcrystalline cellulose. In addition, the tablet coating contains iron oxide yellow E172 (100 mg tablet only), macrogol/PEG, polyvinyl alcohol, talc, and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Active ingredient made in Belgium.

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

Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Licensed from Mitsubishi Tanabe Pharma Corporation

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