

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204042Orig1s026

Trade Name: **INVOKANA**

Generic Name: **Canagliflozin**

Sponsor: **Janssen Research & Development, LLC**

Approval Date: **07/25/2017**

Indications: 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

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	X
Administrative/Correspondence Document(s)	X

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APPROVAL LETTER



NDA 204042/ S-026

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
Attention: Sukhdev K. Saran
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Saran:

Please refer to your supplemental New Drug Application (sNDA) dated and received June 15, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invokana (canagliflozin) tablets.

We also refer to our letter dated May 16, 2017, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for products containing canagliflozin. This information pertains to the risk of lower limb amputation.

This sNDA provides for revisions to the labeling for Invokana, consistent with our May 16, 2017, letter and the labeling comments provided to you via teleconferences on June 21 and July 14, 2017, and via email correspondences on July 7, 12, 13, and 14, 2017.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below and indicated in the enclosed labeling.

- Revision dates updated to reflect the date of approval of this supplement.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide) with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes with the revisions listed above approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Liz Godwin, Regulatory Project Manager, at 240-402-3438.

Sincerely,

{See appended electronic signature page}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Invokana Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER R PIPPINS
07/25/2017

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LABELING

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

WARNING: LOWER LIMB AMPUTATION

See full prescribing information for complete boxed warning.

- In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, INVOKANA has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg (5.1)
- Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA for infections or ulcers of the lower limbs, and discontinue if these occur. (5.1)

RECENT MAJOR CHANGES

Boxed Warning 07/2017
Warnings and Precautions (5.1) 07/2017

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 m² or greater and require additional glycemic control (2.1)
- Assess renal function before initiating and periodically thereafter. (2.2)
- Limit the dose of INVOKANA to 100 mg once daily in patients who have an eGFR of 45 to less than 60 mL/min/1.73 m² (2.2)
- Initiation or use of INVOKANA is not recommended if eGFR is below 45 mL/min/1.73 m² (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

- Lower Limb Amputation: See boxed warning (5.1)
- 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 (5.2)

- Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue INVOKANA, evaluate and treat promptly. Before initiating INVOKANA, consider risk factors for ketoacidosis. Patients on INVOKANA may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis (5.3)
- Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy (5.4)
- Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia (2.2, 5.5, 6.1, 8.6)
- Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.6)
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKANA (5.7)
- Genital mycotic infections: Monitor and treat if indicated (5.8)
- Hypersensitivity reactions: Discontinue INVOKANA and monitor until signs and symptoms resolve (5.9)
- Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKANA (5.10)
- Increased LDL-C: Monitor LDL-C and treat if appropriate (5.11)

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: Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- Lactation: INVOKANA is not recommended when breastfeeding (8.2)
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume (5.2, 8.5)
- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.2, 5.4, 8.6)
- Hepatic impairment: Not recommended with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LOWER LIMB AMPUTATION

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Patients with Renal Impairment
- 2.3 Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Lower Limb Amputation
- 5.2 Hypotension
- 5.3 Ketoacidosis
- 5.4 Acute Kidney Injury and Impairment in Renal Function
- 5.5 Hyperkalemia
- 5.6 Urosepsis and Pyelonephritis
- 5.7 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- 5.8 Genital Mycotic Infections
- 5.9 Hypersensitivity Reactions
- 5.10 Bone Fracture

- 5.11 Increases in Low-Density Lipoprotein (LDL-C)
- 5.12 Macrovascular Outcomes
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Studies Experience
 - 6.2 Postmarketing Experience
- 7 DRUG INTERACTIONS**
 - 7.1 UGT Enzyme Inducers
 - 7.2 Digoxin
 - 7.3 Positive Urine Glucose Test
 - 7.4 Interference with 1,5-anhydroglucitol (1,5-AG) Assay
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Renal Impairment
 - 8.7 Hepatic Impairment

- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
 - 14.1 Monotherapy
 - 14.2 Combination Therapy
 - 14.3 Studies in Special Populations
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

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

FULL PRESCRIBING INFORMATION

WARNING: LOWER LIMB AMPUTATION

- An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD.
- Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.
- Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.
- Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur [see Warnings and Precautions (5.1)].

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 m² or greater and require additional glycemic control, the dose can be increased to 300 mg once daily [see Warnings and Precautions (5.4), 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 (5.2), Use in Specific Populations (8.5 and 8.6), and Patient Counseling Information (17)].

2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of INVOKANA and periodically thereafter.

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 m².

Initiation of INVOKANA is not recommended in patients with an eGFR less than 45 mL/min/1.73 m².

Use of INVOKANA is not recommended when eGFR is persistently less than 45 mL/min/1.73 m² [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.6)*].

INVOKANA is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see *Contraindications (4)*].

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 m² or greater and require additional glycemic control [see *Drug Interactions (7.1)*].

Consider another antihyperglycemic agent in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² 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, such as anaphylaxis or angioedema [see *Warnings and Precautions (5.9) and Adverse Reactions (6.1, 6.2)*].
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease (ESRD), or patients on dialysis [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. In CANVAS, INVOKANA-treated patients and placebo-treated patients had 5.9 and 2.8 amputations per 1000 patients per year, respectively. In CANVAS-R, INVOKANA-treated patients and placebo-treated patients had 7.5 and 4.2 amputations per 1000 patients per year, respectively. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively [*see Adverse Reactions (6.1)*].

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

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

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

5.2 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 m²), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus [*see Indications and Usage (1)*].

Patients treated with INVOKANA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKANA, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with INVOKANA consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.4 Acute Kidney Injury and Impairment in Renal Function

INVOKANA causes intravascular volume contraction [*see Warnings and Precautions (5.2)*] and can cause renal impairment [*see Adverse Reactions (6.1)*]. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving INVOKANA; some reports involved patients younger than 65 years of age.

Before initiating INVOKANA, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and

concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing INVOKANA in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue INVOKANA promptly and institute treatment.

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)*]. Renal function should be evaluated prior to initiation of INVOKANA and monitored periodically thereafter. Dosage adjustment and more frequent renal function monitoring are recommended in patients with an eGFR below 60 mL/min/1.73 m². Use of INVOKANA is not recommended when eGFR is persistently less than 45 mL/min/1.73 m² and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see *Dosage and Administration (2.2)*, *Contraindications (4)* and *Use in Specific Populations (8.6)*].

5.5 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 at an increased risk of developing hyperkalemia [see *Dosage and Administration (2.2)* and *Adverse Reactions (6.1)*].

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.

5.6 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated [see *Adverse Reactions (6)*].

5.7 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.

5.8 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.

5.9 Hypersensitivity Reactions

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

5.10 Bone Fracture

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

5.11 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 if appropriate after initiating INVOKANA.

5.12 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

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

- Lower Limb Amputation [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Hypotension [see *Warnings and Precautions (5.2)*]
- Ketoacidosis [see *Warnings and Precautions (5.3)*]
- Acute Kidney Injury and Impairment in Renal Function [see *Warnings and Precautions (5.4)*]
- Hyperkalemia [see *Warnings and Precautions (5.5)*]
- Urosepsis and Pyelonephritis [see *Warnings and Precautions (5.6)*]
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues [see *Warnings and Precautions (5.7)*]
- Genital Mycotic Infections [see *Warnings and Precautions (5.8)*]

- Hypersensitivity Reactions [*see Warnings and Precautions (5.9)*]
- Bone Fracture [*see Warnings and Precautions (5.10)*]
- Increases in Low-Density Lipoprotein (LDL-C) [*see Warnings and Precautions (5.11)*]

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 HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m²).

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
Urinary tract infections [‡]	3.8%	5.9%	4.4%
Increased urination [§]	0.7%	5.1%	4.6%
Thirst [#]	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	N=425	N=430
Female genital mycotic infections [†]	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	N=408	N=404
Male genital mycotic infections [¶]	0.7%	4.2%	3.8%

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

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

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

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

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

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

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

Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions for canagliflozin was 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 HbA_{1C} 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 m²).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool,

INVOKANA was also associated with the adverse reactions of fatigue (1.8% 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 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

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

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

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

Lower Limb Amputation

An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively [see *Warnings and Precautions (5.1)*].

Table 2: CANVAS AMPUTATIONS

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (Pooled) N=2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

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

Table 3: CANVAS-R AMPUTATIONS

	Placebo N=2903	INVOKANA 100 mg (with up-titration to 300 mg) N=2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

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

Volume Depletion-Related Adverse Reactions

INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²), and age 75 years and older (Table 4) [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.2), and *Use in Specific Populations* (8.5 and 8.6)].

Table 4: 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

Falls

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

Impairment in Renal Function

INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 5). Patients with moderate renal impairment at baseline had larger mean changes.

Table 5: 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 m² and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

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 m² (mean baseline eGFR 39 mL/min/1.73 m²) [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 2.2% 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 m² (mean baseline eGFR 48 mL/min/1.73 m²), the overall 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 has been 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 (5.4)*].

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 2.8%, 10.6%, and 11.6% 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. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively [*see Warnings and Precautions (5.8)*].

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively. In the pooled analysis of 8 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 (5.8)*].

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 (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 6) [see *Warnings and Precautions (5.7)*].

Table 6: 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)

Bone Fracture

The occurrence of bone fractures was evaluated in a pool of nine clinical trials with a mean duration of exposure to INVOKANA of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, INVOKANA 100 mg, and INVOKANA 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., fall from no more than standing height), and affect the upper extremities [*see Warnings and Precautions (5.10)*].

Laboratory and Imaging Tests

Increases in Serum Potassium

In a pooled population of patients (N=723) with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m²), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers [*see Warnings and Precautions (5.4 and 5.5) and Use in Specific Populations (8.6)*].

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 percent 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 percent 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 (5.11)*].

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.

Decreases in Bone Mineral Density

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) [see *Clinical Studies (14.3)*]. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

6.2 Postmarketing Experience

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

Ketoacidosis [*see Warnings and Precautions (5.3)*]

Acute Kidney Injury and Impairment in Renal Function [*see Warnings and Precautions (5.4)*]

Anaphylaxis, Angioedema [*see Warnings and Precautions (5.9)*]

Urosepsis and Pyelonephritis [*see Warnings and Precautions (5.6)*]

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 m², and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m² receiving concurrent therapy with a UGT inducer and require additional glycemic control [*see Dosage and Administration (2.3) and 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.

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

Risk Summary

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

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

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Animal Data

Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that

correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1 month recovery period.

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats [*see Data*]. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

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

Data

Animal Data

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

8.4 Pediatric Use

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

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; a more prominent increase in the incidence was seen in patients who were 75 years and older [see *Dosage and Administration (2.1) and Adverse Reactions (6.1)*]. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

8.6 Renal Impairment

The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m²) [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 m²). Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) 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. Severe elevations (greater than or equal to 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 [see *Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.4, and 5.5), 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 m²), 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)*].

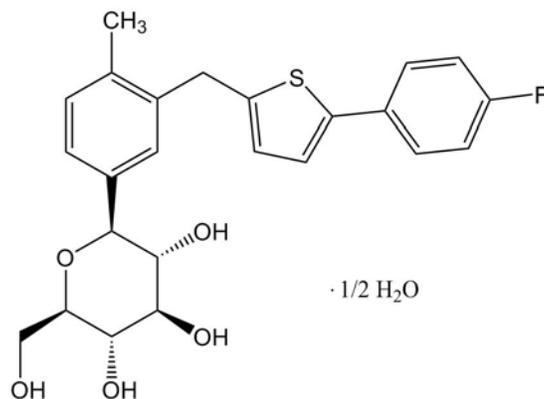
10 OVERDOSAGE

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

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 $C_{24}H_{25}FO_5S \cdot 1/2 H_2O$ and 453.53, respectively. The structural formula for canagliflozin is:



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

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

Inactive ingredients of the core tablet are croscarmellose sodium, 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).

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 (UGE).

12.2 Pharmacodynamics

Following single and multiple oral doses of canagliflozin in patients with type 2 diabetes, dose-dependent decreases in the renal threshold for glucose (RT_G) and increases in urinary glucose excretion were observed. From a starting RT_G value of approximately 240 mg/dL, canagliflozin at 100 mg and 300 mg once daily suppressed RT_G throughout the 24-hour period. 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. The reductions in RT_G led to increases in mean UGE of approximately 100 g/day in subjects with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin. 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.

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 83.5 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metabolism

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites.

CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

Excretion

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

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

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

Specific Populations

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 m²), 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 m², 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 (5.4)*].

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)*].

Pharmacokinetic 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 the pharmacokinetics of canagliflozin [see *Use in Specific Populations (8.5)*].

Pediatric

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

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 7: Effect of Co-Administered Drugs on Systemic Exposures of Canagliflozin

Co-Administered Drug	Dose of Co-Administered Drug*	Dose of Canagliflozin*	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect=1.0	
			AUC [†] (90% CI)	C _{max} (90% CI)
See Drug Interactions (7.1) 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 8: Effect of Canagliflozin on Systemic Exposure of Co-Administered Drugs

Co-Administered Drug	Dose of Co-Administered Drug*	Dose of Canagliflozin*	Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect = 1.0	
			AUC [†] (90% CI)	C _{max} (90% CI)

See Drug Interactions (7.2) for the clinical relevance of the following:					
Digoxin	0.5 mg QD first day followed by 0.25 mg QD for 6 days	300 mg QD for 7 days	digoxin	1.20 (1.12; 1.28)	1.36 (1.21; 1.53)
No dose adjustments of co-administered drug required for the following:					
Acetaminophen	1,000 mg	300 mg BID for 25 days	acetaminophen	1.06 [†] (0.98; 1.14)	1.00 (0.92; 1.09)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	ethinyl estradiol	1.07 (0.99; 1.15)	1.22 (1.10; 1.35)
			levonorgestrel	1.06 (1.00; 1.13)	1.22 (1.11; 1.35)
Glyburide	1.25 mg	200 mg QD for 6 days	glyburide	1.02 (0.98; 1.07)	0.93 (0.85; 1.01)
			3-cis-hydroxy-glyburide	1.01 (0.96; 1.07)	0.99 (0.91; 1.08)
			4-trans-hydroxy-glyburide	1.03 (0.97; 1.09)	0.96 (0.88; 1.04)
Hydrochlorothiazide	25 mg QD for 35 days	300 mg QD for 7 days	hydrochlorothiazide	0.99 (0.95; 1.04)	0.94 (0.87; 1.01)
Metformin	2,000 mg	300 mg QD for 8 days	metformin	1.20 (1.08; 1.34)	1.06 (0.93; 1.20)
Simvastatin	40 mg	300 mg QD for 7 days	simvastatin	1.12 (0.94; 1.33)	1.09 (0.91; 1.31)
			simvastatin acid	1.18 (1.03; 1.35)	1.26 (1.10; 1.45)
Warfarin	30 mg	300 mg QD for 12 days	(R)-warfarin	1.01 (0.96; 1.06)	1.03 (0.94; 1.13)
			(S)-warfarin	1.06 (1.00; 1.12)	1.01 (0.90; 1.13)
			INR	1.00 (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

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

INVOKANA (canagliflozin) has been studied as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and sitagliptin, 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), both as add-on combination therapy with metformin and sulfonylurea, and a sulfonylurea (glimepiride), both as add-on combination therapy with metformin. 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 HbA_{1C} compared to placebo. Reductions in HbA_{1C} were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

14.1 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 m². Patients taking other antihyperglycemic agents (N=281) discontinued the agent and underwent an 8-week washout followed by a 2-week, single-blind, placebo run-in period. Patients not taking oral antihyperglycemic agents (N=303) entered the 2-week, single-blind, placebo run-in period directly. After the placebo run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily for 26 weeks.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} (p<0.001 for both doses) compared to placebo. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo (see Table 9). 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 9: 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)
HbA_{1C} (%)			
Baseline (mean)	7.97	8.06	8.01
Change from baseline (adjusted mean)	0.14	-0.77	-1.03
Difference from placebo (adjusted mean) (95% CI) [†]		-0.91 [‡] (-1.09; -0.73)	-1.16 [‡] (-1.34; -0.99)
Percent of Patients Achieving HbA_{1C} < 7%	21	45 [‡]	62 [‡]
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	166	172	173
Change from baseline (adjusted mean)	8	-27	-35
Difference from placebo (adjusted mean) (95% CI) [†]		-36 [‡] (-42; -29)	-43 [‡] (-50; -37)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	229	250	254
Change from baseline (adjusted mean)	5	-43	-59
Difference from placebo (adjusted mean) (95% CI) [†]		-48 [‡] (-59.1; -37.0)	-64 [‡] (-75.0; -52.9)
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 m². Patients already on the required metformin dose (N=1009) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients taking less than the required metformin dose or patients on metformin in combination with another antihyperglycemic agent (N=275) were switched to metformin monotherapy (at doses described above) for at least 8 weeks before entering the 2-week, single-blind, placebo run-in. After the placebo run-in period, patients were randomized to 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 HbA_{1C} (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 HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin (see Table 10). 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 10: 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)
HbA_{1C} (%)			
Baseline (mean)	7.96	7.94	7.95
Change from baseline (adjusted mean)	-0.17	-0.79	-0.94
Difference from placebo (adjusted mean) (95% CI) [†]		-0.62 [‡] (-0.76; -0.48)	-0.77 [‡] (-0.91; -0.64)
Percent of patients achieving HbA_{1C} < 7%	30	46 [‡]	58 [‡]
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	173

Change from baseline (adjusted mean)	2	-27	-38
Difference from placebo (adjusted mean) (95% CI) [†]		-30 [‡] (-36; -24)	-40 [‡] (-46; -34)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	249	258	262
Change from baseline (adjusted mean)	-10	-48	-57
Difference from placebo (adjusted mean) (95% CI) [†]		-38 [‡] (-49; -27)	-47 [‡] (-58; -36)
Body Weight			
Baseline (mean) in kg	86.7	88.7	85.4
% change from baseline (adjusted mean)	-1.2	-3.7	-4.2
Difference from placebo (adjusted mean) (95% CI) [†]		-2.5 [‡] (-3.1; -1.9)	-2.9 [‡] (-3.5; -2.3)

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

[†] Least squares mean adjusted for baseline value and stratification factors

[‡] p<0.001

Initial Combination Therapy with Metformin

A total of 1186 patients with type 2 diabetes inadequately controlled with diet and exercise participated in a 26-week double-blind, active-controlled, parallel-group, 5-arm, multicenter study to evaluate the efficacy and safety of initial therapy with INVOKANA in combination with metformin XR. The median age was 56 years, 48% of patients were men, and the mean baseline eGFR was 87.6 mL/min/1.73 m². The median duration of diabetes was 1.6 years, and 72% of patients were treatment naïve. After completing a 2-week single-blind placebo run-in period, patients were randomly assigned for a double-blind treatment period of 26 weeks to 1 of 5 treatment groups (Table 11). The metformin XR dose was initiated at 500 mg/day for the first week of treatment and then increased to 1000 mg/day. Metformin XR or matching placebo was up-titrated every 2-3 weeks during the next 8 weeks of treatment to a maximum daily dose of 1500 to 2000 mg/day, as tolerated; about 90% of patients reached 2000 mg/day.

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

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

Efficacy Parameter	Metformin XR (N=237)	INVOKANA 100 mg (N=237)	INVOKANA 300 mg (N=238)	INVOKANA 100 mg + Metformin XR (N=237)	INVOKANA 300 mg + Metformin XR (N=237)
HbA_{1C} (%)					
Baseline (mean)	8.81	8.78	8.77	8.83	8.90
Change from baseline (adjusted mean) [†]	-1.30	-1.37	-1.42	-1.77	-1.78
Difference from canagliflozin 100 mg				-0.40 [‡] (-0.59, -0.21)	

(adjusted mean) (95% CI) †					
Difference from canagliflozin 300 mg (adjusted mean) (95% CI) †					-0.36‡ (-0.56, -0.17)
Difference from metformin XR (adjusted mean) (95% CI) †		-0.06‡‡ (-0.26, 0.13)	-0.11‡‡ (-0.31, 0.08)	-0.46‡ (-0.66, -0.27)	-0.48‡ (-0.67, -0.28)
Percent of patients achieving HbA_{1C} < 7%	38	34	39	47 ^{§§}	51 ^{§§}

* Intent-to-treat population

† Least squares mean adjusted for covariates including baseline value and stratification factor

‡ Adjusted p=0.001 for superiority

‡‡ Adjusted p=0.001 for non-inferiority

§§ Adjusted p<0.05

¶ There were 121 patients without week 26 efficacy data. Analyses addressing missing data gave consistent results with the results provided in this table.

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

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 m². 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 12 and Figure 1, at the end of treatment, INVOKANA 100 mg provided similar reductions in HbA_{1C} from baseline compared to glimepiride when added to metformin therapy. INVOKANA 300 mg provided a greater reduction from baseline in HbA_{1C} compared to glimepiride, and the relative treatment difference was -0.12% (95% CI: -0.22; -0.02). As shown in Table 12, treatment with INVOKANA 100 mg and 300 mg daily provided greater improvements in percent body weight change, relative to glimepiride.

Table 12: 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)
HbA_{1C} (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI) [†]	-0.01 [‡] (-0.11; 0.09)	-0.12 [‡] (-0.22; -0.02)	
Percent of patients achieving HbA _{1C} < 7%	54	60	56
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	165	164	166
Change from baseline (adjusted mean)	-24	-28	-18
Difference from glimepiride (adjusted mean) (95% CI) [†]	-6 (-10; -2)	-9 (-13; -5)	
Body Weight			
Baseline (mean) in kg	86.8	86.6	86.6
% change from baseline (adjusted mean)	-4.2	-4.7	1.0
Difference from glimepiride (adjusted mean) (95% CI) [†]	-5.2 [§] (-5.7; -4.7)	-5.7 [§] (-6.2; -5.1)	

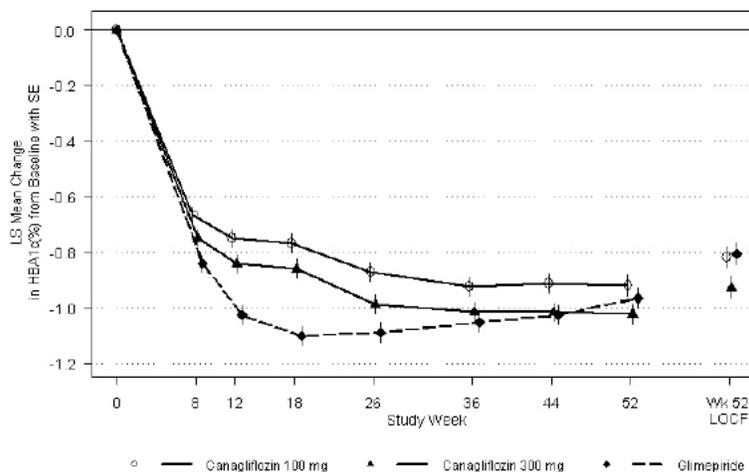
* Intent-to-treat population using last observation in study prior to glycemic rescue therapy

[†] 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 HbA_{1C} 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 m². 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 13, at the end of treatment, INVOKANA 100 mg and 300 mg daily provided statistically significant (p<0.001 for both doses) improvements in HbA_{1C} relative to placebo when added to sulfonylurea. INVOKANA 300 mg once daily compared to placebo resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, (33% vs 5%), greater reductions in fasting plasma glucose (-36 mg/dL vs +12 mg/dL), and greater percent body weight reduction (-2.0% vs -0.2%).

Table 13: 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)
HbA_{1C} (%)			
Baseline (mean)	8.49	8.29	8.28
Change from baseline (adjusted mean)	0.04	-0.70	-0.79
Difference from placebo (adjusted mean) (95% CI) [†]		-0.74 [‡] (-1.15; -0.33)	-0.83 [‡] (-1.24; -0.41)

* Intent-to-treat population using last observation in 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 m². 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 HbA_{1C} (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 HbA_{1C} less than 7%, in a significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin and sulfonylurea (see Table 14).

Table 14: 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)
HbA_{1C} (%)			
Baseline (mean)	8.12	8.13	8.13
Change from baseline (adjusted mean)	-0.13	-0.85	-1.06
Difference from placebo (adjusted mean) (95% CI) [†]		-0.71 [‡] (-0.90; -0.52)	-0.92 [‡] (-1.11; -0.73)
Percent of patients achieving A_{1C} < 7%	18	43 [‡]	57 [‡]
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	170	173	168
Change from baseline (adjusted mean)	4	-18	-31
Difference from placebo (adjusted mean) (95% CI) [†]		-22 [‡] (-31; -13)	-35 [‡] (-44; -25)
Body Weight			
Baseline (mean) in kg	90.8	93.5	93.5
% change from baseline (adjusted mean)	-0.7	-2.1	-2.6
Difference from placebo (adjusted mean) (95% CI) [†]		-1.4 [‡] (-2.1; -0.7)	-2.0 [‡] (-2.7; -1.3)

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

[†] Least squares mean adjusted for baseline value and stratification factors

[‡] p<0.001

Add-on Combination Therapy With Metformin and Sitagliptin

A total of 217 patients with type 2 diabetes inadequately controlled on the combination of metformin (greater than or equal to 1,500 mg/day) and sitagliptin 100 mg/day (or equivalent fixed-dose combination) participated in a 26-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of INVOKANA in combination with metformin and sitagliptin. The mean age was 57 years, 58% of patients were men, 73% of patients were Caucasian, 15% were Asian, and 12% were Black or African-American. The mean baseline eGFR was 90 mL/min/1.73 m² and the mean baseline BMI was 32 kg/m². The mean duration of diabetes

was 10 years. Eligible patients entered a 2-week, single-blind, placebo run-in period and were subsequently randomized to INVOKANA 100 mg or placebo, administered once daily as add-on to metformin and sitagliptin. Patients with a baseline eGFR of 70 mL/min/1.73 m² or greater who were tolerating INVOKANA 100 mg and who required additional glycemic control (fasting finger stick 100 mg/dL or greater at least twice within 2 weeks) were up-titrated to INVOKANA 300 mg. While up-titration occurred as early as Week 4, most (90%) patients randomized to INVOKANA were up-titrated to INVOKANA 300 mg by 6 to 8 weeks.

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

Table 15: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin and Sitagliptin

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

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

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

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

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

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

p<0.001

INVOKANA Compared to Sitagliptin, Both as Add-on Combination Therapy With Metformin 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 m². 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 16 and Figure 2, at the end of treatment, INVOKANA 300 mg provided greater HbA_{1C} reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea (p<0.05). INVOKANA 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg. A mean change in systolic blood pressure from baseline of -5.06 mmHg was observed with INVOKANA 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

Table 16: 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)
HbA_{1C} (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI) [†]	-0.37 [‡] (-0.50; -0.25)	
Percent of patients achieving HbA_{1C} < 7%	48	35
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	170	164
Change from baseline (adjusted mean)	-30	-6
Difference from sitagliptin (adjusted mean) (95% CI) [†]	-24 (-30; -18)	
Body Weight		
Baseline (mean) in kg	87.6	89.6
% change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI) [†]	-2.8 [§] (-3.3; -2.2)	

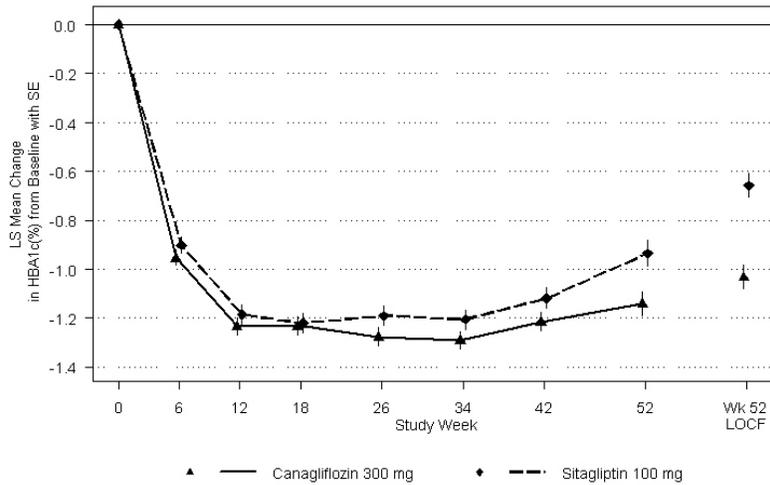
* Intent-to-treat population using last observation in study prior to glycemic rescue therapy

[†] Least squares mean adjusted for baseline value and stratification factors

[‡] 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 HbA_{1C} Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



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 m². 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 end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} (p<0.001 for both doses) compared to placebo when added to metformin and pioglitazone. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reduction in fasting plasma glucose (FPG) and in percent body weight reduction compared to placebo when added to metformin and pioglitazone (see Table 17). Statistically significant (p<0.05 for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -4.1 mmHg and -3.5 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 17: 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)
HbA_{1C} (%)			
Baseline (mean)	8.00	7.99	7.84
Change from baseline (adjusted mean)	-0.26	-0.89	-1.03
Difference from placebo (adjusted mean) (95% CI) [†]		-0.62 [‡] (-0.81; -0.44)	-0.76 [‡] (-0.95; -0.58)
Percent of patients achieving HbA_{1C} < 7%	33	47 [‡]	64 [‡]
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	164
Change from baseline (adjusted mean)	3	-27	-33
Difference from placebo (adjusted mean) (95% CI) [†]		-29 [‡] (-37; -22)	-36 [‡] (-43; -28)
Body Weight			
Baseline (mean) in kg	94.0	94.2	94.4
% change from baseline (adjusted mean)	-0.1	-2.8	-3.8
Difference from placebo (adjusted mean) (95% CI) [†]		-2.7 [‡] (-3.6; -1.8)	-3.7 [‡] (-4.6; -2.8)

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

[†] Least squares mean adjusted for baseline value and stratification factors

[‡] p<0.001

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 m². Patients on basal, bolus, or basal/bolus insulin for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. Approximately 70% of patients were on a background basal/bolus insulin regimen. After the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to insulin. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups.

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA_{1C} (p<0.001 for both doses) compared to placebo when added to insulin. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA_{1C} less than 7%, in significant reductions in fasting plasma glucose (FPG), and in percent body weight reductions compared to placebo (see Table 18). 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 18: 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)
HbA_{1C} (%)			
Baseline (mean)	8.20	8.33	8.27
Change from baseline (adjusted mean)	0.01	-0.63	-0.72
Difference from placebo (adjusted mean) (95% CI) [†]		-0.65 [‡] (-0.73; -0.56)	-0.73 [‡] (-0.82; -0.65)
Percent of patients achieving HbA _{1C} < 7%	8	20 [‡]	25 [‡]
Fasting Plasma Glucose (mg/dL)			
Baseline	169	170	168
Change from baseline (adjusted mean)	4	-19	-25
Difference from placebo (adjusted mean) (97.5% CI) [†]		-23 [‡] (-29; -16)	-29 [‡] (-35; -23)
Body Weight			
Baseline (mean) in kg	97.7	96.9	96.7
% change from baseline (adjusted mean)	0.1	-1.8	-2.3
Difference from placebo (adjusted mean) (97.5% CI) [†]		-1.9 [‡] (-2.2; -1.6)	-2.4 [‡] (-2.7; -2.1)

* Intent-to-treat population using last observation in 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 m². 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 HbA_{1C} ($p < 0.001$ for both doses) of -0.57% (95% CI: -0.71; -0.44) for INVOKANA 100 mg and -0.70% (95% CI: -0.84; -0.57) for INVOKANA 300 mg. 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 m² to less than 50 mL/min/1.73 m² 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 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 m². 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 HbA_{1C} relative to placebo (-0.30% [95% CI: -0.53; -0.07] and -0.40%, [95% CI: -0.64; -0.17], respectively) [*see Warnings and Precautions (5.4), 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 physical activity, periodic blood glucose monitoring and HbA_{1C} 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.

Lower Limb Amputation

Inform patients that INVOKANA is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop [*see Boxed Warning and Warnings and Precautions (5.1)*].

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 (5.2)*].

Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of INVOKANA. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical advice immediately [*see Warnings and Precautions (5.3)*].

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of INVOKANA. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue INVOKANA use in those settings [*see Warnings and Precautions (5.4)*].

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur [*see Warnings and Precautions (5.6)*].

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 (5.8)*].

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice [*see Warnings and Precautions (5.8)*].

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians.

Bone Fracture

Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk.

Pregnancy

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

Lactation

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

Active ingredient made in Belgium

Manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

Finished product manufactured by:

Janssen Ortho LLC

Gurabo, PR 00778

Or

Janssen Cilag SpA

Latina, Italy

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:

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

You may be at a higher risk of lower limb amputation if you:

- have a history of amputation
- have heart disease or are at risk for heart disease
- have had blocked or narrowed blood vessels, usually in your leg
- have damage to the nerves (neuropathy) in your leg
- have had diabetic foot ulcers or sores

Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Your doctor may decide to stop your INVOKANA for a while if you have any of these signs or symptoms.

Talk to your doctor about proper foot care.

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

You may be at higher risk of dehydration if you:

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

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

- **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
- 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, mouth, 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 a history of amputation.
- have heart disease or are at risk for heart disease.
- have had blocked or narrowed blood vessels, usually in your leg.
- have damage to the nerves (neuropathy) in your leg.
- have had diabetic foot ulcers or sores.
- have kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems with urination.
- are on a low sodium (salt) diet. Your doctor may change your diet or your dose of INVOKANA.
- are going to have surgery.
- are eating less due to illness, surgery, or a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short-term (“binge” drinking).
- have ever had an allergic reaction to INVOKANA.
- have other medical conditions.
- are pregnant or plan to become pregnant. INVOKANA may harm your unborn baby. If you become pregnant while taking INVOKANA, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. INVOKANA may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking INVOKANA. Do not breastfeed while 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)
- phenytoin or phenobarbital (used to control seizures)
- digoxin (Lanoxin®)* (used to treat heart problems)
- rifampin (used to treat or prevent tuberculosis)
- ritonavir (Norvir®, Kaletra®)* (used to treat HIV infection)

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

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

How should I take 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.
- 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 A_{1c}.

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?”

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

If you get any of these symptoms during treatment with INVOKANA, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- kidney problems.** Sudden kidney injury has happened to people taking INVOKANA. Talk to your doctor right away if you:
 - reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
 - you start to lose liquids from your body for example, from vomiting, diarrhea or being in the sun too long
- a high amount of potassium in your blood (hyperkalemia)**
- serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking INVOKANA. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people may also have a fever, back pain, nausea, or vomiting.
- low blood sugar (hypoglycemia).** If you take 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:

o headache	o drowsiness	o weakness	o confusion	o dizziness
o irritability	o hunger	o fast heartbeat	o sweating	o 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.
- broken bones (fractures).** Bone fractures have been seen in patients taking INVOKANA. Talk to your doctor about factors that may increase your risk of bone fracture.

The most common side effects of INVOKANA include:

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

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.**

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.

*The brands listed are trademarks of their respective owners and are not trademarks of Janssen Pharmaceuticals, Inc.

Active ingredient made in Belgium. Manufactured for: Janssen Pharmaceuticals, Inc., Titusville, NJ 08560. Manufactured by: Janssen Ortho LLC, Gurabo, PR 00778 or Janssen Cilag SpA, Latina, Italy. Licensed from Mitsubishi Tanabe Pharma Corporation. © 2013 Janssen Pharmaceutical Companies

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

Revised 07/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204042Orig1s026

OTHER REVIEW(S)

MEMORANDUM TO FILE

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

NDA/BLA #s: NDA 204042, NDA 204353, NDA 205879
PRODUCTS: Invokana (canagliflozin), Invokamet (canagliflozin and metformin), Invokamet XR (canagliflozin and metformin extended-release)
APPLICANTS: Janssen Pharmaceuticals, Inc. (Janssen)
FROM: Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety, Division of Metabolism and Endocrinology
DATE: July 25, 2017
TOPICS: Safety Labeling Changes, canagliflozin products and lower limb amputations,
ADDENDUM
TSI #: 1680

PURPOSE

This memorandum to file is an addendum to the memorandum filed on May 16, 2017,¹ regarding the Division of Metabolism and Endocrinology Products' (DMEP) requirement for safety labeling changes (SLC) to address the safety issue of lower limb amputations identified postapproval for canagliflozin products.

BACKGROUND

Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Currently approved canagliflozin products are listed in Table 1.

Table 1. Canagliflozin Products

NDA	Brand name	Active ingredient(s)
<i>Janssen Pharmaceuticals, Inc.</i>		
204042	Invokana	canagliflozin
204353	Invokamet	canagliflozin and metformin
205879	Invokamet XR	canagliflozin and metformin extended-release

Canagliflozin, a member of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor class, works by inhibiting the sodium-glucose co-transporter 2, which is expressed in the proximal renal tubule and is responsible for the majority of the reabsorption of filtered glucose. Inhibition of SGLT-2 increases urinary glucose excretion.

¹ Pippins J. DDS Memorandum. DARRTS Reference ID: 4098560. May 16, 2017.

SLC NOTIFICATION

On May 16, 2017, DMEP issued an SLC notification letter to Janssen Pharmaceuticals, Inc. (Janssen) stating that since approval the Agency has become aware of the risk of lower limb amputation in patients treated with products containing canagliflozin, based on the topline results of the CANVAS and CANVAS-R trials, submitted on April 10, 2017. This information was considered to be “new safety information” as defined in section 505-1(b)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA).

The SLC notification letter specified the addition of a *Boxed Warning* and a *Warning and Precautions* statement to the product labels, as follows (language below is from the Invokana label, and is representative of the changes across the class):

FULL PRESCRIBING INFORMATION

WARNING: RISK OF LOWER LIMB AMPUTATION

- **An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials in patients with type 2 diabetes who had cardiovascular disease (CVD) or were at risk for CVD.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
- **Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur [see *Warnings and Precautions (5.1)*].**

5. WARNINGS AND PRECAUTIONS

5.1 Amputations

An approximately 2-fold increased risk of lower limb amputations associated with INVOKANA use was observed in CANVAS and CANVAS-R, two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively. In CANVAS, use of INVOKANA increased the risk of lower limb amputations from 2.8 amputations per 1000 patients per year to 5.9 amputations per 1000 patients per year (Number Needed to Harm: 323). In CANVAS-R, the use of INVOKANA increased the risk of lower limb amputations from 4.2 amputations per 1000

patients per year to 7.5 amputations per 1000 patients per year (Number Needed to Harm: 270). The risk of lower limb amputations was observed at both the 100 mg and 300 mg doses. The amputation results for CANVAS and CANVAS-R are shown in Table 1 and 2, respectively.

Table 1: CANVAS AMPUTATIONS

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (Pooled) N=2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

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

Table 2: CANVAS-R AMPUTATIONS

	Placebo N=2903	INVOKANA 100 mg (with up-titration to 300 mg) N=2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

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

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

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

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Monitor patients receiving INVOKANA for signs and symptoms of infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

Additionally, the SLC notification also specified corresponding changes to Highlights, Section 6, and Section 17, and instructed the applicant to revise the Medication Guides to conform to the changes in the prescribing information.

RESPONSE TO SLC NOTIFICATION

Janssen responded to the May 16, 2017, SLC notification letter with submission of the supplements listed in Table 2.

Table 2. Responses to May 16, 2017, SLC notification

NDA	Brand name	Active ingredient(s)	Response to SLC
<i>Janssen Pharmaceuticals, Inc.</i>			
204042	Invokana	canagliflozin	S-026
204353	Invokamet	canagliflozin and metformin	S-023
205879	Invokamet XR	canagliflozin and metformin extended-release	S-005

The supplements proposed substantial revisions to the labeling outlined in the SLC notification letter. Most notably, (b) (4)

[Redacted]

[Redacted] (b) (4)

Regarding Janssen’s proposed changes to the text of the new Warnings and Precautions, while some revisions were reasonable (e.g., movement of data tables from Section 5 to Section 6) other changes were not, as DMEP found them to be (b) (4)

On June 21, 2017, a teleconference was held between DMEP and Janssen to discuss their proposed alternative labeling language. (b) (4)

Details of this discussion are captured in the internal meeting minutes for this teleconference.² Following the teleconference, Janssen submitted amended labeling (b) (4) and eliminated changes to the text that DMEP had found to be risk mitigating. There was some additional back and forth between the company and the DMEP over the description of the patient population, but ultimately Janssen agreed to the text “patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease.” Additional changes, based on recommendations from the Office of Prescription Drug Promotion (OPDP),³ were also made.

The Division of Medical Policy Programs (DMPP) reviewed the Medication Guides submitted in response to the SLC notification letter and recommended some changes in order to increase the use of patient-friendly language, improve consistency with the Prescribing Information, and decrease redundancy.⁴ These changes were relayed to Janssen, who responded with concerns about the wording of the text describing the occurrence of multiple and bilateral amputations. At Janssen’s request, a teleconference was held on July 14, 2017, to discuss their concerns. FDA participants included both DMEP and DMPP. For a summary of the details of this teleconference please see the associated internal meeting minutes.⁵ DMEP and Janssen ultimately agreed upon the following text:

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

INVOKANA can cause important side effects, including:

Amputations. INVOKANA may increase your risk of lower limb amputations.

Amputations mainly involve removal of the toe or part of the foot, however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some of both sides of the body.

CONCLUSION

DMEP has reached agreement with Janssen on labeling language addressing the May 16, 2017, SLC notification letter regarding the risk of lower limb amputation in patients treated with products containing canagliflozin. Supplements NDA 202042/S-026 (Invokana), NDA 204353/S-023 (Invokamet), and NDA 205879/S-005 (Invokamet XR) are ready for approval. A

² Godwin, E. Memorandum of Teleconference. DARRTS Reference ID: 4120683. July 6, 2017.

³ Ramachandra, M. OPDP Labeling Review. DARRTS Reference ID: 4119042. June 30, 2017.

⁴ Scales, T. Patient Labeling Review. DARRTS Reference ID: 4117240. June 27, 2017.

⁵ Hanan, E. Memorandum of Teleconference. DARRTS Reference ID: 4125483. July 17, 2017.

“call-out box” will be added to the top of the May 16, 2017, Drug Safety Communication instructing users to search the Drugs@ FDA website for final approved SLC labeling.

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/s/

JENNIFER R PIPPINS
07/25/2017

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 204042/ S-026 Prior Approval Supplement

Name of Drug: Invokana (canagliflozin) tablets

Applicant: Janssen Pharmaceuticals, Inc. (Janssen)

Labeling Reviewed

Submission Date: June 15, 2017

Receipt Date: June 15, 2017

Background and Summary Description:

On May 16, 2017, a Safety Labeling Change (SLC) Notification letter was issued for all currently approved products containing canagliflozin as follows: Invokana (canagliflozin) tablets (NDA 204042), Invokamet (canagliflozin and metformin hydrochloride) tablets (NDA 204353), and Invokamet XR (canagliflozin and metformin hydrochloride extended release) tablets (NDA 205879).

The SLC Notification letter required the applicant of these products to add language describing an increased risk of lower limb amputations in patients treated with products containing canagliflozin, based on topline results of Janssen’s cardiovascular outcomes trials, CANVAS (DIA3008; NCT01032629) and CANVAS-R (DIA4003; NCT01989754), submitted on April 10, 2017 (See Dr. Jennifer Pippins’s review in DARRTS dated May 16, 2017, for additional information). The new language was required to be added to the prescribing information (PI) and patient labeling (Medication Guide [MG]).

On June 15, 2017, Janssen submitted prior approval supplements for each of the three applications with proposed modifications from the text provided by FDA for the PI. The supplements submitted in response to this SLC are listed in the table below.

Applicant	NDA/ Supplement	Product
Janssen Pharmaceuticals, Inc.	NDA 204042/ S-026	Invokana (canagliflozin) tablets
Janssen Pharmaceuticals, Inc.	NDA 204353/ S-023	Invokamet (canagliflozin and metformin hydrochloride) tablets

Janssen Pharmaceuticals, Inc.	NDA 205879/ S-005	Invokamet XR (canagliflozin and metformin hydrochloride extended release) tablets
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A teleconference was arranged with Janssen for June 21, 2017, to discuss the extensive revisions proposed by Janssen for the PI, most of which were not acceptable to DMEP (refer to the internal meeting minutes filed on July 6, 2017, for additional information). In addition, the following internal consult reviews were provided:

- Division of Medical Policy Programs (DMPP): June 27, 2017
- Office of Prescription Drug Promotion (OPDP): June 30, 2017
- Division of Medication Error Prevention and Analysis (DMEPA): July 5, 2017

The proposed revised labeling submitted by Janssen following the teleconference, along with the consultant reviews, were reviewed by DMEP and the applicant was asked to make revisions. A second teleconference was held with Janssen on July 14, 2017, to finalize the language for the MG (refer to the email correspondence filed on July 14, 2017, and the internal meeting minutes filed on July 17, 2017, for additional information).

Materials Reviewed

This review compared the following labeling for Invokana (canagliflozin) tablets:

Labeling Reviewed	Final Proposed Labeling Submission Date	Currently Approved (supplement and date)
Prescribing Information	July 17, 2017	NDA 204042/ S-018 February 1, 2017
Medication Guide	July 17, 2017	NDA 204042/ S-018 February 1, 2017

Review

Each piece of proposed labeling was compared to the currently approved version, using the Microsoft Word electronic comparison function. The changes in the proposed labeling are consistent with the SLC-required changes, as documented in the May 16, 2017, SLC Notification letter and the labeling comments sent on June 23, July 7, July 12, July 13, and July 14, 2017.

The following significant changes are noted below, underline is text added to currently approved labeling; strikethrough is text deleted from currently approved labeling.

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Recommendations

The labeling was reviewed and agreed upon by the DMEP, OPDP, DMPP, and DMEPA.

An approval letter should be drafted and issued for Invokana (canagliflozin) tablets, NDA 204042 (S-026), for the version of labeling submitted on July 17, 2017.

Liz Godwin, MSHS, CCRP	7/24/2017
<hr/>	
Regulatory Project Manager	Date
Julie Van der Waag, MPH	7/24/2017
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Chief, Project Management Staff	Date

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/s/

ELIZABETH R GODWIN
07/25/2017

MEMORANDUM
REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 30, 2017

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: 204042/S-026
204353/ S-023
205879/S-005

Product Name and Strength: Invokana (canagliflozin), tablet, 100 mg and 300 mg

Invokamet (canagliflozin and metformin), tablet, 50 mg/500 mg, 50 mg/1,000 mg, and 150 mg/1,000 mg

Invokamet XR (canagliflozin and metformin extended release), tablet, 50 mg/500 mg, 50 mg/1,000 mg, and 150 mg/1,000 mg

Applicant/Sponsor Name: Janssen Pharmaceuticals, Inc.

Submission Date: June 15, 2017

OSE RCM #: 2017-1184

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised prescribing information (PI) and medication guides for Invokana (canagliflozin), Invokamet (canagliflozin and metformin), and Invokamet XR (canagliflozin and metformin extended release) to determine if they are acceptable from a medication error perspective. Janssen submitted a Prior Approval Supplement in response to the May 16, 2017 Safety Labeling Change notification for canagliflozin products regarding increased risk of lower limb amputation based on topline results of cardiovascular outcomes trials. Thus, they have

proposed changes to the prescribing information (Highlights of Prescribing Information Boxed Warning and Warnings and Precautions section; Full Prescribing Information Boxed Warning, Section 5 Warnings and Precautions, Section 6 Adverse Reactions, Section 17 Patient Counseling Information) and the medication guide.

2 CONCLUSION

We defer to the review team for analysis of the proposed changes to the various sections of the prescribing information. The revised prescribing information and medication guide for Invokana, Invokamet, and Invokamet XR are acceptable from a medication error perspective. We have no further recommendations at this time.

Appendix A. Prescribing Information and Medication Guides Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Invokana, Invokamet, and Invokamet XR labeling submitted by Janssen on June 15, 2017.

- Invokana (NDA 204042)

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- Invokamet (NDA 204353)

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- Invokamet XR (NDA 205879)

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^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ARIANE O CONRAD
06/30/2017

HINA S MEHTA
07/05/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 30, 2017

To: Elizabeth Godwin, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Meena Ramachandra, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204042/S-026 Invokana (canagliflozin)
NDA 204353/S-023 Invokamet (canagliflozin/metformin)
NDA 205879/S-005 Invokamet XR (canagliflozin/metformin
extended release)

Focused Review: OPDP labeling comments for safety labeling
change

On June 16, 2017, OPDP received a consult request from DMEP to perform a focused review of proposed package inserts (PI) and Medication Guides (MG) based on safety labeling changes regarding increased risk of lower limb amputation for INVOKANA[®] (canagliflozin) tablets, for oral use, INVOKAMET[®] (canagliflozin and metformin hydrochloride) tablets, for oral use and INVOKAMET[®] XR (canagliflozin/metformin extended release) tablets, for oral use.

OPDP's review of the proposed PIs is based on the labeling sent by Elisabeth Godwin via email on June 26, 2017. OPDP's comments are reflected in the attached labeling.

OPDP concurs with DMPP's proposed changes to the Medication Guide as discussed in their Patient Labeling Review dated June 27, 2017 in DARRTS.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Meena Ramachandra at 240-402-1348 or Meena.Ramachandra@fda.hhs.gov.

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/s/

MEENA RAMACHANDRA
06/30/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: June 27, 2017

To: Jean-Marc Guettier, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Focused Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): Invokana (canagliflozin)
Invokamet (canagliflozin/metformin)
Invokamet XR (canagliflozin/metformin)

Dosage Form and Route: Tablets

Application Type/Number: NDA 204042/S-026
NDA 204353/S-023
NDA 205879/S-005

TSI Number: 1680

Applicant: Janssen Research & Development, LLC. (Janssen)

1 INTRODUCTION

On June 15, 2017, Janssen submitted for the Agency's review a Safety labeling - Prior Approval Supplement for New Drug Applications NDA 204042 for INVOKANA (canagliflozin) tablets, for oral use approved March 29, 2013, NDA 204353 for INVOKAMET (canagliflozin / metformin hydrochloride) tablets, for oral use approved August 8, 2014, and NDA 205879 for INVOKAMET XR (canagliflozin / metformin hydrochloride extended release) approved on September 20, 2017 indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on June 16, 2017, for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for INVOKANA (canagliflozin) tablets, for oral use, INVOKAMET (canagliflozin / metformin hydrochloride) tablets, for oral use, and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft INVOKANA (canagliflozin) tablets, for oral use, INVOKAMET (canagliflozin / metformin hydrochloride) tablets, for oral use, and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use MGs received on June 15, 2017, received by DMPP on June 26, 2017.
- Draft INVOKANA (canagliflozin) tablets, for oral use, INVOKAMET (canagliflozin / metformin hydrochloride) tablets, for oral use, and INVOKAMET XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use Prescribing Information (PI) received on June 15, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on June 26, 2017.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our focused review of the MGs we:

- simplified wording and clarified concepts where possible
- ensured that the MGs are consistent with the Prescribing Information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MGs meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MGs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused review of the MGs are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MGs.

Please let us know if you have any questions.

25 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TWANDA D SCALES
06/27/2017

MARCIA B WILLIAMS
06/27/2017

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204042Orig1s026

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 14, 2017

Application Numbers: NDA 204042/S-026
NDA 204353/S-023
NDA 205879/S-005

Product Names: Invokana (canagliflozin) tablets
Invokamet (canagliflozin and metformin hydrochloride) tablets
Invokamet XR (canagliflozin and metformin hydrochloride extended-release) tablets

Applicant Name: Janssen Pharmaceuticals

Subject: Discussion of the applicant's proposed revisions to Safety Labeling Changes required by FDA to be added to the approved labeling for canagliflozin products

FDA Participants

Division of Metabolism and Endocrinology Products

Jennifer Pippins, MD, MPH Deputy Director for Safety
Elisabeth Hanan, MS Safety Regulatory Project Manager

Division of Medical Policy Programs

CAPT Twanda Scales, RN, MSN/Ed Patient Labeling Reviewer

Applicant Participants

Clinical

Mehul Desai, MD Senior Director, Medical Leader

Compound Development Team

Kirk Ways, MD, PhD VP, Therapeutic Development Head

Medical Affairs

Paul Burton, MD VP, Medical Affairs Internal Medicine

Global Regulatory Affairs

Craig Ostroff, PharmD, RPh VP, CVM Global Regulatory Affairs
Jacqueline Coelln-Hough, RPh Senior Director, Global Regulatory Affairs
Lori Birkenberger, PhD Director, Global Regulatory Affairs
Sukhdev Saran, MBA Director, Global Regulatory Affairs

Global Medical Safety

Amy Freedman Therapeutic Area Safety Head, CV/ Metabolism

1.0 BACKGROUND:

Please refer to the internal meeting minutes filed on July 6, 2017, for additional background information regarding these Safety Labeling Change (SLC) supplements. Additional rounds of comments and revisions for both the prescribing information (PIs) and Medication Guides (MGs) occurred following that teleconference, as documented in email correspondence filed on July 7, 12, and 13, 2017. On July 14, 2017, FDA and Janssen discussed the final MG language via email (reference email correspondence filed on July 14, 2017); however, due to the upcoming end of the SLC discussion period (July 15, 2017), it was necessary to hold a teleconference to reach alignment on the final language for the MG.

FDA sent their final proposed language via email as follows:

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

INVOKANA can cause important side effects, including:

Amputations. INVOKANA may increase your risk of lower limb amputations.

Amputations mainly involve removal of the toe or part of the foot, however, amputations involving the leg, below and above the knee, have also occurred. (b) (4)

Janssen responded with the following proposal (addition in red):

(b) (4)

The teleconference discussion focused on the last sentence of this section. Additional revisions to this language are documented in the email correspondence filed on July 14, 2017.

2.0 DISCUSSION:

Janssen raised the following concerns regarding the final sentence of the MG section outlined above:

- Use of the word “some” is vague and may cause confusion and undue alarm in patients without additional context. Janssen is concerned that patients may discontinue their drug and not start another treatment.
- The phrase is not consistent with the text in the PI.
- Janssen’s proposed language is consistent with informed consent (IC) documents currently in use for canagliflozin clinical trials.

(b) (4)

FDA responded with the following points:

- The MG is written at a different level of detail than the PI; healthcare providers (HCPs) are expected to act as a learned intermediary to explain the details of the risks described in the MG.
- IC documents are used in a different setting (clinical trials), and are not under FDA's purview, as compared with MGs, which are intended for use in a patient care setting with approved drugs.
- Ms. Scales stated that it is very rare to include clinical data in MGs; this has only been done for a few products after much careful vetting with the patient labeling team.
- Dr. Pippins reminded Janssen that FDA has already accepted many of their proposed revisions to the MG language in order to increase the precision of the language, even though these changes were not always ideal with respect to the use of patient-friendly language. Further changes negatively impacting the use of patient-friendly language were not acceptable.
- Dr. Pippins also stated that while FDA acknowledged Janssen's comments on the importance of recognizing the rarity of amputation events, FDA was also considering the strength of the amputation signal, which was seen across two independent randomized clinical trials and at two doses within a single trial, in determining how to approach labeling.

Following extensive discussion and multiple revisions, both FDA and Janssen agreed on the following language for the MG:

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

INVOKANA can cause important side effects, including:

Amputations. INVOKANA may increase your risk of lower limb amputations.

Amputations mainly involve removal of the toe or part of the foot, however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body.

Janssen documented concurrence with this language via email, as documented in the email correspondence filed on July 14, 2017.

3.0 ACTION ITEM:

Janssen to submit final labeling for these supplements on Monday, July 17, 2017.
(completed on July 17, 2017)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELISABETH A HANAN
07/17/2017

From: [Saran, Sukhdev \[JRDUS\]](#)
To: [Hanan, Elisabeth](#); [Godwin, Elizabeth](#); [Porter, Brandon \[JRDUS\]](#)
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments
Date: Friday, July 14, 2017 4:57:08 PM
Attachments: [image001.png](#)
[mg_info.txt](#)

Hi Elisabeth,

Janssen agrees with the final language below.

We would like to thank you for the very helpful discussion and in reaching agreement on this wording.

I will send the labeling documents to the NDA's on Monday.

Thanks,
Sukhdev

From: Hanan, Elisabeth [mailto:Elisabeth.Hanan@fda.hhs.gov]
Sent: Friday, July 14, 2017 4:48 PM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Godwin, Elizabeth <Elisabeth.Godwin@fda.hhs.gov>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev,

As discussed, here is the final language:

FDA – FINAL PROPOSAL:

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

INVOKANA can cause important side effects, including:

Amputations. INVOKANA may increase your risk of lower limb amputations. Amputations mainly involve removal of the toe or part of the foot, however, amputations involving the leg, below and above the knee, have also occurred.

(b) (4)

Thank you,
Elisabeth

From: [Saran, Sukhdev \[JRDUS\]](#)
To: [Hanan, Elisabeth](#); [Godwin, Elisabeth](#)
Cc: [Porter, Brandon \[JRDUS\]](#)
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments
Date: Friday, July 14, 2017 4:36:07 PM
Attachments: [mg_info.txt](#)

Hi Elisabeth,

Janssen proposal:



Thanks,
Sukhdev

From: Hanan, Elisabeth [mailto:Elisabeth.Hanan@fda.hhs.gov]
Sent: Friday, July 14, 2017 4:24 PM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Godwin, Elisabeth <Elisabeth.Godwin@fda.hhs.gov>
Cc: Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev,

Please see below for a minor modification proposed for the language:



Thanks,
Elisabeth

From: Saran, Sukhdev [JRDUS] [mailto:SSaran@its.jnj.com]
Sent: Friday, July 14, 2017 4:15 PM
To: Hanan, Elisabeth; Godwin, Elisabeth

Cc: Porter, Brandon [JRDUS]

Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Elisabeth,

Can you please call back into the TC?

Thanks,

Sukhdev

From: Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]

Sent: Friday, July 14, 2017 4:07 PM

To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Godwin, Elizabeth <Elisabeth.Godwin@fda.hhs.gov>

Cc: Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>

Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev,

Here is FDA's proposed final language currently under discussion:



Thanks,

Elisabeth

From: Hanan, Elisabeth

Sent: Friday, July 14, 2017 3:15 PM

To: Saran, Sukhdev [JRDUS]; Godwin, Elizabeth

Cc: Porter, Brandon [JRDUS]

Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev,

This is to confirm receipt of the dial-in information; we will speak to you at 3:30pm.

Thanks,

Elisabeth

From: Saran, Sukhdev [JRDUS] [<mailto:SSaran@its.jnj.com>]

Sent: Friday, July 14, 2017 3:10 PM
To: Hanan, Elisabeth; Godwin, Elizabeth
Cc: Porter, Brandon [JRDUS]
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Elisabeth,

We would like the opportunity to speak with you. Below is the TC dial-information:

SUKHDEV SARAN invites you to attend an audio conference.



Thank you,
Sukhdev

From: Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]
Sent: Friday, July 14, 2017 2:59 PM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>
Cc: Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev,

Your proposed additional text (highlighted in yellow below) is unacceptable, as we do not consider such language to be either appropriate or necessary for the MG. We consider the version sent to you at 1:28pm today to be final. If still needed, we will accommodate a teleconference. We are available at 3:30.



Thank you,
Elisabeth

From: Saran, Sukhdev [JRDUS] [<mailto:SSaran@its.jnj.com>]
Sent: Friday, July 14, 2017 2:36 PM

To: Godwin, Elizabeth; Hanan, Elisabeth
Cc: Porter, Brandon [JRDUS]; Saran, Sukhdev [JRDUS]
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Elisabeth,

We would propose the change below. The word “some” is vague. Our proposed text is supported by the data and provides information to the patient in a manner that can be understood by them (i.e. patient friendly plain language). This type of description is also used in the Informed Consent documents.

Please advise if this proposal is acceptable. If not, we are available for a TC.



We will make the correction to the word “ (b) (4) ” as noted.

Thank you,
Sukhdev

From: Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]
Sent: Friday, July 14, 2017 1:28 PM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev,

Our written responses are below; we request a response as soon as possible.

Please confirm receipt.

Thank you,
Elisabeth

[Redacted]

We acknowledge your proposed revised language for the Medication Guide provided to us by email on July 14, 2017. We have considered your proposal, and agree in part. The various iterations are provided below, with our final proposal highlighted in green:

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

We acknowledge your proposed revised language for the PI, Section 8, provided to us via ESG submission to NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 on July 13, 2017.

We do not agree with your revision. According to the draft PLLR Guidance (attached and excerpted below) only the first word (“ [Redacted] (b) (4) ”) is capitalized. We request that you reject your revision.

[Redacted] (b) (4)

We believe that this email should suffice to resolve all issues pertaining to labeling, and request that you submit final labeling by COB today; however, we acknowledge your request from earlier today for a teleconference. If you consider a teleconference to still be necessary we will attempt to arrange it for this afternoon. We remind you that the end of the discussion period is today.

From: Saran, Sukhdev [JRDUS] [<mailto:SSaran@its.jnj.com>]
Sent: Friday, July 14, 2017 11:55 AM
To: Godwin, Elizabeth; Porter, Brandon [JRDUS]; Hanan, Elisabeth
Cc: Saran, Sukhdev [JRDUS]
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Elisabeth,

Thank you, we would also like to reach alignment with you today on the labeling language. Below is our proposed language and supporting rationale.

Thank you,
Sukhdev

From: Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]
Sent: Friday, July 14, 2017 11:22 AM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev,

We cannot commit to holding a teleconference until we see the nature of your concerns with the proposed MGs; however, we are eager to reach alignment with you today on the labeling language due to the end of the SLC discussion period.

Thanks,
Elisabeth

From: Saran, Sukhdev [JRDUS] [<mailto:SSaran@its.jnj.com>]
Sent: Friday, July 14, 2017 11:06 AM
To: Hanan, Elisabeth; Godwin, Elizabeth; Porter, Brandon [JRDUS]
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Elisabeth,

We can provide via email our concerns with the proposed language, however, we strongly feel that it is critical that we speak and review the data that supports the appropriate language.

Can the Agency confirm that no action letter would be issued until we have had a discussion?

Thank you,
Sukhdev

From: Hanan, Elisabeth [<mailto:Elisabeth.Hanan@fda.hhs.gov>]
Sent: Friday, July 14, 2017 10:50 AM

To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Godwin, Elizabeth <Elizabeth.Godwin@fda.hhs.gov>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukdev,

Because there are multiple teams involved with review of the Medication Guides, **we ask that you submit in writing (via email) your specific concerns with the proposed language.** We can then work to schedule a teleconference with the appropriate individuals, if warranted.

Thank you,
Elisabeth

From: Saran, Sukhdev [JRDUS] [<mailto:SSaran@its.jnj.com>]
Sent: Friday, July 14, 2017 10:42 AM
To: Godwin, Elizabeth; Porter, Brandon [JRDUS]
Cc: Hanan, Elisabeth
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Elisabeth,

Thank you for speaking with me today. We would like to have TC with the Agency today on the proposed language for the medication guide. Please advise if this would be feasible. My cell number is (b) (6).

Thank you,
Sukhdev

From: Godwin, Elizabeth [<mailto:Elizabeth.Godwin@fda.hhs.gov>]
Sent: Thursday, July 13, 2017 8:43 AM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Cc: Hanan, Elisabeth <Elisabeth.Hanan@fda.hhs.gov>
Subject: [EXTERNAL] NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev and Brandon,

Please see the attached Medication Guides with FDA comments for NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005. We request that you send the revised labeling by **noon tomorrow, July 14, 2017.**

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments

and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state “COMPANY’S response to FDA change” or “COMPANY comment.”

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELISABETH A HANAN
07/14/2017

From: [Saran, Sukhdev \[JRDUS\]](#)
To: [Godwin, Elizabeth](#); [Porter, Brandon \[JRDUS\]](#)
Cc: [Hanan, Elisabeth](#)
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments
Date: Thursday, July 13, 2017 9:13:06 AM
Attachments: [image001.png](#)
[mg_alert.txt](#)

Hi Liz,
Confirming receipt.
Thank you,
Sukhdev

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Thursday, July 13, 2017 8:43 AM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Cc: Hanan, Elisabeth <Elisabeth.Hanan@fda.hhs.gov>
Subject: [EXTERNAL] NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev and Brandon,

Please see the attached Medication Guides with FDA comments for NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005. We request that you send the revised labeling by **noon tomorrow, July 14, 2017**.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

Liz Godwin, MSHS, CCRP
Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



APPEARS THIS WAY ON
ORIGINAL

11 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH R GODWIN
07/13/2017

From: [Saran, Sukhdev \[JRDUS\]](#)
To: [Godwin, Elizabeth](#); [Porter, Brandon \[JRDUS\]](#)
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments
Date: Wednesday, July 12, 2017 12:12:15 PM
Attachments: [image001.png](#)
[mg_info.txt](#)

Hi Liz,
Confirming receipt.
Thank you,
Sukhdev

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Wednesday, July 12, 2017 12:04 PM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev and Brandon,

Please see the attached labels and Medication Guides with FDA comments for NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005. We request that you send the revised labeling by **tomorrow, July 13, 2017**. Please note, comments on the Medication Guides will be sent separately.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

From: Godwin, Elizabeth
Sent: Friday, July 07, 2017 9:22 AM
To: 'Saran, Sukhdev [JRDUS]'; Porter, Brandon [JRDUS]
Subject: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev and Brandon,

Please see the attached labels and Medication Guides with FDA comments for NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005. We request that you send the revised labeling by COB

Tuesday, July 11, 2017.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

Please confirm receipt and let me know if you have any questions.

Thanks,

Liz

Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Tel: 240-402-3438

Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
07/12/2017

From: [Saran, Sukhdev \[JRDUS\]](#)
To: [Godwin, Elizabeth](#); [Porter, Brandon \[JRDUS\]](#)
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments
Date: Friday, July 07, 2017 9:27:57 AM
Attachments: [image001.png](#)
[mg_info.txt](#)

Hi Liz,
Confirming receipt.
Thank you,
Sukhdev

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Friday, July 07, 2017 9:22 AM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hi Sukhdev and Brandon,

Please see the attached labels and Medication Guides with FDA comments for NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005. We request that you send the revised labeling by COB Tuesday, July 11, 2017.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

Liz Godwin, MSHS, CCRP
Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov





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/s/

ELIZABETH R GODWIN
07/07/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 21, 2017

Application Numbers: NDA 204042/ S-026
NDA 204353/ S-023
NDA 205879/ S-005

Product Names: Invokana (canagliflozin) tablets
Invokamet (canagliflozin and metformin hydrochloride) tablets
Invokamet XR (canagliflozin and metformin hydrochloride extended release) tablets

Sponsor/Applicant Name: Janssen Pharmaceuticals

Subject: Discussion of the applicant's proposed revisions to Safety Labeling Changes required by FDA to be added to the approved labeling for canagliflozin products

FDA Participants

Jean-Marc Guettier, MD Director, DMEP
Jennifer Pippins, MD, MPH Deputy Director for Safety, DMEP
Monika Houstoun, PharmD Associate Director of Labeling, DMEP
Elisabeth Hanan, MS Safety Regulatory Project Manager, DMEP
Liz Godwin, MSHS, CCRP Regulatory Project Manager, DMEP

Applicant Participants

Quantitative Sciences

Gordon Law, PhD Director, Statistical Leader
George Capuano, PhD Associate Director, Clinical Biostatistics

Clinical

Mehul Desai, MD Senior Director, Medical Leader
Ngozi Erundu, MD, PhD Senior Director, Clinical Leader

Compound Development Team

Norman Rosenthal, MD VP, Canagliflozin Compound Development Team Leader
Kirk Ways, MD, PhD VP, Therapeutic Development Head
James List, MD Global Therapeutic Head, CVM

Medical Affairs

Paul Burton, MD VP, Medical Affairs Internal Medicine

Global Regulatory Affairs

Craig Ostroff, PharmD, RPh VP, CVM Global Regulatory Affairs
Jacqueline Coelln-Hough, RPh Senior Director, Global Regulatory Affairs

Lori Birkenberger, PhD Director, Global Regulatory Affairs
Sukhdev Saran, MBA Director, Global Regulatory Affairs

Global Medical Safety

Don Sun, GMS Physician
Amy Freedman, Therapeutic Area Safety Head, CV/ Metabolism

1.0 BACKGROUND:

On May 16, 2017, Safety Labeling Change (SLC) Notification letters were issued for all currently approved products containing canagliflozin as follows: Invokana (canagliflozin) tablets (NDA 204042), Invokamet (canagliflozin and metformin hydrochloride) tablets (NDA 204353), and Invokamet XR (canagliflozin and metformin hydrochloride extended release) tablets (NDA 205879).

The SLC notification letter required the applicant of these products to add language describing an increased risk of lower limb amputations in patients treated with products containing canagliflozin, based on topline results of Janssen’s cardiovascular outcomes trials, CANVAS (DIA3008; NCT01032629) and CANVAS-R (DIA4003; NCT01989754), submitted on April 10, 2017 (See Dr. Jennifer Pippins’s review in DARRTS dated May 16, 2017, for additional information). The new language was required to be added to the prescribing information (PI) and patient labeling (Medication Guide [MG]).

On June 15, 2017, Janssen submitted prior approval supplements for each of the three applications with proposed modifications from the text provided by FDA for the PI. A teleconference was arranged with Janssen for June 21, 2017, to discuss the PASs due to the extensive revisions proposed by Janssen.

2.0 DISCUSSION:

FDA led the discussion by reviewing Janssen’s proposed modifications for the PI, following each point with FDA’s response as listed below. Following the overview of FDA’s position, Janssen provided additional comments on some points as denoted by “Additional Discussion” below.

- **Boxed Warning**

-



(b) (4)

(b) (4)

- **Warnings and Precautions**

- *FDA summarized Janssen’s recommendation that some of the language FDA proposed to include in Section 5 be relocated to Section 6, based on the rationale that FDA Guidance recommends use of a “succinct description” in Section 5.*
 - **FDA agreed, stating it is reasonable to move the data tables to Section 6.**
- *FDA summarized Janssen’s recommendation that the Warnings and Precautions section include incidence rates for amputation.*
 - **FDA agreed.**

(b) (4)



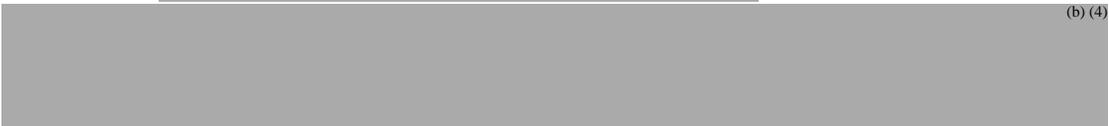
- *FDA summarized Janssen's recommendation that information regarding trial duration be relocated to Section 6.*
 - **FDA: agreed.**



- *FDA summarized Janssen's recommendation for deletion of text describing the Number Needed to Harm (NNH), which is based on rationale that NNH is not a metric commonly used by providers and is not interpretable unless put in the context of benefit.*
 - **FDA agreed. While noting that in some cases it may be reasonable to include NNH, FDA acknowledged that NNH is not commonly used.**



- *FDA noted Janssen’s recommendation to change the term “infections” to “lower limb infections.”*
 - **FDA agreed.**
- *FDA summarized Janssen’s recommended revisions to the language describing preceding events.*
 - **FDA agreed in part and disagreed in part. Specifically, FDA agreed with deleting ischemia, given the lower percentage compared to other preceding events.**



(b) (4)

- *FDA summarized Janssen's recommendation for the addition of the sentence, "Counsel patients about the importance of routine preventative foot care."*
 - **FDA agreed.**

(b) (4)

- **Section 17**

- *FDA summarized Janssen's recommendation for addition of language on counseling patients regarding preventative foot care.*

- **FDA agreed.**



Following discussion of the proposed changes to the PI, FDA addressed several questions from Janssen regarding the SLC process moving forward as outlined below.

- FDA stated it would return labels with edits for each product PI to Janssen, and that it would consider these updated versions to be essentially final. Janssen inquired if they would have further opportunity to comment; FDA replied that

they have opportunity to comment until the end of discussion period (effectively July 14th) but that they should keep in mind FDA's perspective that the label is near final. FDA noted that it does not intend to extend the discussion period.

- FDA stated that comments on the Medication Guides would be forthcoming.
- Janssen inquired whether a change in the BW title, so as to indicate that amputations are seen in a high-CV risk population, would be acceptable. FDA did not agree, as it would find the additional text to be unnecessary and potentially detrimental from a readability perspective. FDA noted that it will eliminate the words "Risk Of" in the BW title (i.e., so that the BW title reads "Lower Limb Amputations"), in accordance with best labeling practices.

3.0 ACTION ITEMS:

- FDA will provide revised PIs to Janssen by June 23, 2017.
- Comments regarding the MGs will be sent at a later date.

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/s/

ELIZABETH R GODWIN
07/06/2017

From: [Saran, Sukhdev \[JRDUS\]](#)
To: [Godwin, Elizabeth](#); [Porter, Brandon \[JRDUS\]](#)
Subject: RE: NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments
Date: Friday, June 23, 2017 3:59:52 PM
Attachments: [image001.png](#)
[mg_info.txt](#)

Hi Liz,
Confirming receipt. We will review and respond as requested.
Thank you,
Sukhdev

From: Godwin, Elizabeth [mailto:Elizabeth.Godwin@fda.hhs.gov]
Sent: Friday, June 23, 2017 3:52 PM
To: Saran, Sukhdev [JRDUS] <SSaran@its.jnj.com>; Porter, Brandon [JRDUS] <BPorter3@its.jnj.com>
Subject: [EXTERNAL] NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005 - Invokana, Invokamet, and Invokamet XR - Labels with FDA Comments

Hello Sukhdev and Brandon,

Please see the attached labels with FDA comments for NDA 204042/S-026, NDA 204353/S-023, and NDA 205879/S-005. We request that you send the revised labeling by COB Friday, June 30, 2017.

We refer you to the teleconference held on June 21, 2017, during which we relayed the rationale underlying our response to your proposed revisions. Regarding version control, please note that we have made revisions to the versions of the labels included in the SLC notification (i.e., and not to the versions you submitted on June 15, 2017).

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to the this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

Please confirm receipt and let me know if you have any questions.

Thanks,
Liz

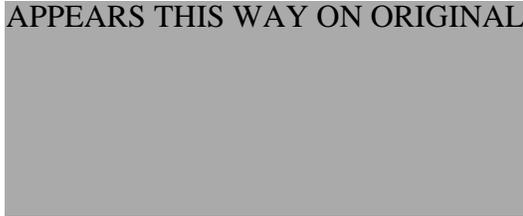
Liz Godwin, MSHS, CCRP

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3438
Elizabeth.Godwin@fda.hhs.gov



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/s/

ELIZABETH R GODWIN
06/23/2017

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

FROM: Liz Godwin, RPM, DMEP, ODE II, 240-402-3438

DATE
6/16/2017

IND NO.

NDA NO.
204042/ S-026
204353/ S-023
205879/S-005

TYPE OF DOCUMENT
SLC Prior Approval Supplement

DATE OF DOCUMENT
June 15, 2017

NAME OF DRUG
Invokana (canagliflozin)
Invokamet (canagliflozin and metformin)
Invokamet XR (canagliflozin and metformin extended release)

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
SGLT2

DESIRED COMPLETION DATE
July 7, 2017

NAME OF FIRM: Janssen

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | | <input type="checkbox"/> MEDICATION ERRORS |
| <input type="checkbox"/> MEETING PLANNED BY | | <input type="checkbox"/> OTHER (SPECIFY BELOW): |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: DMEP received Prior Approval Supplements in response to our May 16, 2017, Safety Labeling Change notification for the canagliflozin products. Due to the short review period for this supplement, we request that the PIs and MGs be reviewed as quickly as possible (no more than 2 weeks, sooner if possible). **Due to the very tight timeline the consult request for the three canagliflozin labels is for a focused review pertaining only to the SLC-related changes.**

Invokana

Cover Letter: <\\CDSESUB1\evsprod\NDA204042\0197\m1\us\cover.pdf>

EDR Location: <\\CDSESUB1\evsprod\NDA204042\0197>

Invokamet

EDR Location: <\\CDSESUB1\evsprod\NDA204353\0136>

Invokamet XR

EDR Location: \\CDSESUB1\evsprod\NDA205879\0033	
SIGNATURE OF REQUESTER Liz Godwin	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ELIZABETH R GODWIN
06/16/2017

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-OPDP-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Liz Godwin, RPM/ ODE II/ DMEP/ 240-402-3438
---------------------------------	--

REQUEST DATE: 6/16/2017	IND NO.	NDA/BLA NO. NDA 204042/ S-026 NDA 204353/ S-023 NDA 205879/ S-005	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG: Invokana (canagliflozin) Invokamet (canagliflozin and metformin) Invokamet XR (canagliflozin and metformin extended release)	PRIORITY CONSIDERATION: Priority	CLASSIFICATION OF DRUG SGLT2	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) July 28, 2017 (or earlier if possible)
---	--	--	---

NAME OF FIRM: Janssen	PDUFA Date: July 30, 2017
---------------------------------	---------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS
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EDR link to submission:

Invokana
 Cover Letter: <\\CDSESUB1\evsprod\NDA204042\0197\m1\us\cover.pdf>
 EDR Location: <\\CDSESUB1\evsprod\NDA204042\0197>

Invokamet
 EDR Location: <\\CDSESUB1\evsprod\NDA204353\0136>

Invokamet XR
 EDR Location: <\\CDSESUB1\evsprod\NDA205879\0033>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by

audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: DMEP received Prior Approval Supplements in response to our May 16, 2017, Safety Labeling Change notification for the canagliflozin products. The overall timeframe for this supplement is 30 days, we plan to have the SCPIs available around July 14. Due to the short review period for this supplement, we request that the PIs and MGs be reviewed as quickly as possible (no more than 2 weeks, sooner if possible).

SIGNATURE OF REQUESTER
Liz Godwin

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

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/s/

ELIZABETH R GODWIN
06/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION			
TO: CDER-DMPP-PatientLabelingTeam			FROM: (Name/Title, Office/Division/Phone number of requestor) Liz Godwin, RPM/ ODE II/ DMEP/ 240-402-3438		
REQUEST DATE: 6/16/2017		NDA/BLA NO.: NDA 204042/ S-026 NDA 204353/ S-023 NDA 205879. S-005	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)		
NAME OF DRUG: Invokana (canagliflozin) Invokamet (canagliflozin and metformin) Invokamet XR (canagliflozin and metformin extended release)	PRIORITY CONSIDERATION: Priority		CLASSIFICATION OF DRUG: SGLT2	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) July 28, 2017 (or earlier if possible)	
SPONSOR: Janssen			PDUFA Date: July 30, 2017		
TYPE OF LABEL TO REVIEW					
TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA/ANDA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION	
EDR link to submission: Invokana Cover Letter: \\CDSESUB1\evsprod\NDA204042\0197\m1\us\cover.pdf EDR Location: \\CDSESUB1\evsprod\NDA204042\0197 Invokamet EDR Location: \\CDSESUB1\evsprod\NDA204353\0136 Invokamet XR EDR Location: \\CDSESUB1\evsprod\NDA205879\0033					
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.					

COMMENTS/SPECIAL INSTRUCTIONS:

DMEP received Prior Approval Supplements in response to our May 16, 2017, Safety Labeling Change notification for the canagliflozin products. The overall timeframe for this supplement is 30 days, we plan to have the SCPIs available around July 14. Due to the short review period for this supplement, we request that the MGs be reviewed as quickly as possible (no more than 2 weeks, sooner if possible).

SIGNATURE OF REQUESTER
Liz Godwin

SIGNATURE OF RECEIVER

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/s/

ELIZABETH R GODWIN
06/16/2017