CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204042Orig1s013

Trade Name: **INVOKANA**

Generic Name: Canagliflozin

Sponsor: Janssen Pharmaceuticals, Inc.

Approval Date: 12/04/2015

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204042/S-013

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
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 October 21, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invokana (canagliflozin) tablets, 100 mg and 300 mg.

We also refer to our letter dated September 25, 2015, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for sodium-glucose cotransporter-2 (SGLT-2) inhibitor products. This information pertains to the risk of ketoacidosis and urosepsis in patients treated with SGLT-2 inhibitors.

This "Prior Approval" sNDA provides for revisions to the labeling to address the risks of ketoacidosis and urosepsis, with the use of SGLT-2 inhibitors, consistent with our September 25, 2015, letter.

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 date changed 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 package insert and Medication Guide) with the addition of any labeling changes in pending "Changes Being Effected" (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 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.

POSTMARKETING REQUIREMENT UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

As previously communicated to you in our letter dated September 25, 2015, we have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of ketoacidosis in patients treated with SGLT-2 inhibitors.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3005-1 An enhanced pharmacovigilance study of ketoacidosis in patients treated with canagliflozin. The study will include reports of ketoacidosis or diabetic ketoacidosis for a period of 5 years, and will include assessment and analysis of spontaneous reports of ketoacidosis in patients treated with canagliflozin, with specialized follow-up to collect additional information on these cases.

We refer to your submission dated October 20, 2015, which states your intention to conduct one study to address this postmarketing requirement (PMR) for all currently approved products containing canagliflozin. Therefore, this PMR will also apply to Invokamet (canagliflozin and metformin HCl) tablets, per our approval letter issued to NDA 204353/S-012.

The timetable you submitted via email on November 12, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2016
Interim Report Submission:	12/2017
	12/2018
	12/2019
	12/2020
Study Completion:	06/2021
Final Report Submission:	12/2021

Submit the protocol to your IND 076479, with a cross-reference letter to this NDA. Submit all interim and final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to

submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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 Abolade (Bola) Adeolu, Regulatory Project Manager, at 301-796-4264.

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

ENCLOSURE:
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
12/04/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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

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

Warnings and Precautions (5.2)	12/2015
Warnings and Precautions (5.5)	12/2015
Warnings and Precautions (5.9)	09/2015

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

INVOKANA is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)

Limitation of Use:

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

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

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

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

Tablets: 100 mg, 300 mg (3)

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

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

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

- Hypotension: Before initiating INVOKANA, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or if on diuretics, ACEi, or ARB. Monitor for signs and symptoms during therapy (5.1)
- 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 (5.2)
- Impairment in renal function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR below 60 mL/min/1.73 m^2 (5 3)
- Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia (2.2, 5.4, 6.1, 8.6)
- Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.5)
- Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with INVOKANA (5.6)
- Genital mycotic infections: Monitor and treat if indicated (5.7)
- Hypersensitivity reactions: Discontinue INVOKANA and monitor until signs and symptoms resolve (5.8)
- Bone fracture: Consider factors that contribute to fracture risk before initiating INVOKANA (5.9)
- Increased LDL-C: Monitor LDL-C and treat if appropriate (5.10)

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

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

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

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

- UGT inducers (e.g., rifampin): Canagliflozin exposure is reduced. Consider increasing dose from 100 mg to 300 mg (2 3, 7.1)
- Digoxin: Monitor digoxin levels (7.2)

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

- Pregnancy: No adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Nursing mothers: Discontinue drug or nursing (8.3)
- Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume (5.1, 8.5)
- Renal impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function (2.2, 5.3, 8.6)
- Hepatic impairment: Not recommended with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dose of INVOKANA (canagliflozin) is 100 mg once daily, taken before the first meal of the day. In patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control, the dose can be increased to 300 mg once daily *[see Warnings and Precautions (5.3), Clinical Pharmacology (12.2), and Patient Counseling Information (17)]*.

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

2.2 Patients with Renal Impairment

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

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

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

Assessment of renal function is recommended prior to initiation of INVOKANA therapy and periodically thereafter. INVOKANA should be discontinued when eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions (5.8)]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease (ESRD), or patients on dialysis *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

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

5.2 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. 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).

5.3 Impairment in Renal Function

INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions (6.1)]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

5.4 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.

5.5 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)]*.

5.6 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.

5.7 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.

5.8 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications (4) and Adverse Reactions (6.1)]*.

5.9 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)]*.

5.10 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.

5.11 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

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

- Hypotension *[see Warnings and Precautions (5.1)]*
- Ketoacidosis *[see Warnings and Precautions (5.2)]*

- Impairment in Renal Function *[see Warnings and Precautions (5.3)]*
- Hyperkalemia *[see Warnings and Precautions (5.4)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.5)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.6)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.7)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*
- Bone Fracture *[see Warnings and Precautions (5.9)]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions (5.10)]*

6.1 Clinical Studies Experience

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

Pool of Placebo-Controlled Trials

The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14)]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

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

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections[†]	3.2%	10.4%	11.4%
Urinary tract infections[‡]	4.0%	5.9%	4.3%
Increased urination[§]	0.8%	5.3%	4.6%

Male genital mycotic infections[¶]	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst[#]	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

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

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

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

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

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

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

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

Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions 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 HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg, and 1.1% with INVOKANA 300 mg).

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

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

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

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

Volume Depletion-Related Adverse Reactions

INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 2) *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), and Use in Specific Populations (8.5 and 8.6)]*.

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

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

***** Includes placebo and active-comparator groups

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

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 3). Patients with moderate renal impairment at baseline had larger mean changes.

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

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

* Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

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

18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 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 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), 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 (5.3)]*.

Genital Mycotic Infections

In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. 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 (5.7)]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In 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 (5.7)]*.

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 4) *[see Warnings and Precautions (5.6)]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

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

Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)][†]	14 (2.5)	10 (1.8)	16 (2.7)

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

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

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 (5.9)]*.

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 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions (5.3 and 5.4) 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 (5.10)]*.

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 (5.2)]*

Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.5)]*

7 DRUG INTERACTIONS

7.1 UGT Enzyme Inducers

Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

7.2 Digoxin

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

7.3 Positive Urine Glucose Test

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

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

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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 HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

8.6 Renal Impairment

The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3)]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2). 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 (5.1, 5.3, and 5.4), and Adverse Reactions (6.1)]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

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

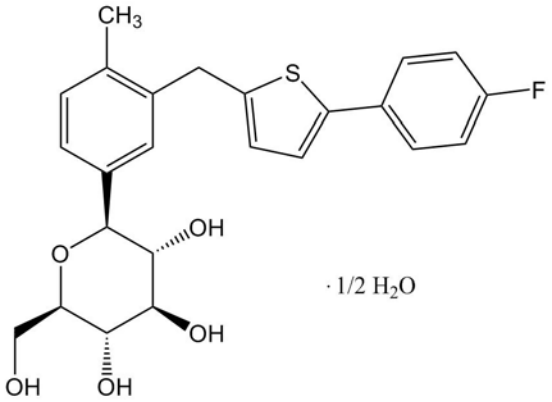
10 OVERDOSAGE

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

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

11 DESCRIPTION

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



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

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

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

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

Metabolism

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

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

Excretion

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

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

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

Specific Populations

Renal Impairment

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

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

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

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 5: Effect of Co−Administered Drugs on Systemic Exposures of Canagliflozin

Co-Administered Drug	**Dose of Co-Administered Drug***	**Dose of Canagliflozin***	**Geometric Mean Ratio (Ratio With/Without Co-Administered Drug) No Effect=1.0**	
			AUC† (90% CI)	**C_{max} (90% CI)**
See *Drug Interactions (7.1)* for the clinical relevance of the following:				
Rifampin	600 mg QD for 8 days	300 mg	0.49 (0.44; 0.54)	0.72 (0.61; 0.84)
No dose adjustments of INVOKANA required for the following:				
Cyclosporine	400 mg	300 mg QD for 8 days	1.23 (1.19; 1.27)	1.01 (0.91; 1.11)
Ethinyl estradiol and levonorgestrel	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel	200 mg QD for 6 days	0.91 (0.88; 0.94)	0.92 (0.84; 0.99)
Hydrochlorothiazide	25 mg QD for 35 days	300 mg QD for 7 days	1.12 (1.08; 1.17)	1.15 (1.06; 1.25)
Metformin	2,000 mg	300 mg QD for 8 days	1.10 (1.05; 1.15)	1.05 (0.96; 1.16)
Probenecid	500 mg BID for 3 days	300 mg QD for 17 days	1.21 (1.16; 1.25)	1.13 (1.00; 1.28)

* Single dose unless otherwise noted

† AUC_{inf} for drugs given as a single dose and AUC_{24h} for drugs given as multiple doses
QD = once daily; BID = twice daily

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

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

13.2 Animal Toxicology and/or Pharmacology

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

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

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

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

14 CLINICAL STUDIES

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

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

14.1 Monotherapy

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

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo. INVOKANA

100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo (see Table 7). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -3.7 mmHg and -5.4 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 7: Results from 26-Week Placebo-Controlled Clinical Study with INVOKANA as Monotherapy*

Efficacy Parameter	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
HbA1C (%)			
Baseline (mean)	7.97	8.06	8.01
Change from baseline (adjusted mean)	0.14	-0.77	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.91‡ (-1.09; -0.73)	-1.16‡ (-1.34; -0.99)
Percent of Patients Achieving HbA1C < 7%	21	45‡	62‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	166	172	173
Change from baseline (adjusted mean)	8	-27	-35
Difference from placebo (adjusted mean) (95% CI)†		-36‡ (-42; -29)	-43‡ (-50; -37)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	229	250	254
Change from baseline (adjusted mean)	5	-43	-59
Difference from placebo (adjusted mean) (95% CI)†		-48‡ (-59.1; -37.0)	-64‡ (-75.0; -52.9)
Body Weight			
Baseline (mean) in kg	87.5	85.9	86.9
% change from baseline (adjusted mean)	-0.6	-2.8	-3.9
Difference from placebo (adjusted mean) (95% CI)†		-2.2‡ (-2.9; -1.6)	-3.3‡ (-4.0; -2.6)

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

14.2 Combination Therapy

Add-on Combination Therapy with Metformin

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

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

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin (see Table 8). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -5.4 mmHg and -6.6 mmHg with INVOKANA 100 mg and 300 mg, respectively.

Table 8: Results from 26-Week Placebo-Controlled Clinical Study of INVOKANA in Combination with Metformin*

Efficacy Parameter	Placebo + Metformin (N=183)	INVOKANA 100 mg + Metformin (N=368)	INVOKANA 300 mg + Metformin (N=367)
HbA1C (%)			
Baseline (mean)	7.96	7.94	7.95
Change from baseline (adjusted mean)	-0.17	-0.79	-0.94
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.76; -0.48)	-0.77‡ (-0.91; -0.64)
Percent of patients achieving HbA1C < 7%	30	46‡	58‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	173
Change from baseline (adjusted mean)	2	-27	-38
Difference from placebo (adjusted mean) (95% CI)†		-30‡ (-36; -24)	-40‡ (-46; -34)
2-hour Postprandial Glucose (mg/dL)			
Baseline (mean)	249	258	262
Change from baseline (adjusted mean)	-10	-48	-57
Difference from placebo (adjusted mean) (95% CI)†		-38‡ (-49; -27)	-47‡ (-58; -36)
Body Weight			
Baseline (mean) in kg	86.7	88.7	85.4
% change from baseline (adjusted mean)	-1.2	-3.7	-4.2
Difference from placebo (adjusted mean) (95% CI)†		-2.5‡ (-3.1; -1.9)	-2.9‡ (-3.5; -2.3)

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

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

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

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

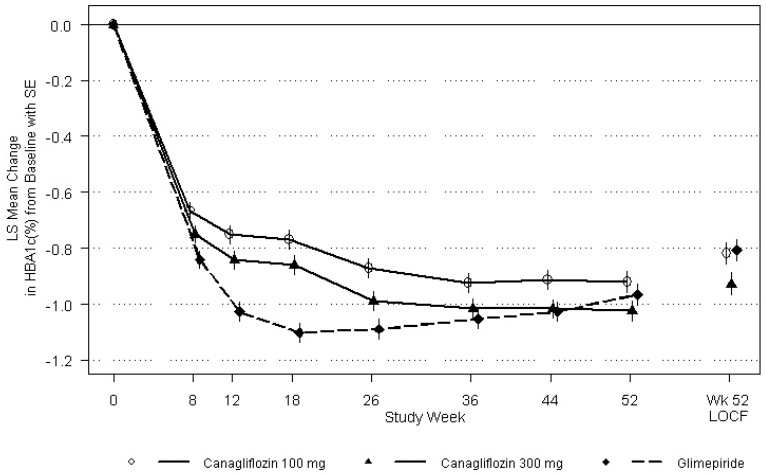
As shown in Table 9 and Figure 1, at the end of treatment, INVOKANA 100 mg provided similar reductions in HbA1C from baseline compared to glimepiride when added to metformin therapy. INVOKANA 300 mg provided a greater reduction from baseline in HbA1C compared to glimepiride, and the relative treatment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

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

Efficacy Parameter	INVOKANA 100 mg + Metformin (N=483)	INVOKANA 300 mg + Metformin (N=485)	Glimepiride (titrated) + Metformin (N=482)
HbA1C (%)			
Baseline (mean)	7.78	7.79	7.83
Change from baseline (adjusted mean)	-0.82	-0.93	-0.81
Difference from glimepiride (adjusted mean) (95% CI)†	-0.01‡ (-0.11; 0.09)	-0.12‡ (-0.22; -0.02)	
Percent of patients achieving HbA1C < 7%	54	60	56
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	165	164	166
Change from baseline (adjusted mean)	-24	-28	-18
Difference from glimepiride (adjusted mean) (95% CI)†	-6 (-10; -2)	-9 (-13; -5)	
Body Weight			
Baseline (mean) in kg	86.8	86.6	86.6
% change from baseline (adjusted mean)	-4.2	-4.7	1.0
Difference from glimepiride (adjusted mean) (95% CI)†	-5.2§ (-5.7; -4.7)	-5.7§ (-6.2; -5.1)	

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

Figure 1: Mean HbA1C Change at Each Time Point (Completers) and at Week 52 Using Last Observation Carried Forward (mITT Population)



Add-on Combination Therapy With Sulfonylurea

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

As shown in Table 10, at the end of treatment, INVOKANA 100 mg and 300 mg daily provided statistically significant (p<0.001 for both doses) improvements in HbA1C relative to placebo when added to sulfonylurea. INVOKANA 300 mg once daily compared to placebo resulted in a greater proportion of patients achieving an HbA1C less than 7%, (33% vs 5%), greater reductions in fasting plasma glucose (-36 mg/dL vs +12 mg/dL), and greater percent body weight reduction (-2.0% vs -0.2%).

Table 10: Results from 18-Week Placebo–Controlled Clinical Study of INVOKANA in Combination with Sulfonylurea*

Efficacy Parameter	Placebo + Sulfonylurea (N=45)	INVOKANA 100 mg + Sulfonylurea (N=42)	INVOKANA 300 mg + Sulfonylurea (N=40)
HbA1C (%)			
Baseline (mean)	8.49	8.29	8.28
Change from baseline (adjusted mean)	0.04	-0.70	-0.79
Difference from placebo (adjusted mean) (95% CI)†		-0.74‡ (-1.15; -0.33)	-0.83‡ (-1.24; -0.41)

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

Add-on Combination Therapy With Metformin and Sulfonylurea

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

At the end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin and sulfonylurea. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in a significant reduction in fasting plasma glucose (FPG), and in percent body weight reduction compared to placebo when added to metformin and sulfonylurea (see Table 11).

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

Efficacy Parameter	Placebo + Metformin and Sulfonylurea (N=156)	INVOKANA 100 mg + Metformin and Sulfonylurea (N=157)	INVOKANA 300 mg + Metformin and Sulfonylurea (N=156)
HbA1C (%)			
Baseline (mean)	8.12	8.13	8.13
Change from baseline (adjusted mean)	-0.13	-0.85	-1.06
Difference from placebo (adjusted mean) (95% CI)†		-0.71‡ (-0.90; -0.52)	-0.92‡ (-1.11; -0.73)
Percent of patients achieving A1C < 7%	18	43‡	57‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	170	173	168
Change from baseline (adjusted mean)	4	-18	-31
Difference from placebo (adjusted mean) (95% CI)†		-22‡ (-31; -13)	-35‡ (-44; -25)
Body Weight			
Baseline (mean) in kg	90.8	93.5	93.5
% change from baseline (adjusted mean)	-0.7	-2.1	-2.6
Difference from placebo (adjusted mean) (95% CI)†		-1.4‡ (-2.1; -0.7)	-2.0‡ (-2.7; -1.3)

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

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

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

As shown in Table 12 and Figure 2, at the end of treatment, INVOKANA 300 mg provided greater HbA1C reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea ($p<0.05$). INVOKANA 300 mg resulted in a mean percent change in body weight from baseline of -2.5% compared to +0.3% with sitagliptin 100 mg. A mean change in systolic

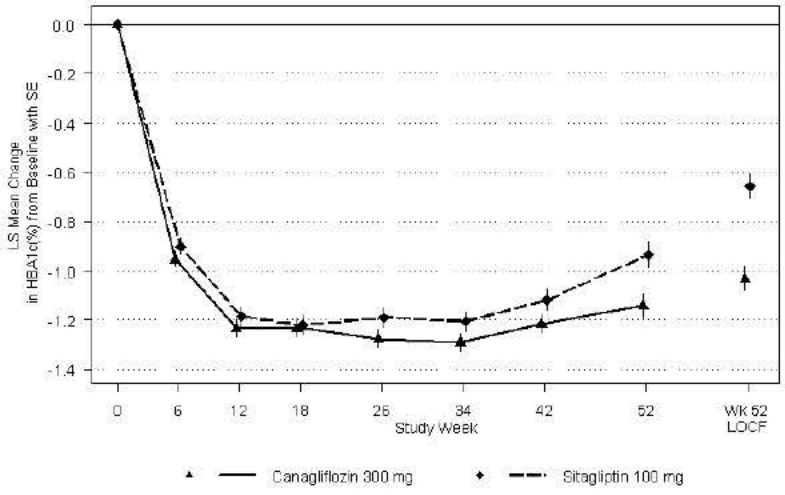
blood pressure from baseline of -5.06 mmHg was observed with INVOKANA 300 mg compared to +0.85 mmHg with sitagliptin 100 mg.

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

Efficacy Parameter	INVOKANA 300 mg + Metformin and Sulfonylurea (N=377)	Sitagliptin 100 mg + Metformin and Sulfonylurea (N=378)
HbA1C (%)		
Baseline (mean)	8.12	8.13
Change from baseline (adjusted mean)	-1.03	-0.66
Difference from sitagliptin (adjusted mean) (95% CI)†	-0.37‡ (-0.50; -0.25)	
Percent of patients achieving HbA1C < 7%	48	35
Fasting Plasma Glucose (mg/dL)		
Baseline (mean)	170	164
Change from baseline (adjusted mean)	-30	-6
Difference from sitagliptin (adjusted mean) (95% CI)†	-24 (-30; -18)	
Body Weight		
Baseline (mean) in kg	87.6	89.6
% change from baseline (adjusted mean)	-2.5	0.3
Difference from sitagliptin (adjusted mean) (95% CI)†	-2.8§ (-3.3; -2.2)	

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

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



Add-on Combination Therapy With Metformin and Pioglitazone

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

At the of end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to metformin and pioglitazone. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reduction in fasting plasma glucose (FPG) and in percent body weight reduction compared to placebo when added to metformin and pioglitazone (see Table 13). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -4.1 mmHg and -3.5 mmHg with INVOKANA 100 mg and 300 mg, respectively.

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

Efficacy Parameter	Placebo + Metformin and Pioglitazone (N=115)	INVOKANA 100 mg + Metformin and Pioglitazone (N=113)	INVOKANA 300 mg + Metformin and Pioglitazone (N=114)
HbA1C (%)			
Baseline (mean)	8.00	7.99	7.84
Change from baseline (adjusted mean)	-0.26	-0.89	-1.03
Difference from placebo (adjusted mean) (95% CI)†		-0.62‡ (-0.81; -0.44)	-0.76‡ (-0.95; -0.58)
Percent of patients achieving HbA1C < 7%	33	47‡	64‡
Fasting Plasma Glucose (mg/dL)			
Baseline (mean)	164	169	164
Change from baseline (adjusted mean)	3	-27	-33
Difference from placebo (adjusted mean) (95% CI)†		-29‡ (-37; -22)	-36‡ (-43; -28)
Body Weight			
Baseline (mean) in kg	94.0	94.2	94.4
% change from baseline (adjusted mean)	-0.1	-2.8	-3.8
Difference from placebo (adjusted mean) (95% CI)†		-2.7‡ (-3.6; -1.8)	-3.7‡ (-4.6; -2.8)

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

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

A total of 1718 patients with type 2 diabetes inadequately controlled on insulin greater than or equal to 30 units/day or insulin in combination with other antihyperglycemic agents participated in an 18-week, double-blind, placebo-controlled substudy of a cardiovascular study to evaluate the efficacy and safety of INVOKANA in combination with insulin. The mean age was 63 years, 66% of patients were men, and the mean baseline eGFR was 75 mL/min/1.73 m^2. Patients on basal, bolus, or basal/bolus insulin for at least 10 weeks entered a 2-week, single-blind, placebo run-in period. Approximately 70% of patients were on a background basal/bolus insulin regimen. After the run-in period, patients were randomized to INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily as add-on to insulin. The mean daily insulin dose at baseline was 83 units, which was similar across treatment groups.

At the of end of treatment, INVOKANA 100 mg and 300 mg once daily resulted in a statistically significant improvement in HbA1C ($p<0.001$ for both doses) compared to placebo when added to insulin. INVOKANA 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1C less than 7%, in significant reductions in fasting plasma glucose (FPG), and in percent body weight reductions compared to placebo (see Table 14). Statistically significant ($p<0.001$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo were -2.6 mmHg and -4.4 mmHg with INVOKANA 100 mg and 300 mg, respectively.

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

Efficacy Parameter	Placebo + Insulin (N=565)	INVOKANA 100 mg + Insulin (N=566)	INVOKANA 300 mg + Insulin (N=587)
HbA1C (%)			
Baseline (mean)	8.20	8.33	8.27
Change from baseline (adjusted mean)	0.01	-0.63	-0.72
Difference from placebo (adjusted mean) (95% CI)†		-0.65‡ (-0.73; -0.56)	-0.73‡ (-0.82; -0.65)
Percent of patients achieving HbA1C < 7%	8	20‡	25‡
Fasting Plasma Glucose (mg/dL)			
Baseline	169	170	168
Change from baseline (adjusted mean)	4	-19	-25
Difference from placebo (adjusted mean) (97.5% CI)†		-23‡ (-29; -16)	-29‡ (-35; -23)

Body Weight			
Baseline (mean) in kg	97.7	96.9	96.7
% change from baseline (adjusted mean)	0.1	-1.8	-2.3
Difference from placebo (adjusted mean) (97.5% CI)[†]		-1.9[‡] (-2.2; -1.6)	-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 m^2. Patients were randomized to the addition of INVOKANA 100 mg, INVOKANA 300 mg, or placebo, administered once daily. At the end of treatment, INVOKANA provided statistically significant improvements from baseline relative to placebo in HbA1C (p<0.001 for both doses) of -0.57% (95% CI: -0.71; -0.44) for INVOKANA 100 mg and -0.70% (95% CI: -0.84; -0.57) for INVOKANA 300 mg. Statistically significant (p<0.001 for both doses) reductions from baseline in fasting plasma glucose (FPG) and body weight were also observed in this study relative to placebo *[see Use in Specific Populations (8.5)]*.

Moderate Renal Impairment

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

At the end of treatment, INVOKANA 100 mg and INVOKANA 300 mg daily provided greater reductions in HbA1C relative to placebo (-0.30% [95% CI: -0.53; -0.07] and -0.40%, [95% CI: -0.64; -0.17], respectively) *[see Warnings and Precautions (5.3), 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 HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests

Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension

Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions (5.1)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis has 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 (5.2)]*.

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 (5.5)]*.

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 (5.7)]*.

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 (5.7)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

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.

Active ingredient made in Belgium

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

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

Licensed from Mitsubishi Tanabe Pharma Corporation

Medication Guide
INVOKANA® (in-vo-KAHN-uh)
(canagliflozin)
Tablets

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

INVOKANA can cause important side effects, including:

- **Dehydration. INVOKANA can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).**
  You may be at higher risk of dehydration if you:
  - have low blood pressure
  - take medicines to lower your blood pressure, including diuretics (water pill)
  - are on a low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older
- **Vaginal yeast infection.** Women who take INVOKANA may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take INVOKANA may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around penis

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

What is INVOKANA?

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

Who should not take INVOKANA?

Do not take INVOKANA if you:

- are allergic to canagliflozin or any of the ingredients in INVOKANA. See the end of this Medication Guide for a list of ingredients in INVOKANA. Symptoms of allergic reaction to INVOKANA may include:
  - rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing
- have severe kidney problems or are on dialysis.

What should I tell my doctor before taking INVOKANA?

Before you take INVOKANA, tell your doctor if you:

- have kidney problems.
- have liver problems.
- 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. It is not known if INVOKANA will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if INVOKANA passes into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking INVOKANA.

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

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

- diuretics (water pills)
- 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 A1C.

What are the possible side effects of INVOKANA?

INVOKANA may cause serious side effects including:

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

- **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 can be life-threatening and may need to be treated in a hospital. **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**
- **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. Licensed from Mitsubishi Tanabe Pharma Corporation.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised DEC/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s013

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
Division of Metabolism and Endocrinology Products (DMEP)

Applications: NDA 204042/S-013
NDA 204353/S-012

Names of Drugs: Invokana (canagliflozin) tablets
Invokamet (canagliflozin and metformin HCl) tablets

Applicant: Janssen Pharmaceuticals, Inc.

Background and Summary

On September 25, 2015, Safety Labeling Change (SLC) notification letters were issued for all currently approved sodium-glucose cotransporter-2 (SGLT-2) inhibitor products as follows: Invokana (canagliflozin) tablets (NDA 204042), Invokamet (canagliflozin and metformin HCl) tablets (NDA 204353), Farxiga (dapagliflozin) tablets (NDA 202293), Xigduo XR (dapagliflozin and metformin HCl extended release) tablets (NDA 205649), Jardiance (empagliflozin) tablets (NDA 204629), Synjardy (empagliflozin and metformin hydrochloride) tablets (NDA 206111), and Glyxambi (empagliflozin and linagliptin) tablets (NDA 206073). The SLC letters required the applicants of these products to add language regarding postmarketing cases of ketoacidosis and urosepsis in patients treated with SGLT-2 inhibitors (see Dr. Jennifer Pippins' review in DARRTS dated December 3, 2015). The new language was required to be added to the package inserts (PIs) and patient labeling of all seven products. The changes required for the patient labeling incorporated comments provided via consult review from DMPP.

All three applicants submitted supplements in response to this SLC notification as required for the seven products by October 23, 2015. These supplements included the revised PIs and and patient labeling (Medication Guide or Patient Package Insert, as applicable) with proposed modifications from the changes proposed by FDA in the SLC notification letters. The following is the list of supplements that were submitted in response to the SLC notification:

Applicant	NDA/Supplement	Product
Janssen Pharmaceuticals, Inc.	NDA 204042/S-013	Invokana (canagliflozin) tablets
	NDA 204353/S-012	Invokamet (canagliflozin and metformin HCl) tablets
AstraZeneca AB	NDA 202293/S-008	Farxiga (dapagliflozin) tablets
	NDA 205649/S-003	Xigduo XR (dapagliflozin and metformin HCl extended release) tablets
Boehringer Ingelheim Pharmaceuticals, Inc.	NDA 204629/S-007	Jardiance (empagliflozin) tablets
	NDA 206111/S-002	Synjardy (empagliflozin and metformin hydrochloride) tablets
	NDA 206073/S-003	Glyxambi (empagliflozin and linagliptin) tablets

DMEP (Dr. Jennifer Pippins, in collaboration with the clinical team) reviewed the PIs and asked

the applicants to make revisions. The revised PIs were found acceptable.

This labeling review is for the canagliflozin products.

Materials Reviewed

Labeling Reviewed	Submission Date	Currently Approved (supplement and date)
Invokana (canagliflozin) tablets		
Package Insert	November 20, 2015	NDA 204042/S-006 September 10, 2015
Medication Guide		
Invokamet (canagliflozin and metformin HCl) tablets		
Package Insert	November 20, 2015	NDA 204353/S-003 September 10, 2015
Medication Guide		

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 Dr. Pippins's clinical review, or are considered annual-reportable changes.

Recommendations

The labeling was reviewed and found acceptable by Dr. Jennifer Rodriguez Pippins. The supplement is ready for approval.

Reviewed by: Elisabeth A. Hanan, Regulatory Project Manager
(see appended signature page)

Concurrency by: Julie Van der Waag, Chief, Project Management Staff

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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
12/03/2015

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 202293, NDA 205649 NDA 204629, NDA 206073, NDA 206111
PRODUCTS:	Invokana (canagliflozin), Invokamet (canagliflozin and metformin) Farxiga (dapagliflozin), Xigduo XR (dapagliflozin and metformin) Jardiance (empagliflozin), Glyxambi (empagliflozin and linagliptin), Synjardy (empagliflozin and metformin)
APPLICANTS:	Janssen Pharmaceuticals (canagliflozin products) Astra Zeneca AB (dapagliflozin products) Boehringer Ingelheim Pharmaceuticals (empagliflozin products)
FROM:	Jennifer Rodriguez Pippins, M.D., M.P.H. Deputy Director for Safety, Division of Metabolism and Endocrinology
DATE:	December 3, 2015
TOPIC:	Safety Labeling Changes and new Postmarketing Requirement, sodium-glucose cotransporter-2 (SGLT-2) inhibitor class
TSI #:	1383 (ketoacidosis), 1512 (urosepsis)

PURPOSE

This memorandum to file pertains to the Division of Metabolism and Endocrinology Products' (DMEP) requirement for safety labeling changes (SLC) to address two safety issues identified postapproval for the sodium-glucose cotransporter-2 (SGLT-2) inhibitor class: ketoacidosis (tracked safety issue [TSI] 1383) and urosepsis (TSI 1512). In addition, a new postmarketing requirement for an enhanced pharmacovigilance (ePV) study of ketoacidosis is also being required.

BACKGROUND

The SGLT-2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2DM). They are a relatively new class of antidiabetic agents. The first member of the class to receive FDA approval was canagliflozin in 2013; dapagliflozin and empagliflozin each followed in 2014, and these three molecular entities are also available as fixed dose combinations with other antidiabetic agents (Table 1).

Table 1. SGLT-2 Inhibitors

NDA	Brand name	Active ingredient(s)
Janssen Pharmaceuticals		
204042	Invokana	canagliflozin
204353	Invokamet	canagliflozin and metformin
Astra Zeneca AB		
202293	Farxiga	dapagliflozin

205649	Xigduo XR	dapagliflozin and metformin
Boehringer Ingelheim Pharmaceuticals		
204629	Jardiance	empagliflozin
206073	Glyxambi	empagliflozin and linagliptin
206111	Synjardy	empagliflozin and metformin

The mechanism of action for this class is inhibition of 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.

Ketoacidosis

Initial Case Series

Ketoacidosis was identified as a potential safety issue from a signal generated by routine screening of FDA Adverse Event Reporting System (FAERS) spontaneous reports conducted by the Division of Pharmacovigilance I (DPVI) for canagliflozin, the first approved SGLT-2 inhibitor. DPVI conducted a disproportionality analysis for the SGLT-2 inhibitor class, and observed disproportionate data mining scores for diabetic ketoacidosis (DKA) for this class compared to other antidiabetic agents. In response to this signal, DPVI conducted a review which included an evaluation of FAERS data and a review of the published literature.[1] This initial DPV review searched the FAERS database for cases of DKA through June 6, 2014; the search was conducted for canagliflozin and dapagliflozin only, as they were the only two SGLT-2 approved at the time. A case of DKA was defined as a FAERS report with all of the following elements:

- Temporal association between canagliflozin or dapagliflozin exposure and the onset of DKA, ketoacidosis, or ketosis, and a measure of time to onset
- DKA reported or diagnosed by a healthcare provider
- Emergency room visit and/or hospitalization for the treatment of DKA

The above search strategy yielded 20 cases. No additional cases were identified from the literature. Among the 20 cases, the SGLT-2 inhibitor was being used to treat T2DM in 14 cases, type 1 diabetes mellitus (T1DM) in 3 cases, and unspecified in 3 cases. It should be noted that the SGLT-2 class is not indicated for the treatment of TIDM.[2] The median time to onset of DKA was 14.5 days (range, 1 to 175 days). The primary outcome was listed as hospitalization in 16 cases, death in 1 case, and "other serious" in 3 cases. Thirteen cases reported at least one laboratory diagnostic criteria for DKA, such as anion gap acidosis, ketonemia, or reduced serum bicarbonate. Serum glucose was reported in only 8 cases. While values ranged widely (116 mg/dL to 1211 mg/dL), the presence of only mildly elevated serum glucose in multiple cases was notable. In a majority of cases (n=13) drug was discontinued. Twelve cases noted a history of prior insulin use, 4 cases noted the absence of prior insulin use, and insulin use status was not reported in 4 cases. The most commonly noted concurrent events were dehydration (n=5) and viral illness (n=4). Table 2, adapted from the DPVI review, further summarizes the case series.

[1] Chamberlain C. DPVI Review. DARRTS Reference ID: 3633765. September 24, 2014.
[2] The product labels include a "limitation of use" statement informing prescribers that drug is not recommended in patients with T1DM or for the treatment of DKA.

Table 2. Diabetic Ketoacidosis Reported with SGLT-2 Inhibitor Use, March 2013, through June 6, 2014

Descriptive characteristics of case series, N=20	
Number of cases by approved SGLT-2 inhibitor	
Canagliflozin	13
Dapagliflozin	7
Origin of report	
Domestic	14
Foreign	6
Age (years), n=16	
Mean	56
Median	55
Range	32-86
Sex	
Female	12
Male	6
Not reported	2
Indication	
T2DM	14
T1DM	3
Not reported	3
Time to onset (days)	
Mean	40
Median	15
Range	1 to 175
Drug Discontinued	
Yes	13
Unknown	7
Primary outcome	
Death	1
Hospitalization	16
Other serious	3
Prior insulin use	
Yes	12
No	4
Not reported	4
Concurrent event	
Dehydration	5
Viral illness	4
Urosepsis	1
Sinus infection	1

While the ability to fully delineate the nature of this safety issue was limited by the overall modest number of events in this first case series, several features stood out. First, the data

supported causal association given the temporal association between drug use and event. Second, the occurrence of events with both canagliflozin and dapagliflozin suggested a class effect. Third, the serious nature of the events, all of which resulted in hospitalization or emergency department use, was notable.

With regard to the actual nature of the adverse event, the limited information made full characterization somewhat difficult. Diabetic ketoacidosis (DKA) is often a diagnosis of exclusion, and its diagnosis requires robust clinical information to allow the elimination of alternative causes of acidosis. As is usual for FAERS data, the level of clinical detail was somewhat limited. In addition, diagnosis of DKA also involves documentation of the typical triad of hyperglycemia, acidosis, and ketonemia. Not all these laboratory data were available from FAERS; moreover, in some cases the blood glucose levels were only slightly increased. While DKA in the absence of marked hyperglycemia (i.e., "euglycemic DKA") is not unheard of, it is unusual. The cases also suggested the possibility alternative etiologies of high-anion gap acidosis other than DKA. For example, the concurrent event of reduced caloric intake suggested the possibility of starvation ketosis, while the concurrent event of alcohol use suggested the possibility of alcohol-related ketosis. Finally, the presentation was not typical for DKA as most patients had T2DM. The possibility that patients' disease was misclassified was considered, but there was no clear evidence of this.

To further understand this safety issue, DMEP conducted a clinical review.[3] This review included a summary of pre-approval controlled data pertinent to ketoacidosis. It noted that in the original canagliflozin NDA there was a small but non-significant imbalance in the incidence of serious adverse events of DKA favoring placebo; no imbalance was observed when both serious and non-serious adverse events of DKA were considered together. Only a single event of DKA was noted in the dapagliflozin review; subsequent data mining suggested 3 additional possible cases with dapagliflozin. The empagliflozin review noted that a greater percentage of patients treated with empagliflozin demonstrated shifts in sodium bicarbonate levels from normal to low, or had a possibly clinically significant low serum bircarbonate, but there was no imbalance in the incidence of acid-base disorders. DMEP's clinical review of this safety issue also includes a discussion of the complexity of diabetes classification, and raised the possibility that some patients in the case series may have had "ketosis-prone diabetes," which is characterized by the occurrence of DKA or ketosis in the absence of the classic phenotype of autoimmune T1DM.

Both the original DPV review and DMEP review concurred that the addition of a Warning and Precautions statement describing this safety concern was warranted. In order to inform health care providers and patients of this safety issue, a Drug Safety Communication (DSC) was issued on May 15, 2015. Issuing of this DSC allowed FDA to communicate our safety concern while we continued our review of the safety issue and discussions on the content of labeling.

Follow-up Case Series

In order to further elucidate this safety issue, a follow-up review was conducted by DPV.[4] The review includes an evaluation of FAERS data, a medical literature review, and initiation of

[3] Pratt V. DMEP Review. DARRTS Reference ID: 3731067. April 17, 2015.
[4] Chamberlain C. DPVI Review. DARRTS Reference ID: 3792892. July 16, 2015.

exploratory analyses using Sentinel. As the basis of the SLC action is the postmarketing data, this summary review focuses on the results of the FAERS evaluation. The FAERS database was searched for cases of diabetic ketoacidosis (DKA) from June 6, 2014 (the data-lock date for the initial DPV review) through May 1, 2015; this time the search was conducted for all three members of the SGLT-2 inhibitor class. A case of DKA was defined as a FAERS report with all of the following elements:

- DKA, ketoacidosis, ketosis, or hyperosmolar hyperglycemic state reported or diagnosed by a healthcare provider
- A measure of time to onset from SGLT-2 inhibitor exposure to DKA, ketoacidosis, ketosis, or hyperosmolar hyperglycemic state
- Emergency room or urgent care visit and/or hospitalization for the treatment of DKA, ketoacidosis, ketosis or hyperosmolar hyperglycemic state

The above search strategy yielded 54 cases. Among the 54 cases, the SGLT-2 inhibitor was being used to treat T2DM in 31 cases, T1DM in 12 cases, latent autoimmune diabetes of adults (LADA) in 1 case, and unspecified in 10 cases. In the 10 cases not reporting diabetes type, nine were taking concomitant oral antidiabetic agents, which is suggestive of T2DM. The median time to onset was 53 days (range, 2 to 365 days). The primary outcome was hospitalization in 50 cases, "life threatening" in 16 cases, "other serious" in 13 cases, and emergency department in 1 case. Thirty-two cases reported at least one laboratory diagnostic criteria for DKA, such as anion gap acidosis, ketonemia, or reduced serum biacarbonate. Serum glucose was reported in 33 cases. While values ranged widely (90 mg/dL to 1366 mg/dL), the mean serum glucose level was 290 mg/dL and the median 220 mg/dL. Two additional cases reported mild hyperglycemia or normoglycemia. In a majority of cases (n=45) drug was discontinued. Twenty-six cases noted a history of concurrent insulin use, twenty noted the absence of concurrent insulin, and insulin use status was not reported in 8 cases. The majority of cases (n=35) reported a concurrent event, including changes in insulin dose and infection. Dehydration was common at presentation. Table 3, adapted from the DPVI review, further summarizes the case series.

Table 3. Diabetic Ketoacidosis Reported with SGLT-2 Inhibitor Use, June 6, 2014, through May 1, 2015

Descriptive characteristics of case series, N=54	
Number of cases by approved SGLT-2 inhibitor	
Canagliflozin Dapagliflozin Empagliflozin	35 15 4
Origin of report	
Domestic Foreign	40 14
Age (years), n=46	
Mean Median Range	47 48 16-77
Sex	

Female	27
Male	27
Indication	
T2DM	31
T1DM	12
LADA	1
Not reported	10
Time to onset (days)	
Mean	79
Median	53
Range	2 to 365
Drug Discontinued	
Yes	45
No	4
Not reported	5
Primary outcome	
Death	0
Hospitalization	50
Life-threatening	16
Other serious	13
Emergency Department	1
Concurrent insulin use	
Yes	26
No	20
Not reported	8
Concurrent event	
Yes	35
No	1
Not reported	18

Evaluation of the second case series provided confirmation of several key features of this safety issue. First, the continued receipt of reports, now including ones for the third approved SGLT-2 inhibitor, underscored the relevance of this safety issue across the entire class. Second, causality continued to be supported by the temporal association observed between drug use and event. Third, the fact that all cases involved hospitalization or emergency department presentation provided additional evidence of the seriousness of the events.

Review of the 54 cases again demonstrated that events occurred both in patients with T2DM as well as in patients with T1DM. In addition, the phenomenon of ketosis in the presence of only modestly elevated serum glucose was confirmed. The presence of concurrent events precluded describing the events specifically as DKA; rather, based on the available information, they may be accurately described as events of ketoacidosis associated with SGLT-2 inhibitor use in diabetics. Contributing factors include insulin dose reduction, reduced caloric intake, and alcohol abuse.

Based on the two DPV reviews, and after discussion between DMEP and DPV, language for a SLC notification requiring a new Warning and Precautions statement describing ketoacidosis was drafted. In addition, consideration was given as to whether additional studies would be useful to inform this safety issue. DMEP and DPV concluded that an enhanced pharmacovigilance (ePV) study of five years duration, with specialized follow-up to collect additional information on ketoacidosis cases, would be useful to the FDA's ongoing evaluation of this safety issue. The wording of the SLC and PMR notification is provided later on in this review.

Urosepsis and Pyelonephritis

Urosepsis was identified as a safety signal during routine pharmacovigilance for canagliflozin. In response to this signal, DPVI conducted a review of FAERS data and the medical literature.[5] This DPV review searched the FAERS database for cases of urosepsis through October 8, 2014; the search was conducted for all three members of the SGLT-2 inhibitor class. A case of urosepsis was defined as a FAERS report with all of the following elements:

- Hospitalization or death
- Evidence of infection of the genitourinary tract or kidney with one of the following:
    - sepsis by diagnosis (urosepsis, septicemia, sepsis)
    - fever
    - elevated white blood cell count
    - positive blood culture results
- Emergency room visit and/or hospitalization for the treatment of DKA

Reports were excluded if they:

- Contained strong confounders (e.g., immunosuppressive treatment)
- Were non-spontaneous
- Described a pre-existing renal or urinary tract abnormality suggestive of obstruction

The above search strategy yielded 19 cases. No additional cases were identified from the literature. The median time to onset was 46 days (range, 2 to 270 days). The primary outcome was hospitalization in all 19 cases; four of those hospitalizations involved ICU admissions. Two patients required hemodialysis for renal failure. In a majority of cases (n=15) drug was discontinued. Eight cases reported microbiology data; in all eight cases, blood cultures were positive for E. coli. In most cases (n=16) whether or not a patient had a history of prior UTI was not reported. Hemoglobin A1c data was available in some instances, as follows: 6.5-7.5% (n=2), 7.6-8.9% (n=2), and 9.0 to 13.1% (n=4). Table 4, adapted from the DPVI review, further summarizes the case series.

Table 4. Urosepsis Reported with SGLT-2 Inhibitor Use, March 2013, through October 8, 2014

Descriptive characteristics of case series, N=19
Number of cases by approved SGLT-2 inhibitor

[5] Chamberlain C. DPVI Review. DARRTS Reference ID: 3730950. April 13, 2015.

Canagliflozin Dapagliflozin Empagliflozin	10 9 0
Origin of report	
Domestic Foreign	11 8
Age (years), n=18	
Mean Median Range	60 62 18-80
Sex	
Female Male	10 9
Time to onset (days), n=14	
Mean Median Range	59 46 2 to 270
Drug Discontinued	
Yes No Not reported	15 1 3
Primary outcome	
Death Hospitalization • ICU admission	0 19 4
Blood culture organism	
E. coli Not reported	8 11
Prior history of UTI	
Yes No Not reported	1 2 16
HgA1c, n=8	
6.5-7.5% 7.6-8.9% 9.0-13.1%	2 2 4

This case series, while modest in size, is notable for the severity of events, which resulted in hospitalization including several cases of ICU admission. While cases were identified only for canagliflozin and dapagliflozin, this was not unexpected, given that empagliflozin was approved only two months prior to the data-lock for the DPV review. A subsequent DVP review[6] was conducted to determine whether cases for empagliflozin had accrued. This second review searched the FAERS database from August 1, 2014 through July 26, 2015, and included both

[6] Chamberlain C. DPVI Review. DARRTS Reference ID: 3802239. August 5, 2015.

monotherapy and combination empagliflozin products. Three cases of urosepsis, pyelonephritis, or complicated UTI were identified.

While diabetics are at increased baseline risk for UTI, causality is supported by the pre-market clinical trial data across the SGLT-2 inhibitor class, which demonstrated imbalances in UTI in patients treated with drug compared to placebo. In addition, while preliminary data from the recently completed empagliflozin cardiovascular outcomes trial (EMPA-REG) demonstrates that UTI events are balanced overall, there is an increased incidence in urosepsis with empagliflozin (rate of 0.10-0.18 per 100 patient-years) compared to placebo (rate of 0.05 per 100 patients-years).[7] Causality is also supported by the mechanism of SGLT-2 inhibition, which acts by increasing urinary glucose excretion; it is conceivable that higher urinary glucose concentrations may increase risk the of infection.

Current labeling with respect to UTI is heterogeneous across the class, with empagliflozin having a Warnings and Precautions statement for UTI, in addition to reporting data in Section 6, Adverse Reactions, while canagliflozin and dapagliflozin only include data in Section 6. Urosepsis is currently only included in the canagliflozin label, where it appears in a footnote to a table in Section 6.

Based on the totality of the data, DMEP concurred with DPV's recommendation for labeling changes. DMEP concluded that a new Warnings and Precautions statement on urosepsis and pyelonephritis was required.

SLC and PMR NOTIFICATION

On September 25, 2015, DMEP notified the application holders for the seven currently approved DPP-4 inhibitor products that since approval the Agency had become aware of the risks of ketoacidosis and urosepsis associated with the SGLT-2 inhibitor class. 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 main change to prescribing information outlined in the SLC notification letters was the addition of two new Warnings and Precautions statements to Section 5:

> ***Section 5.X 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 (SGLT-2) inhibitors, including DRUG. DRUG is not indicated for the treatment of patients with type 1 diabetes mellitus [see Indications and Usage (1)].*
>
> *Patients treated with DRUG 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 DRUG may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected DRUG should be*

[7] Boehringer Ingelheim/FDA teleconference held August 19, 2015.

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

Section 5.Y 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 DRUG. 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)].

The SLC notification letter also specified corresponding language in Section 17 (Patient Counseling Information), as well as in patient labeling. The patient labeling language was reviewed by the Division of Medical Policy Programs (DMPP) prior to issuing the SLC notification letters.

It should be noted that (b) (4)

In addition to the SLC, the letter issued on September 25, 2015, also notified the application holders of the new PMR:

An enhanced pharmacovigilance study of ketoacidosis in patients treated with DRUG. The study will include reports of ketoacidosis or diabetic ketoacidosis for a period of 5 years, and will include assessment and analysis of spontaneous reports of ketoacidosis in patients treated with DRUG, with specialized follow-up to collect additional information on these cases.

The application holders were asked to submit a timetable for PMR milestones.

APPLICANTS' RESPONSES

Only a single discussion period was held for this SLC.

Canagliflozin

Janssen Pharmaceuticals, the application holder for Invokana (canagliflozin) and Invokamet (canagliflozin and metformin), responded to DMEP's September 25, 2015 SLC Labeling Notification by submitting prior approval supplements (NDA 204042 S-13, NDA 204353 S-12) on October 21, 2015. While the language for the Warnings and Precautions statements was generally consistent with that contained in the SLC notification, Janssen proposed (b) (4) DMEP did not agree with this addition, (b) (4) Moreover, the (b) (4) . Finally, (b) (4)

For all these reasons the proposed changes were rejected.

Dapagliflozin

Astra Zeneca AB (dapagliflozin products), the application holder for Farxiga (dapagliflozin) and Xigduo XR (dapagliflozin and metformin), responded to DMEP's September 25, 2015 SLC Labeling Notification by submitting prior approval supplements (NDA 202293 S-8, NDA 205649 S-3) on October 23, 2015. Astra Zeneca proposed a number of revisions to (b) (4) Notable among these were (b) (4) DMEP concluded that these (b) (4), and so the proposed changes were rejected.

Empagliflozin

Boehringer Ingelheim Pharmaceuticals, the application holder for Jardiance (empagliflozin), Glyxambi (empagliflozin and linagliptin), and Synjardy (empagliflozin and metformin), responded to DMEP's September 25, 2015 SLC Labeling Notification by submitting prior approval supplements (NDA 204629 S-7, NDA 206073 S-3, NDA 206111 S-2) on October 22, 2015. Boehringer Ingelheim proposed minor revisions, some of which were accepted.

During review of the submitted labeling, two issues were raised by DPVI regarding the language pertaining to ketoacidosis. DPVI recommended revision of "alcohol abuse" to "alcohol use," stating that in some cases only minor alcohol use was reported. DMEP reviewed all cases (n=7)

mentioning alcohol use from DPVI's second review. Among the seven cases, at least four strongly suggested excessive drinking. Given that alcohol abuse is an established risk factor for ketoacidosis, and given that the term "alcohol use" not clearly defined, DMEP decided to retain the term "alcohol abuse." DPVI also recommended addition of the term "dehydration" as a predisposing factor. DMEP disagreed, as our analysis of the cases suggested that in many cases dehydration was likely to be a result of ketoacidosis, rather than a cause. Moreover, dehydration alone is not understood to be ketogenic. DMEP did concur that dehydration was a presenting feature in many cases, and agreed to add "dehydration" to the text describing patient presentation.

Additional minor changes were made to the text of the Warnings and Precautions statement and to the patient labeling. These changes were harmonized across the SGLT-2 inhibitor class. DMEP and the application holders reached agreement on the content of labeling on November 20, 2015. In addition, the companies agreed to the new postmarketing requirement for an enhanced pharmacovigilance study of ketoacidosis. The PMR will be conducted according to the following schedule:

Final Protocol Submission:	June 2016
Interim Report Submission:	December 2017
	December 2018
	December 2019
	December 2020
Study Completion:	June 2021
Final Report:	December 2021

CONCLUSION

DMEP and the application holders for the SGLT-2 inhibitor class (canagliflozin, dapagliflozin, and empagliflozin) have reached agreement on revised labeling incorporating the new safety information describing postmarketing reports of ketoacidosis as well as urosepsis and pyelonephritis with this class of drugs. The supplements submitted in response to the SLC notification are ready for approval. In addition, the application holders have agreed to new postmarketing requirement for an enhanced pharmacovigilance study of ketoacidosis. A Drug Safety Communication on these safety topics will be issued on the same day that the supplements are approved.

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/s/

JENNIFER R PIPPINS
12/03/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076479
NDA 204042

ADVICE/INFORMATION REQUEST

Janssen Research & Development, L.L.C.
Attention: Sukhdev K. Saran
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Saran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA), and to your New Drug Application (NDA) submitted under section 505(b) of the FDCA, both for Invokana (canagliflozin) tablets.

We also refer to our communication to you on June 4, 2015, concerning the Drug Safety Communication (DSC) issued by the FDA on May 15, 2015, regarding sodium-glucose cotransporter-2 (SGLT2) inhibitors and the risk of ketoacidosis. We also refer to the updated DSC issued by the FDA on December 4, 2015, as well as the approval letter for NDA 204042/S-013, also issued on December 4, 2015.

We also refer to your amendment dated June 11, 2015, containing your response to our June 4, 2015, communication and a Case Report Form for Diabetic Ketoacidosis. Finally, we refer to your amendment dated June 19, 2015, containing your updated Investigators Brochure.

We have the following comments and recommendations:

1. Reconsent all patients currently enrolled in ongoing clinical trials so as to fully inform patients of the risk of ketoacidosis with SGLT2 exposure.

2. Update Investigator Brochures to reflect the current understanding of the risk of ketoacidsosis with SGLT2 exposure.

3. Describe the methods you will use for case detection in your program. We recommend that you develop a dedicated Case Report Form (CRF) to prospectively capture ketoacidosis events. The form should be completed by investigators at every visit. We recognize that presenting symptoms and signs of acidosis and ketoacidosis can be vague; to that extent, we encourage you to consider the possibility of a ketoacidosis event for all adverse events that could be consistent with signs and symptoms of severe acidosis involving an emergency room visit, a hospitalization, or that otherwise meet the

regulatory definition of a serious adverse event (such as death). Also describe other methods, besides prospective eCRF capture, that will be used to query data accumulated to date or ensure completeness of ascertainment for potential prospective events (for example, data mining for adverse event terms or laboratory abnormalities potentially consistent with ketoacidosis etc.).

4. We recommend that potential ketoacidosis events undergo adjudication by a team separate from the development team who remains blinded to treatment allocation. Describe the adjudication process in detail including but not limited to; the operational plan, the retrieval process for data to be used to constitute the adjudication package (for example, source documentation) and the information that will constitute a full or complete adjudication package. Provide case definitions for ketoacidosis to be used in adjudication and justification for your chosen case definitions. Your case definitions should be adequately sensitive to capture possible cases, but should also incorporate methods to determine the likelihood that events represent actual ketoacidosis. We recommend that you implement multiple standardized case definitions that recognize that all data may not be available to adjudicate all cases and that span the range possibility of an event from certain to probable to unlikely or to unclassifiable.

5. We recommend adding the following MedDRA Preferred Terms in your search criteria for diabetic ketoacidosis in addition to your proposed list of Lower Level Terms: Blood ketone body, blood ketone body increased, blood ketone body present, diabetic hyperosmolar coma, diabetic ketoacidotic hyperglycemic coma, diabetic metabolic decompensation, diabetes with hyperosmolarity, hyperglycemic seizure, hyperosmolar hyperglycemic state, hyperosmolar state, ketonuria, ketosis, diabetic hyperglycemic coma.

6. In your Diabetic Ketoacidosis Form, we recommend adding generalized malaise and shortness of breath on the list of symptoms to check off under "Did the patient have symptoms", as these signs and symptoms were also present in the post-marketing reports.

In addition, we remind you that you must comply with reporting requirements for an active IND (see information below), and for an approved NDA (21 CFR 314.80 and 314.81).

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at 301-796-4264.

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

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/s/

JENNIFER R PIPPINS
12/23/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #	NDA 204042/S-013 (Invokana)
Product Name:	NDA 204353/S-012 (Invokamet)

PMR Description: An enhanced pharmacovigilance study of ketoacidosis in patients treated with canagliflozin. The study will include reports of ketoacidosis or diabetic ketoacidosis for a period of 5 years, and will include assessment and analysis of spontaneous reports of ketoacidosis in patients treated with canagliflozin, with specialized follow-up to collect additional information on these cases.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	06/2016
	Interim Report Submission:	12/2017
		12/2018
		12/2019
		12/2020
	Study Completion:	06/2021
	Final Report Submission:	12/2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This safety issue was identified post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Routine post-approval pharmacovigilance identified a potential signal of ketoacidosis for the SGLT2 inhibitor class of antidiabetic agents. A subsequent search of the FAERS database identified postmarketing cases of ketoacidosis; an initial DPV review (September 27, 2014) identified 20 cases, while a follow-up DPV review (July 16, 2015) identified an additional 54 cases. These postmarketing cases were considered to be "new safety information" and served as the basis of a letter issued on September 25, 2015, notifying application holders of required Safety Labeling Changes and the plan for the enhanced pharmacovigilance PMR described in this template.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☒ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An enhanced pharmacovigilance study of ketoacidosis in patients treated with canagliflozin. The study will include reports of ketoacidosis or diabetic ketoacidosis for a period of 5 years, and will include assessment and analysis of spontaneous reports of ketoacidosis in patients treated with canagliflozin, with specialized follow-up to collect additional information on these cases.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation)

Enhanced pharmacovigilance

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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/s/

JENNIFER R PIPPINS
12/04/2015

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, November 06, 2015 2:33 PM
To: Saran, Sukhdev [JRDUS]
Cc: Adeolu, Abolade
Subject: SGLT2 SLC Labeling

Dear Sukhdev,

Attached are the PIs for NDAs 204042 and 204353. Please respond by COB, Friday, November 13.

Thanks,
Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

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/s/

ABOLADE ADEOLU
11/08/2015

From:	Van der Waag, Julie
To:	"ssaran@its.jnj.com"
Cc:	Adeolu, Abolade
Subject:	NDA 204042/S-013 Invokana
Date:	Thursday, October 29, 2015 10:01:00 AM

Sukhdev,

With reference to (b) (4) , we request that you resubmit the Clinical Overview as an amendment in support of S-013, submitted on October 21, 2015. Please include all individual subject narratives in your submission.

Thanks,

Julie

Julie Van der Waag
Chief, Regulatory Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.vanderwaag@fda.hhs.gov

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/s/

JULIE C VAN DER WAAG
10/29/2015