**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

# 204629Orig1s007

***Trade Name:*** **JARDIANCE**

***Generic Name:*** Empagliflozin

***Sponsor:*** Boehringer Ingelheim Pharmaceuticals, Inc.

***Approval Date:*** 12/04/2015

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

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**204629Orig1s007**

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204629/S-007

**SUPPLEMENT APPROVAL**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director, Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your supplemental New Drug Application (sNDA) dated and received October 22, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jardiance (empagliflozin) tablets, 10 mg and 25 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, text for the patient package insert) 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:

3004-1 An enhanced pharmacovigilance study of ketoacidosis in patients treated with empagliflozin. 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 empagliflozin, with specialized follow-up to collect additional information on these cases.

We refer to your submission dated October 22, 2015, which states your intention to conduct one study to address this postmarketing requirement (PMR) for all currently approved products containing empagliflozin. Therefore, this PMR will also apply to Glyxambi (empagliflozin and linagliptin) tablets and Synjardy (empagliflozin and metformin hydrochloride) tablets, per our approval letters issued to NDA 206073/S-003 and NDA 206111/S-002, respectively.

The timetable you submitted on November 19, 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 102145, 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 Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

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

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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.**

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/s/

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JENNIFER R PIPPINS
12/04/2015

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**204629Orig1s007**

# LABELING

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use JARDIANCE safely and effectively. See full prescribing information for JARDIANCE.**

**JARDIANCE® (empagliflozin) tablets, for oral use**
**Initial U.S. Approval: 2014**

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

Warnings and Precautions (5.2, 5.4) 12/2015

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

JARDIANCE 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 the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1.1)

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

- The recommended dose of JARDIANCE is 10 mg once daily, taken in the morning, with or without food (2.1)
- Dose may be increased to 25 mg once daily (2.1)
- Assess renal function before initiating JARDIANCE. Do not initiate JARDIANCE if eGFR is below 45 mL/min/1.73 $m^2$ (2.2)
- Discontinue JARDIANCE if eGFR falls persistently below 45 mL/min/1.73 $m^2$ (2 2)

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

Tablets: 10 mg, 25 mg (3)

**----------CONTRAINDICATIONS----------**

- History of serious hypersensitivity reaction to JARDIANCE (4)
- Severe renal impairment, end-stage renal disease, or dialysis (4)

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

- *Hypotension* Before initiating JARDIANCE assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. 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 JARDIANCE, evaluate and treat promptly. Before initiating JARDIANCE, consider risk factors for ketoacidosis. Patients on JARDIANCE 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)
- *Urosepsis and Pyelonephritis* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.4)
- *Hypoglycemia* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating JARDIANCE (5.5)
- *Genital mycotic infections* Monitor and treat as appropriate (5.6)
- *Increased LDL-C* Monitor and treat as appropriate (5.7)
- *Macrovascular outcomes*: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE (5.8)

**----------ADVERSE REACTIONS----------**

- The most common adverse reactions associated with JARDIANCE (5% or greater incidence) were urinary tract infections and female genital mycotic infections (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda gov/medwatch.**

**----------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 JARDIANCE or discontinue nursing (8.3)
- *Geriatric patients* Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.1, 5.3, 8.5)
- *Patients with renal impairment* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.3, 8.6)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 12/2015**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



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

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

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

### 1.1 Limitation of Use

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food. In patients tolerating JARDIANCE, the dose may be increased to 25 mg *[see Clinical Studies (14)]*.

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

### 2.2 Patients with Renal Impairment

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

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

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 $m^2$.

JARDIANCE should be discontinued if eGFR is persistently less than 45 mL/min/1.73 $m^2$ *[see Warnings and Precautions (5.1, 5.3), and Use in Specific Populations (8.6)]*.

## 3 DOSAGE FORMS AND STRENGTHS

- JARDIANCE (empagliflozin) 10 mg tablets are pale yellow, round, biconvex and bevel-edged, film-coated tablets debossed with “S 10” on one side and the Boehringer Ingelheim company symbol on the other side.
- JARDIANCE (empagliflozin) 25 mg tablets are pale yellow, oval, biconvex, film-coated tablets debossed with “S 25” on one side and the Boehringer Ingelheim company symbol on the other side.

## 4 CONTRAINDICATIONS

- History of serious hypersensitivity reaction to JARDIANCE.
- Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations (8.6)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypotension

JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE *[see Adverse Reactions (6.1)]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations (8.5)]*.

### 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 JARDIANCE. JARDIANCE is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with JARDIANCE 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 JARDIANCE may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE 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 JARDIANCE, 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 JARDIANCE consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

### 5.3 Impairment in Renal Function

JARDIANCE increases serum creatinine and decreases eGFR *[see Adverse Reactions (6.1)]*. The risk of impaired renal function with JARDIANCE is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients *[see Use in Specific Populations* (*8.5, 8.6)]*. Renal function should be evaluated prior to initiating JARDIANCE and periodically thereafter.

### 5.4 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 JARDIANCE. 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)]*.

### 5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE.

### 5.6 Genital Mycotic Infections
JARDIANCE increases the risk for genital mycotic infections *[see Adverse Reactions (6.1)]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.

### 5.7 Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with JARDIANCE *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

### 5.8 Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE 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)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.7)]*

### 6.1 Clinical Trials 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 rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg
The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (14)]*.

These data reflect exposure of 1976 patients to JARDIANCE with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), JARDIANCE 10 mg (N=999), or JARDIANCE 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 $m^2$).

Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline, occurred more commonly on JARDIANCE than on placebo and occurred in greater than or equal to 2% of patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg.

**Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with JARDIANCE and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of JARDIANCE Monotherapy or Combination Therapy**

| | Number (%) of Patients | | |
|---|---|---|---|
| | **Placebo N=995** | **JARDIANCE 10 mg N=999** | **JARDIANCE 25 mg N=977** |
| Urinary tract infection[a] | 7.6% | 9.3% | 7.6% |
| Female genital mycotic infections[b] | 1.5% | 5.4% | 6.4% |
| Upper respiratory tract infection | 3.8% | 3.1% | 4.0% |
| Increased urination[c] | 1.0% | 3.4% | 3.2% |
| Dyslipidemia | 3.4% | 3.9% | 2.9% |
| Arthralgia | 2.2% | 2.4% | 2.3% |
| Male genital mycotic infections[d] | 0.4% | 3.1% | 1.6% |
| Nausea | 1.4% | 2.3% | 1.1% |

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis
[b]Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), JARDIANCE 10 mg (N=443), JARDIANCE 25 mg (N=420).
[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia
[d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

*Volume Depletion*
JARDIANCE causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg respectively. JARDIANCE may increase the risk of hypotension in patients at risk for volume contraction *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.5, 8.6)]*.

*Increased Urination*
In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on JARDIANCE than on placebo (see Table 1). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

*Impairment in Renal Function*
Use of JARDIANCE was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes *[see Warnings and Precautions (5.3)* and *Use in Specific Populations (8.5, 8.6)]*.

**Table 2 Changes from Baseline in Serum Creatinine and eGFR in the Pool of Four 24-week Placebo-Controlled Studies and Renal Impairment Study**

| | | Pool of 24-Week Placebo-Controlled Studies | | |
|---|---|---|---|---|
| | | **Placebo** | **JARDIANCE 10 mg** | **JARDIANCE 25 mg** |
| Baseline Mean | N | 825 | 830 | 822 |
| | Creatinine (mg/dL) | 0.84 | 0.85 | 0.85 |
| | eGFR (mL/min/1.73 $m^2$) | 87.3 | 87.1 | 87.8 |
| Week 12 Change | N | 771 | 797 | 783 |
| | Creatinine (mg/dL) | 0.00 | 0.02 | 0.01 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | -1.3 | -1.4 |
| Week 24 Change | N | 708 | 769 | 754 |
| | Creatinine (mg/dL) | 0.00 | 0.01 | 0.01 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | -0.6 | -1.4 |
| | | **Moderate Renal Impairment[a]** | | |
| | | **Placebo** | | **JARDIANCE 25 mg** |
| Baseline | N | 187 | -- | 187 |
| | Creatinine (mg/dL) | 1.49 | -- | 1.46 |
| | eGFR (mL/min/1.73 $m^2$) | 44.3 | -- | 45.4 |
| Week 12 Change | N | 176 | -- | 179 |
| | Creatinine (mg/dL) | 0.01 | -- | 0.12 |
| | eGFR (mL/min/1.73 $m^2$) | 0.1 | -- | -3.8 |
| Week 24 Change | N | 170 | -- | 171 |
| | Creatinine (mg/dL) | 0.01 | -- | 0.10 |
| | eGFR (mL/min/1.73 $m^2$) | 0.2 | -- | -3.2 |
| Week 52 Change | N | 164 | -- | 162 |
| | Creatinine (mg/dL) | 0.02 | -- | 0.11 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | -- | -2.8 |

[a]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 $m^2$

*Hypoglycemia*
The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when JARDIANCE was administered with insulin or sulfonylurea *[see Warnings and Precautions (5.5)]*.

**Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies**

| **Monotherapy (24 weeks)** | **Placebo (n=229)** | **JARDIANCE 10 mg (n=224)** | **JARDIANCE 25 mg (n=223)** |
|---|---|---|---|
| Overall (%) | 0.4% | 0.4% | 0.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Metformin (24 weeks)** | **Placebo + Metformin (n=206)** | **JARDIANCE 10 mg + Metformin (n=217)** | **JARDIANCE 25 mg + Metformin (n=214)** |
| Overall (%) | 0.5% | 1.8% | 1.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Metformin + Sulfonylurea (24 weeks)** | **Placebo (n=225)** | **JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)** | **JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)** |
| Overall (%) | 8.4% | 16.1% | 11.5% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Pioglitazone +/- Metformin (24 weeks)** | **Placebo (n=165)** | **JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)** | **JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)** |
| Overall (%) | 1.8% | 1.2% | 2.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Basal Insulin (18 weeks[c])** | **Placebo (n=170)** | **JARDIANCE 10 mg (n=169)** | **JARDIANCE 25 mg (n=155)** |
| Overall (%) | 20.6% | 19.5% | 28.4% |
| Severe (%) | 0% | 0% | 1.3% |
| **In Combination with MDI Insulin +/- Metformin (18 weeks[c])** | **Placebo (n=188)** | **JARDIANCE 10 mg (n=186)** | **JARDIANCE 25 mg (n=189)** |
| Overall (%) | 37.2% | 39.8% | 41.3% |
| Severe (%) | 0.5% | 0.5% | 0.5% |

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Insulin dose could not be adjusted during the initial 18 week treatment period

*Genital Mycotic Infections*
In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg.

Genital mycotic infections occurred more frequently in female than male patients (see Table 1).

Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%).

*Urinary Tract Infections*
In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.5)]*.

*Laboratory Tests*
Increase in Low-Density Lipoprotein Cholesterol (LDL-C)
Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions (5.7)]*. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit
In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

### 6.2 Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of JARDIANCE. 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 (5.4)]*

## 7 DRUG INTERACTIONS
### 7.1 Diuretics
Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion *[see Warnings and Precautions (5.1)]*.

### 7.2 Insulin or Insulin Secretagogues
Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia *[see Warnings and Precautions (5.5)]*.

### 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

*Pregnancy Category C*

There are no adequate and well-controlled studies of JARDIANCE in pregnant women. JARDIANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

Empagliflozin was not teratogenic in embryo-fetal development studies in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg. At higher doses, causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154 times the 25 mg maximum clinical dose in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139 times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose).

### 8.3 Nursing Mothers

It is not known if JARDIANCE is excreted in human milk. Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. 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 JARDIANCE, a decision should be made whether to discontinue nursing or to discontinue JARDIANCE, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness of JARDIANCE in pediatric patients under 18 years of age have not been established.

### 8.5 Geriatric Use

No JARDIANCE dosage change is recommended based on age *[see Dosage and Administration (2)]*. A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment *[see Use in Specific Populations (8.6)]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

### 8.6 Renal Impairment

The efficacy and safety of JARDIANCE were evaluated in a study of patients with mild and moderate renal impairment *[see Clinical Studies (14.3)]*. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 $m^2$, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 $m^2$ and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 $m^2$. The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.3)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. JARDIANCE is not expected to be effective in these patient populations *[see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.1, 5.3)]*.

### 8.7 Hepatic Impairment

JARDIANCE may be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

## 10 OVERDOSAGE

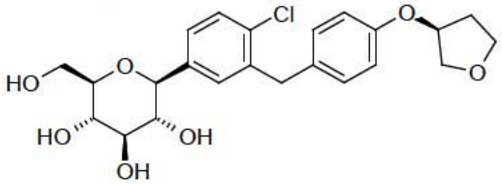
In the event of an overdose with JARDIANCE, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

## 11 DESCRIPTION

JARDIANCE tablets contain empagliflozin, an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:




Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

Each film-coated tablet of JARDIANCE contains 10 mg or 25 mg of empagliflozin (free base) and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and yellow ferric oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

### 12.2 Pharmacodynamics

*Urinary Glucose Excretion*

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of JARDIANCE and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg JARDIANCE once daily *[see Clinical Studies (14)]*.

*Urinary Volume*

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

*Cardiac Electrophysiology*

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of JARDIANCE 25 mg, JARDIANCE 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

### 12.3 Pharmacokinetics

*Absorption*

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and $C_{max}$ were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and $C_{max}$ decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

*Distribution*

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [$^{14}$C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

*Metabolism*

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of

empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

*Elimination*
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [$^{14}$C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

*Specific Populations*
Renal Impairment
In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 $m^2$), moderate (eGFR: 30 to less than 60 mL/min/1.73 $m^2$), and severe (eGFR: less than 30 mL/min/1.73 $m^2$) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Hepatic Impairment
In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and $C_{max}$ increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Effects of Age, Body Mass Index, Gender, and Race
Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin *[see Use in Specific Populations (8.5)]*.

Pediatric
Studies characterizing the pharmacokinetics of empagliflozin in pediatric patients have not been performed.

*Drug Interactions*
*In vitro* Assessment of Drug Interactions
*In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin also does not inhibit UGT1A1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

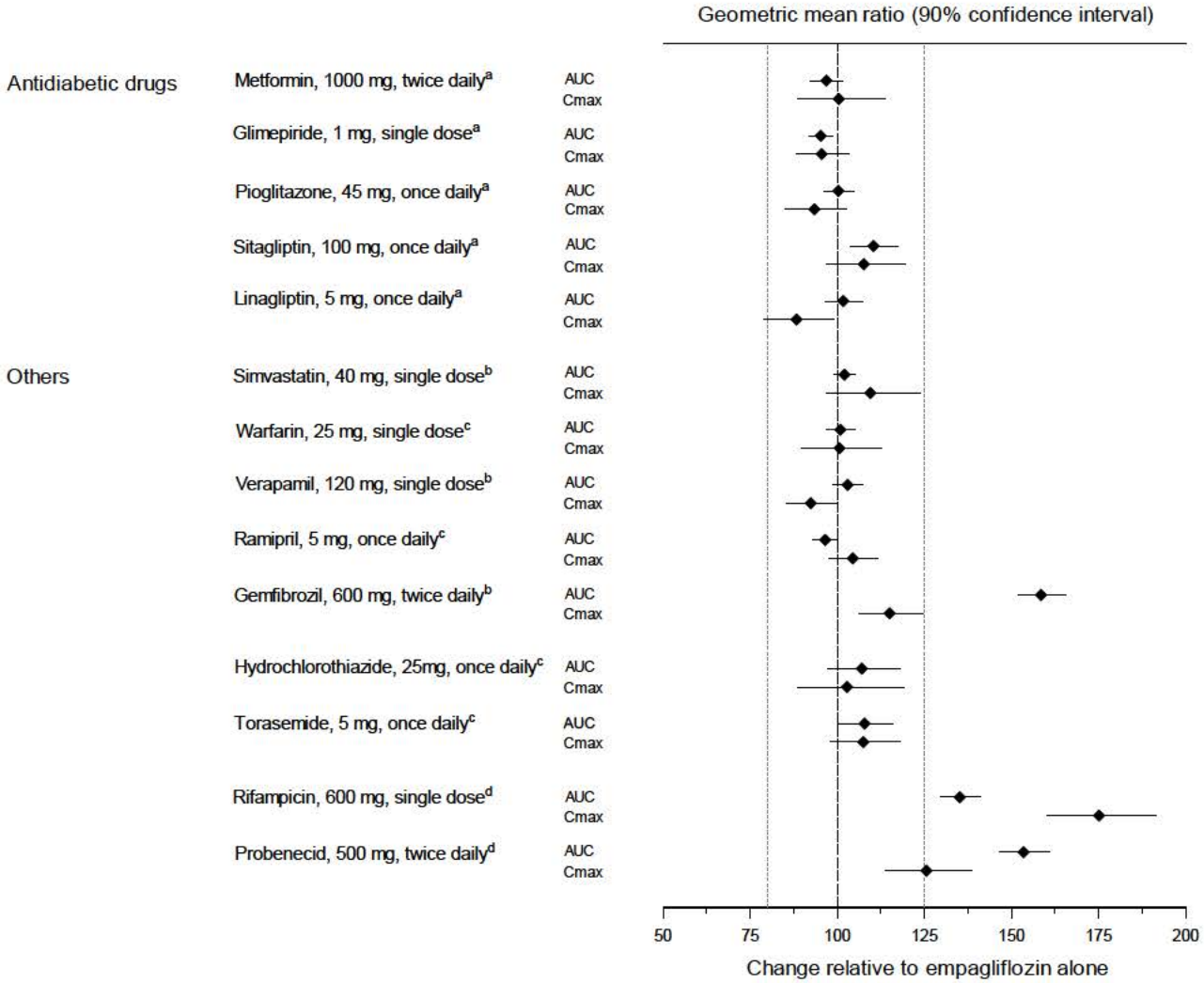
Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human

uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

*In vivo* Assessment of Drug Interactions

No dose adjustment of JARDIANCE is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, hydrochlorothiazide, and torasemide in healthy volunteers (see Figure 1). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

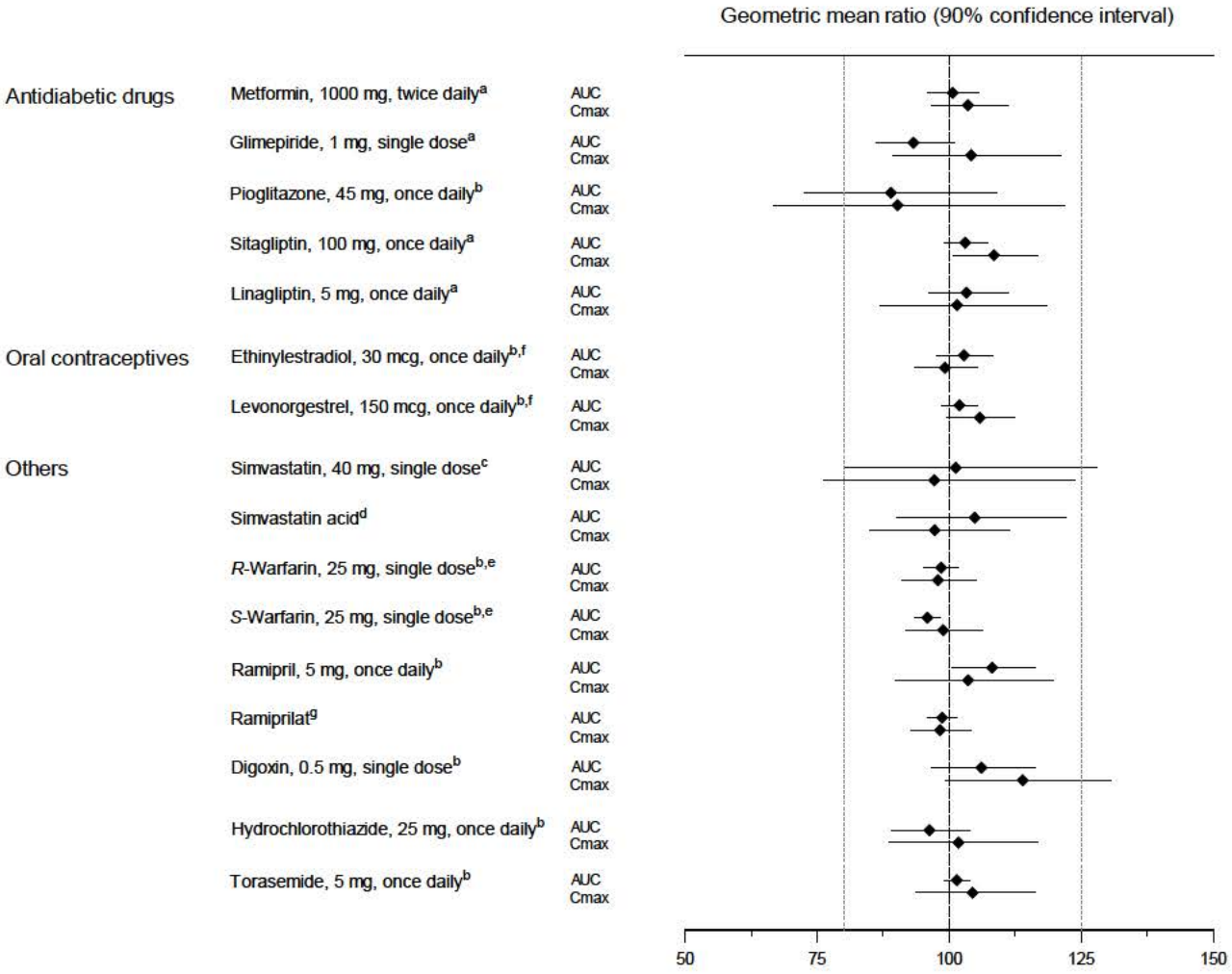
**Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and $C_{max}$ Ratios [reference lines indicate 100% (80% - 125%)]**




[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

**Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and $C_{max}$ Ratios [reference lines indicate 100% (80% - 125%)]**




[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg.

Mutagenesis

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y $tk^{+/-}$ mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Impairment of Fertility

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

## 14 CLINICAL STUDIES

JARDIANCE has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, linagliptin, and insulin. JARDIANCE has also been studied in patients with type 2 diabetes with mild or moderate renal impairment.

In patients with type 2 diabetes, treatment with JARDIANCE reduced hemoglobin A1c (HbA1c), compared to placebo. The reduction in HbA1c for JARDIANCE compared with placebo was observed across subgroups including gender, race, geographic region, baseline BMI and duration of disease.

### 14.1 Monotherapy

A total of 986 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE monotherapy.

Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10% were randomized to placebo, JARDIANCE 10 mg, JARDIANCE 25 mg, or a reference comparator.

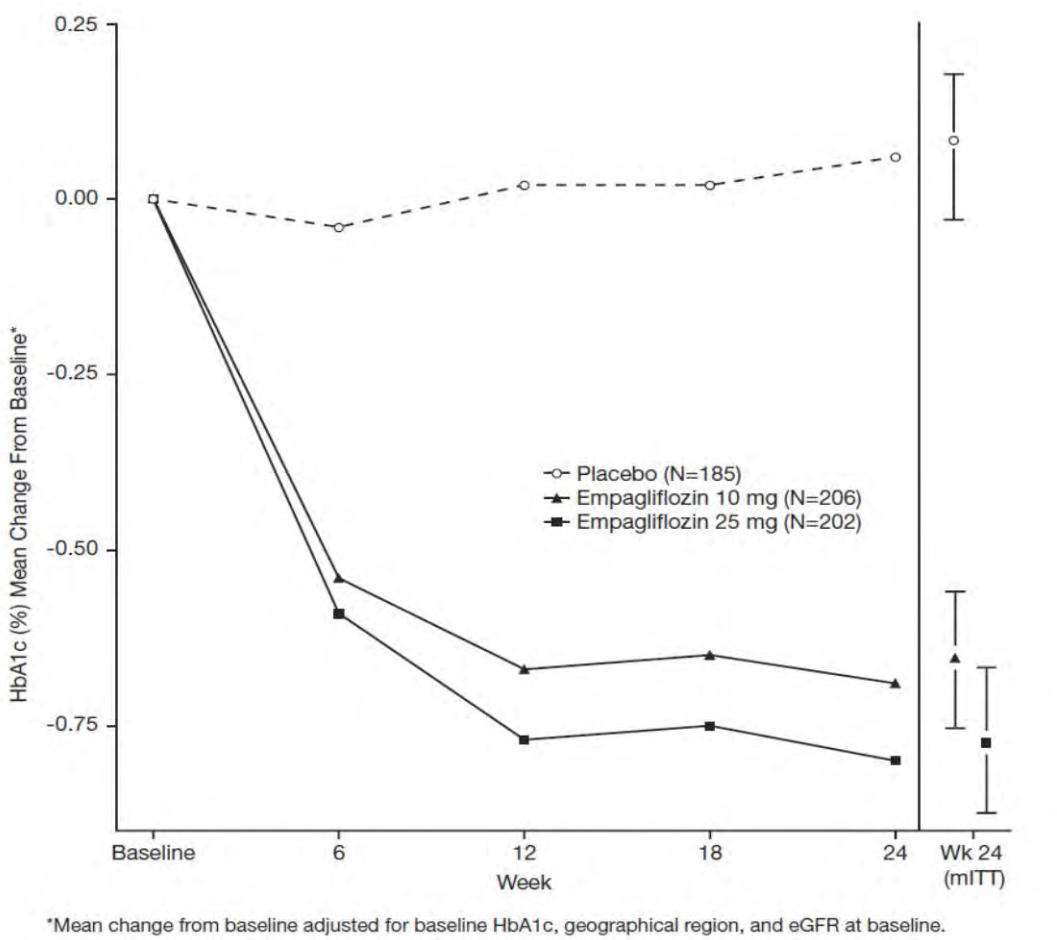
At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), fasting plasma glucose (FPG), and body weight compared with placebo (see Table 4 and Figure 3).

**Table 4 Results at Week 24 From a Placebo-Controlled Monotherapy Study of JARDIANCE**

| | JARDIANCE 10 mg N=224 | JARDIANCE 25 mg N=224 | Placebo N=228 |
|---|---|---|---|
| **HbA1c (%)[a]** | | | |
| Baseline (mean) | 7.9 | 7.9 | 7.9 |
| Change from baseline (adjusted mean) | -0.7 | -0.8 | 0.1 |
| Difference from placebo (adjusted mean) (97.5% CI) | -0.7[b] (-0.9, -0.6) | -0.9[b] (-1.0, -0.7) | -- |
| Patients [n (%)] achieving HbA1c <7% | 72 (35%) | 88 (44%) | 25 (12%) |
| **FPG (mg/dL)[c]** | | | |
| Baseline (mean) | 153 | 153 | 155 |
| Change from baseline (adjusted mean) | -19 | -25 | 12 |
| Difference from placebo (adjusted mean) (95% CI) | -31 (-37, -26) | -36 (-42, -31) | -- |
| **Body Weight** | | | |
| Baseline (mean) in kg | 78 | 78 | 78 |
| % change from baseline (adjusted mean) | -2.8 | -3.2 | -0.4 |
| Difference from placebo (adjusted mean) (95% CI) | -2.5[b] (-3.1, -1.9) | -2.8[b] (-3.4, -2.2) | -- |

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.4%, 9.4%, and 30.7% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA derived p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for JARDIANCE 10 mg, n=223, for JARDIANCE 25 mg, n=223, and for placebo, n=226

**Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT Population) - LOCF**




*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, p-value=0.0231) in patients randomized to 10 mg of JARDIANCE and by -3.4 mmHg (placebo-corrected, p-value=0.0028) in patients randomized to 25 mg of JARDIANCE.

### 14.2 Combination Therapy

*Add-On Combination Therapy with Metformin*

A total of 637 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered an open-label 2 week placebo run-in. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10% were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 5).

**Table 5 Results at Week 24 From a Placebo-Controlled Study for JARDIANCE used in Combination with Metformin**

| | **JARDIANCE 10 mg + Metformin N=217** | **JARDIANCE 25 mg + Metformin N=213** | **Placebo + Metformin N=207** |
|---|---|---|---|
| **HbA1c (%)[a]** | | | |
| Baseline (mean) | 7.9 | 7.9 | 7.9 |
| Change from baseline (adjusted mean) | -0.7 | -0.8 | -0.1 |
| Difference from placebo + metformin (adjusted mean) (95% CI) | -0.6[b] (-0.7, -0.4) | -0.6[b] (-0.8, -0.5) | -- |
| Patients [n (%)] achieving HbA1c <7% | 75 (38%) | 74 (39%) | 23 (13%) |
| **FPG (mg/dL)[c]** | | | |
| Baseline (mean) | 155 | 149 | 156 |
| Change from baseline (adjusted mean) | -20 | -22 | 6 |
| Difference from placebo + metformin (adjusted mean) | -26 | -29 | -- |
| **Body Weight** | | | |
| Baseline mean in kg | 82 | 82 | 80 |
| % change from baseline (adjusted mean) | -2.5 | -2.9 | -0.5 |
| Difference from placebo (adjusted mean) (95% CI) | -2.0[b] (-2.6, -1.4) | -2.5[b] (-3.1, -1.9) | -- |

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.7%, 14.1%, and 24.6% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

[c]FPG (mg/dL); for JARDIANCE 10 mg, n=216, for JARDIANCE 25 mg, n=213, and for placebo, n=207

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-corrected, p-value <0.0001) for JARDIANCE 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for JARDIANCE 25 mg.

*Add-On Combination Therapy with Metformin and Sulfonylurea*
A total of 666 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin plus a sulfonylurea.

Patients with inadequately controlled type 2 diabetes on at least 1500 mg per day of metformin and on a sulfonylurea, entered a 2 week open-label placebo run-in. At the end of the run-in, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 6).

**Table 6 Results at Week 24 from a Placebo-Controlled Study for JARDIANCE in Combination with Metformin and Sulfonylurea**

| | **JARDIANCE 10 mg + Metformin + SU N=225** | **JARDIANCE 25 mg + Metformin + SU N=216** | **Placebo + Metformin + SU N=225** |
|---|---|---|---|
| **HbA1c (%)[a]** | | | |
| Baseline (mean) | 8.1 | 8.1 | 8.2 |
| Change from baseline (adjusted mean) | -0.8 | -0.8 | -0.2 |
| Difference from placebo (adjusted mean) (95% CI) | -0.6[b] (-0.8, -0.5) | -0.6[b] (-0.7, -0.4) | -- |
| Patients [n (%)] achieving HbA1c <7% | 55 (26%) | 65 (32%) | 20 (9%) |
| **FPG (mg/dL)[c]** | | | |
| Baseline (mean) | 151 | 156 | 152 |
| Change from baseline (adjusted mean) | -23 | -23 | 6 |
| Difference from placebo (adjusted mean) | -29 | -29 | -- |
| **Body Weight** | | | |
| Baseline mean in kg | 77 | 78 | 76 |
| % change from baseline (adjusted mean) | -2.9 | -3.2 | -0.5 |
| Difference from placebo (adjusted mean) (95% CI) | -2.4[b] (-3.0, -1.8) | -2.7[b] (-3.3, -2.1) | -- |

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 17.8%, 16.7%, and 25.3% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for JARDIANCE 10 mg, n=225, for JARDIANCE 25 mg, n=215, for placebo, n=224

*In Combination with Linagliptin as Add-On to Metformin Therapy*
A total of 686 patients with type 2 diabetes participated in a double-blind, active-controlled study to evaluate the efficacy and safety of JARDIANCE 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10.5% were randomized 1:1:1:1:1 to one of 5 active-treatment arms of JARDIANCE 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg JARDIANCE as a fixed dose combination tablet.

At Week 24, JARDIANCE 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin. Treatment with

JARDIANCE/linagliptin 25 mg/5 mg or JARDIANCE/linagliptin 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference in body weight compared to JARDIANCE alone.

*Active-Controlled Study versus Glimepiride in Combination with Metformin*
The efficacy of JARDIANCE was evaluated in a double-blind, glimepiride-controlled, study in 1545 patients with type 2 diabetes with insufficient glycemic control despite metformin therapy.

Patients with inadequate glycemic control and an HbA1c between 7% and 10% after a 2-week run-in period were randomized to glimepiride or JARDIANCE 25 mg.

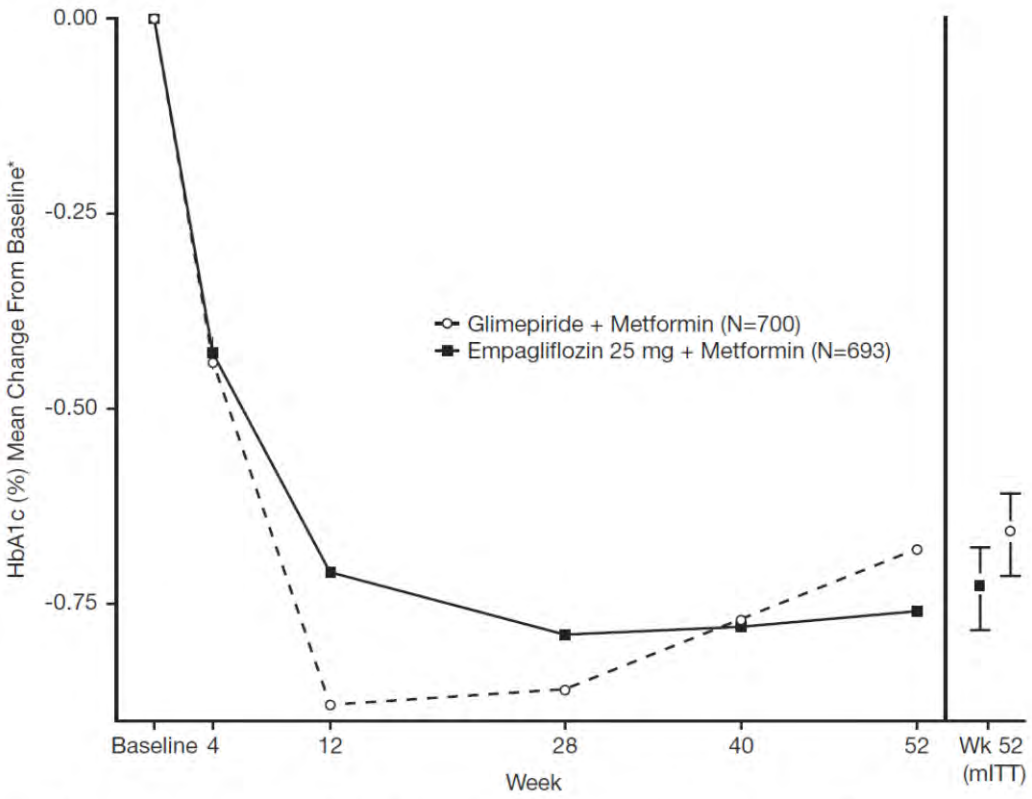
At Week 52, JARDIANCE 25 mg and glimepiride lowered HbA1c and FPG (see Table 7, Figure 4). The difference in observed effect size between JARDIANCE 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day.

**Table 7 Results at Week 52 from an Active-Controlled Study Comparing JARDIANCE to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

| | **JARDIANCE 25 mg + Metformin N=765** | **Glimepiride + Metformin N=780** |
|---|---|---|
| **HbA1c (%)[a]** | | |
| Baseline (mean) | 7.9 | 7.9 |
| Change from baseline (adjusted mean) | -0.7 | -0.7 |
| Difference from glimepiride (adjusted mean) (97.5% CI) | -0.07[b] (-0.15, 0.01) | -- |
| **FPG (mg/dL)[d]** | | |
| Baseline (mean) | 150 | 150 |
| Change from baseline (adjusted mean) | -19 | -9 |
| Difference from glimepiride (adjusted mean) | -11 | -- |
| **Body Weight** | | |
| Baseline mean in kg | 82.5 | 83 |
| % change from baseline (adjusted mean) | -3.9 | 2.0 |
| Difference from glimepiride (adjusted mean) (95% CI) | -5.9[c] (-6.3, -5.5) | -- |

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to JARDIANCE 25 mg and glimepiride, respectively.
[b]Non-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)
[c]ANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[d]FPG (mg/dL); for JARDIANCE 25 mg, n=764, for placebo, n=779

**Figure 4 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF**




*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

At Week 52, the adjusted mean change from baseline in systolic blood pressure was -3.6 mmHg, compared to 2.2 mmHg for glimepiride. The differences between treatment groups for systolic blood pressure was statistically significant (p-value <0.0001).

At Week 104, the adjusted mean change from baseline in HbA1c was -0.75% for JARDIANCE 25 mg and -0.66% for glimepiride. The adjusted mean treatment difference was -0.09% with a 97.5% confidence interval of (-0.32%, 0.15%), excluding the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day. The Week 104 analysis included data with and without concomitant glycemic rescue medication, as well as off-treatment data. Missing data for patients not providing any information at the visit were imputed based on the observed off-treatment data. In this multiple imputation analysis, 13.9% of the data were imputed for JARDIANCE 25 mg and 12.9% for glimepiride.

At Week 104, JARDIANCE 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for JARDIANCE 25 mg vs. +1.3 kg for glimepiride; ANCOVA-LOCF, p-value <0.0001).

*Add-On Combination Therapy with Pioglitazone with or without Metformin*
A total of 498 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with pioglitazone, with or without metformin.

Patients with inadequately controlled type 2 diabetes on metformin at a dose of at least 1500 mg per day and pioglitazone at a dose of at least 30 mg per day were placed into an open-label placebo run-in for 2 weeks. Patients with inadequate glycemic control and an HbA1c between 7% and 10% after the run-in period were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 10 mg or 25 mg daily resulted in statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 8).

**Table 8 Results of Placebo-Controlled Study for JARDIANCE in Combination Therapy with Pioglitazone**

| | **JARDIANCE 10 mg + Pioglitazone N=165** | **JARDIANCE 25 mg + Pioglitazone N=168** | **Placebo + Pioglitazone N=165** |
|---|---|---|---|
| **HbA1c (%)[a]** | | | |
| Baseline (mean) | 8.1 | 8.1 | 8.2 |
| Change from baseline (adjusted mean) | -0.6 | -0.7 | -0.1 |
| Difference from placebo + pioglitazone (adjusted mean) (95% CI) | -0.5[b] (-0.7, -0.3) | -0.6[b] (-0.8, -0.4) | -- |
| Patients [n (%)] achieving HbA1c <7% | 36 (24%) | 48 (30%) | 12 (8%) |
| **FPG (mg/dL)[c]** | | | |
| Baseline (mean) | 152 | 152 | 152 |
| Change from baseline (adjusted mean) | -17 | -22 | 7 |
| Difference from placebo + pioglitazone (adjusted mean) (97.5% CI) | -23[b] (-31.8, -15.2) | -28[b] (-36.7, -20.2) | -- |
| **Body Weight** | | | |
| Baseline mean in kg | 78 | 79 | 78 |
| % change from baseline (adjusted mean) | -2.0 | -1.8 | 0.6 |
| Difference from placebo (adjusted mean) (95% CI) | -2.6[b] (-3.4, -1.8) | -2.4[b] (-3.2, -1.6) | -- |

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 10.9%, 8.3%, and 20.6% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for JARDIANCE 10 mg, n=163

*Add-On Combination with Insulin with or without Metformin and/or Sulfonylureas*
A total of 494 patients with type 2 diabetes inadequately controlled on insulin, or insulin in combination with oral drugs participated in a double-blind, placebo-controlled study to evaluate the efficacy of JARDIANCE as add-on therapy to insulin over 78 weeks.

Patients entered a 2-week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or sulfonylurea background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of JARDIANCE 10 mg, JARDIANCE 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. For the remaining 60 weeks, insulin could be adjusted. The mean total daily insulin dose at baseline for JARDIANCE 10 mg, 25 mg, and placebo was 45 IU, 48 IU, and 48 IU, respectively.

JARDIANCE used in combination with insulin (with or without metformin and/or sulfonylurea) provided statistically significant reductions in HbA1c and FPG compared to placebo after both 18 and 78 weeks of treatment (see Table 9). JARDIANCE 10 mg or 25 mg daily also resulted in statistically significantly greater percent body weight reduction compared to placebo.

**Table 9 Results at Week 18 and 78 for a Placebo-Controlled Study for JARDIANCE in Combination with Insulin**

| | 18 weeks (no insulin adjustment) | | | 78 weeks (adjustable insulin dose after 18 weeks) | | |
|---|---|---|---|---|---|---|
| | **JARDIANCE 10 mg + Insulin N=169** | **JARDIANCE 25 mg + Insulin N=155** | **Placebo + Insulin N=170** | **JARDIANCE 10 mg + Insulin N=169** | **JARDIANCE 25 mg + Insulin N=155** | **Placebo + Insulin N=170** |
| **HbA1c (%)[a]** | | | | | | |
| Baseline (mean) | 8.3 | 8.3 | 8.2 | 8.3 | 8.3 | 8.2 |
| Change from baseline (adjusted mean) | -0.6 | -0.7 | 0 | -0.4 | -0.6 | 0.1 |
| Difference from placebo (adjusted mean) (97.5% CI) | -0.6[b] (-0.8, -0.4) | -0.7[b] (-0.9, -0.5) | -- | -0.5[b] (-0.7, -0.3) | -0.7[b] (-0.9, -0.5) | -- |
| Patients (%) achieving HbA1c <7% | 18.0 | 19.5 | 5.5 | 12.0 | 17.5 | 6.7 |
| **FPG (mg/dL)** | | | | | | |
| Baseline (mean) | 138 | 146 | 142 | 138 | 146 | 142 |
| Change from baseline (adjusted mean, SE) | -17.9 (3.2) | -19.1 (3.3) | 10.4 (3.1) | -10.1 (3.2) | -15.2 (3.4) | 2.8 (3.2) |
| Difference from placebo (adjusted mean) (95% CI) | -28.2[b] (-37.0, -19.5) | -29.5[b] (-38.4, -20.6) | -- | -12.9[c] (-21.9, 3.9) | -17.9[b] (-27.0, -8.8) | -- |
| **Body Weight** | | | | | | |
| Baseline mean in kg | 92 | 95 | 90 | 92 | 95 | 90 |
| % change from baseline (adjusted mean) | -1.8 | -1.4 | -0.1 | -2.4 | -2.4 | 0.7 |
| Difference from placebo (adjusted mean) (95% CI) | -1.7[d] (-3.0, -0.5) | -1.3[e] (-2.5, -0.0) | -- | -3.0[b] (-4.4, -1.7) | -3.0[b] (-4.4, -1.6) | -- |

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 18 and 78. At Week 18, 21.3%, 30.3%, and 21.8% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively. At Week 78, 32.5%, 38.1% and 42.4% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively

[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, and region; FPG: MMRM model includes baseline FPG, baseline HbA1c, treatment, region, visit and visit by treatment interaction. Body weight: MMRM model includes baseline body weight, baseline HbA1c, treatment, region, visit and visit by treatment interaction.

[c]p-value=0.0049

[d]p-value=0.0052

[e]p-value=0.0463

*Add-on Combination with MDI Insulin with or without Metformin*
A total of 563 patients with type 2 diabetes inadequately controlled on multiple daily injections (MDI) of insulin (total daily dose >60 IU), alone or in combination with metformin, participated in a double-blind, placebo-controlled study to evaluate the efficacy of JARDIANCE as add-on therapy to MDI insulin over 18 weeks.

Patients entered a 2-week placebo run-in period on MDI insulin with or without metformin background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of JARDIANCE 10 mg, JARDIANCE 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. The mean total daily insulin dose at baseline for JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo was 88.6 IU, 90.4 IU, and 89.9 IU, respectively.

JARDIANCE 10 mg or 25 mg daily used in combination with MDI insulin (with or without metformin) provided statistically significant reductions in HbA1c compared to placebo after 18 weeks of treatment (see Table 10).

**Table 10 Results at Week 18 for a Placebo-Controlled Study for JARDIANCE in Combination with Insulin and with or without Metformin**

| | **JARDIANCE 10 mg + Insulin +/- Metformin N=186** | **JARDIANCE 25 mg + Insulin +/- Metformin N=189** | **Placebo + Insulin +/- Metformin N=188** |
|---|---|---|---|
| **HbA1c (%)[a]** | | | |
| Baseline (mean) | 8.4 | 8.3 | 8.3 |
| Change from baseline (adjusted mean) | -0.9 | -1.0 | -0.5 |
| Difference from placebo (adjusted mean) (95% CI) | -0.4[b] (-0.6, -0.3) | -0.5[b] (-0.7, -0.4) | -- |

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 18. At Week 18, 23.7%, 22.8% and 23.4% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, geographical region, and background medication).

During an extension period with treatment for up to 52 weeks, insulin could be adjusted to achieve defined glucose target levels. The change from baseline in HbA1c was maintained from 18 to 52 weeks with both JARDIANCE 10 mg and 25 mg. After 52 weeks, JARDIANCE 10 mg or 25 mg daily resulted in statistically greater percent body weight reduction compared to placebo (p-value <0.0001). The mean change in body weight from baseline was -1.95 kg for JARDIANCE 10 mg, and -2.04 kg for JARDIANCE 25 mg.

### 14.3 Renal Impairment
A total of 738 patients with type 2 diabetes and a baseline eGFR less than 90 mL/min/1.73 $m^2$ participated in a randomized, double-blind, placebo-controlled, parallel-group to evaluate the efficacy and safety of JARDIANCE in patients with type 2 diabetes and renal impairment. The trial population comprised of 290 patients with mild renal impairment (eGFR 60 to less than 90 mL/min/1.73 $m^2$), 374 patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 $m^2$), and 74 with severe renal impairment (eGFR less than 30 mL/min/1.73 $m^2$). A total of 194 patients with moderate renal impairment had a baseline eGFR of 30 to less than 45 mL/min/1.73 $m^2$ and 180 patients a baseline eGFR of 45 to less than 60 mL/min/1.73 $m^2$.

At Week 24, JARDIANCE 25 mg provided statistically significant reduction in HbA1c relative to placebo in patients with mild to moderate renal impairment (see Table 11). A statistically significant reduction relative to

placebo was also observed with JARDIANCE 25 mg in patients with either mild [-0.7 (95% CI: -0.9, -0.5)] or moderate [-0.4 (95% CI: -0.6, -0.3)] renal impairment and with JARDIANCE 10 mg in patients with mild [-0.5 (95% CI: -0.7, -0.3)] renal impairment.

The glucose lowering efficacy of JARDIANCE 25 mg decreased with decreasing level of renal function in the mild to moderate range. Least square mean Hb1Ac changes at 24 weeks were -0.6%, -0.5%, and -0.2% for those with a baseline eGFR of 60 to less than 90 mL/min/1.73 $m^2$, 45 to less than 60 mL/min/1.73 $m^2$, and 30 to less than 45 mL/min/1.73 $m^2$, respectively *[see Dosage and Administration (2) and Use in Specific Populations (8.6)]*. For placebo, least square mean HbA1c changes at 24 weeks were 0.1%, -0.1%, and 0.2% for patients with a baseline eGFR of 60 to less than 90 mL/min/1.73 $m^2$, 45 to less than 60 mL/min/1.73 $m^2$, and 30 to less than 45 mL/min/1.73 $m^2$, respectively.

**Table 11 Results at Week 24 (LOCF) of Placebo-Controlled Study for JARDIANCE in Patients with Type 2 Diabetes and Renal Impairment**

| | **Mild and Moderate Impairment[b]** |
|---|---|
| | **JARDIANCE 25 mg** |
| **HbA1c** | |
| Number of patients | n=284 |
| Comparison vs placebo (adjusted mean) (95% CI) | -0.5[a] (-0.6, -0.4) |

[a]p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication)
[b]eGFR 30 to less than 90 mL/min/1.73 $m^2$- Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 24.6% and 26.2% was imputed for patients randomized to JARDIANCE 25 mg and placebo, respectively.

For patients with severe renal impairment, the analyses of changes in HbA1c and FPG showed no discernible treatment effect of JARDIANCE 25 mg compared to placebo *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

JARDIANCE tablets are available in 10 mg and 25 mg strengths as follows:

**10 mg tablets:** pale yellow, round, biconvex and bevel-edged, film-coated tablets debossed with “S 10” on one side and the Boehringer Ingelheim company symbol on the other side.
Bottles of 30 (NDC 0597-0152-30)
Bottles of 90 (NDC 0597-0152-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0152-37), institutional pack.

**25 mg tablets:** pale yellow, oval, biconvex film-coated tablets, debossed with “S 25” on one side and the Boehringer Ingelheim company symbol on the other side.
Bottles of 30 (NDC 0597-0153-30)
Bottles of 90 (NDC 0597-0153-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0153-37), institutional pack.

Dispense in a well-closed container as defined in the USP.

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Instructions
Instruct patients to read the Patient Information before starting JARDIANCE therapy and to reread it each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Inform patients of the potential risks and benefits of JARDIANCE 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 JARDIANCE only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

Inform patients that the most common adverse reactions associated with the use of JARDIANCE are urinary tract infections and mycotic genital infections.

Inform female patients of child bearing age that the use of JARDIANCE during pregnancy has not been studied in humans, and that JARDIANCE should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal data, JARDIANCE may cause fetal harm in the second and third trimesters. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue JARDIANCE or nursing, taking into account the importance of the drug to the mother. It is not known if JARDIANCE is excreted in breast milk; however, based on animal data, JARDIANCE may cause harm to nursing infants.

Hypotension
Inform patients that hypotension may occur with JARDIANCE and advise them to contact their healthcare provider 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 JARDIANCE. 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 JARDIANCE 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 (5.4)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)
Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

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 chronic and recurrent infections. 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 (5.6)]*.

Laboratory Tests
Inform patients that renal function should be assessed prior to initiation of JARDIANCE and monitored periodically thereafter.

Inform patients that elevated glucose in urinalysis is expected when taking JARDIANCE.

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels toward the normal range. Hemoglobin A1c monitoring is especially useful for evaluating long-term glycemic control.

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304562-03

**PATIENT INFORMATION**
**JARDIANCE® (jar DEE ans)**
**(empagliflozin)**
**Tablets**

**What is the most important information I should know about JARDIANCE?**

JARDIANCE can cause serious side effects, including:

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

  You may be at higher risk of dehydration if you:
  - have low blood pressure
  - take medicines to lower your blood pressure, including diuretics (water pill)
  - are on low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older
- **Vaginal yeast infection.** Women who take JARDIANCE 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 JARDIANCE 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 JARDIANCE?**

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

**Who should not take JARDIANCE?**

**Do not take JARDIANCE if you:**

- are allergic to empagliflozin or any of the ingredients in JARDIANCE. See the end of this leaflet for a list of ingredients in JARDIANCE.
- have severe kidney problems or are on dialysis

**What should I tell my doctor before using JARDIANCE?**

**Before you take JARDIANCE, tell your doctor if you:**

- have kidney problems
- have liver problems
- have a history of urinary tract infections or problems with urination
- 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 any other medical conditions
- are pregnant or planning to become pregnant. It is not known if JARDIANCE 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 JARDIANCE passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take JARDIANCE.

**Tell your doctor about all the medicines you take,** including prescription and over-the-counter medicines,

vitamins, and herbal supplements.

JARDIANCE may affect the way other medicines work, and other medicines may affect how JARDIANCE works.

**Especially tell your doctor if you take:**
- diuretics (water pills)
- insulin or other medicines that can lower your blood sugar

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

**How should I take JARDIANCE?**

- Take JARDIANCE exactly as your doctor tells you to take it.
- Take JARDIANCE by mouth 1 time in the morning each day, with or without food.
- Your doctor may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of JARDIANCE at the same time. Talk with your doctor if you have questions about a missed dose.
- Your doctor may tell you to take JARDIANCE along with other diabetes medicines. Low blood sugar can happen more often when JARDIANCE is taken with certain other diabetes medicines. See **"What are the possible side effects of JARDIANCE?"**
- If you take too much JARDIANCE, 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 that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JARDIANCE.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin HbA1c.
- When taking JARDIANCE, you may have sugar in your urine, which will show up on a urine test.

**What are the possible side effects of JARDIANCE?**

**JARDIANCE may cause serious side effects, including:**
- See "**What is the most important information I should know about JARDIANCE?**"
- **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 JARDIANCE. Ketoacidosis can be life-threatening and may need to be treated in a hospital. **Ketoacidosis can happen with JARDIANCE even if your blood sugar is less than 250 mg/dL. Stop taking JARDIANCE and call your doctor right away if you get any of the following symptoms**:
  - o nausea
  - o vomiting
  - o stomach-area (abdominal) pain
  - o tiredness
  - o trouble breathing

  If you get any of these symptoms during treatment with JARDIANCE, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking JARDIANCE. 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 also may have a fever, back pain, nausea or vomiting.
- **Low blood sugar (hypoglycemia).** If you take JARDIANCE 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 JARDIANCE. Signs and symptoms of low blood sugar may include:
  - o headache
  - o drowsiness
  - o weakness
  - o irritability
  - o hunger
  - o fast heartbeat
  - o confusion
  - o shaking or feeling jittery
  - o dizziness
  - o sweating
- **Kidney problems,** especially in people 75 years of age or older and people who already have kidney problems
- **Increased fats in your blood (cholesterol)**

These are not all the possible side effects of JARDIANCE. 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.

**How should I store JARDIANCE?**

Store JARDIANCE at room temperature between 68°F to 77°F (20°C to 25°C).

**General information about the safe and effective use of JARDIANCE.**

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use JARDIANCE for a condition for which it is not prescribed. Do not give JARDIANCE to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about JARDIANCE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about JARDIANCE that is written for health professionals.

For more information about JARDIANCE, go to www.jardiance.com, scan the code below, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

**What are the ingredients in JARDIANCE?**

**Active Ingredient:** empagliflozin

**Inactive Ingredients:** lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and yellow ferric oxide.

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IT6062D
304561-03

IT6063D
304562-03

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: December 2015

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**204629Orig1s007**

# OTHER REVIEW(S)

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

**Applications:** NDA 204629/S-007
NDA 206111/S-002
NDA 206073/S-003

**Names of Drugs:** Jardiance (empagliflozin) tablets
Synjardy (empagliflozin and metformin hydrochloride) tablets
Glyxambi (empagliflozin and linagliptin) tablets

**Applicant:** Boehringer Ingelheim 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 | NDA 204629/S-007 | Jardiance (empagliflozin) tablets |

| Applicant | NDA/Supplement | Product |
|---|---|---|
| Pharmaceuticals, Inc. | 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 empagliflozin products.

## Materials Reviewed

| Labeling Reviewed | Submission Date | Currently Approved (supplement and date) |
|---|---|---|
| **Jardiance (empagliflozin) tablets** | | |
| Package Insert | December 1, 2015 | NDA 204629/S-001, S-002, S-003 June 26, 2015 |
| Patient Package Insert | | |
| **Synjardy (empagliflozin and metformin hydrochloride) tablets** | | |
| Package Insert | December 1, 2015 | NDA 206111/S-000 August 26, 2015 |
| Medication Guide | | |
| **Glyxambi (empagliflozin and linagliptin) tablets** | | |
| Package Insert | November 20, 2015 | NDA 206073/S-001 August 28, 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, with the exception of one addition made to the package insert for Glyxambi (empagliflozin and linagliptin) tablets. The phrase, "mouth ulcerations, stomatitis," was added to the end of the list of adverse reactions included in Section 6.2, Postmarketing Experience, for consistency with the approved labeling for Tradjenta (linagliptin) tablets and Jentadueto (linagliptin and metformin) tablets (see labeling review documented by Richard Whitehead on July 27, 2015, for NDA 201280/S-011 and NDA 201281/S-008).

## 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.**

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/s/

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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**

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| | |
|---|---|
| **NDA/BLA #s:** | NDA 204042, NDA 204353<br>NDA 202293, NDA 205649<br>NDA 204629, NDA 206073, NDA 206111 |
| **PRODUCTS:** | Invokana (canagliflozin), Invokamet (canagliflozin and metformin)<br>Farxiga (dapagliflozin), Xigduo XR (dapagliflozin and metformin)<br>Jardiance (empagliflozin), Glyxambi (empagliflozin and linagliptin), Synjardy (empagliflozin and metformin) |
| **APPLICANTS:** | Janssen Pharmaceuticals (canagliflozin products)<br>Astra Zeneca AB (dapagliflozin products)<br>Boehringer Ingelheim Pharmaceuticals (empagliflozin products) |
| **FROM:** | Jennifer Rodriguez Pippins, M.D., M.P.H.<br>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) |

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## 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<br>Dapagliflozin<br>Empagliflozin | 35<br>15<br>4 |
| *Origin of report* | |
| Domestic<br>Foreign | 40<br>14 |
| *Age (years), n=46* | |
| Mean<br>Median<br>Range | 47<br>48<br>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<br>Dapagliflozin<br>Empagliflozin | 10<br>9<br>0 |
| *Origin of report* | |
| Domestic<br>Foreign | 11<br>8 |
| *Age (years), n=18* | |
| Mean<br>Median<br>Range | 60<br>62<br>18-80 |
| *Sex* | |
| Female<br>Male | 10<br>9 |
| *Time to onset (days), n=14* | |
| Mean<br>Median<br>Range | 59<br>46<br>2 to 270 |
| *Drug Discontinued* | |
| Yes<br>No<br>Not reported | 15<br>1<br>3 |
| *Primary outcome* | |
| Death<br>Hospitalization<br>• ICU admission | 0<br>19<br>4 |
| *Blood culture organism* | |
| E. coli<br>Not reported | 8<br>11 |
| *Prior history of UTI* | |
| Yes<br>No<br>Not reported | 1<br>2<br>16 |
| *HgA1c, n=8* | |
| 6.5-7.5%<br>7.6-8.9%<br>9.0-13.1% | 2<br>2<br>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.


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. (b) (4)

*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. (b) (4)

*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/

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JENNIFER R PIPPINS
12/03/2015

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**204629Orig1s007**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**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 204629/S-007 (Jardiance) |
| Product Name: | NDA 206073/S-003 (Glyxambi)<br>NDA 206111/S-002 (Synjardy) |
| PMR Description: | An enhanced pharmacovigilance study of ketoacidosis in patients treated with empagliflozin. 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 empagliflozin, 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 empagliflozin. 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 empagliflozin, 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

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**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.*

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/s/

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JENNIFER R PIPPINS
12/04/2015

| | |
|---|---|
| **From:** | daniel.coleman@boehringer-ingelheim.com |
| **To:** | White, Michael G (CDER) |
| **Cc:** | chung.lee-sogaard@boehringer-ingelheim.com; heidi.reidies@boehringer-ingelheim.com; joachim.troost@boehringer-ingelheim.com |
| **Subject:** | RE: new empa family SLC labeling revision |
| **Date:** | Wednesday, November 25, 2015 1:08:09 PM |

Thanks Mike,
We are looking into it.
Hope you have a great Thanksgiving!
Dan

**From:** White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
**Sent:** Wednesday, November 25, 2015 12:16 PM
**To:** Coleman,Dr.,Daniel (MED) BIP-US-R; Reidies,Heidi (MED) BIP-US-R; Troost,Dr.,Joachim (MED) BIP-US-R
**Cc:** Lee-Sogaard,Dr.,Chung (MED) BIP-US-R
**Subject:** new empa family SLC labeling revision

Dan & Joachim/Heidi,

I wanted to give you a heads up that we will shortly be sending new labeling revisions for the ketoacidosis/urosepsis SLC with some changes made for consistency between the products in the Patient Information and Med Guide of Jardiance and Synjardy. Glyxambi is not affected.

We'll be asking for concurrence by Monday, November 30th. We'd like another formal submission of the draft label as well (which can come a day later, but the sooner the better).

Look for the emails with the labels shortly and have a great Thanksgiving!

-Mike

**Michael G. White, PhD**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

| | |
|---|---|
| **From:** | White, Michael G (CDER) |
| **To:** | "daniel.coleman@boehringer-ingelheim.com" |
| **Subject:** | NDA204629/S-007, Jardiance: Round 3 FDA DRAFT Safety Labeling Change |
| **Date:** | Wednesday, November 25, 2015 12:51:15 PM |
| **Attachments:** | Jardiance proposed_FDA_11-25-15.doc |

Dear Dr. Coleman,

We have identified some inconsistencies between the draft labels of the empagliflozin products submitted on November 20, 2015, in response to the Safety Labeling Change for ketoacidosis and urosepsis for SGLT-2 inhibitors. Therefore, we have attached a third round of FDA edits of the draft labeling for sNDA 204629/S-007, Jardiance (empagliflozin) tablets. While we consider this to be final labeling, we remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. If you wish to add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timeline we ask the you complete your review and return comments *as soon as possible* and no later than the close of business, **Monday, November 30.**

Please confirm receipt of this email, and let me know if you have any questions.

Kind regards,

-Mike

**Michael G. White, PhD**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

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/s/

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MICHAEL G WHITE
11/25/2015

**From:** daniel.coleman@boehringer-ingelheim.com
**To:** White, Michael G (CDER)
**Subject:** RE: Empagliflozin SLCs: Round 2 FDA DRAFT Safety Labeling Change
**Date:** Wednesday, November 18, 2015 3:10:00 PM

OK
Thanks

**From:** White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
**Sent:** Wednesday, November 18, 2015 3:08 PM
**To:** Coleman,Dr.,Daniel (MED) BIP-US-R
**Cc:** Troost,Dr.,Joachim (MED) BIP-US-R; Lee-Sogaard,Dr.,Chung (MED) BIP-US-R
**Subject:** Empagliflozin SLCs: Round 2 FDA DRAFT Safety Labeling Change

Hi Dan,

Just to clarify, the draft labeling that was sent is considered to have the FDA's final comments.

Please send your concurrence with this final labeling via email by the close of business tomorrow (Thursday, November 19). You should submit the final labeling as an amendment to your sNDA no later than Monday, November 23.

Thanks, and let me know if you have any questions,

-Mike
**Michael G. White, PhD**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

**From:** daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]
**Sent:** Wednesday, November 18, 2015 1:25 PM
**To:** White, Michael G (CDER)
**Subject:** RE: NDA204629/S-007, Jardiance: Round 2 FDA DRAFT Safety Labeling Change

Receipt confirmed.
Thanks Mike.

**From:** daniel.coleman@boehringer-ingelheim.com
**To:** White, Michael G (CDER)
**Subject:** RE: NDA204629/S-007, Jardiance: Round 2 FDA DRAFT Safety Labeling Change
**Date:** Wednesday, November 18, 2015 1:25:32 PM

Receipt confirmed.
Thanks Mike.

**From:** White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
**Sent:** Wednesday, November 18, 2015 1:13 PM
**To:** Coleman,Dr.,Daniel (MED) BIP-US-R
**Subject:** NDA204629/S-007, Jardiance: Round 2 FDA DRAFT Safety Labeling Change

Dear Dr. Coleman,

Attached are the second round of FDA edits of the draft labeling for sNDA 204629/S-007, Jardiance (empagliflozin) tablets, pertaining to the Safety Labeling Change for ketoacidosis and urosepsis for SGLT-2 inhibitors. While we consider this to be final labeling, we remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. If you wish to add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timeline we ask the you complete your review and return comments *as soon as possible* and no later than the close of business, **Thursday, November 19.**

Please confirm receipt of this email, and let me know if you have any questions.

Kind regards,

-Mike

**Michael G. White, PhD**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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

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/s/

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MICHAEL G WHITE
11/18/2015

| | |
|---|---|
| **From:** | daniel.coleman@boehringer-ingelheim.com |
| **To:** | White, Michael G (CDER) |
| **Subject:** | RE: NDA204629/S-007, Jardiance: FDA DRAFT Safety Labeling Change (also NDA206073 & NDA206111) |
| **Date:** | Tuesday, November 10, 2015 4:23:28 PM |

Thanks so much for your patient clarification Mike.
Best regards,
Dan

---

**From:** White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
**Sent:** Tuesday, November 10, 2015 2:52 PM
**To:** Coleman,Dr.,Daniel (MED) BIP-US-R
**Subject:** RE: NDA204629/S-007, Jardiance: FDA DRAFT Safety Labeling Change (also NDA206073 & NDA206111)

Hi Dan,

Yes, the sentence in my last email should have been worded "we propose the following change to the fourth paragraph of 5.2," since we are now proposing to delete the words (b) (4) You should delete those words if you agree with our proposal.

Best,

-Mike
**Michael G. White, PhD**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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**From:** daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]
**Sent:** Tuesday, November 10, 2015 2:04 PM
**To:** White, Michael G (CDER)
**Subject:** RE: NDA204629/S-007, Jardiance: FDA DRAFT Safety Labeling Change (also NDA206073 & NDA206111)

Dear Mike,
Thanks very much for the quick response.
Please confirm our understanding that we should delete the words
(b) (4)
in the fourth paragraph of 5.2.
Your note suggests that this was proposed in the revisions you previously sent, but perhaps they were inadvertently not deleted in the text we got.
Thanks,

Dan

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**From:** White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
**Sent:** Tuesday, November 10, 2015 1:12 PM
**To:** Coleman,Dr.,Daniel (MED) BIP-US-R; Lee-Sogaard,Dr.,Chung (MED) BIP-US-R; Troost,Dr.,Joachim (MED) BIP-US-R
**Subject:** RE: NDA204629/S-007, Jardiance: FDA DRAFT Safety Labeling Change (also NDA206073 & NDA206111)

Dear Dan,

The review team's response to your question received in your November 10th, 2015, email is copied below. Our response applies to the Safety Labeling Change for ketoacidosis and urosepsis for all three of the BI's SGLT-2 inhibitor products: sNDA 204629/S-007 (Jardiance), sNDA 206073/S-003 (Glyxambi), and sNDA 206111/S-002 (Synjardy). As such, BI's contacts for those products were copied on this email.

> Thanks very much for your comment.
>
> The third paragraph of Section 5.2 has the following language:
>
> (b) (4)
>
> The fourth paragraph of Section 5.2 has the following language:
>
> (b) (4)
>
> The patient labeling includes the following language in the section titled "What should I tell my doctor before taking DRUG":
>
> (b) (4) is a patient-friendly term, and is appropriate for inclusion in the Mediation Guide.
>
> **Therefore, we proposed the following change to the fourth paragraph of 5.2:**
>
> (b) (4)

Please let me know if you have any further questions and please confirm receipt of this email.

Kind regards,

-Mike

**Michael G. White, PhD**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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**From:** daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]
**Sent:** Tuesday, November 10, 2015 11:28 AM
**To:** White, Michael G (CDER)
**Subject:** RE: NDA204629/S-007, Jardiance: FDA DRAFT Safety Labeling Change

Dear Mike,
When the JARDIANCE team was reviewing the FDA edits to our proposed labeling for the DKA SLC, we noted the following:

> The text in the Patient Information section states:
> are eating less due to illness, surgery or dieting
>
> While the text in section 5.2 Ketoacidosis states:
> … reduced caloric intake due to illness or surgery, …

Could you kindly share the FDA rationale for excluding the concept of "dieting" from the text in 5.2?

Thanks,
Dan

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**From:** White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
**Sent:** Friday, November 06, 2015 1:37 PM
**To:** Coleman,Dr.,Daniel (MED) BIP-US-R
**Subject:** NDA204629/S-007, Jardiance: FDA DRAFT Safety Labeling Change

Dear Dr. Coleman,

Attached are the FDA edits of the draft labeling for sNDA 204629/S-007, Jardiance (empagliflozin) tablets, pertaining to the Safety Labeling Change for ketoacidosis and urosepsis for SGLT-2 inhibitors. We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only

show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. If you wish to add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timeline we ask the you complete your review and return comments *as soon as possible* and no later than the close of business, **Friday, November 13.**

Please confirm receipt of this email, and let me know if you have any questions.

Kind regards,

-Mike

**Michael G. White, PhD**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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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.**

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/s/

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MICHAEL G WHITE
11/10/2015

| | |
|---|---|
| **From:** | White, Michael G (CDER) |
| **To:** | "daniel.coleman@boehringer-ingelheim.com" |
| **Subject:** | NDA204629/S-007, Jardiance: FDA DRAFT Safety Labeling Change |
| **Date:** | Friday, November 06, 2015 1:36:42 PM |
| **Attachments:** | NDA 204629 Jardiance (empa) SLC FDA Nov 6 2015.doc |

Dear Dr. Coleman,

Attached are the FDA edits of the draft labeling for sNDA 204629/S-007, Jardiance (empagliflozin) tablets, pertaining to the Safety Labeling Change for ketoacidosis and urosepsis for SGLT-2 inhibitors. We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. If you wish to add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timeline we ask the you complete your review and return comments *as soon as possible* and no later than the close of business, **Friday, November 13.**

Please confirm receipt of this email, and let me know if you have any questions.

Kind regards,

-Mike

**Michael G. White, PhD**
Regulatory Project Manager
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32 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.**

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/s/

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MICHAEL G WHITE
11/06/2015