CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204629Orig1s001

Trade Name: **JARDIANCE**

Generic Name: Empagliflozin

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date: 06/26/2015

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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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204629/S-001, S-002, and S-003

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel 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 Applications (sNDAs) dated and received August 29, 2014 (S-001), and September 3, 2014 (S-002 and S-003), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jardiance (empagliflozin) tablets.

We acknowledge receipt of your amendments dated January 23 (S-002), March 13 (S-003), and June 12, 2015 (S-001, S-002, and S-003).

These "Prior Approval" supplemental new drug applications propose to update the Jardiance label to include information described in the following studies, as well as other minor editorial revisions:

S-001 proposes to updated the Jardiance labeling with data from Study 1245.28, a randomized, double-blind active-controlled study comparing empagliflozin to glimepiride in patients with type 2 diabetes and insufficient glycemic control despite metformin treatment.

S-002 proposes to updated the Jardiance labeling with data from Study 1245.49, a randomized, double-blind, placebo-controlled study of empagliflozin (10 mg and 25 mg administered orally once daily) in patients with type 2 diabetes mellitus and insufficient glycemic control on a multiple daily injection insulin regimen alone or with metformin.

S-003 proposes to update the Jardiance labeling with data from Study 1275.1, a randomized, double-blind, active-controlled study to evaluate the efficacy and safety of Jardiance 10 mg or 25 mg in combination with linagliptin 5 mg as an add-on to metformin therapy compared to the individual components in patients with type 2 diabetes.

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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and 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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes 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 these supplemental applications, you are exempt from this requirement.

PROMOTIONAL MATERIALS

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

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

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.

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}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

JEAN-MARC P GUETTIER
06/26/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

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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

----------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)
- *Impairment in renal function* Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR below 60 mL/min/1.73 m^2 (5 2)
- *Hypoglycemia* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating JARDIANCE (5.3)
- *Genital mycotic infections* Monitor and treat as appropriate (5.4)
- *Urinary tract infections* Monitor and treat as appropriate (5.5)
- *Increased LDL-C* Monitor and treat as appropriate (5.6)
- *Macrovascular outcomes*: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE (5.7)

----------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, 5.2, 8.5)
- *Patients with renal impairment* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.2, 8.6)

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

Revised: 6/2015

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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, 5.2), 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)]*.

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5.2 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.

5.3 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.

5.4 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.

5.5 Urinary Tract Infections

JARDIANCE increases the risk for urinary tract infections *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

5.6 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.

5.7 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)]*
- Impairment in Renal Function *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.3)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.4)]*
- Urinary Tract Infections *[see Warnings and Precautions (5.5)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.6)]*

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.

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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.

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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 (5.2)* 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

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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 (5.3)]*.

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%).

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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 (5.5) 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 (5.6)]*. 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.

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 (5.3)]*.

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.

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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

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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 (5.2)]*, 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, 5.2)]*.

8.7 Hepatic Impairment

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

10 OVERDOSAGE

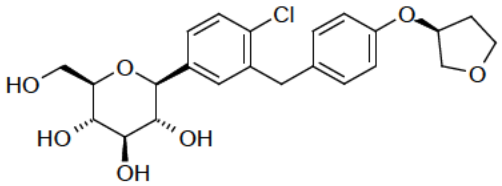
In the event of an overdose with JARDIANCE, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal 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.

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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,

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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

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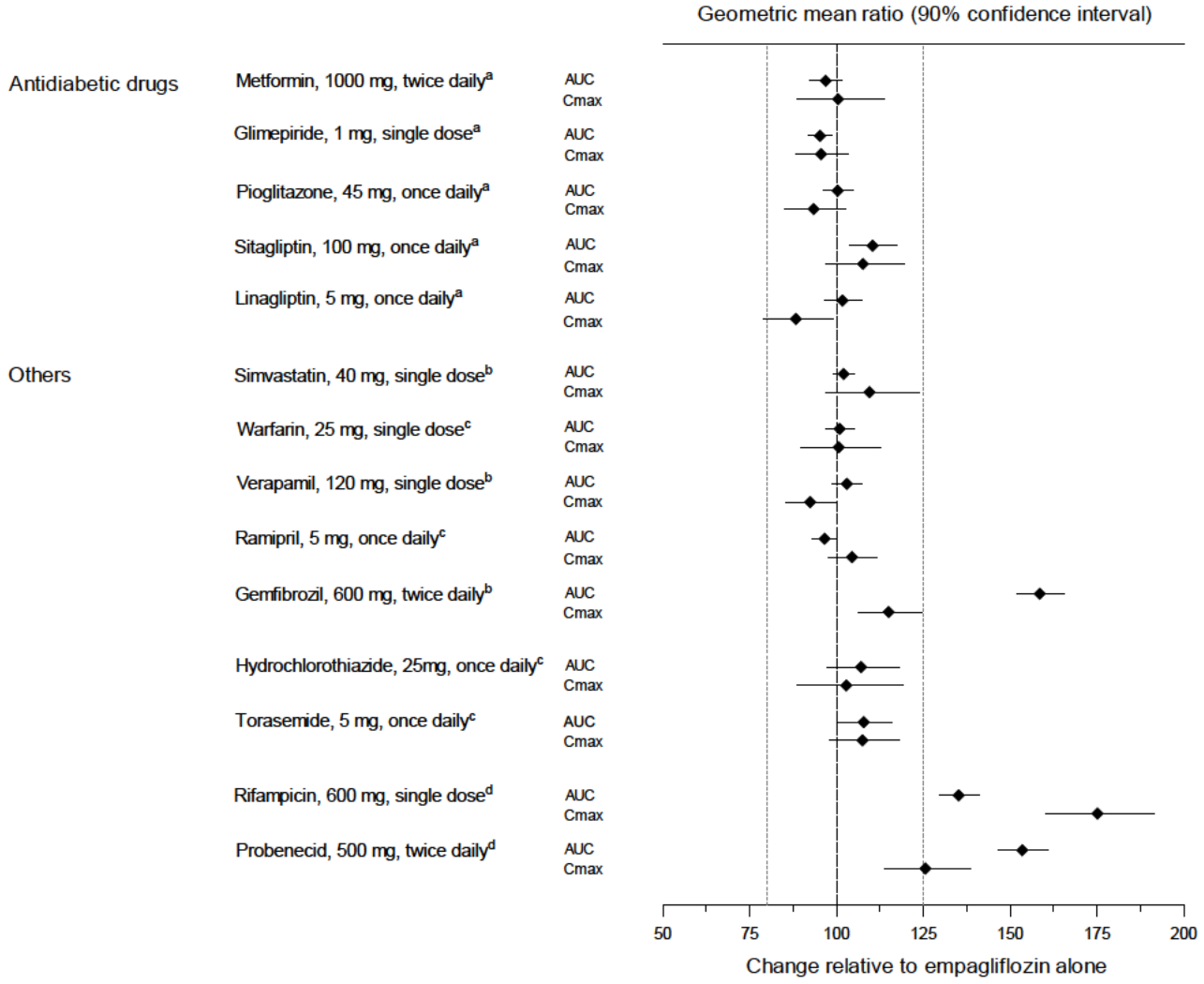
were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, hydrochlorothiazide, and torasemide in healthy volunteers (see Figure 1). The observed increases in overall exposure (AUC) of empagliflozin following 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

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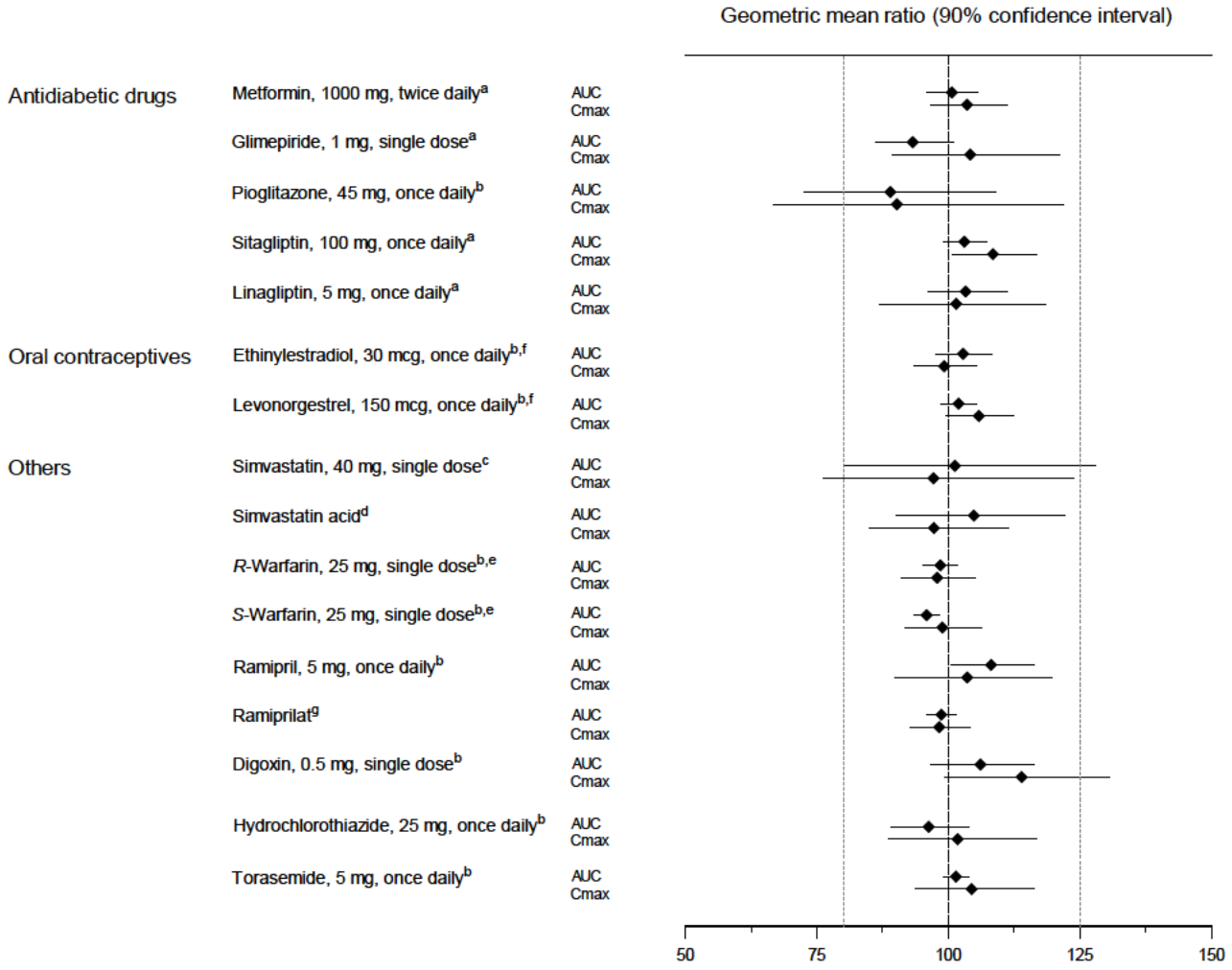
Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

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).

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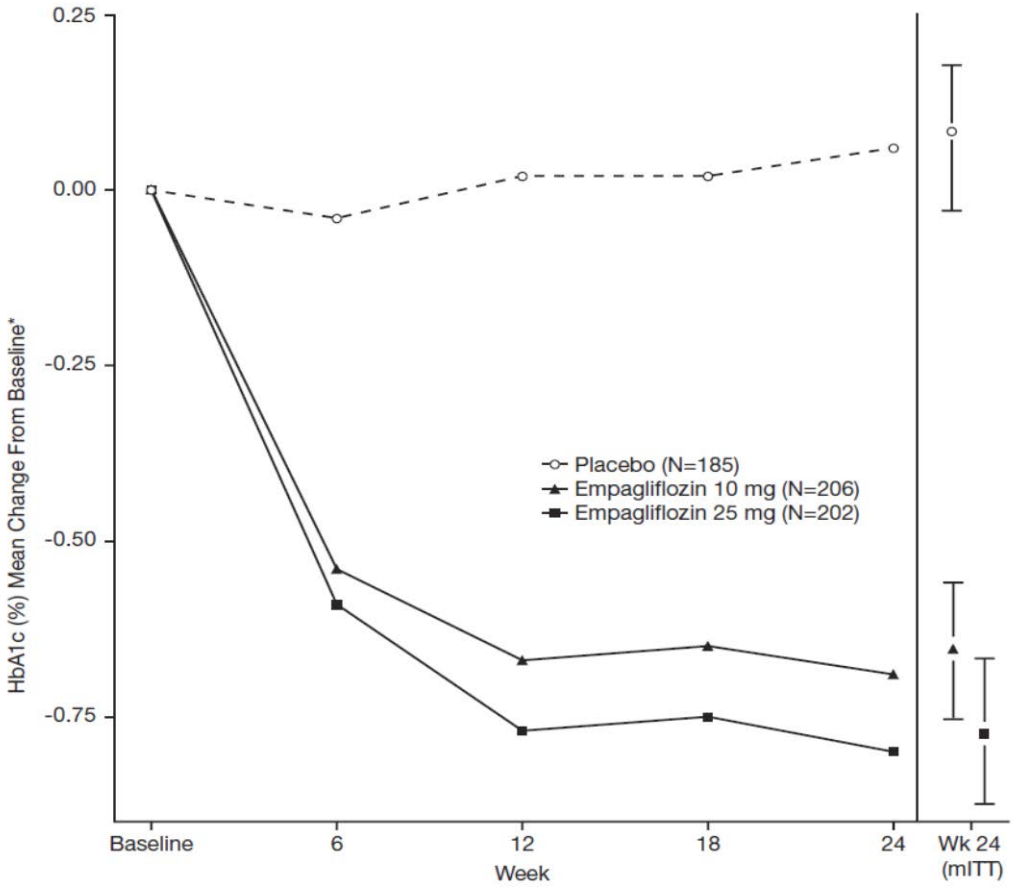
Table 4 Results at Week 24 From a Placebo-Controlled Monotherapy Study of JARDIANCE

	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.

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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

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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

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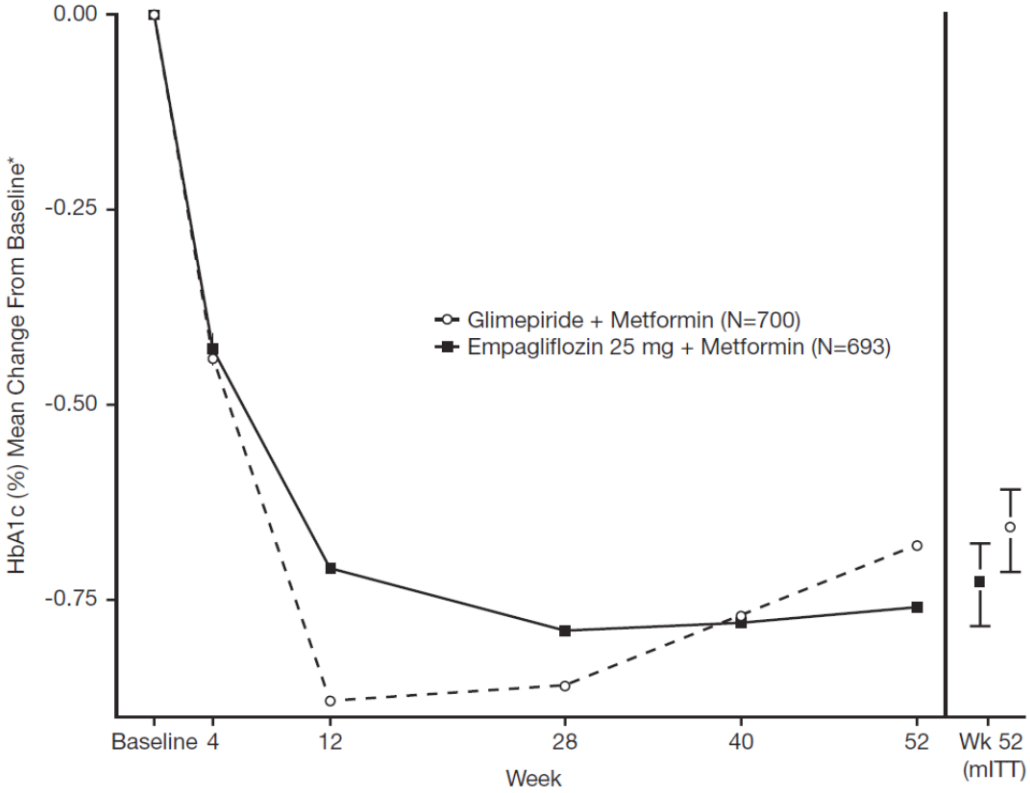
Figure 4 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF



*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).

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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.

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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

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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

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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.

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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.

Urinary Tract Infections

Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

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 (5.4)]*.

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

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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 (5.4)]*.

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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PATIENT INFORMATION

JARDIANCE® (jar DEE ans)
(empagliflozin)
Tablets

Read this Patient Information before you start taking JARDIANCE and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

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).

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- 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
- 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.

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- 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?"**
- **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:
  - headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heart beat
  - sweating
  - shaking or feeling jittery
- **kidney problems,** especially in people 75 years of age or older and people who already have kidney problems
- **increased fats in your blood (cholesterol)**

The most common side effects of JARDIANCE include:

- urinary tract infection. Signs and symptoms of a urinary tract infection may include burning feeling when passing urine, urine that looks cloudy, pain in the pelvis, or back pain.

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.

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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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s001

CROSS DISCIPLINE TEAM LEADER REVIEW

CLINICAL REVIEW/CROSS-DISCIPLINE MEMORANDUM

Application Type	Efficacy Supplement
Application Number(s)	NDA-204629, Supplement 1, 2, and 3
Received Date(s)	August 29, 2014 (Suppl 1) September 3, 2014 (Suppl 2 and Suppl 3)
PDUFA Goal Date	June 29, 2015 (Suppl 1) July 3, 2015 (Suppl 2 and Suppl 3)
Division / Office	Division of Metabolism and Endocrine Products
Reviewer Name(s)	William H. Chong
Review Completion Date	June 15, 2015
Established Name	Empagliflozin
Trade Name	Jardiance
Therapeutic Class	Sodium glucose co-transporter-2 inhibitor
Applicant	Boehringer-Ingelheim
Formulation(s)	Oral tablet
Dosing Regimen	10 mg, 25 mg once daily
Indication(s)	Adjunct to diet and exercise to improve glycemic control
Intended Population(s)	Adults with type 2 diabetes mellitus

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

As this review/memorandum covers three supplements, I will outline my recommendations for each supplement separately.

Supplement-1: I recommend approval of this supplement which consists of a clinical study (Study 1245.28) of empagliflozin versus glimepiride. Though 52 week data from this study is already included in the empagliflozin label, additional data out to 104 weeks has been submitted and I agree that the data support noninferiority of empagliflozin 25 mg compared to glimepiride at 104 weeks. (b) (4)

Supplement-2: I recommend approval of this supplement which consists of a clinical study (Study 1245.49) of empagliflozin versus placebo on a background of basal/bolus insulin with or without concomitant metformin. Insulin dose was fixed for the first 18 weeks (i.e., time to primary endpoint). I agree that the data support concluding that the addition of empagliflozin improves glycemic control compared to placebo in this context. (b) (4)

Supplement-3: I recommend approval of this supplement which consists of a factorial study (Study 1275.1) of empagliflozin + linagliptin versus the individual components. This study was previously reviewed and was the basis for approval of the empagliflozin/linagliptin fixed combination drug product. I agree that this study has shown improved glycemic control with initiation of empagliflozin and linagliptin compared to initiation of either alone in subjects already treated with metformin. I do not agree that this study informs the use of empagliflozin as the therapeutic regimen studied is not relevant to the use of empagliflozin, but is more informative for the approved empagliflozin/linagliptin fixed combination drug product. However, the sponsor has cited recently approved labeling which includes description of studies with this design to supporting their position that inclusion of this study in the empagliflozin label is appropriate. Given this precedence, I find it difficult to argue against including it in the label. However, I would limit the presentation to text only.

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1.2 Risk Benefit Assessment

All three supplements suggest that when used as studied, there is improved glycemic control. Based on findings from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study, these findings are expected to result in improvement in clinical outcomes. Risks in each study were consistent with what would be expected with use of the study drug(s). Based on this, I do not believe that the data alter the original risk-benefit assessment for empagliflozin.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the data reviewed in these supplements, I do not recommend a risk evaluation and mitigation strategy.

1.4 Recommendations for Postmarket Requirements and Commitments

Based on the data reviewed in these supplements, I do not recommend any additional postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. By inhibiting glucose reabsorption in the kidney, empagliflozin increases the urinary excretion of glucose and thus reduces plasma glucose levels.

2.2 Tables of Currently Available Treatments for Proposed Indications

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes are:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- DPP-4 inhibitors
- GLP-1 analogues

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- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

2.3 Availability of Proposed Active Ingredient in the United States

Empagliflozin was approved for use in the United States on August 1, 2014. It is available by prescription.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety concerns with SGLT2 inhibitors include:

- Volume depletion/hypotension
- Impairment of renal function
- Genitourinary infections (especially genital mycotic infections)
- Increases in low density lipoprotein cholesterol (LDL-C)
- Hypoglycemia with concomitant insulin or insulin secretagogue therapy
- Anion gap acidosis

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There was no presubmission activity for these efficacy supplements.

2.6 Other Relevant Background Information

All of these of these studies were previously submitted to different NDA's in support of fixed combination drug products (FCDPs). Study 1275.1 (Supplement-3) was submitted to support the empagliflozin/linagliptin (Empa-Lina; NDA-206073) FCDP. This study was also submitted to the empagliflozin/metformin (Empa-Met; NDA-206111) FCDP for additional safety information. Study 1245.28 (Supplement-1) was submitted to support the efficacy and safety, and study 1245.49 (Supplement-2) was submitted to support the safety of the Empa-Met FCDP.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No issues with submission quality or integrity were identified.

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3.2 Compliance with Good Clinical Practices

No concerns for noncompliance with good clinical practice were identified.

3.3 Financial Disclosures

Review of the submitted financial disclosure information does not raise concerns for bias. See section 8.3 for completed Financial Disclosure Review Templates for Supplement-1 and Supplement-3. See Dr. Lungu's review for detailed discussion of the financial disclosures for Supplement-2.

4 Sources of Clinical Data

4.1 Tables of Studies/Clinical Trials

Each efficacy supplement is supported by a single clinical study.

Supplement Number	Study Number	Description
1	1245.28	Double-blind, active controlled study comparing empagliflozin to glimepiride. - Note: 52 week data submitted as part of the initial empagliflozin NDA (b) (4)
2	1245.49	Double-blind, placebo-controlled study comparing empagliflozin to placebo on a background of multiple daily injections of insulin + /- metformin - Note: This study was also submitted to the Empa-Met fixed combination drug product NDA.
3	1275.1	Double-blind, active-controlled study comparing the combination of empagliflozin and linagliptin compared to the individual components. - Note: This study was submitted to the Empa-Lina fixed combination drug product NDA.

4.2 Review Strategy

The focus of this review/memorandum will be Supplement-1 (Study 1245.28). Supplement-2 (Study 1245.49) was separately reviewed by Dr. Andreea Lungu as part of NDA-204629 and by Dr. Shuxian Sinks as part of NDA-206111. The study submitted to support Supplement-3 was the focus of the Empa-Lina FCDP review (NDA-206073). This study was previously reviewed by Dr. Jennifer Clark and myself as part of the review for NDA-206073. Findings from Supplement-2 and Supplement-3 will be briefly discussed in this review/memorandum. For detailed discussion of the findings from study 1245.49 and study 1275.1, see Dr. Lungu's primary clinical review of Supplement-2, Dr. Sinks' primary statistical review under NDA-

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206111, Dr. Clark's review under NDA-206073, and my review/memorandum of the Empa-Lina FCDP (NDA-206073).

4.3 Discussion of Individual Studies/Clinical Trials

Study 1245.28 is an active controlled study of empagliflozin 25 vs. glimepiride 1 to 4 mg as add-on to metformin. The duration of this study is 104 weeks with another 104 week extension. In this study, the active comparator (i.e. glimepiride) was initiated at 1 mg/day and was then up-titrated by 1 mg/day every 4 weeks to a maximum dose of 4 mg if fasting blood glucose was > 110 mg/dL. If there was concern for an increased risk of hypoglycemia, up-titration could be held. Glimepiride could be down-titrated for concern of hypoglycemia. The 52 week data from this study were reviewed during the initial NDA review and are included in the current empagliflozin label. The additional data submitted with the efficacy supplement is for the completed 104 week study period.

Study 1245.49 was a placebo-controlled study of empagliflozin added to basal/bolus insulin with or without metformin. Insulin dose was to be kept stable for the first 18 weeks (time to primary endpoint), and then titration of insulin was allowed after that.

Study 1275.1 was a factorial study designed to explore the effect of empagliflozin + linagliptin compared to empagliflozin or linagliptin alone in either treatment naïve subjects or in subjects already treated with metformin.

See Dr. Lungu's primary clinical review of Supplement-2 and my review/memorandum of the Empa-Lina FCDP (NDA-206073) for additional discussion of the design of study 1245.49 and 1275.1, respectively.

5 Review of Efficacy

<u>Efficacy Summary</u>

In Supplement-1, the Applicant has demonstrated that at 104 weeks empagliflozin 25 mg shows similar efficacy for glycemic control compared to glimepiride at a mean dose of 2.7 mg. (b) (4) (b) (4) (b) (4) Thus, I believe concluding noninferiority is the

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appropriate conclusion. (b) (4)

In Supplement-2, the Applicant has demonstrated that the addition of empagliflozin on a background of basal/bolus insulin with or without metformin results in improved glycemic control compared to placebo at 18 weeks. (b) (4) (b) (4)

In Supplement-3, the Applicant has demonstrated that initiating treatment with empagliflozin and linagliptin in subjects already treated with metformin results in better glycemic control compared to the addition of empagliflozin or linagliptin alone. Of note, a separate the treatment naïve population from this study failed to demonstrate statistical significance for the comparison of the combination versus empagliflozin.

5.1 Indication

No changes to the current indication are proposed with these efficacy supplements. The current indication for empagliflozin is "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

5.1.1 Methods

Efficacy findings from study 1245.28 and 1245.49 were reviewed by Dr. Shuxian Sinks as part of her review of NDA-206111 (Empa-Met FCDP), and the efficacy findings from study 1275.1 were reviewed by Dr. Jennifer Clark as part of her review of NDA-206073 (Empa-Lina FCDP). Detailed discussion of the efficacy findings are presented in those reviews. For the purposes of this review, I will focus on the updated findings with regard to efficacy in study 1245.28 and on the findings from 1245.49.

5.1.2 Demographics

Baseline demographics were generally balanced for the studies included in these supplements. Detailed presentation of baseline demographics for study 1275.1 and study 1245.49 are found in my review for the Empa-Lina FCDP and in Dr. Lungu's review of Supplement-2, respectively.

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The baseline demographics for study 1245.28 were previously discussed in Dr. Sinks' review for the Empa-Met FCDP (NDA-206111), and are reproduced here (Table 1).

Table 1: Baseline demographics for Study 1245.28

	Empa 25 N=765	Glimepiride N=780
Age (years)		
– Mean (SD)	56.2 (10.3)	55.7 (10.44)
Age (years), N (%)		
– 50 to <65	395 (51.6)	417 (53.5)
– 65 to <75	145 (19.0)	125 (16.0)
– <50	197 (25.8)	212 (27.2)
– ≥75	28 (3.7)	26 (3.3)
Ethnic, N (%)		
– Hispanic	153 (20.0)	159 (20.4)
– Non-Hispanic	612 (80.0)	621 (79.6)
Race, N (%)		
– Asian	254 (33.2)	253 (32.4)
– Black	12 (1.6)	8 (1.0)
– Native Hawaiian	1 (0.1)	0 (0.0)
– White	498 (65.1)	519 (66.5)
Region, N (%)		
– Asia	215 (28.1)	219 (28.1)
– Europe	317 (41.4)	322 (41.3)
– Latin America	136 (17.8)	140 (17.9)
– North America	97 (12.7)	99 (12.7)
Sex, N (%)		
– Male	432 (56.5)	421 (54.0)
eGFR, N (%)		
– 30 to <60	13 (1.7)	22 (2.8)
– 60 to <90	439 (57.4)	440 (56.4)
– ≥90	313 (40.9)	318 (40.8)
HbA1c		
– Mean (SD)	7.9 (0.81)	7.9 (0.86)
HbA1c , N (%)		
– <8.5	584 (76.3)	589 (75.5)
– ≥8.5	181 (23.7)	191 (24.5)

Empa = empagliflozin; eGFR = estimated glomerular filtration rate as calculated by modification of diet in renal disease equation and expressed in ml/min/1.73 m^2
Source: Adapted from Table 3, Table 6 and Table 7 of Dr. Sinks' review for NDA-206111 (Empa-Met FCDP)

5.1.3 Subject Disposition

For discussion of the disposition of subjects in study 1275.1 and 1245.49 see my review in NDA-206073 (Empa-Lina FCDP) and Dr. Sinks' review in NDA-206111 (Empa-Met FCDP). There was no notable difference between treatment arms with regard to subject disposition for these studies.

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In study 1245.28, there were 765 subjects exposed to empagliflozin 25 mg and 780 subjects exposed to glimepiride (Table 2). At 104 weeks, there were 545 (71.2%) still receiving empagliflozin and 510 (65.4%) still receiving glimepiride. The primary reason for this small difference appeared to be subjects choosing to not continue into the extension, and "other". There were slightly more subjects from the empagliflozin arm that prematurely discontinued for the reason of "other AE".

Table 2: Disposition of subjects in Study 1245.28 at 104 weeks

	Empa 25		Glimepiride	
	N	%	N	%
Treated	765	100	780	100
– Still on study medication	545	71.2	510	65.4
– Did not continue to extension period	95	12.4	128	16.4
Prematurely discontinued study medication				
– AE-Unexpected worsening of pre-existing disease	2	0.3	4	0.5
– AE-Unexpected worsening of disease under study	3	0.4	8	1.0
– Other AE	33	4.3	22	2.8
– Lack of efficacy	3	0.4	3	0.4
– Non-complaint with protocol	6	0.8	13	1.7
– Lost to follow-up	16	2.1	15	1.9
– Withdrawal by subject	37	4.8	31	4.0
– Other	25	3.3	46	5.9

Empa = empagliflozin; AE = adverse event
Source: Reproduced from Table 3 of Dr. Sinks' review for NDA-206111 (Empa-Met FCDP)

5.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for all three studies (study 1275.1, study 1245.49, and study 1245.28) was change from baseline in HbA1c. This was assessed at 24 weeks, 18 weeks, and 52/104 weeks, respectively. From study 1275.1, the Empa-Lina FCDP showed statistically significantly greater reduction in HbA1c compared to the individual components when used on a background of metformin therapy (for details, see Dr. Jennifer Clark's statistical review for NDA-206073). From study 1245.49, both empagliflozin arms showed a statistically significantly greater reduction in HbA1c compared to placebo (Table 3).

Table 3: Change from baseline in HbA1c for Study 1245.49 at 18 weeks

	N	Baseline Mean (SE)	Change from Baseline (SE)	Difference	97.5% CI	p-value
Placebo	188	8.3 (0.72)	-0.56 (0.06)			
Empa 10	186	8.4 (0.74)	-1.0 (0.06)	-0.43	(-0.61, -0.26)	<0.0001
Empa 25	189	8.3 (0.72)	-1.1 (0.06)	-0.53	(-0.70, -0.35)	<0.0001

SE = standard error; CI = confidence interval; Empa = empagliflozin
Source: Adapted from Table 13 of Dr. Sinks' review for NDA-206111 (Empa-Met FCDP)

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[redacted] (b) (4) (b) (4) (b) (4) As a result, I believe that using the 52 week data (as currently presented in the label) is (b) (4) appropriate and (b) (4) accurate. Concluding noninferiority at 104 weeks seems reasonable, (b) (4) [redacted]

Table 4: Change from baseline in HbA1c for Study 1245.28 at 104 weeks

	N	Baseline Mean (SE)	Change from Baseline (SE)	Difference	97.5% CI	p-value[1]	p-value[2]
Glimepiride	780	7.9 (0.86)	-0.65 (0.03)				
Empa 25	765	7.9 (0.81)	-0.78 (0.03)	-0.13	(-0.24, -0.02)	<0.0001	0.008

[1] for non-inferiority; [2] for superiority
SE = standard error; CI = confidence interval; Empa = empagliflozin
Source: Adapted from Table 12 of Dr. Sinks' review for NDA-206111 (Empa-Met FCDP)

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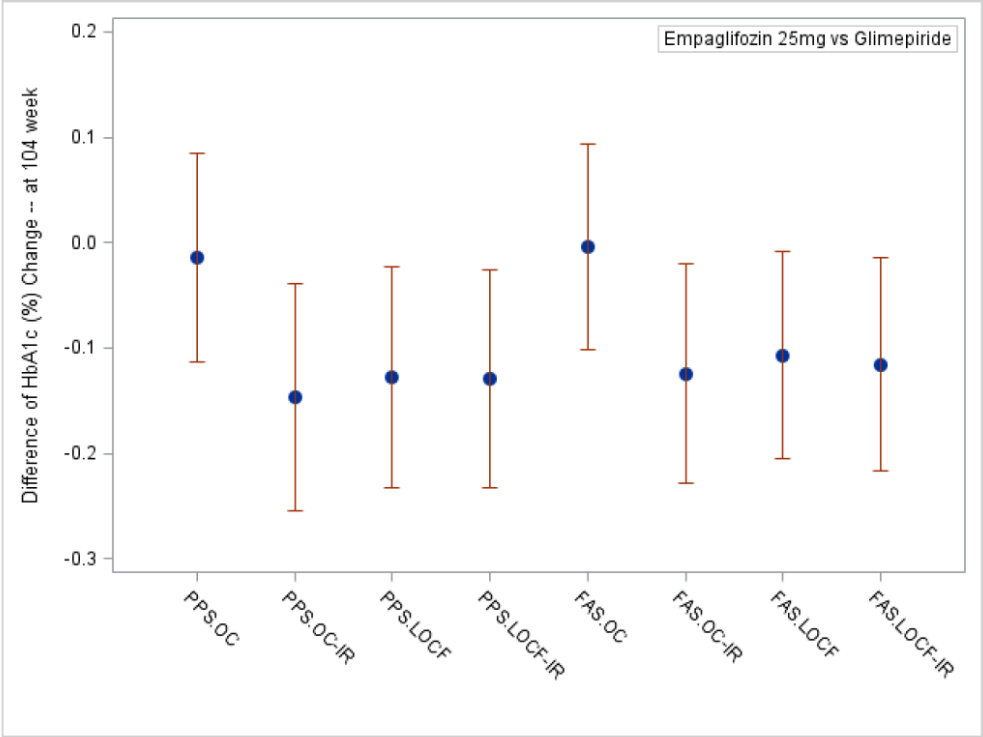
Figure 1 Summary of Sensitivity Analysis on Change in HbA1c (ANCOVA) for Study 1245.28



Source: Excerpted from Dr. Sinks' Review for NDA-206111

5.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints that were tested in a hierarchical fashion for study 1245.28 and study 1245.49 are presented in Table 2 of Dr. Sinks' review for the Empa-Met FCDP (NDA-206111, excerpted below). For discussion of the secondary endpoint tested in study 1275.1, see Dr. Clark's review and my review/memorandum for the Empa-Lina FCDP (NDA-206073).

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Table 2 Summary of Key Secondary Endpoints for Reviewed Phase III studies		
Hierarchical Testing Order	**Study 1245.28**	**Study 1245.49**
1	Change from baseline in Body weight at 52 and 104 weeks	Change from baseline in insulin at 52 weeks
2	Occurrence of Confirmed symptomatic hypoglycaemic events during 52 and 104 weeks	Change from baseline in body weight at 52 weeks
3	Change in blood pressure (SBP and DBP) from baseline at 52 and 104 weeks	Change from baseline in HbA1c at 52 weeks

For study 1245.28, Dr. Sinks does not discuss the endpoint of confirmed symptomatic hypoglycemic events. Hypoglycemia will be discussed below in section 6.2.5.1. She concludes that the results support superiority of empagliflozin compared to glimepiride for the other secondary endpoints in this study (Table 5).

Table 5: Secondary endpoints from study 1245.28 at 104 weeks

	N	Baseline Mean (SE)	Change from Baseline (SE)	Difference	97.5% CI	p-value
Body Weight						
Glimepiride	780	83 (19.2)	1.37 (0.16)			
Empa 25	765	83 (19.2)	-2.88 (0.16)	-4.2	(-4.7, -3.8)	<0.0001
SBP						
Glimepiride	780	133 (15.9)	0.32 (0.47)			
Empa 25	765	133 (15.9)	-4.92 (0.47)	-5.2	(-6.7, -3.8)	<0.0001
DBP						
Glimepiride	780	79 (9.2)	-0.38 (0.30)			
Empa 25	765	79 (9.6)	-2.73 (0.30)	-2.4	(-3.3, -1.6)	<0.0001

SE = standard error; CI = confidence interval; Empa = empagliflozin; SBP = systolic blood pressure; DBP = diastolic blood pressure
Source: Adapted from Table 12 of Dr. Sinks' Review from NDA-206111

For analysis of the secondary endpoints in study 1245.49, Dr. Sinks used the full analysis set in contrast to the Applicant which utilized the per protocol/completer set. The results were generally similar. There was a decrease in total daily insulin dose with empagliflozin compared to placebo (-8.8 units for Empa 10 vs. placebo; -11.2 units for Empa 25 vs. placebo; Table 6). While this difference in insulin dose is statistically significant, the clinical significance of this is unclear. At 52 weeks, both doses of empagliflozin were superior to placebo for change in body

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weight and change in HbA1c. However, it should be noted that the adequacy of insulin titration is in question as mean fasting plasma glucose at 52 weeks was not within the target range of 70 to 100 mg/dL. As noted in Table 20 of Dr. Lungu's review, the placebo arm had mean fasting plasma glucose values of 151.6 mg/dL at baseline, 156.4 mg/dL at 18 weeks, and 152.7 mg/dL at 52 weeks. It is unclear why glycemic targets were not achieved during the titratable insulin period. (b) (4)

Table 6: Secondary endpoints from Study 1245.49 at 52 weeks

	N	Baseline mean (SE)	Change from baseline (SE)	Difference	97.5% CI	p-value
Insulin dose						
Placebo	115	89.94 (4.08	9.54 (2.31)			
Empa 10	118	88.57 (3.43)	1.86 (2.02)	-8.83	(-15.69, -1.97)	0.004
Empa 25	117	90.38 (4.09)	-1 (2.21)	-11.22	(-18.09, -4.36)	0.0003
Body weight						
Placebo	188	96 (17.5)	0.67 (0.34)			
Empa 10	186	97 (17.9)	-1.7 (0.35)	-2.3	(-3.3, -1.3)	<0.0001
Empa 25	189	96 (17.3)	-2.3 (0.34)	-2.9	(-4.0, -1.9)	<0.0001
HbA1c						
Placebo	188	8.3 (0.72)	-0.7 (0.07)			
Empa 10	186	8.4 (0.74)	-1.1 (0.07)	-0.39	(-0.60, -0.18)	<0.0001
Empa 25	189	8.3 (0.72)	-1.2 (0.07)	-0.53	(-0.74, -0.32)	<0.0001

SE = standard error; CI = confidence interval; Empa = empagliflozin
Source: Adapted from Table 11.4.12.1: 2 of the study report for study 1245.49 and Table 13 of Dr. Sinks' Review from NDA-206111

5.1.6 Subpopulations

Sub-groups analyzed by Dr. Sinks included groups based on intrinsic factors (i.e., age, race, gender, geographic region) and disease-related factors (i.e., duration of diabetes, baseline HbA1c, renal function). If a sub-group contained < 20 subjects, that sub-group was excluded from analysis.

In study 1245.28, there was no evidence for significant heterogeneity of treatment effect by gender, race, or region. There did appear to be an age interaction with treatment effect with a greater reduction in HbA1c seen in younger subjects compared to older subjects (Figure 1). Similar findings were seen in the empagliflozin review.

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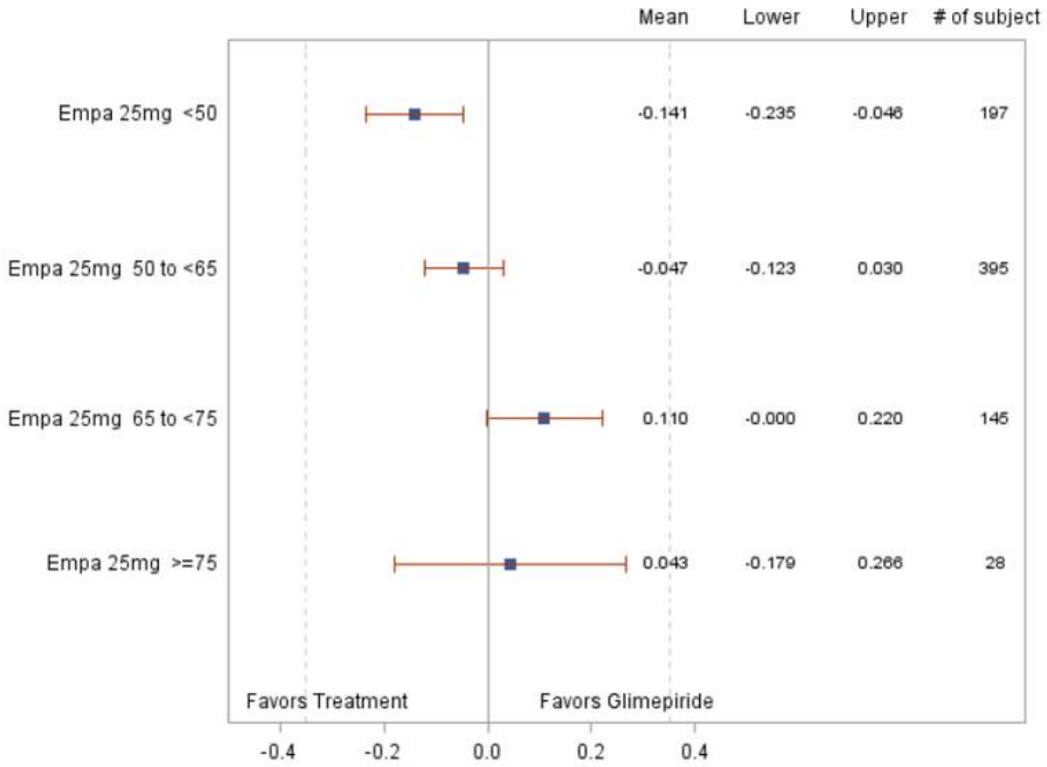
Figure 1: Change in HbA1c from baseline by age sub-groups for Study 1245.28 at 104 weeks



Source: Adapted from Figure 6 of Dr. Sinks' Review from NDA-206111

For study 1245.49, no heterogeneity of treatment effect by gender, age, or region was seen. The background therapy for this study was multiple daily injections of insulin with or without metformin. No heterogeneity of treatment effect by background therapy was seen (see Figure 7 of Dr. Sinks' Review, excerpted below).

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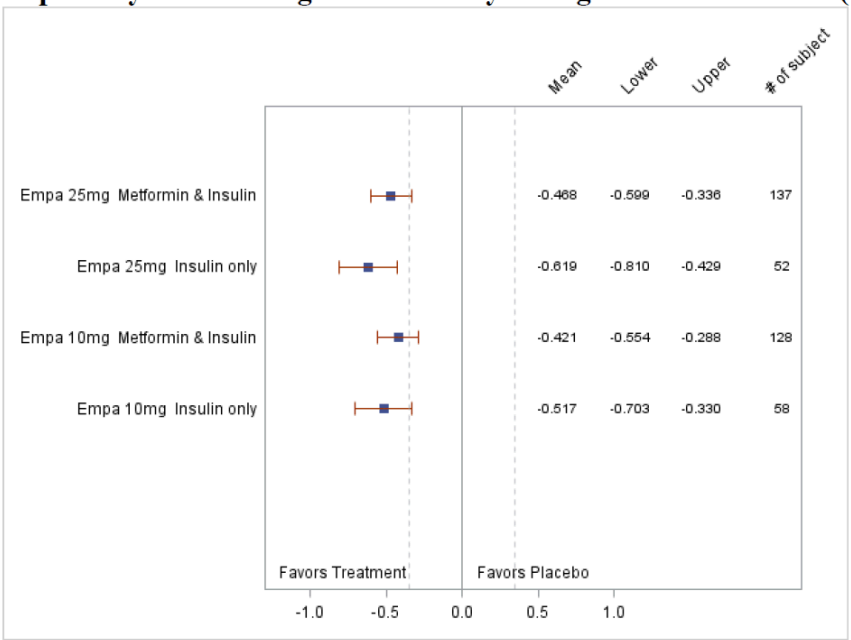
Figure 7 Subgroup Analysis on Change in HbA1c by Background Medication (Study 1245.49)



5.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

Improved glycemic control was seen with empagliflozin compared to placebo at 52 weeks in study 1245.49. In study 1245.28, the effect on glycemic control with empagliflozin appeared to be maintained and non-inferior to glimepiride at 104 weeks

5.1.8 Additional Efficacy Issues/Analyses

(b) (4)

One efficacy issue from Study 1275.1 is the apparent absence of additional efficacy in the treatment naïve population for Empa/Lina 25/5 over Empa 25 alone. This finding in itself did not preclude a recommendation of approval for the Empa/Lina FCDP, (b) (4)

As discussed above, it is unclear whether the insulin titration was adequate in the period after 18 weeks in Study 1245.49. Similar to the issues identified in Study 1245.28 with regard to the

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adequacy of the comparator, the validity of the results at 52 weeks for this study are in question as there are potential issues with the fairness of comparison.

6 Review of Safety

Safety Summary

Safety findings from these three supplements were generally consistent with the labeled safety concerns for the study drug(s). There were no findings to suggest an increased risk of death with empagliflozin. Findings for serious adverse events and class related safety concerns were consistent with what is known and in the approved label. The safety results of these three studies suggest that there is potential for adverse effects on renal function, increased risk for genitourinary infections, and increased risk for hypoglycemia and hypotension. This is consistent with the current label. No new safety signals or concerning increases in incidence of known safety signals were identified during review of these three supplements.

6.1 Methods

For the review of safety, each study was reviewed independently. Safety data was not pooled for purposes of these supplements. Details of the approach to evaluating safety for supplement-2 (i.e., study 1245.49), and supplement-3 (i.e., study 1275.1) are discussed in Dr. Lungu's review and my review of the Empa-Lina FCDP (NDA-206073), respectively. For review of the additional data from study 1245.28, I relied primarily on the presented findings from the study report.

6.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety discussion will focus on the findings at 104 weeks from Study 1245.28. Safety findings from Study 1245.49 and Study 1275.1 will be briefly discussed. For more detailed discussion of these two studies, see Dr. Lungu's clinical review of Supplement-2 and my review/memorandum for the Empa-Lina FCDP NDA (NDA-206073), respectively.

6.1.2 Categorization of Adverse Events

The analysis of on-treatment adverse events (AEs) was based on all events with an onset after the first dose of study medication up to seven days after the last dose of study medication. Events that occurred more than seven days after the last dose of study medication were considered post-treatment events.

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Analysis of adverse events of interest was performed using MedDRA queries. For hepatic injury and decreased renal function, standardized MedDRA queries (SMQs) were used. For urinary tract infection, genital infection, volume depletion, bone fractures, and malignancies, custom MedDRA queries (CMQs) were used.

6.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. Safety for each efficacy supplement was evaluated individually. No pooling of safety data was performed across studies.

6.2 Major Safety Results

6.2.1 Deaths

For discussion of deaths in Study 1245.49 and Study 1275.1, see Dr. Lungu's primary review of Supplement-2 and my review of the Empa/Lina FCDP (NDA-206073). There was no concerning imbalance in deaths observed in either of these studies.

In Study 1245.28, there were a total of ten deaths during the 104 week period with one additional death occurring after 104 weeks but before database lock (Table 7). These deaths were evenly split between the empagliflozin arm and the glimepiride arm (5 [0.7%] with empagliflozin vs. 6 [0.8%] with glimepiride). Review of the causes of death does not implicate any particular etiology in either treatment arm.

Table 7: Summary of deaths in Study 1245.28

Subject ID	Age/Gender	Days[1]	Cause of death
Empagliflozin			
(b) (6)	59/M	29	Pancreatic cancer
	59/F	281	Multiorgan failure secondary to septic shock from pneumonia and infectious diarrhea
	71/F	14	Sudden death
	75/F	33	Metastatic lung cancer
	48/M	270	Renal failure and liver failure
	74/F	788	Respiratory failure with concomitant acute myeloid leukemia
	57/M	450	Hepatic carcinoma
	66/M	441	Myocardial infarction with left ventricular rupture and cardiac tamponade
	49/M	754	Septic shock from post-CABG infection
	61/F	338	Non-small cell lung cancer with malignant pericardial and

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(b) (6)			malignant pleural effusions
	50/F	300	Myocardial infarction

[1] days from start of study medication; [2] event occurred after 104 week period but before database lock
ID = identification; M = male; F = female; CABG = coronary artery bypass graft
Source: Adapted from Table 12.3.1: 1 from the 104 week study report for 1245.28 and review of narratives

6.2.2 Nonfatal Serious Adverse Events

For discussion of nonfatal serious adverse events (SAEs) in Study 1245.49 and Study 1275.1, see Dr. Lungu's primary review for Supplement-2 and my review of the Empa/Lina FCDP (NDA-206073), respectively. There were no concerning findings with regard to SAEs in either of these studies.

In Study 1245.28, there were slightly more SAEs in the empagliflozin arm than in the glimepiride arm (15.6% vs. 11.4%; Table 8). In review of the reported preferred terms (PTs), certain terms showed a numerical imbalance not favoring empagliflozin. These included "Cerebrovascular accident", "Gastrointestinal hemorrhage", "Inguinal hernia", and "Fall". Though these numerical imbalances are intriguing, there are an insufficient number of events to draw meaningful conclusions. Review of the narratives for "Cerebrovascular accident" and for "Fall" events did not lead to suspicion of causality. Though a numerical imbalance in stroke events was noted in the original NDA review, a more complete assessment of cardiovascular risk is being performed in a dedicated cardiovascular outcomes study. Though the primary endpoint for that study is a composite[1], there should be additional information on stroke events to allow for further consideration of this risk. With regards to falls, there are limited events to draw meaningful conclusions. Further, the fall events do not appear to be associated with an increase in fractures which is arguably the clinical outcome of concern with falls. Analyzing the risk for falls also needs to be caveated with the fact that there was limited information in the narratives regarding symptoms at the time of the fall that might help in assigning causality to treatment, or attribution to other adverse events of concern (e.g., hypoglycemia or hypotension).

[1] In the ongoing cardiovascular outcomes trial, the primary endpoint of major adverse cardiovascular events is a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

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Table 8: Nonfatal serious adverse events occurring in ≥ 2 subjects (either treatment arm) at 104 weeks for Study 1245.28

System Organ Class – Preferred Term	Empagliflozin N=765 Pt-yrs=1464.1				Glimepiride N=780 Pt-yrs=1477.7			
	n	%	#	per 100	n	%	#	per 100
Overall SAE	119	15.6	195	13.3	89	11.4	175	11.8
Blood and lymphatic system disorders	2	0.3	2	0.1	3	0.4	9	0.6
Cardiac disorders	14	1.8	16	1.1	23	2.9	24	1.6
– Acute myocardial infarction	1	0.1	1	0.1	5	0.6	6	0.4
– Angina unstable	4	0.5	4	0.3	2	0.3	2	0.1
– Coronary artery disease	2	0.3	2	0.1	5	0.6	5	0.3
– Myocardial ischemia	0	0	0	0	3	0.4	3	0.2
Ear and labyrinth disorders	0	0	0	0	3	0.4	3	0.2
Eye disorders	3	0.4	3	0.2	6	0.8	8	0.5
– Retinal detachment	1	0.1	1	0.1	3	0.4	4	0.3
Gastrointestinal disorders	22	2.9	22	1.5	17	2.2	22	1.5
– Gastrointestinal hemorrhage	3	0.4	3	0.2	0	0	0	0
– Inguinal hernia	3	0.4	3	0.2	0	0	0	0
General disorders and administration site conditions	5	0.7	5	0.3	7	0.9	7	0.5
– Chest pain	1	0.1	1	0.1	3	0.4	3	0.2
Hepatobiliary disorders	5	0.7	5	0.3	6	0.8	6	0.4
Infections and infestations	25	3.3	26	1.8	15	1.9	15	1.0
– Gastroenteritis	3	0.4	3	0.2	0	0	0	0
– Viral infection	3	0.4	3	0.2	0	0	0	0
Injury, poisoning and procedural complications	25	3.3	26	1.8	15	1.9	16	1.1
– Fall	7	0.9	7	0.5	1	0.1	1	0.1
Metabolism and nutrition disorders	2	0.3	2	0.1	4	0.5	4	0.3
Musculoskeletal and connective tissue disorders	15	2.0	15	1.0	13	1.7	14	0.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16	2.1	17	1.2	10	1.3	11	0.7
Nervous system disorders	19	2.5	20	1.4	12	1.5	14	0.9
– Cerebrovascular accident	6	0.8	7	0.5	1	0.1	1	0.1
Psychiatric disorders	2	0.3	2	0.1	3	0.4	3	0.2
Renal and urinary disorders	6	0.8	7	0.5	2	0.3	2	0.1
Reproductive system and breast disorders	8	1.0	8	0.5	3	0.4	3	0.2
– Benign prostatic hyperplasia	3	0.4	3	0.2	1	0.1	1	0.1

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System Organ Class – Preferred Term	Empagliflozin N=765 Pt-yrs=1464.1				Glimepiride N=780 Pt-yrs=1477.7			
	n	%	#	per 100	n	%	#	per 100
Respiratory, thoracic and mediastinal disorders	8	1.0	8	0.5	2	0.3	2	0.1
Surgical and medical procedures	4	0.5	4	0.3	2	0.3	2	0.1
Vascular disorders	2	0.3	2	0.1	4	0.5	4	0.3

Pt-yrs = patient-years; n = number of subjects with event; % = percentage of subjects with event; # = number of events; per 100 = events per 100 subject years
Source: Adapted from review of the submitted datasets (AE.xpt, DM.xpt), Table 12.1: 1, and Table 12.3.2.1: 1 of the study report for Study 1245.28

Overall, review of the nonfatal serious adverse events from these three supplements does not warrant changes to the currently approved labeling. Further assessment of adverse events, particularly cardiovascular risk, is being performed as part of an ongoing cardiovascular outcomes study.

6.2.3 Dropouts and/or Discontinuations

For discussion of the dropouts/discontinuations in Study 1245.49 and Study 1275.1, see the reviews by Dr. Lungu for Supplement-2 and my review of the Empa-Lina FCDP NDA, respectively. There were no concerning findings with regard to dropouts/discontinuations in either study.

In Study 1245.28, more subjects discontinued study drug in the glimepiride arm than in the empagliflozin arm (33.2% vs. 27.5%; Table 9). A main reason for this difference comes from the number of subjects that chose not to continue into the extension period. Discontinuations due to adverse events were similar between treatment arms.

Table 9: Subject disposition at 104 weeks in Study 1245.28

	Empagliflozin		Glimepiride	
Treated	**765**		**780**	
	N	**%**	**N**	**%**
Prematurely discontinued study drug	210	27.5	259	33.2
– Did not continue into extension	93	12.2	127	16.3
– Adverse event	35	4.6	32	4.1

Source: Adapted from Table 15.1.1: 2 of the study report for Study 1245.28

There was no apparent imbalance in premature discontinuation for any of the supplements.

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6.2.4 Significant Adverse Events

Significant adverse events were defined by the Applicant as non-serious AEs that led to premature discontinuation of study drug, or that were marked as significant by the investigator or clinical monitor (as outlined in ICH E3). No substantial imbalances in significant adverse events were noted in the reviews of study 1245.49 or study 1275.1.

There were slightly more significant adverse events in the glimepiride arm compared to the empagliflozin arm (5.0% with glimepiride vs. 3.8% with empagliflozin; Table 10). Events from the "Infections and infestations" system organ class were more common significant adverse event with empagliflozin than with glimepiride, while the preferred term "Hypoglycemia" was a more common significant adverse event with glimepiride compared to empagliflozin. There were also more events reported in the "Reproductive system and breast disorder" system organ class with empagliflozin. Review of the terms supports that the findings for significant adverse events in study 1245.28 are consistent with other safety findings and consistent with the currently approved label.

Table 10: Incidence of significant adverse events (according to ICH E3) at 104 weeks for study 1245.28

- Includes only those system organ classes and preferred terms reported in ≥ 2 subjects regardless of treatment arm

System organ class – **Preferred term**	**Empa**		**Glimepiride**	
	N	**%**	**N**	**%**
Number of subjects	**765**	**100**	**780**	**100**
Total with other significant adverse events	29	3.8	39	5.0
Infections and infestations	10	1.3	2	0.3
– Vaginal infection	2	0.3	0	0
Metabolism and nutrition disorders	7	0.9	21	2.7
– Hypoglycemia	2	0.3	18	2.3
– Hyperglycemia	3	0.4	2	0.3
– Decreased appetite	2	0.3	0	0
Nervous system disorders	2	0.3	7	0.9
– Tremor	0	0	4	0.5
– Dizziness	0	0	3	0.4
Gastrointestinal disorders	4	0.5	2	0.3
– Nausea	2	0.3	0	0
Hepatobiliary disorders	2	0.3	2	0.3
Skin and subcutaneous tissue disorders	2	0.3	3	0.4
– Hyperhidrosis	0	0	2	0.3
Musculoskeletal and connective tissue disorders	3	0.4	0	0
Reproductive system and breast disorders	3	0.4	0	0
– Balanitis	3	0.4	0	0
General disorders and administration site conditions	3	0.4	0	0
– Thirst	2	0.3	0	0

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System organ class – Preferred term	Empa		Glimepiride	
	N	%	N	%
Number of subjects	**765**	**100**	**780**	**100**
Investigations	2	0.3	3	0.4
– Blood creatine phosphokinase increased	0	0	2	0.3

Empa = empagliflozin
Source: Adapted from Table 7.13 of the 104 week study report for study 1245.28

6.2.5 Submission Specific Primary Safety Concerns

For discussion of the adverse events of special interest in Study 1245.49 and Study 1275.1, see the reviews by Dr. Lungu for Supplement-2 and my review of the Empa-Lina FCDP NDA, respectively. In general, the safety findings from these studies are consistent with the current approved labeling. The following discussion will focus on the safety findings from study 1245.28 at 104 weeks.

6.2.5.1 Hypoglycemia

In Study 1245.28, hypoglycemia was defined as:

Symptomatic without glucose:	No plasma glucose, plus typical symptoms
Symptomatic with glucose > 70mg/dL:	Plasma glucose ≥ 70 mg/dL plus typical symptoms
Asymptomatic:	Plasma glucose ≤ 70 mg/dL, no symptoms
Documented symptomatic with glucose ≥ 54 mg/dL, < 70 mg/dL	Plasma glucose ≥ 54 mg/dL, ≤ 70 mg/dL plus typical symptoms
Documented symptomatic with glucose < 54, mg/dL:	Plasma glucose < 54 mg/dL plus typical symptoms
Severe:	Event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions

In addition, hypoglycemic events were identified as "confirmed" events if there was a plasma glucose ≤ 70 mg/dL or if assistance was required.

Comparing the empagliflozin treated subjects with the glimepiride treated subjects demonstrated a greater frequency of confirmed hypoglycemic events (Table 11). This difference in hypoglycemia occurred early in the study (Figure 2).

Table 11: Frequency of hypoglycemic events in Study 1245.28

	Empagliflozin		Glimepiride	
Treated	**765**		**780**	
	N	**%**	**N**	**%**
Confirmed hypoglycemia	19	2.5	189	24.2
– Symptomatic	13	1.7	168	21.5

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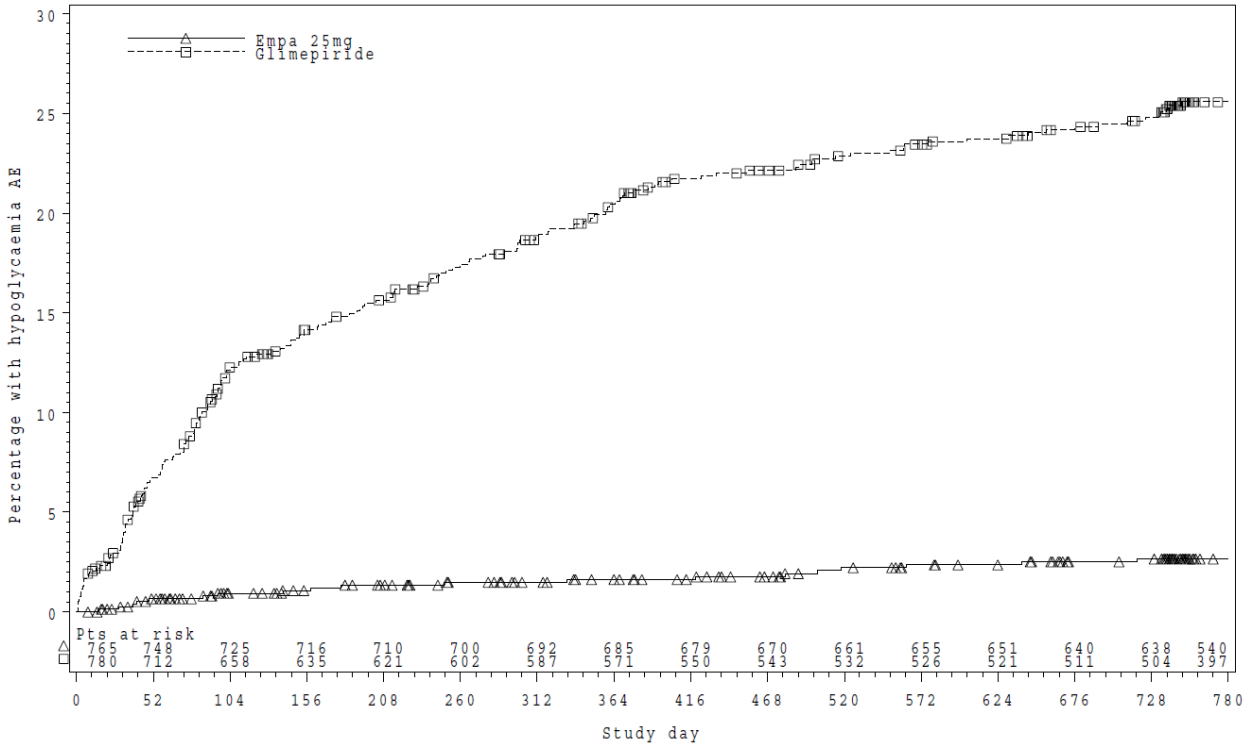
– Asymptomatic	8	1.0	43	5.5
Severe	0	0	2	0.3
Documented symptomatic, glucose < 54 mg/dL	5	0.7	62	7.9
Documented symptomatic, glucose ≥ 54, ≤ 70 mg/dL	8	1.0	104	13.3
Asymptomatic, glucose ≤ 70 mg/dL	6	0.8	21	2.7

Source: Adapted from Table 12.3.3.1.1: 1 of the study report for Study 1245.28

Figure 2: Kaplan-Meier analysis of hypoglycemic events in Study 1245.28



Source: Excerpted from Figure 15.3.2.3: 1 of the study report for Study 1245.28

In looking at the findings for hypoglycemia, there is a greater risk for hypoglycemia with glimepiride than with empagliflozin. Given the different mechanisms of action and what is already known of the hypoglycemic risk of these drugs from different classes, this is hardly surprising. However, the incidence of "confirmed" hypoglycemia may be misleading as it includes events that were asymptomatic and events with plasma glucose levels in a range which may not be consistent with clinically important hypoglycemia (e.g., ≥ 54 mg/dL). Looking at only "severe" events and "documented symptomatic" events with a plasma glucose < 54 mg/dL a difference remains, but it is less striking. Regardless of this observation, I believe that safety data from placebo-controlled studies provide the clearest understanding of a drug's safety profile and that safety data from active comparator studies should not be included unless there is a clear risk message to be communicated. Otherwise it could be misinterpreted as a safety benefit which

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when taken from a study not specifically designed to assess for a safety benefit would be an unsubstantiated claim. The Applicant has not proposed including hypoglycemia information from this study, and I agree with this approach.

Notably, in study 1245.49, the incidence of hypoglycemia was similar across arms at 52 weeks, though there were more events of "severe" intensity with empagliflozin. This is discussed in Dr. Lungu's review. Looking at the incidence at 18 weeks may be more informative, as this was during the fixed insulin dose period. At 18 weeks, the incidence of hypoglycemia was higher in the empagliflozin 25 mg arm compared to placebo (Table 12).

Table 12: Hypoglycemia at 18 weeks for study 1245.49

	Placebo N=188	**Empa 10 N=186**	**Empa 25 N=189**
	n (%)	**n (%)**	**n (%)**
Number of subjects with confirmed hypoglycemic adverse events	70 (37.2)	74 (39.8)	78 (41.3)
– Confirmed symptomatic hypoglycemic adverse events	60 (31.9)	59 (31.7)	67 (35.4)
– Confirmed asymptomatic hypoglycemic adverse events	24 (12.8)	27 (14.5)	31 (16.4)
Severity of hypoglycemia (worst episode)			
– Episode requiring assistance ("severe hypoglycemic episode")	1 (0.5)	1 (0.5)	1 (0.5)
– Sympt. and glucose < 54 mg/dL and no assistance required	38 (20.2)	36 (19.4)	47 (24.9)
– Sympt. and 54 mg/dL ≤ glucose ≤ 70 mg/dL and no assistance required	21 (11.2)	22 (11.8)	19 (10.1)
– Asympt. and glucose ≤ 70 mg/dL	10 (5.3)	15 (8.1)	11 (5.8)
Intensity of event (worst episode)			
– Severe	1 (0.5)	1 (0.5)	1 (0.5)
– Moderate	16 (8.5)	14 (7.5)	13 (6.9)
– Mild	53 (28.2)	59 (31.7)	64 (33.9)
Subjects with actions taken			
– Therapy required	8 (4.3)	11 (5.9)	11 (5.8)
– Action taken with antidiabetic background medication due to AE within 14 days	20 (10.6)	29 (15.6)	27 (14.3)
– Action taken with trial drug	0	0	0
– Requiring or prolonging hospitalization	0	0	0

Empa = empagliflozin; Sympt. = symptomatic; Asympt. = asymptomatic; AE = adverse event
Source: Adapted from Table 15.3.2.5: 3 of the study report for study 1245.49

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6.2.5.2 Decreased renal function

In Study 1245.28, analysis of decreased renal function was performed by adverse event reports and by laboratory findings.

Analysis of adverse events was performed using the standardized MedDRA query (SMQ) "acute renal failure". Based on this SMQ, there was a suggestion of an increase in renal adverse events, but there were too few events to draw meaningful conclusions (Table 13).

Table 13: Incidence of renal failure adverse events in Study 1245.28

	Empagliflozin		Glimepiride	
Subjects	**765**		**780**	
	N	**%**	**N**	**%**
Acute renal failure SMQ	7	0.9	5	0.6
Preferred terms				
– Renal impairment	4	0.5	4	0.5
– Renal failure	3	0.4	0	0
– Renal failure acute	1	0.1	1	0.1

SMQ = standardized MedDRA query
Source: Adapted from Table 7.28 from the Appendix to the study report for Study 1245.28

For the analysis of decreased renal function, the Applicant has used serum creatinine to identify events. Serum creatinine values were also reviewed to identify potential cases (defined as increase in serum creatinine ≥ 2x baseline and greater than upper limit of reference range). Based on this definition, there was no increase in decreased renal function with empagliflozin (Table 14).

Table 14: Incidence of decrease renal function based on serum creatinine criteria in Study 1245.28

	Empagliflozin		Glimepiride	
Subjects	**765**		**780**	
	N	**%**	**N**	**%**
Increase in serum creatinine ≥ 2x baseline and > ULRR	2	0.3	4	0.5

ULRR = upper limit of reference range
Source: Adapted from Table 15.3.3.4.1: 2 of the study report for Study 1245.28

Evaluation of renal function by estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation was also performed. Changes from baseline in eGFR were small for both groups (+1.69 ml/min/1.73 m^2 for empagliflozin vs. -1.84 ml/min/1.73 m^2 for glimepiride at 104 weeks). There were no clear or meaningful differences in

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changes in renal impairment category as defined by eGFR from baseline and last value on treatment (Table 15). Comparing eGFR from baseline to minimum value on treatment yielded similar findings (Table 16).

Table 15: Percentage of subjects with change in renal impairment category from baseline to last value on treatment for Study 1245.28

		Last value on treatment					
Baseline	**Subjects**	**Normal**		**Mild**		**Moderate**	
		N	**%**	**N**	**%**	**N**	**%**
Empagliflozin							
– Normal	301	230	76.4	69	22.9	2	0.7
– Mild	428	95	22.2	315	73.6	17	4.0
– Moderate	13	1	7.7	5	38.5	7	53.8
Glimepiride							
– Normal	309	224	72.5	80	25.9	5	1.6
– Mild	426	54	12.7	340	79.8	32	7.5
– Moderate	22	0	0	11	50.0	11	50.0

Source: Adapted from Table 15.3.3.4.2: 4 of the study report for Study 1245.28

Table 16: Percentage of subjects with change in renal impairment category from baseline to minimum value on treatment for Study 1245.28

		Minimum value on treatment					
Baseline	**Subjects**	**Normal**		**Mild**		**Moderate**	
		N	**%**	**N**	**%**	**N**	**%**
Empagliflozin							
– Normal	301	140	46.5	159	52.8	2	0.7
– Mild	428	20	4.7	348	81.3	59	13.8
– Moderate	13	0	0	1	7.7	12	92.3
Glimepiride							
– Normal	309	142	46.0	162	52.4	5	1.6
– Mild	426	11	2.6	342	80.3	72	16.9
– Moderate	22	0	0	8	36.4	14	63.6

Source: Adapted from Table 15.3.3.4.2: 4 of the study report for Study 1245.28

These findings are consistent with the observations from the empagliflozin NDA review and are consistent with the approved labeling. I do not recommend any changes to the label with regard to these events.

6.2.5.3 Hepatic injury

In Study 1245.28, liver injury events were analyzed using SMQs and laboratory tests.

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Four SMQs were used to evaluate the frequency of hepatic injury events. These were "Liver related investigations, signs and symptoms", "Cholestasis and jaundice of hepatic origin", "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions", and "Hepatitis, non-infectious". No SMQ was reported with a greater frequency in the empagliflozin arm (Table 17).

Table 17: Frequency of hepatic injury by adverse event reports for study 1245.28

	Empagliflozin		Glimepiride	
Subjects	765		780	
	N	%	N	%
Hepatic injury adverse event	14	1.8	33	4.2
SMQ				
– Liver related investigations, signs and symptoms	3	0.4	20	2.6
– Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	9	1.2	13	1.7
– Hepatitis, non-infectious	1	0.1	3	0.4
– Cholestasis and jaundice of hepatic origin	1	0.1	2	0.3

SMQ = standardized MedDRA query
Source: Adapted from Table 7.29 of the Appendix to the study report for Study 1245.28

Comparison of elevations in liver enzymes similarly did not demonstrate an increased incidence in the empagliflozin arm (Table 18).

One subject from the empagliflozin arm was reported to have ALT/AST ≥ 10x ULRR based on local laboratory assessments and is not included in this category in Table 18. This subject was included in the counts for "ALT/AST ≥ 5x ULRR". Review of the narrative for this subject [redacted] (b) (6) stated that the subject had a history of elevated liver enzymes, but the values obtained at screening were acceptable. Elevations in ALT and AST were noted during the study (even prior to randomization), but no action was taken with regard to study drug. Notably, there was no concurrent increase in bilirubin. Study drug was eventually discontinued (658 days after randomization) due to complaints of loose stools. Interestingly, the ALT and AST elevations improved after this. The investigator postulates that the liver enzyme elevation was related to alcohol consumption, but alcohol use was not confirmed by the subject. Though the improvement after discontinuation is consistent with a drug related event, the timing of the rise and the absence of concurrent bilirubin changes go against this being a severe hepatotoxic event.

There was also a subject in the empagliflozin group [redacted] (b) (6) with liver enzyme elevations (based on local laboratory results, not central laboratory results) concerning

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for Hy's Law[2]. This subject is not included in Table 18. This subject died of renal and hepatic insufficiency complicated by coagulopathy and gastrointestinal bleeding 277 days after randomization. Prior to death, increased ascites/waist circumference and jaundice were reported, along with increased alcohol intake. From the laboratory data included in the submitted narrative, the alkaline phosphatase was not increased ≥ 2x ULRR (unlike the case from the glimepiride arm). Autopsy showed liver cirrhosis and esophageal varices. Though the laboratory findings are consistent with Hy's Law, there is a plausible alternative explanation of alcoholic cirrhosis. This case was reviewed during the initial NDA review. Though concerning, it does not raise sufficient concern to withdraw empagliflozin or lead me to recommend labeling hepatic injury. Liver injury will be further explored in the ongoing cardiovascular outcomes trial.

Table 18: Frequency of increased liver enzymes based on central laboratory measurements in Study 1245.28

	Empagliflozin		**Glimepiride**	
Subjects	**765**		**780**	
	N	**%**	**N**	**%**
ALT/AST ≥ 3x ULRR	7	0.9	9	1.2
ALT/AST ≥ 5x ULRR	2	0.3	1	0.1
ALT/AST ≥ 10x ULRR	1	0.1	0	0
ALT/AST ≥ 20x ULRR	0	0	0	0
ALT and/or AST ≥ 3x ULRR with T. Bili ≥ 2x ULRR	0	0	1	0.1
– Alkaline phosphatase < 2x ULRR	0	0	0	0
– Alkaline phosphatase ≥ 2x ULRR	0	0	1	0.1

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range; T. Bili = total bilirubin
Source: Adapted from Table 15.3.3.3: 1 of the study report for Study 1245.28

Based on the information from study 1245.28, there does not appear to be evidence of drug-induced liver injury for empagliflozin. I do not recommend any changes to the label with regard to these events.

6.2.5.4 Urinary tract infections

The analysis of urinary tract infection events was based on a custom MedDRA query created by the Applicant (Table 27). Based on this approach, the incidence of urinary tract infections was similar between treatment arms in study 1245.28 (Table 19). Though the overall incidence was similar, it is notable that there were more fungal urinary tract infections. These observations are

[2] Biochemical criteria for Hy's Law (used for predicting whether there is a risk for severe drug-induced liver injury) are aminotransferases ≥ 3x ULRR with T. Bili ≥ 2x ULRR and without alkaline phosphatase ≥ 2x ULRR

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consistent with the currently approved labeling which warns against increased risk for urinary tract infections and of increased risk for genital mycotic infections. I do not recommend any changes to the label with regard to these events.

Table 19: Urinary tract infection events in study 1245.28 at 104 weeks

	Empagliflozin		Glimepiride	
	N	%	N	%
Number of subjects	765	100.0	780	100.0
Subjects with urinary tract infection events[1]	105	13.7	102	13.1
– Urinary tract infection	95	12.4	99	12.7
– Cystitis	6	0.8	2	0.3
– Urinary tract infection fungal	4	0.5	0	0.0
– Asymptomatic bacteriuria	2	0.3	2	0.3
– Genitourinary tract infection	2	0.3	1	0.1
– Bacteriuria	1	0.1	1	0.1
– Cystitis escherichia	1	0.1	0	0.0
– Escherichia urinary tract infection	1	0.1	0	0.0
– Fungal cystitis	1	0.1	0	0.0
– Kidney infection	1	0.1	0	0.0
– Pyelonephritis acute	1	0.1	0	0.0
– Urinary tract infection bacterial	1	0.1	0	0.0

[1] based on Applicant defined custom MedDRA query
Source: Adapted from Table 12.3.3.3: 1 of the 104 week study report for Study 1245.28

6.2.5.5 Genital infections

The analysis of genital infection events was based on a custom MedDRA query created by the Applicant (Table 28). Based on this approach, there was a higher incidence of genital infections with empagliflozin than with glimepiride in study 1245.28 (Table 20). This is consistent with the currently approved labeling which warns against increased risk for genital mycotic infections. I do not recommend any changes to the label with regard to these events.

Table 20: Genital infections in study 1245.28 at 104 weeks

	Empagliflozin		Glimepiride	
	N	%	N	%
Number of subjects	765	100.0	780	100.0
Subjects with genital infection events[1]	90	11.8	17	2.2
– Balanitis	17	2.2	4	0.5
– Vulvovaginal candidiasis	16	2.1	3	0.4
– Vaginal infection	12	1.6	1	0.1
– Vulvovaginal mycotic infection	9	1.2	2	0.3
– Balanitis candida	7	0.9	0	0.0
– Genital infection fungal	5	0.7	0	0.0
– Vulvovaginitis	5	0.7	1	0.1
– Balanoposthitis	4	0.5	0	0.0

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	Empagliflozin		Glimepiride	
	N	%	N	%
– Genital infection	4	0.5	0	0.0
– Cervicitis	3	0.4	2	0.3
– Epididymitis	2	0.3	0	0.0
– Genital candidiasis	2	0.3	0	0.0
– Genitourinary tract infection	2	0.3	1	0.1
– Prostatitis	2	0.3	0	0.0
– Vaginitis bacterial	1	0.1	2	0.3
– Cellulitis of male external genital organ	1	0.1	0	0.0
– Orchitis	0	0.0	1	0.1
– Pelvic inflammatory disease	0	0.0	1	0.1
– Penile infection	1	0.1	0	0.0
– Posthitis	1	0.1	0	0.0
– Vulvitis	1	0.1	0	0.0

[1] based on Applicant defined custom MedDRA query
Source: Adapted from Table 12.3.3.4: 1 of the 104 week study report for study 1245.28

6.2.5.6 Volume depletion events

Volume depletion events were assessed using an Applicant defined custom MedDRA query. The terms included were:

Blood pressure ambulatory decreased	Blood pressure decreased	Blood pressure systolic decreased
Dehydration	Hypotension	Hypovolemia
Orthostatic hypotension	Syncope	

Though there was no marked imbalance between treatment arms, more events of hypotension were reported in the empagliflozin treated subjects (Table 21). This is consistent with the current labeling. I do not recommend any changes to the label with regard to these events.

Table 21: Volume depletion events in study 1245.28 at 104 weeks

	Empagliflozin		Glimepiride	
	N	%	N	%
Number of subjects	765	100.0	780	100.0
Subjects with volume depletion events[1]	11	1.4	8	1.3
– Hypotension	6	0.8	3	0.4
– Syncope	2	0.3	4	0.4
– Dehydration	0	0.0	3	0.4
– Orthostatic hypotension	2	0.3	0	0.0
– Blood pressure decreased	1	0.1	0	0.0

[1] based on Applicant defined custom MedDRA query
Source: Adapted from Table 12.3.3.5: 1 of the 104 week study report for study 1245.28

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6.2.5.7 Fractures

Fractures were assessed using an Applicant defined custom MedDRA query. Based on this, there was no evidence of increased risk for fracture events (19 [2.5%] with empagliflozin vs. 17 [2.2%] with glimepiride. I do not recommend any changes to the label with regard to these events.

6.2.5.8 Malignancies

A custom MedDRA query was utilized by the Applicant to explore malignancy events. Based on this, there were slightly more malignancy events with empagliflozin (15 [2.0%] with empagliflozin vs. 9 [1.2%] for glimepiride). However, no single type of cancer drove this numeric imbalance. I do not recommend any changes to the label with regard to these events.

6.3 Supportive Safety Results

For detailed discussion of the supportive safety results from study 1275.1 and study 1245.49, see my review of the Empa-Lina FCDP (NDA-206073) and Dr. Lungu's review of Supplement-2 for NDA-204629. The findings were in general consistent with the approved label. Dr. Lungu did note an increase in events of vertigo and dizziness, but she concludes that these events may be related to the labeled safety events of hypoglycemia and/or hypotension. This portion of the review will focus on the findings from study 1245.28 at 104 weeks.

6.3.1 Common Adverse Events

In study 1245.28, the most common adverse events came from the "Infections and infestations" system organ class (Table 22). The incidence of events was balanced between treatment arms (53.5% for empagliflozin vs. 50.5% for glimepiride). Events from the "Metabolism and nutrition disorders" SOC was the next most common. There was a higher incidence in the glimepiride arm, and this was primarily driven by differences in the preferred terms "Hypoglycemia" and "Hyperglycemia".

Table 22: Adverse events occurring in ≥ 5% of subjects for either treatment group at 104 weeks at the preferred term level for study 1245.28

System organ class – Preferred term	Empagliflozin N=765		Glimepiride N=780	
	N	%	N	%
Infections and infestations	409	53.5	394	50.5
– Urinary tract infection	95	12.4	99	12.7
– Nasopharyngitis	76	9.9	89	11.4
– Upper respiratory tract infection	79	10.3	74	9.5
– Influenza	51	6.7	51	6.5

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System organ class – Preferred term	Empagliflozin N=765		Glimepiride N=780	
	N	%	N	%
Metabolism and nutrition disorders	202	26.4	407	52.2
– Hypoglycemia	32	4.2	197	25.3
– Hyperglycemia	105	13.7	168	21.5
– Dyslipidemia	41	5.4	39	5.0
Nervous system disorders	163	21.3	176	22.6
– Headache	48	6.3	55	7.1
– Dizziness	49	6.4	49	6.3
Vascular disorders	68	8.9	104	13.3
– Hypertension	41	5.4	77	9.9
Respiratory, thoracic and mediastinal disorders	96	12.5	106	13.6
– Cough	42	5.5	47	6.0
Gastrointestinal disorders	194	25.4	216	27.7
– Diarrhea	39	5.1	51	6.5
Musculoskeletal and connective tissue disorders	240	31.4	251	32.2
– Arthralgia	44	5.8	66	8.5
– Back pain	63	8.2	64	8.2
– Pain in extremity	39	5.1	32	4.1

Source: Adapted from Table 12.2.2.1: 1 of the 104 week study report for study 1245.28

As it is possible that potential safety signals may be missed by looking at system organ class or preferred terms only, I also looked at the high level group terms for imbalances (Table 23). There was a higher incidence of urinary tract symptoms, fungal infections, renal disorders, and both male and female genitourinary events with empagliflozin than with glimepiride. This is consistent with the approved labeling. Of note, conjunctivitis was also seen more commonly in the empagliflozin treated arm. Though unexpected, I do not believe this to be a significant safety concern and would not recommend any labeling changes based on this observation.

Table 23: Incidence of treatment emergent adverse events in > 2% of empagliflozin treated subjects by High level group term at 104 weeks for study 1245.28

High level group term – Preferred term[1]	Empagliflozin N=765		Glimepiride N=780	
	N	%	N	%
Infections - pathogen unspecified	357	46.7	349	44.7
Musculoskeletal and connective tissue disorders NEC	153	20.0	137	17.6
Glucose metabolism disorders (incl diabetes mellitus)	148	19.3	365	46.8
Gastrointestinal signs and symptoms	97	12.7	104	13.3
General system disorders NEC	97	12.7	114	14.6
Viral infectious disorders	94	12.3	89	11.4
Urinary tract signs and symptoms	91	11.9	46	5.9
– Pollakiuria	24	3.1	8	1
– Polyuria	17	2.2	2	0.3
– Microalbuminuria	14	1.8	10	1.3
– Dysuria	12	1.6	6	0.8
– Hematuria	8	1	10	1.3

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High level group term – **Preferred term**[1]	**Empagliflozin N=765**		**Glimepiride N=780**	
	N	**%**	**N**	**%**
– Nocturia	7	0.9	3	0.4
– Urinary retention	3	0.4	2	0.3
Joint disorders	90	11.8	122	15.6
Neurological disorders NEC	86	11.2	93	11.9
Injuries NEC	75	9.8	93	11.9
Respiratory disorders NEC	73	9.5	78	10.0
Gastrointestinal motility and defecation conditions	71	9.3	96	12.3
Fungal infectious disorders	69	9.0	36	4.6
– Vulvovaginal candidiasis	16	2.1	3	0.4
– Vulvovaginal mycotic infection	9	1.2	2	0.3
– Balanitis candida	8	1	0	0
– Fungal infection	8	1	7	0.9
– Candida infection	6	0.8	1	0.1
– Onychomycosis	5	0.7	6	0.8
– Urinary tract infection fungal	5	0.7	0	0
– Genital infection fungal	4	0.5	0	0
– Tinea pedis	3	0.4	8	1
Lipid metabolism disorders	62	8.1	75	9.6
Epidermal and dermal conditions	61	8.0	74	9.5
Headaches	54	7.1	67	8.6
Vascular hypertensive disorders	47	6.1	81	10.4
Bacterial infectious disorders	35	4.6	29	3.7
Ocular infections, irritations and inflammations	32	4.2	22	2.8
– Conjunctivitis	19	2.5	12	1.5
Muscle disorders	29	3.8	39	5.0
Gastrointestinal inflammatory conditions	28	3.7	26	3.3
Upper respiratory tract disorders (excl infections)	26	3.4	21	2.7
Inner ear and VIIIth cranial nerve disorders	25	3.3	22	2.8
Male reproductive tract infections and inflammations	25	3.3	6	0.8
– Balanitis	17	2.2	5	0.6
– Balanoposthitis	4	0.5	0	0.0
Bone and joint injuries	24	3.1	43	5.5
Peripheral neuropathies	23	3.0	19	2.4
Anterior eye structural change, deposit and degeneration	20	2.6	19	2.4
Depressed mood disorders and disturbances	20	2.6	18	2.3
Prostatic disorders (excl infections and inflammations)	20	2.6	12	1.5
– Benign prostatic hyperplasia	11	1.4	7	0.9
– Prostatomegaly	5	0.7	3	0.4
– Prostatism	4	0.5	1	0.1
Sleep disorders and disturbances	20	2.6	25	3.2
Tendon, ligament and cartilage disorders	20	2.6	27	3.5
Vulvovaginal disorders (excl infections and inflammations)	20	2.6	7	0.9
– Vulvovaginal pruritus	12	1.6	3	0.4
– Vaginal discharge	3	0.4	1	0.1
– Vulvovaginal dryness	3	0.4	0	0.0
Dental and gingival conditions	19	2.5	15	1.9
Body temperature conditions	17	2.2	16	2.1

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High level group term – Preferred term[1]	Empagliflozin N=765		Glimepiride N=780	
	N	%	N	%
Metabolic, nutritional and blood gas investigations	16	2.1	35	4.5
Renal disorders (excl nephropathies)	16	2.1	7	0.9
– Renal cyst	8	1.0	2	0.3
– Renal impairment	4	0.5	4	0.5
– Hydronephrosis	3	0.4	1	0.1
– Renal failure	3	0.4	0	0.0
Skin appendage conditions	16	2.1	18	2.3

[1] preferred terms shown for those events occurring in >2 empagliflozin subjects from high level group terms with notably higher incidence in empagliflozin compared to glimepiride
NEC = not elsewhere classified
Source: Reviewer generated using JMP v11.1.1 based on the submitted AE.xpt and DM.xpt files for study 1245.28

6.3.2 Laboratory Findings

The findings with regard to laboratory tests for these supplements were generally consistent with what was seen during the review of the empagliflozin NDA. Detailed discussion of the findings for study 1245.49 and study 1275.1 can be found in the review by Dr. Lungu and in my review of the Empa/Lina FCDP. Selected findings from study 1245.28 will be discussed here.

Consistent with the previous observations, treatment with empagliflozin resulted in increases in mean hematocrit, decreases in serum bicarbonate, and increases in cholesterol (Table 24). Findings for categorical shifts of hematocrit and cholesterol were consistent with these observations (Table 25), as were findings for Applicant defined "possible clinically significant abnormalities" (Table 26).

Table 24: Mean changes in selected laboratory parameters at 104 weeks for study 1245.28

	N	Mean at baseline (SD)	Mean last value (SD)	Change from baseline (SD)
Hematocrit (%)				
Empagliflozin	740	42.8 (4.8)	47.1 (5.4)	4.3 (4.4)
Glimepiride	740	42.6 (5.2)	43.2 (0.6)	0 (2.8)
Serum bicarbonate (mEq/L)				
Empagliflozin	737	24.4 (2.9)	23.2 (2.8)	-1.2 (3.0)
Glimepiride	757	24.2 (2.9)	23.3 (2.8)	-0.8 (2.9)
Total cholesterol (mg/dL)				
Empagliflozin	712	162.9 (57.4)	177.3 (60.3)	14.4 (49.6)
Glimepiride	712	160.5 (53.9)	166.1 (58.3)	5.6 (49.3)
LDL cholesterol				
Empagliflozin	711	72.0 (26.0)	77.1 (27.21)	5.1 (21.4)
Glimepiride	711	71.6 (25.2)	73.0(26.6)	1.38 (21.6)

SD = standard deviation; LDL = low density lipoprotein
Source: Adapted from Table 15.3.3.2: 1 from the 1004 week study report for study 1245.28

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Table 25: Categorical shifts in selected laboratory parameters at 104 weeks for study 1245.28

		Last value on treatment		
Baseline	**Total at baseline**	**< LLRR N (%)**	**In RR N (%)**	**> ULRR N (%)**
Hematocrit				
Empagliflozin				
– < LLRR	39	7 (17.9)	32 (82.1)	0
– In RR	691	6 (0.9)	622 (90.0)	63 (9.1)
– > ULRR	10	0	4 (40.0)	6 (60.0)
Glimepiride				
– < LLRR	49	19 (38.8)	29 (59.2)	1 (2.0)
– In RR	692	30 (4.3)	648 (93.6)	14 (2.0)
– > ULRR	12	0	9 (75.0)	3 (25.0)
Total cholesterol				
Empagliflozin				
– < LLRR	84	39 (46.4)	44 (52.4)	1 (1.2)
– In RR	462	22 (4.8)	331 (71.6)	109 (23.6)
– > ULRR	166	2 (1.2)	44 (26.5)	120 (72.3)
Glimepiride				
– < LLRR	83	49 (59.0)	31 (37.3)	3 (3.6)
– In RR	477	30 (6.3)	370 (77.6)	77 (16.1)
– > ULRR	156	3 (1.9)	57 (36.5)	96 (61.5)
LDL cholesterol				
Empagliflozin				
– < LLRR	0	0	0	0
– In RR	615	0	539 (87.6)	76 (12.4)
– > ULRR	96	0	33 (34.4)	63 (65.6)
Glimepiride				
– < LLRR	0	0	0	0
– In RR	620	0	569 (91.8)	51 (8.2)
– > ULRR	96	0	46 (47.9)	50 (52.1)

LLRR = lower limit of reference range; RR = reference range; ULRR = upper limit of reference range
Source: Adapted from Table 15.3.3.2: 2 of the 104 week study report for study 1245.28

Table 26: Incidence of possible clinically significant abnormalities for selected laboratory parameters at 104 weeks in study 1245.28

	N	**PCSA Low N (%)**	**PCSA High N (%)**
Hematocrit[1]			
– Empagliflozin	733	6 (0.8)	12 (1.6)
– Glimepiride	749	17 (2.3)	7 (0.9)
Serum bicarbonate[2]			
– Empagliflozin	730	29 (4.0)	16 (2.2)
– Glimepiride	745	19 (2.6)	12 (1.6)

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	N	PCSA Low N (%)	PCSA High N (%)
Total cholesterol[3]			
– Empagliflozin	704	--	62 (8.8)
– Glimepiride	719	--	49 (6.8)

[1] for hematocrit, criteria were: low = less than 32%, high = greater than 55%; [2] for serum bicarbonate, criteria were: low = less than 18 mEq/L, high = greater than 32 mEq/L; [3] for total cholesterol, only high criteria were defined (greater than 6.5 mmol/L)
PCSA Low = possible clinically significant low abnormality; PCSA High = possible clinically significant high abnormality
Source: Adapted from Table 15.3.3.2: 4 of the 104 week study report for study 1245.28

Though there appears to be an association between empagliflozin use and lower serum bicarbonate, this did not translate into an increase in clinical acidosis events. However, anion gap acidosis has been identified as a concern in the postmarketing setting and is a tracked safety issue. This topic is currently being further evaluated with the assistance of the Office of Surveillance and Epidemiology.

6.3.3 Vital Signs

Blood pressure was evaluated as a secondary efficacy endpoint. For discussion of blood pressure findings, see section 5.1.5. Heart rate was also assessed throughout the study. There were small changes from baseline to week 104 (mean change from baseline with empagliflozin = -1.36 beats per minute; mean change from baseline with glimepiride = +0.59 beats per minute). It is not clear that this change is clinically meaningful.

6.4 Other Safety Explorations

6.4.1 Dose Dependency for Adverse Events

From the original review of empagliflozin, it was noted that dose dependency for adverse events was observed for some events and in some sub-groups. Older subjects and subjects with renal impairment were noted to have an apparent dose dependent risk for genitourinary infections, volume depletion/hypotension, and renal failure.

Discussion of dose dependency for adverse events for study 1245.49 and study 1275.1 are found in Dr. Lungu's review and in my review of the Empa-Lina FCDP, respectively. There was no exploration for dose dependency in study 1245.28 as only one dose of empagliflozin was studied.

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6.4.2 Time Dependency for Adverse Events

A suggestion for early changes in renal function was observed in the original NDA review for empagliflozin. Genital infections also appeared to accumulate at an increased rate compared to placebo.

Discussion of time dependency for adverse events for study 1245.49 and study 1275.1 are found in Dr. Lungu's review and in my review of the Empa-Lina FCDP, respectively. For study 1245.28, no new findings for time dependency were identified.

6.4.3 Drug-Demographic Interactions

In the original empagliflozin review, it was noted that older subjects appeared to be at greater risk for certain type of adverse events (i.e., renal failure, genitourinary infections, volume depletion).

Discussion of demographic interactions for safety in study 1245.49 and study 1275.1 are found in Dr. Lungu's review and in my review of the Empa-Lina FCDP, respectively. .No new findings for demographic interactions were identified in review of the updated study 1245.28.

6.5 Additional Safety Evaluations

6.5.1 Human Carcinogenicity

See section 6.2.5.8 for discussion malignancy events in study 1245.28. Also see my review of the Empa-Lina FCDP (NDA-206073) and Dr. Lungu's primary review of Supplement-2 for additional discussion of malignancy events in study 1275.1 and 1245.49, respectively.

6.5.2 Human Reproduction and Pregnancy Data

No subjects reported pregnancy while receiving empagliflozin therapy in study 1245.28.

6.5.3 Pediatrics and Assessment of Effects on Growth

No information on use in pediatrics or on effects on growth is included in any of these submissions.

7 Postmarket Experience

In the most recently submitted periodic adverse event report (NDA-204629, SD-170, February 13, 2015) events of diarrhea, nausea, fungal infection, and urinary tract infection were reported

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by > 10 subjects. None of these events was considered to be a serious event. I do not think additional action is needed for these events at this time. Of note, there were two serious events of diabetic ketoacidosis.

Acidosis has been reported in the post-marketing setting with the SGLT2 inhibitor class. No clear imbalance in acid-base disorders was seen in the data submitted to support these efficacy supplements, but it remains an issue of concern and is a tracked safety issue.

8 Appendices

8.1 Labeling Recommendations

(b) (4)

For study 1245.49, (b) (4) I would favor presentation of the 18 week data for glycemic endpoints.

I am uncertain how relevant the results of the factorial study (i.e., study 1275.1) are for the empagliflozin label as the therapeutic regimen studied in this study was simultaneous initiation of empagliflozin and linagliptin. I do not agree that this study informs the use of empagliflozin as the therapeutic regimen studied is not relevant to the use of empagliflozin, but is more informative for the approved empagliflozin/linagliptin fixed combination drug product. However, the sponsor has cited recently approved labeling which includes description of studies with this design to supporting their position that inclusion of this study in the empagliflozin label is appropriate. While I do not favor including this study in the label, I find it difficult to argue against including it in the label given recent precedence. However, I would limit the presentation to text only.

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Labeling negotiations are ongoing at the time of completion of this review. Additional changes may be recommended.

8.2 Advisory Committee Meeting

Not applicable. No advisory committee meeting was held to discuss these efficacy supplements.

8.3 Financial Disclosure Review Templates

Clinical Investigator Financial Disclosure
Review Template – Supplement 1

Application Number: NDA-204629
Submission Date(s): August 29, 2014
Applicant: Boehringer-Ingelheim
Product: Empagliflozin
Reviewer: William H. Chong
Date of Review: December 18, 2014
Covered Clinical Study (Name and/or Number): Study 1245.28: "A phase 3 randomized, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104 weeks extension period in subjects with type 2 diabetes mellitus and insufficient glycemic control despite metformin treatment"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 704		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		

Reference ID: 3784605

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 118		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The financial disclosure information included as part of this supplement does not raise any concerns for potential bias. The majority of investigators (584 of 704) are certified as having no financial arrangements whereby the value of compensation could affect the outcome of the study. Though there are quite a few investigators without certified disclosures, the majority of these are sub-investigators. The reported reason for nearly all of the primary investigators without certified financial disclosures was either no enrolled subjects or the site did not actually initiate participation in the study. There are two primary investigators who did not have certified financial disclosure information due to incomplete financial disclosure questionnaires. Given the design (randomized, double-blind) and size (multi-center, multi-national) of the study, this is unlikely to introduce any bias. There are two investigators with reportable financial disclosures. One investigator's spouse works for a competing company, and the other investigator received cumulative monetary payments in excess of $25,000 for participation in educational programs and advisory boards. Again, the design and size of the study make it unlikely that there is any bias as a result of two investigators with reportable financial disclosures.

Clinical Investigator Financial Disclosure
Review Template – Supplement 3

Application Number: NDA-204629
Submission Date(s): September 3, 2014
Applicant: Boehringer-Ingelheim
Product: Empagliflozin
Reviewer: William H. Chong
Date of Review: December 18, 2014
Covered Clinical Study (Name and/or Number): Study 1275.1: "A phase 3 randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg fixed combination drug product tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated subjects with type 2 diabetes mellitus with insufficient glycemic control"

Reference ID: 3784605

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 965		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 47		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The financial disclosure information included as part of this supplement does not raise any concerns for potential bias. The majority of investigators (918 of 965) are certified as having no financial arrangements whereby the value of compensation could affect the outcome of the study. Though there are 47 investigators without certified disclosures, the reported reasons were either no subject enrollment, no participation, or the study was not initiated at the study site. Given the design (randomized, double-blind) and size (multi-center, multi-national) of the study and the absence of data from these investigators, this is unlikely to introduce any bias.

Reference ID: 3784605

8.4 Preferred terms included in custom MedDRA queries

Table 27: Preferred terms included in Applicant defined custom MedDRA query for urinary tract infection

Acute focal bacterial nephritis	HIV associated nephropathy	Urethral carbuncle
Adenoviral hemorrhagic cystitis	Kidney infection	Urethral papilloma
Asymptomatic bacteriuria	Nephritis	Urethral stricture post infection
Bacterial pyelonephritis	Perinephric abscess	Urethritis
Bacteriuria	Perinephritis	Urethritis chlamydial
Bacteriuria in pregnancy	Polyomavirus−associated nephropathy	Urethritis gonococcal
Bladder candidiasis	Pyelocystitis	Urethritis trichomonal
Candiduria	Pyelonephritis	Urethritis ureaplasmal
Cystitis	Pyelonephritis acute	Urinary bladder abscess
Cystitis bacterial	Pyelonephritis chronic	Urinary tract abscess
Cystitis escherichia	Pyelonephritis fungal	Urinary tract infection
Cystitis gonococcal	Pyelonephritis mycoplasmal	Urinary tract infection bacterial
Cystitis hemorrhagic	Pyelonephritis viral	Urinary tract infection enterococcal
Cystitis helminthic	Pyonephrosis	Urinary tract infection fungal
Cystitis klebsiella	Renal abscess	Urinary tract infection neonatal
Cystitis pseudomonal	Renal cyst infection	Urinary tract infection psuedomonal
Cystitis viral	Renal syphilis	Urinary tract infection staphylococcal
Cytomegalovirus urinary tract infection	Renal tuberculosis	Urinary tract infection viral
Emphysematous cystitis	Streptococcal urinary tract infection	Urogenital infection bacterial
Emphysematous pyelonephritis	Tuberculosis bladder	Urogenital infection fungal
Escherichia urinary tract infection	Tuberculosis of genitourinary system	Urogenital trichomoniasis
Fungal cystitis	Tuberculosis ureter	Urosepsis
Genitourinary chlamydia infection	Ureter abscess	Viral hemorrhagic cystitis
Genitourinary tract gonococcal infection	Ureteritis	
Genitourinary tract infection	Urethral abscess	

Source: Adapted from Listing 2.8 of the Appendix of the study report for Study 1245.28

Table 28: Preferred terms included in Applicant defined custom MedDRA query for genital infection

Bacterial prostatitis	Genitourinary tract infection	Salpingo−oophoritis
Balanitis	Hydrocele male infected	Scrotal abscess
Balanitis candida	Intrauterine infection	Scrotal gangrene
Balanoposthitis	Myometritis	Scrotal infection
Balanoposthitis infective	Oophoritis	Seminal vesicular infection
Bartholin’s abscess	Orchitis	Seminal vesiculitis
Bartholinitis	Ovarian abscess	Spermatic cord funiculitis
Candida cervicitis	Ovarian bacterial infection	Testicular abscess

Reference ID: 3784605

Cellulitis of male external genital organ	Ovarian infection	Toxic shock syndrome staphylococcal
Cervicitis	Parametric abscess	Toxic shock syndrome streptococcal
Cervicitis cystic	Parametritis	Urogenital infection bacterial
Cervicitis streptococcal	Pelvic abscess	Urogenital infection fungal
Clitoris abscess	Pelvic infection	Uterine abscess
Cytolytic vaginosis	Pelvic inflammatory disease	Uterine infection
Endometritis	Pelvic inflammatory disease mycoplasmal	Vaginal abscess
Epididymal infection	Pelvic sepsis	Vaginal cellulitis
Epididymitis	Penile abscess	Vaginal infection
Erosive balanitis	Penile infection	Vaginitis bacterial
Escherichia vaginitis	Perineal abscess	Vaginitis gardnerella
Fallopian tube abscess	Perineal infection	Vaginitis viral
Gangrenous balanitis	Posthitis	Vulval abscess
Genital abscess	Prostate infection	Vulval cellulitis
Genital candidiasis	Prostatic abscess	Vulvitis
Genital herpes zoster	Prostatitis	Vulvovaginal candidiasis
Genital infection	Prostatitis Escherichia coli	Vulvovaginal human papilloma virus infection
Genital infection bacterial	Prostatovesiculitis	Vulvovaginal mycotic infection
Genital infection female	Pyometra	Vulvovaginitis
Genital infection fungal	Pyospermia	Vulvovaginitis streptococcal
Genital infection male	Rectovaginal septum abscess	
Genital infection viral	Salpingitis	

Source: Adapted from Listing 2.8 of the Appendix of the study report for Study 1245.28

Reference ID: 3784605

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

/s/

WILLIAM H CHONG
06/26/2015

JEAN-MARC P GUETTIER
06/26/2015
I concur. Dr. Chong's review is the Divisional summary for this application.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s001

<u>OTHER REVIEW(S)</u>

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 204629/S-001, S-002, S-003

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Jardiance (empagliflozin) tablets

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Receipt Dates: August 29 (S-001), September 3 (S-002), and September 3, 2014 (S-003)

Goal Dates: June 29 (S-001), September 3 (S-002), and September 3, 2015 (S-003)

1. Regulatory History and Applicant's Main Proposals

Empagliflozin is a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2) and was developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Original IND 102145 was opened on April 10, 2008, to study empagliflozin as a treatment for type 2 diabetes. The End-of-Phase 2 meeting was held on January 21, 2010, and the Pre-NDA meeting was held on January 18, 2012. The new drug application for empagliflozin, NDA 204629, was submitted on March 5, 2013. The agency issued a Complete Response for the NDA on March 4, 2014, and a class 1 resubmission of the NDA was submitted on June 3, 2014. NDA 204629 for empagliflozin, proprietary name Jardiance, was approved on August 1, 2014.

S-001, a prior approval efficacy supplement (SE-8) submitted on August 29, 2014, proposes to update the Jardiance labeling with data from Study 1245.28, a randomized, double-blind active-controlled study comparing empagliflozin to glimepiride in patients with type 2 diabetes and insufficient glycemic control despite metformin treatment.

S-002, a prior approval efficacy supplement (SE-8) submitted on September 3, 2014, proposes to update the Jardiance labeling with data from Study 1245.49, a phase III, randomized, double-blind, placebo-controlled safety and efficacy study of empagliflozin (10 mg and 25 mg administered orally once daily) in patients with type 2 diabetes mellitus and insufficient glycemic control on MDI insulin regimen alone or with metformin.

S-003, a prior approval efficacy supplement (SE-8) submitted on September 3, 2014, proposes to update the Jardiance labeling with data from Study 1275.1, a randomized, double-blind, active-controlled study to evaluate the efficacy and safety of Jardiance (10 mg or 25 mg) in combination with linagliptin (5 mg) as an add-on to metformin therapy compared to the individual components.

Reference ID: 3784457

On June 12, 2015, the sponsor amended the supplements in order to combine the proposed changes from all three supplements into a single proposed draft labeling. The Prescribing Information of the combined draft labeling is reviewed below.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Reference ID: 3784457

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

Reference ID: 3784457

Selected Requirements of Prescribing Information

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Reference ID: 3784457

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Reference ID: 3784457

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Reference ID: 3784457

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 3784457

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

Reference ID: 3784457

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "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."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Reference ID: 3784457

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Reference ID: 3784457

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 [text]
  2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 [text]
  5.2 [text]
6 ADVERSE REACTIONS
  6.1 [text]
  6.2 [text]
7 DRUG INTERACTIONS
  7.1 [text]
  7.2 [text]
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Labor and Delivery
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
  9.1 Controlled Substance
  9.2 Abuse
  9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
  12.4 Microbiology
  12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
  14.1 [text]
  14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 3784457

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/s/

MICHAEL G WHITE
06/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # NDA 204629 SUPPL # S-001, S-002, S-003 HFD # 510

Trade Name Jardiance

Generic Name empagliflozin

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known June 26, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

S-001- Study 1245.28: A phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104-week

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extension period in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment

S-002 - Study 1245.49: A phase III, randomized, double-blind, placebo-controlled, parallel group safety and efficacy study of BI 10773 (10 mg and 25 mg administered orally once daily) during 52 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control on MDI insulin regimen alone or with metformin

S-003 - Study 1275.1: A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin-treated patients with type 2 diabetes mellitus with insufficient glycaemic control

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

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(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 204629 Jardiance (empagliflozin) tablets

NDA# 206073 Glyxambi (empagliflozin and linagliptin) tablets

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

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IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

S-001- Study 1245.28: A phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment

S-002 - Study 1245.49: A phase III, randomized, double-blind, placebo-controlled, parallel group safety and efficacy study of BI 10773 (10 mg and 25 mg administered orally once daily) during 52 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control on MDI insulin regimen alone or with metformin

S-003 - Study 1275.1: A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin

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5 mg) for 52 weeks in treatment naïve and metformin-treated patients with type 2 diabetes mellitus with insufficient glycaemic control

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒
*SEE NOTE BELOW

Investigation #2 YES ☐ NO ☒
*SEE NOTE BELOW

Investigation #3 YES ☒ NO ☐

Note: Study 1245.28 and Study 1245.49 were submitted to NDA 206111, empagliflozin and metformin HCl tablets. This NDA would have been approved, but we were not able to reach agreement regarding labeling. A complete response was issued on June 4, 2015.

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study 1275.1was submitted to NDA 206073, which was approved on January 30, 2015.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

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Investigation #2 YES ☐ NO ☒

Investigation #3 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

S-001- Study 1245.28: A phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment

S-002 - Study 1245.49: A phase III, randomized, double-blind, placebo-controlled, parallel group safety and efficacy study of BI 10773 (10 mg and 25 mg administered orally once daily) during 52 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control on MDI insulin regimen alone or with metformin

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 102145 YES ☒ ! NO ☐
! Explain:

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Investigation #2 ! !

IND # 102145 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 ! !

YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

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Name of person completing form: Michael G. White, Ph.D.
Title: Regulatory Project Manager
Date: 6/23/2015

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MICHAEL G WHITE
06/26/2015

JEAN-MARC P GUETTIER
06/26/2015