The format of this leaflet was defined by MoH and its content checked and approved by MoH in February 2017 and updated according to MoH guidelines in December 2017

Jardiance

PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

Jardiance 10 mg film-coated tablets
Jardiance 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Jardiance 10 mg contains 10 mg empagliflozin.
Each film-coated tablet of Jardiance 25 mg contains 25 mg empagliflozin.

3 PHARMACEUTICAL FORM

Film-coated tablet.

For more information on pharmaceutical form see sections 6 & 18 “DOSAGE FORM“ & “ HOW SUPPLIED/STORAGE AND HANDLING”.

4 INDICATIONS AND USAGE

JARDIANCE is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Limitations of Use

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

5 DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

Monotherapy and add-on combination

The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. In patients tolerating empagliflozin 10 mg once daily, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg. *[see Clinical Studies (16)]*.

When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

In patients with volume depletion, correcting this condition prior to initiation of JARDIANCE is recommended *[see Warnings and Precautions (8.1), Use in Specific Populations (11.5)]*.

5.2 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 (8.1, 8.3) and Use in Specific Populations (11.6)]*.

6 DOSAGE FORMS AND STRENGTHS

JARDIANCE tablets are available as:

- 10 mg 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.
- 25 mg pale yellow, oval, biconvex, film-coated tablets debossed with "S 25" on one side and the Boehringer Ingelheim company symbol on the other side.

7 CONTRAINDICATIONS

- History of serious hypersensitivity reaction to empagliflozin or any of the excipients in JARDIANCE [*see Warnings and Precautions (8.7)*].
- Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations (11.6)]*.

8 WARNINGS AND PRECAUTIONS

8.1 Hypotension

JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE *[see Adverse Reactions (9.1)]* 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 (11.5)]*.

8.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1

and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including JARDIANCE. Fatal cases of ketoacidosis have been reported in patients taking JARDIANCE. JARDIANCE is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (4)]*.

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

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

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

8.3 Acute Kidney Injury and Impairment in Renal Function

JARDIANCE causes intravascular volume contraction *[see Warnings and Precautions (8.1)]* and can cause renal impairment *[see Adverse Reactions (9.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including JARDIANCE; some reports involved patients younger than 65 years of age.

Before initiating JARDIANCE, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing JARDIANCE in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE promptly and institute treatment.

JARDIANCE increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating JARDIANCE *[see Adverse Reactions (9.1)]*. Renal function should be evaluated prior to initiation of JARDIANCE and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60

mL/min/1.73 m^2. Use of JARDIANCE is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 [see Dosage and Administration (5.2), Contraindications (7) and Use in Specific Populations (11.6)].

8.4 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including JARDIANCE. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (9)]*.

8.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions (9.1)]*. 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.

8.6 Genital Mycotic Infections

JARDIANCE increases the risk for genital mycotic infections *[see Adverse Reactions (9.1)]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

8.7 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with JARDIANCE. If a hypersensitivity reaction occurs, discontinue JARDIANCE; treat promptly per standard of care, and monitor until signs and symptoms resolve. JARDIANCE is contraindicated in patients with a previous serious hypersensitivity reaction to empagliflozin or any of the excipients in JARDIANCE [*see Contraindications (7)*].

8.8 Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with JARDIANCE *[see Adverse Reactions (9.1)]*. Monitor and treat as appropriate.

8.9 Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative footcare.

9 ADVERSE REACTIONS

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

- Hypotension *[see Warnings and Precautions (8.1)]*

- Ketoacidosis [see Warnings and Precautions (8.2)]
- Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions (8.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (8.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (8.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (8.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (8.7)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (8.8)]*

9.1 Clinical Trials Experience

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

Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg

The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (16)]*.

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

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

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

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

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

[b]Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), JARDIANCE 10 mg (N=443), JARDIANCE 25 mg (N=420).

[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia

[d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

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

Volume Depletion

JARDIANCE causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg respectively. JARDIANCE may increase the risk of hypotension in patients at risk for volume contraction *[see Warnings and Precautions (8.1) and Use in Specific Populations (11.5, 11.6)]*.

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.

Acute Impairment in Renal Function

Treatment with JARDIANCE was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had

larger mean changes *[see Warnings and Precautions (5.3)* and *Use in Specific Populations (11.5, 11.6)]*.

In a long-term cardiovascular outcome trial, the acute impairment in renal function was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes play a role in the renal function changes observed with empagliflozin.

Table 2 Changes from Baseline in Serum Creatinine and eGFR[a] 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[b]		
		Placebo		**JARDIANCE 25 mg**
Baseline Mean	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
Post-treatment change[c]	N	98	--	103
	Creatinine (mg/dL)	0.03	--	0.02
	eGFR (mL/min/1.73 m^2)	0.16	--	1.48

[a]Observed cases on treatment.
[b]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2
[c]Approximately 3 weeks after end of treatment.

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 (8.5)]*.

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

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 +/- Metformin (18 weeks[d])	**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[d])	**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]Treated set (patients who had received at least one dose of study drug
[d]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections

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

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

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

Urinary Tract Infections

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

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Warnings and Precautions (8.4) and Use in Specific Populations (11.5)]*.

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 (8.8)]*. 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.

9.2 Postmarketing Experience

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

- Ketoacidosis [*see Warnings and Precautions (8.2)*]

- Urosepsis and pyelonephritis [*see Warnings and Precautions (8.4)*]
- Angioedema [*see Warnings and Precautions (8.7*)]
- Skin reactions (e.g., rash, urticaria)

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

10 DRUG INTERACTIONS

10.1 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 (8.1)]*.

10.2 Insulin or Insulin Secretagogues

Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia *[see Warnings and Precautions (8.5)]*.

10.3 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.

10.4 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.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

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

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

In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. Empagliflozin was not

teratogenic 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 when administered during organogenesis [see Data].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13 week drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48- times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154 times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues 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).

11.2 Lactation

Risk Summary

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

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise women that use of JARDIANCE is not recommended while breastfeeding.

Data

Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 -5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

11.4 Pediatric Use

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

11.5 Geriatric Use

No JARDIANCE dosage change is recommended based on age *[see Dosage and Administration (5)]*. In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, 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 glycemic efficacy in elderly patients with renal impairment *[see Use in Specific Populations (11.6)]*. 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 (8.1) and Adverse Reactions (9.1)]*.

11.6 Renal Impairment

The efficacy and safety of JARDIANCE were evaluated in a study of patients with mild and moderate renal impairment *[see Clinical Studies (16.1)]*. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 m^2 and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (8.3)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

In a large cardiovascular outcomes study, there were 1819 patients with eGFR below 60 mL/min/1.73 m^2. The cardiovascular death findings in this subgroup were consistent with the overall findings *[see Clinical Studies (16.2)]*.

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 (5.2), Contraindications (7) and Warnings and Precautions (8.1, 8.3)]*.

11.7 Hepatic Impairment

JARDIANCE may be used in patients with hepatic impairment *[see Clinical Pharmacology (14.3)]*.

12 OVERDOSAGE

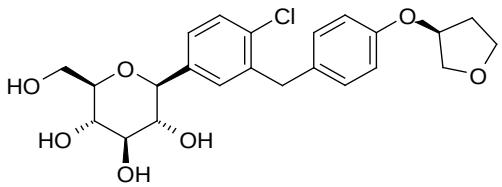
In the event of an overdose with JARDIANCE, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal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

13 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.

14 CLINICAL PHARMACOLOGY

14.1 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.

14.2 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 (16)]*.

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.

14.3 Pharmacokinetics

Absorption

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

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

Distribution

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

Metabolism

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination

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

Specific Populations

Renal Impairment

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

Hepatic Impairment

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%,

and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Effects of Age, Body Mass Index, Gender, and Race

Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin *[see Use in Specific Populations (11.5)]*.

Pediatric

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

Drug Interactions

In vitro Assessment of Drug Interactions

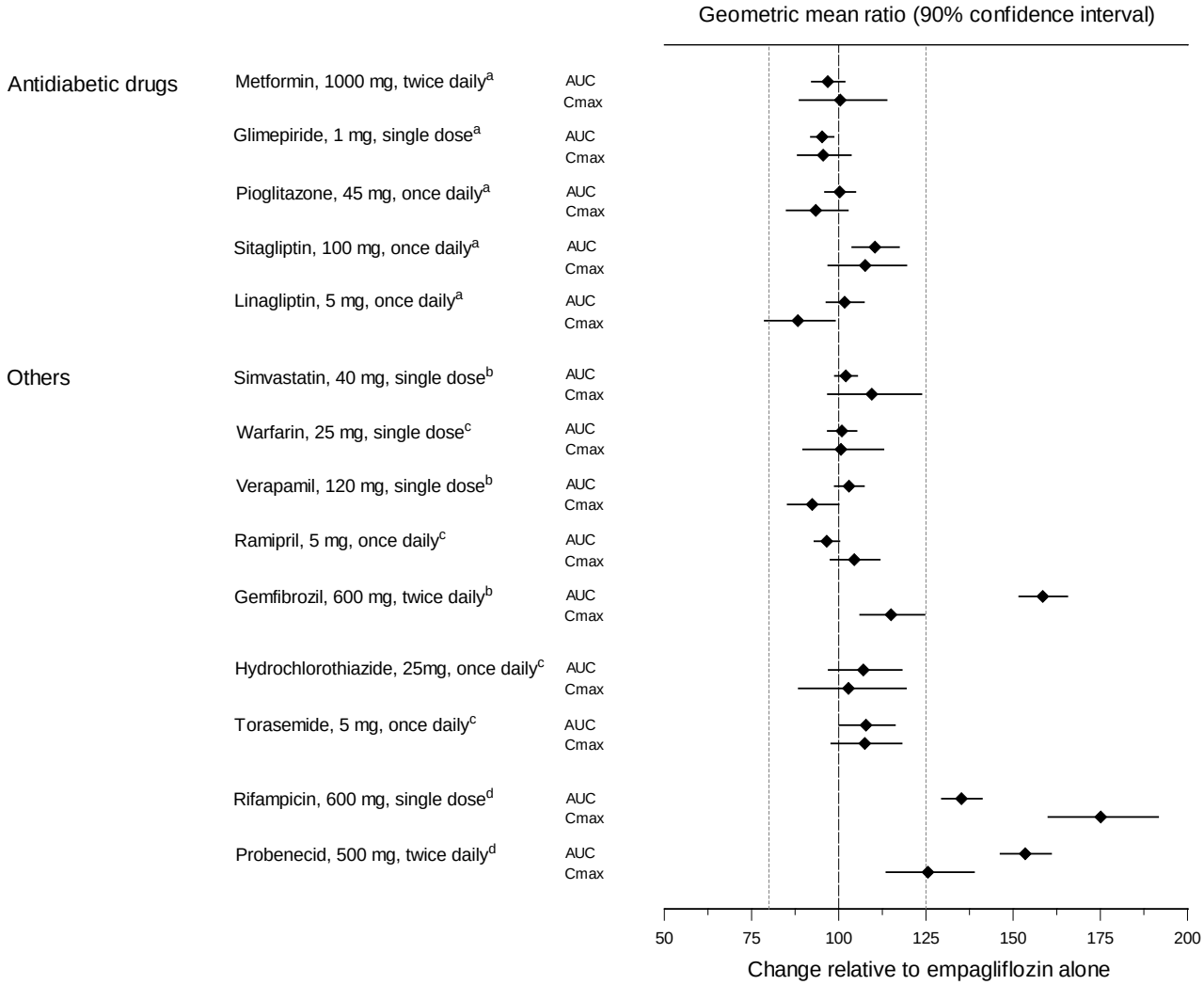
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1,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

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

No dose adjustment of JARDIANCE is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes (see Figure 1). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max}

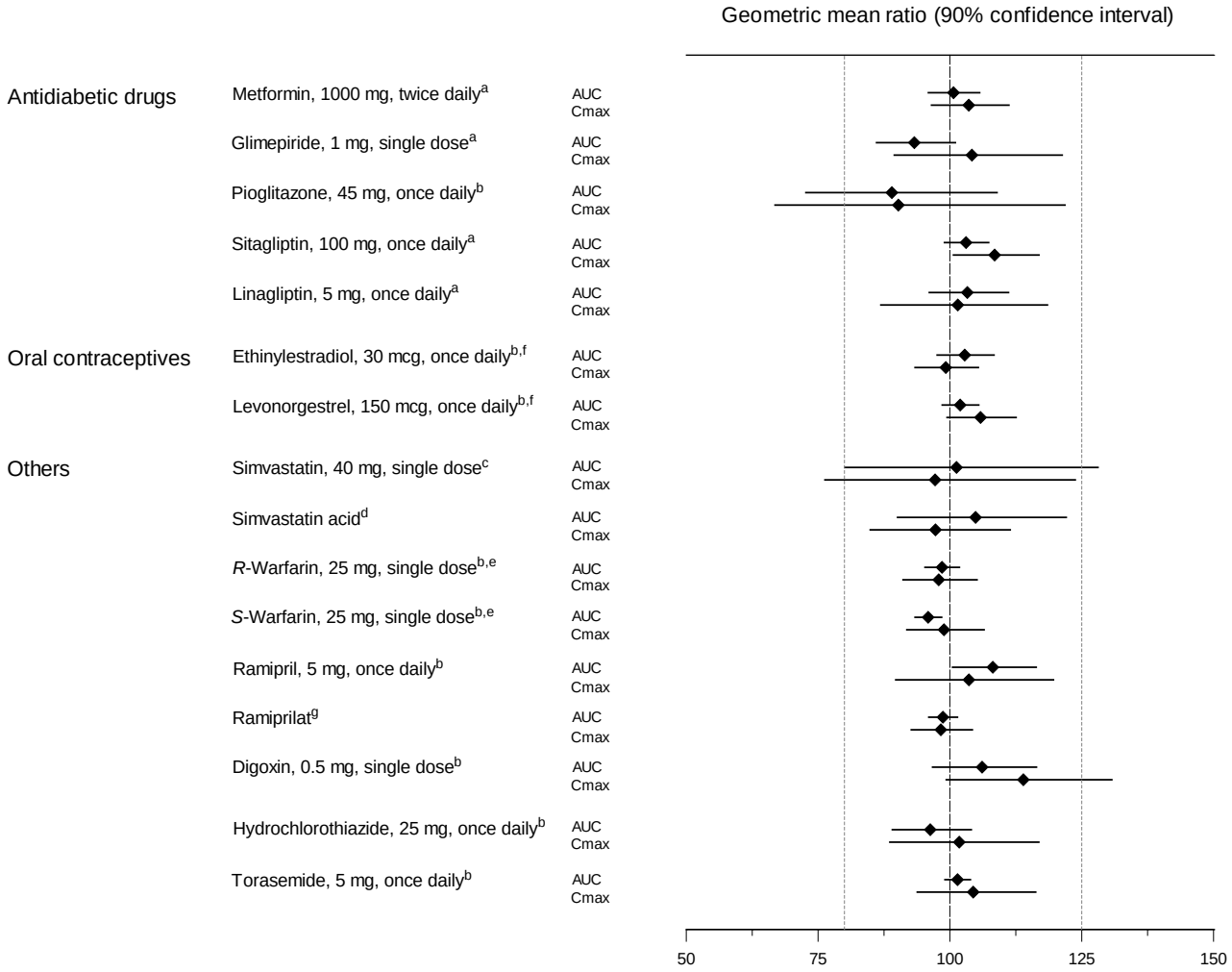


Ratios [reference lines indicate 100% (80% - 125%)]

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

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, 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

15 NONCLINICAL TOXICOLOGY

15.1 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. These tumors

may be associated with a metabolic pathway predominantly present in the male mouse kidney.

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).

16 CLINICAL STUDIES

16.1 Glycemic control

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.

Monotherapy

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

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

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

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

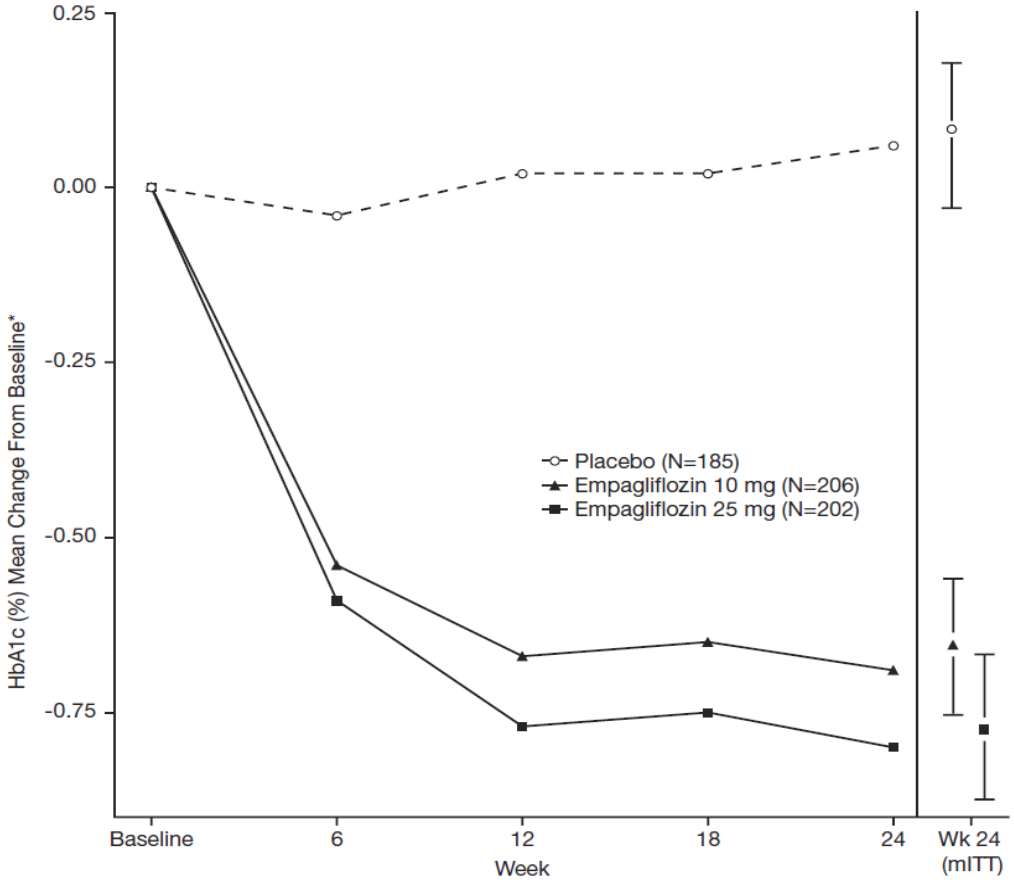
	JARDIANCE 10 mg N=224	**JARDIANCE 25 mg N=224**	**Placebo N=228**
HbA1c (%)[a]			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-0.7[b] (-0.9, -0.6)	-0.9[b] (-1.0, -0.7)	--
Patients [n (%)] achieving HbA1c <7%	72 (35%)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

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.4%, 9.4%, and 30.7% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

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

[c]FPG (mg/dL); for JARDIANCE 10 mg, n=223, for JARDIANCE 25 mg, n=223, and for placebo, n=226

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



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

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

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.

Initial Combination Therapy with Metformin

A total of 1364 patients with type 2 diabetes participated in a double-blind, randomized, active-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin as initial therapy compared to the corresponding individual components.

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 10.5% were randomized to one of 8 active-treatment arms: JARDIANCE 10 mg or 25 mg; metformin 1000 mg, or 2000 mg; JARDIANCE 10 mg in combination with 1000 mg or 2000 mg metformin; or JARDIANCE 25 mg in combination with 1000 mg or 2000 mg metformin.

At Week 24, initial therapy of JARDIANCE in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 6).

Table 6 Glycemic Parameters at 24 Weeks in a Study Comparing JARDIANCE and Metformin to the Individual Components as Initial Therapy

	JARDIANCE 10 mg + Metformin 1000 mg[a] N=161	**JARDIANCE 10 mg + Metformin 2000 mg[a] N=167**	**JARDIANCE 25 mg + Metformin 1000 mg[a] N=165**	**JARDIANCE 25 mg + Metformin 2000 mg[a] N=169**	**JARDIANCE 10 mg N=169**	**JARDIANCE 25 mg N=163**	**Metformin 1000 mg[a] N=167**	**Metfo 2000 N=1**
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.
Comparison vs JARDIANCE (adjusted mean) (95% CI)	-0.6[b] (-0.9,-0.4)	-0.7[b] (-1.0,-0.5)	-0.6[c] (-0.8,-0.3)	-0.7[c] (-1.0,-0.5)	--	--	--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.8[b] (-1.0, -0.6)	-0.3[b] (-0.6,-0.1)	-0.8[c] (-1.0,-0.5)	-0.3[c] (-0.6,-0.1)	--	--	--	--

[a]Metformin total daily dose, administered in two equally divided doses per day.

[b]p-value ≤0.0062 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

[c]p-value ≤0.0056 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

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 7).

Table 7 Results at Week 24 from a Placebo-Controlled Study for JARDIANCE in Combination with Metformin and Sulfonylurea

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

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 17.8%, 16.7%, and 25.3% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

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

[c]FPG (mg/dL); for JARDIANCE 10 mg, n=225, for JARDIANCE 25 mg, n=215, for placebo, n=224

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

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

At Week 24, JARDIANCE 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin. Treatment with JARDIANCE/linagliptin 25 mg/5 mg or JARDIANCE/linagliptin 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference in body weight compared to JARDIANCE alone.

Active-Controlled Study versus Glimepiride in Combination with Metformin

The efficacy of JARDIANCE was evaluated in a double-blind, glimepiride-controlled, study in 1545 patients with type 2 diabetes with insufficient glycemic control despite metformin therapy.

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

At Week 52, JARDIANCE 25 mg and glimepiride lowered HbA1c and FPG (see Table 8, 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 Israel is 8 mg per day.

Table 8 Results at Week 52 from an Active-Controlled Study Comparing JARDIANCE to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

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

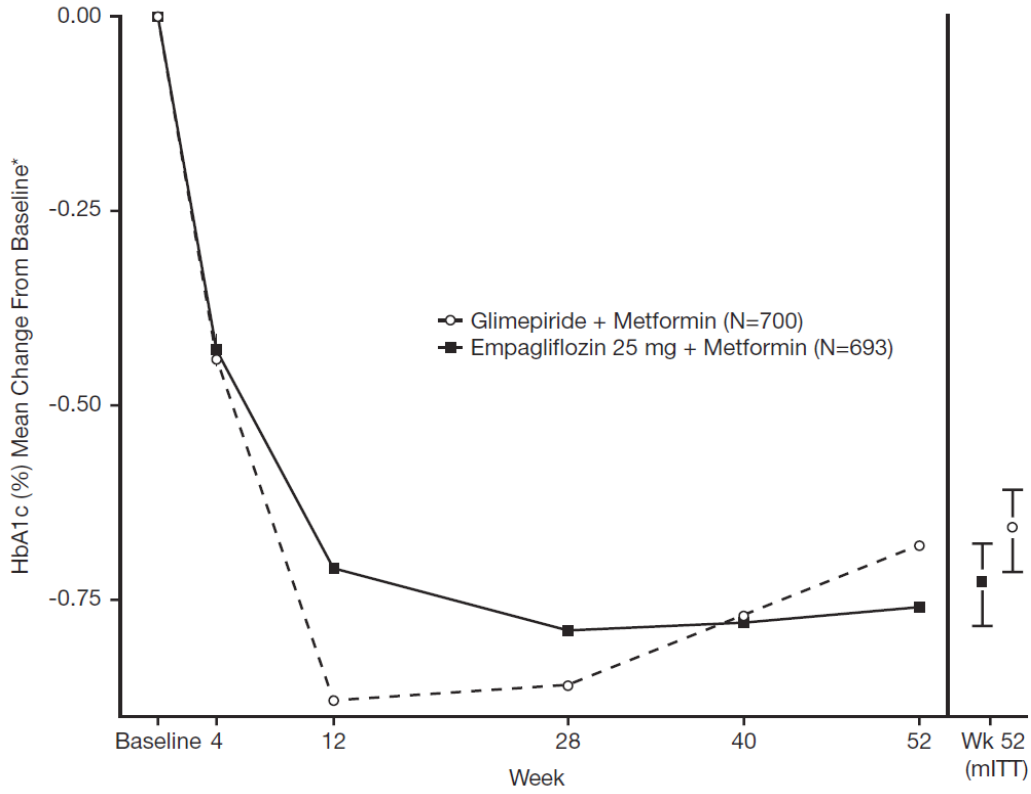
[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to JARDIANCE 25 mg and glimepiride, respectively.

[b]Non-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)

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

[d]FPG (mg/dL); for JARDIANCE 25 mg, n=764, for placebo, n=779

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



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

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

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

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

Add-On Combination Therapy with Pioglitazone with or without Metformin

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

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

Treatment with JARDIANCE 10 mg or 25 mg daily resulted in statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 9)

Table 9 Results of Placebo-Controlled Study for JARDIANCE in Combination Therapy with Pioglitazone

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

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 10.9%, 8.3%, and 20.6% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication. Body weight and FPG: same

model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

[c]FPG (mg/dL); for JARDIANCE 10 mg, n=163

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

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

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

Table 10 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	-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)	--

(adjusted mean) (95% CI)						

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

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

[c]p-value=0.0049

[d]p-value=0.0052

[e]p-value=0.0463

Add-on Combination with MDI Insulin with or without Metformin

A total of 563 patients with type 2 diabetes inadequately controlled on multiple daily injections (MDI) of insulin (total daily dose >60 IU), alone or in combination with metformin, participated in a double-blind, placebo-controlled study to evaluate the efficacy of JARDIANCE as add-on therapy to MDI insulin over 18 weeks.

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

JARDIANCE 10 mg or 25 mg daily used in combination with MDI insulin (with or without metformin) provided statistically significant reductions in HbA1c compared to placebo after 18 weeks of treatment (see Table 11).

Table 11 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.

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

The glucose lowering efficacy of JARDIANCE 25 mg decreased with decreasing level of renal function in the mild to moderate range. Least square mean Hb1Ac changes at 24 weeks were -0.6%, -0.5%, and -0.2% for those with a baseline eGFR of 60 to less than 90 mL/min/1.73 m^2, 45 to less than 60 mL/min/1.73 m^2, and 30 to less than 45 mL/min/1.73 m^2, respectively *[see Dosage and Administration (5) and Use in Specific Populations (11.6)]*. 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 12 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 (5.2) and Use in Specific Populations (11.6)]*.

16.2 Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The effect of JARDIANCE on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease was evaluated in the EMPA-REG OUTCOME study, a multicenter, multi-national, randomized, double-blind parallel group trial. The study compared the risk of experiencing a major adverse cardiovascular event (MACE) between JARDIANCE and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease.
Coadministered antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 7020 patients were treated (JARDIANCE 10 mg = 2345; JARDIANCE 25 mg = 2342; placebo = 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had had diabetes for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators respectively and the mean eGFR was 74 mL/min/1.73 m^2. At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), and sulfonylurea (43%).

All patients had established atherosclerotic cardiovascular disease at baseline including one (82%) or more (18%) of the following; a documented history of coronary artery disease (76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg doses would be combined. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non- inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

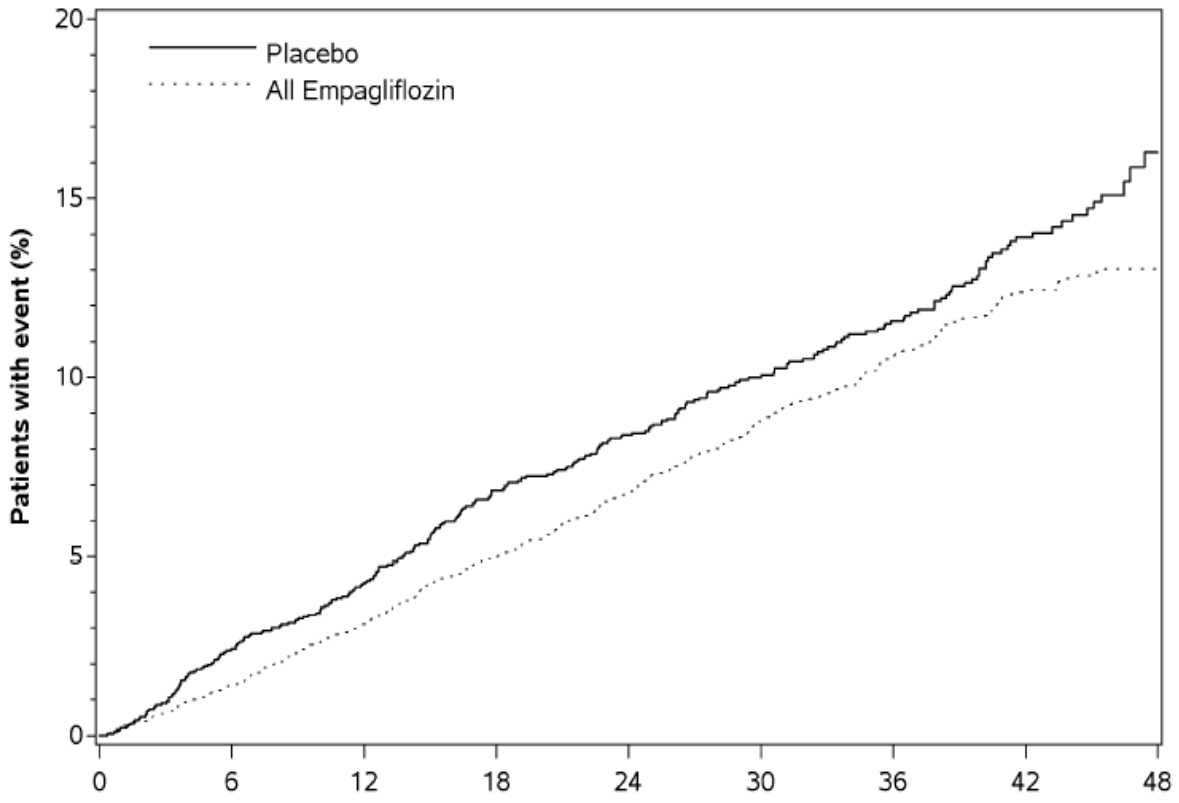
JARDIANCE significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects randomized to empagliflozin (HR: 0.62; 95% CI 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 13 and Figure 5 and 6). Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

Table 13 Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2333	JARDIANCE N=4687	Hazard ratio vs placebo (95% CI)
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
Cardiovascular death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

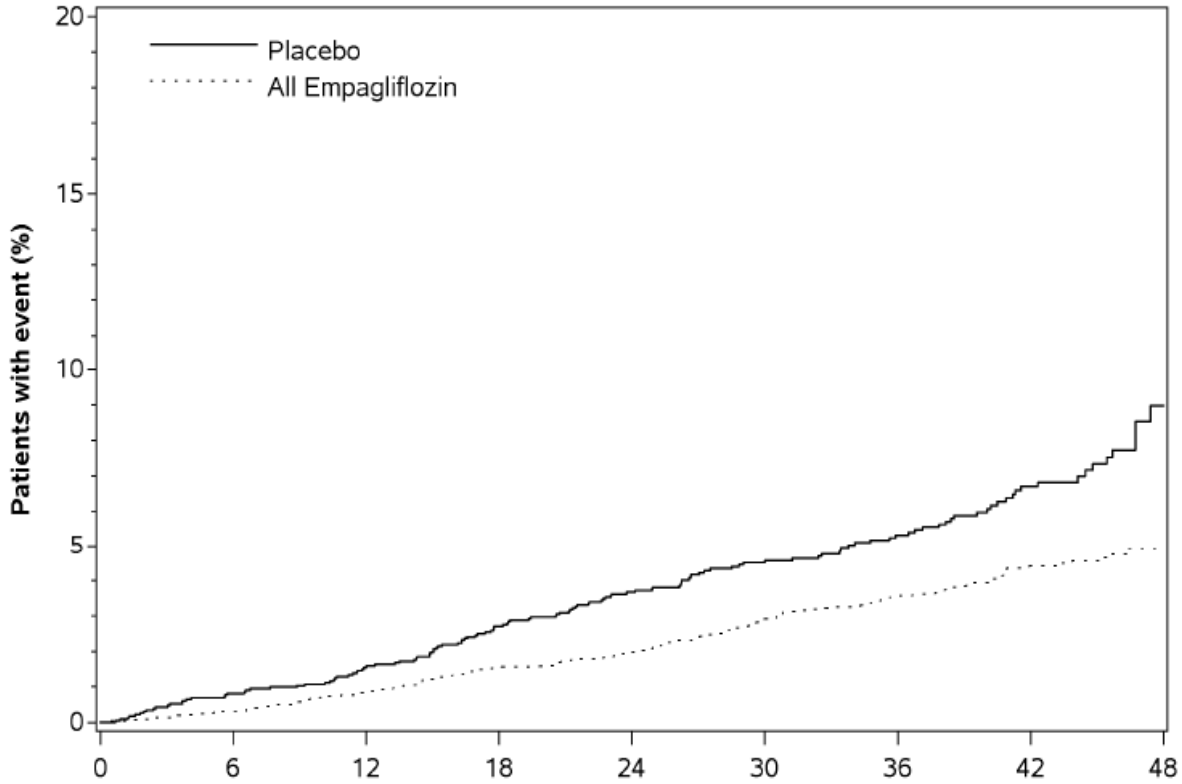
[a]Treated set (patients who had received at least one dose of study drug)
[b]p–value for superiority (2–sided) 0.04
[c]Total number of events

Figure 5 Estimated Cumulative Incidence of First MACE



Subjects at risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
All Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

Figure 6 Estimated Cumulative Incidence of Cardiovascular Death



Subjects at risk									
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177
All Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414

The efficacy of JARDIANCE on cardiovascular death was generally consistent across major demographic and disease subgroups.

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as cardiovascular deaths. The non-cardiovascular deaths were only a small proportion of deaths, and were balanced between the treatment groups (2.1% in patients treated with JARDIANCE, and 2.4% of patients treated with placebo).

18 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.
Cartons containing 3 blister cards of 10 tablets each (3 x 10).

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.
Cartons containing 3 blister cards of 10 tablets each (3 x 10).

Storage
Store below 30°C.

19 MANUFACTURER
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger St. 173, 55216
Ingelheim/Rhein
Germany

20 MARKETING AUTHORISATION HOLDER
Boehringer Ingelheim Israel Ltd.
Medinat Ha-Yehudim 89 St.
P.O. Box 4124
Herzliya Pituach 4676672

21 MARKETING AUTHORISATION NUMBER(S)
Jardiance 10 mg 154-22-34202-00
Jardiance 25 mg 154-23-34203-00

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in February 2017.
Updated: December 2017

Reference: FDA approved USPI December 2017