JARDIANCE DUO

PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (8.1)]*.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see Dosage and Administration (5.2), Contraindications (7), Warnings and Precautions (8.1), Drug Interactions (10), and Use in Specific Populations (11.6, 11.7)]*.

If metformin-associated lactic acidosis is suspected, immediately discontinue JARDIANCE DUO and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (8.1)]*.

1 NAME OF THE MEDICINAL PRODUCT

Jardiance duo	5mg/850mg
Jardiance duo	5mg/1000mg
Jardiance duo	12.5mg/850mg
Jardiance duo	12.5mg/1000mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Jardiance duo 5 mg/850 mg film-coated tablets
Each tablet contains 5 mg empagliflozin and 850 mg metformin hydrochloride.
Jardiance duo 5 mg/1,000 mg film-coated tablets
Each tablet contains 5 mg empagliflozin and 1,000 mg metformin hydrochloride.
Jardiance duo 12.5 mg/850 mg film-coated tablets
Each tablet contains 12.5 mg empagliflozin and 850 mg metformin hydrochloride.
Jardiance duo 12.5 mg/1,000 mg film-coated tablets
Each tablet contains 12.5 mg empagliflozin and 1,000 mg metformin hydrochloride.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

4 INDICATIONS AND USAGE

Jardiance duo is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control

- in patients inadequately controlled on their maximally tolerated dose of metformin alone.
- in patients inadequately controlled with metformin in combination with other glucose-lowering medicinal products, including insulin.
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

5 DOSAGE AND ADMINISTRATION

5.1 Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90 ml/min)

- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating JARDIANCE DUO *[see Warnings and Precautions (8.2)]*.
- Individualize the starting dose of JARDIANCE DUO based on the patient’s current regimen:
  - In patients on metformin hydrochloride, switch to JARDIANCE DUO containing empagliflozin 5 mg with a similar total daily dose of metformin hydrochloride;
  - In patients already treated with empagliflozin and metformin hydrochloride, switch to JARDIANCE DUO containing the same total daily doses of each component.
- Take JARDIANCE DUO twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin *[see Dosage Forms and Strengths (6)]*.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000 mg and empagliflozin 25 mg *[see Dosage and Administration (5.2)]*.

5.2 Recommended Dosage in Patients with Renal Impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis *[see Warnings and Precautions (8.1)]* should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.
If no adequate strength of Jardiance Duo is available, individual monocomponents should be used instead of the fixed dose combination.

GFR ml/min	metformin	empagliflozin
60-89	Maximum daily dose is 2550 mg Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 25 mg.
45-59	Maximum daily dose is 2000 mg The starting dose is at most half of the maximum dose.	No dose adjustment is required.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Empagliflozin is contraindicated.
<30	Metformin is contraindicated	Empagliflozin is contraindicated.

5.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue JARDIANCE DUO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JARDIANCE DUO if renal function is stable *[see Warnings and Precautions (8.1)]*.

6 DOSAGE FORMS AND STRENGTHS

JARDIANCE DUO Tablets:

Empagliflozin Strength	Metformin HCl Strength	Color/Shape	Tablet Markings
5 mg	850 mg	yellowish white, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and “S5” debossed on one side; the other side is debossed with “850”
5 mg	1,000 mg	brownish yellow, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and “S5” debossed on one side; the other side is debossed with “1000”
12.5 mg	850 mg	pinkish white, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and “S12” debossed on one side; the other side is debossed with “850”
12.5 mg	1,000 mg	dark brownish purple, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and “S12” debossed on one side; the other side is debossed with “1000”

7 CONTRAINDICATIONS

JARDIANCE DUO is contraindicated in patients with:

- moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2), end stage renal disease, or dialysis *[see Warnings and Precautions (8.1,) and Use in Specific Populations (11.6)].*
- acute or chronic metabolic acidosis, including diabetic ketoacidosis. *[see Warnings and Precautions (8.1)].*
- hypersensitivity to empagliflozin, metformin, or any of the excipients *[see Description (14)]* in JARDIANCE DUO, reactions such as angioedema have occurred *[see Warnings and Precautions (8.8)]*.

8 WARNINGS AND PRECAUTIONS

General:
JARDIANCE DUO is not indicated for patients with type 1 diabetes.

8.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of JARDIANCE DUO. In JARDIANCE DUO-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue JARDIANCE DUO and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration (5.2)and Clinical Pharmacology (12.3)]*.

- Before initiating JARDIANCE DUO, obtain an estimated glomerular filtration rate (eGFR).
- JARDIANCE DUO is contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2 *[see Contraindications (7)]*..
- Obtain an eGFR at least annually in all patients taking JARDIANCE DUO. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of JARDIANCE DUO with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation *[see Drug Interactions (10)]*. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients.
Assess renal function more frequently in elderly patients *[see Use in Specific Populations 11.5)]*.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop JARDIANCE DUO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart JARDIANCE DUO if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. JARDIANCE DUO should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue JARDIANCE DUO.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving JARDIANCE DUO.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of JARDIANCE DUO in patients with clinical or laboratory evidence of hepatic disease.

8.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. JARDIANCE DUO is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (4)]*.

Patients treated with JARDIANCE DUO 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 DUO may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE DUO 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 dosage reduction, acute febrile illness, reduced

caloric intake 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 DUO, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing JARDIANCE DUO for at least 3 days prior to surgery *[see Clinical Pharmacology (15.2, 15.3)]*.
Consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE DUO in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting JARDIANCE DUO.
Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue JARDIANCE DUO and seek medical attention immediately if signs and symptoms occur.

8.3 Volume Depletion
Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions (9.1)]*. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin . Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension.

Before initiating JARDIANCE DUO in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating JARDIANCE DUO. Monitor for signs and symptoms of volume depletion and renal function after initiating therapy.

8.4 Urosepsis and Pyelonephritis
There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving empagliflozin. Treatment with empagliflozin 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
Insulin and insulin secretagogues are known to cause hypoglycemia. In adult patients, the risk of hypoglycemia may be increased when JARDIANCE DUO is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions (9.1)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

8.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with JARDIANCE DUO presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected,

start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue JARDIANCE DUO, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

8.7 Genital Mycotic Infections

Empagliflozin 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.

8.8 Hypersensitivity Reactions

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

8.9 Vitamin B_{12} Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2- to 3-year intervals in patients on JARDIANCE DUO and manage any abnormalities *[see Adverse Reactions (9.1)]*.

8.10 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:

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (8.1)]*
- Ketoacidosis *[see Warnings and Precautions (8.2)]*
- Volume Depletion *[see Warnings and Precautions (8.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (8.4)]*
- Hypoglycemia *[see Warnings and Precautions (8.5)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) [see Warnings and Precautions (8.6)]
- Genital Mycotic Infections [see Warnings and Precautions (8.7)]
- Hypersensitivity Reactions *[see Warnings and Precautions (8.8)]*
- Vitamin B_{12} Deficiency *[see Warnings and Precautions (8.9)]*

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.

The safety of concomitantly administered empagliflozin (daily dosage 10 mg or 25 mg) and metformin HCl (mean daily dosage of approximately 1,800 mg) has been evaluated in 3,456 adult patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1,271 patients received a daily dosage of empagliflozin 10 mg, and 1,259 patients received a daily dosage of empagliflozin 25 mg. Discontinuation of therapy due to adverse events across treatment groups was 3.0%, 2.8%, and 2.9% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Adverse Reactions in a Clinical Trial with Empagliflozin (Add-On Combination Therapy with Metformin and Sulfonylurea) for Glycemic Control in Adults with Type 2 Diabetes Mellitus

In a 24-week placebo-controlled trial of empagliflozin 10 mg or 25 mg administered once daily added to metformin and sulfonylurea, adverse reactions reported in ≥5% of empagliflozin-treated patients and more commonly than in placebo-treated patients are presented in Table 1 (see also Table 4).

Table 1 Adverse Reactions Reported in ≥5% of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin added on to Metformin plus Sulfonylurea and Greater than with Placebo in a 24-week Placebo Controlled Clinical Trial

Adverse Reactions	Placebo (%) n=225	Empagliflozin 10 mg (%) n=224	Empagliflozin 25 mg (%) n=217
Hypoglycemia	9.8	15.6	12.9
Urinary tract infection	6.7	9.4	6.9
Nasopharyngitis	4.9	8.0	6.0

Empagliflozin

Clinical Trials in Adults with Type 2 Diabetes Mellitus

The data in Table 2 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with basal insulin in adult patients with type 2 diabetes mellitus. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (17)]*.

These data reflect exposure of 1,976 adult patients to empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), empagliflozin 10 mg (N=999), or empagliflozin 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 2 shows adverse reactions (excluding hypoglycemia) that were not present at baseline, occurred more commonly in empagliflozin treated patients than placebo treated patients, and occurred in greater than or equal to 2% of empagliflozin-treated patients.

Table 2 Adverse Reactions Reported in ≥2% of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Trials of Empagliflozin Monotherapy or Combination Therapy

Adverse Reactions	Placebo (%) N=995	Empagliflozin 10 mg (%) N=999	Empagliflozin 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), empagliflozin 10 mg (N=443), empagliflozin 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), empagliflozin 10 mg (N=556), empagliflozin 25 mg (N=557).

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

Volume Depletion

Empagliflozin 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 in adults, 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, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction *[see Use in Specific Populations (11.5, 11.6)]*.

Increased Urination

In the pool of five placebo-controlled clinical trials in adults, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see Table 2). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Hypoglycemia in Clinical Trials with Empagliflozin for Glycemic Control in Adults with Type 2 Diabetes Mellitus

The incidence of hypoglycemia in adults by trial is shown in Table 3. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea.

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**Empagliflozin 10 mg (n=224)**	**Empagliflozin 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)**	**Empagliflozin 10 mg + Metformin (n=217)**	**Empagliflozin 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)**	**Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)**	**Empagliflozin 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)**	**Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)**	**Empagliflozin 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)**	**Empagliflozin 10 mg (n=169)**	**Empagliflozin 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)**	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 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 dosage of trial drug)
[d]Insulin dosage could not be adjusted during the initial 18 week treatment period

Other Adverse Reactions in Clinical Trials with Empagliflozin for Glycemic Control in Adults with Type 2 Diabetes Mellitus

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 empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Discontinuation from trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 or 25 mg.

  Genital mycotic infections occurred more frequently in female than male patients (see Table 2).

  Phimosis occurred more frequently in male patients treated with empagliflozin 10 mg (less than 0.1%) and empagliflozin 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 empagliflozin compared to placebo (see Table 2). 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, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

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

Adverse Reactions with Clinical Trials of Metformin

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Laboratory Test Abnormalities in Clinical Trials of Empagliflozin or Metformin

Empagliflozin

- *Increases in Serum Creatinine and Decreases in eGFR:* Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a trial of adults with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.

- *Increase in Low-Density Lipoprotein Cholesterol (LDL-C):* Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in adults treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. 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 trials in adults, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 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, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Metformin

- Decrease in Vitamin B12: In metformin clinical trials of 29 week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.

9.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use. 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.

Empagliflozin
Gastrointestinal Disorders: Constipation
Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene) , urosepsis and pyelonephritis
Metabolism and Nutrition Disorders: Ketoacidosis
Renal and Urinary Disorders: Acute kidney injury
Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

Metformin HCl
Hepatobiliary Disorders: Cholestatic, hepatocellular, and mixed hepatocellular liver injury

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:https://sideeffects.health.gov.il

10 DRUG INTERACTIONS

See Table 4 for clinically relevant interactions with **JARDIANCE DUO**.

Table 4 Clinically Relevant Interactions with JARDIANCE DUO

Carbonic Anhydrase Inhibitors	
Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with JARDIANCE DUO may increase the risk of lactic acidosis.
Intervention	Consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)].
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving JARDIANCE DUO.
Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating JARDIANCE DUO, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating JARDIANCE DUO. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when JARDIANCE DUO is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of JARDIANCE DUO with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
Intervention	When such drugs are administered to a patient receiving JARDIANCE DUO, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving JARDIANCE DUO, the patient should be observed closely for hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.

Intervention	Monitor serum lithium concentration more frequently during JARDIANCE DUO initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. 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 from empagliflozin, JARDIANCE DUO is not recommended during the second and third trimesters of pregnancy.

The limited available data with JARDIANCE DUO or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, empagliflozin, a component of JARDIANCE DUO, resulted in adverse renal changes in rats when 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. No adverse developmental effects were observed when metformin was administered to pregnant rats or rabbits *(see Data)*.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown.

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, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from postmarketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Empagliflozin: 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).

Metformin HCl: Metformin HCl did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at doses up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2,000 mg, based on body surface area (mg/m^2) for rats and rabbits, respectively.

Empagliflozin and Metformin HCl: No adverse developmental effects were observed when empagliflozin and metformin HCl were coadministered to pregnant rats during the period of organogenesis at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2,000 mg dose.

11.2 Lactation

Risk Summary

There is limited information regarding the presence of JARDIANCE DUO or its components (empagliflozin or metformin) in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk *(see Data)*.

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 patients that use of JARDIANCE DUO is not recommended while breastfeeding.

Data
Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

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 to 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.

11.3 Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

11.4 Pediatric Use
Safety and effectiveness of JARDIANCE DUO in pediatric patients under 18 years of age have not been established.

11.5 Geriatric Use
Assess renal function more frequently in JARDIANCE DUO-treated geriatric patients because there is a greater risk of empagliflozin -associated intravascular volume contraction and symptomatic hypotension in geriatric patients and there is a greater risk of metformin-associated lactic acidosis in geriatric patients *[see Warnings and Precautions (8.1, 8.3)]*.
The recommended dosage for the metformin component of JARDIANCE DUO in geriatric patients should usually start at the lower end of the dosage range.

Empagliflozin
In empagliflozin type 2 diabetes mellitus trials, 2,721 empagliflozin -treated patients were 65 years of age and older and 491 patients were 75 years of age and older. In these trials, volume depletion-related adverse reactions occurred in 2.1%, 2.3%, and 4.4% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively; and urinary tract infections occurred in 10.5%, 15.7%, and 15.1% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively.

Metformin
Clinical studies of metformin did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

11.6 Renal Impairment
JARDIANCE DUO is contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2), end stage renal disease, or dialysis.

Empagliflozin
The glucose lowering benefit of empagliflozin 25 mg decreased in adult patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function *[see Warnings and Precautions (8.2)]*.

Metformin
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. *[see Warnings and Precautions (8.1)]*.

11.7 Hepatic Impairment
Use of metformin HCl in patients with hepatic impairment has been associated with some cases of lactic acidosis. JARDIANCE DUO is not recommended in patients with hepatic impairment *[see Warnings and Precautions (8.1)]*.

13 OVERDOSAGE
In the event of an overdose with JARDIANCE DUO, contact poison control center or a medical toxicologist for additional overdosage management recommendations.

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings and Precautions (8.1)]*. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

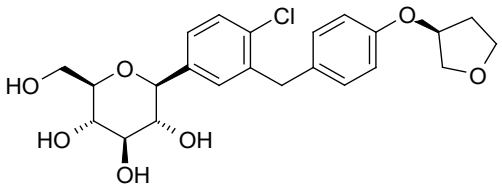
Removal of empagliflozin by hemodialysis has not been studied.

14 DESCRIPTION
JARDIANCE DUO tablets for oral use contain: empagliflozin and metformin HCl.

Empagliflozin
Empagliflozin is an inhibitor of the 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).

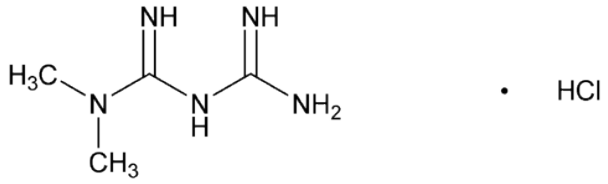
Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



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.

Metformin HCl
Metformin HCl (*N, N*-dimethylimidodicarbonimidic diamide HCl) is a biguanide.
Metformin HCl is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin HCl is freely soluble in water and is practically insoluble in acetone,

ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin HCl is 6.68. The structural formula is:



JARDIANCE DUO
JARDIANCE DUO tablets for oral administration are available in four dosage strengths containing:

- 5 mg empagliflozin and 850 mg metformin HCl
- 5 mg empagliflozin and 1,000 mg metformin HCl
- 12.5 mg empagliflozin and 850 mg metformin HCl
- 12.5 mg empagliflozin and 1,000 mg metformin HCl

Each film-coated tablet of JARDIANCE DUO contains the following inactive ingredients: copovidone, maize starch, magnesium stearate, silica colloidal anhydrous.
Film-coating: iron oxide black and iron oxide red (12.5 mg/850 mg, 12.5 mg/1,000 mg), or iron oxide yellow (5 mg/850 mg, 5 mg/1,000 mg), hypromellose 2910, titanium dioxide, talc, Macrogol 400.

15 CLINICAL PHARMACOLOGY

15.1 Mechanism of Action

JARDIANCE DUO
JARDIANCE DUO contains: empagliflozin, a SGLT2 inhibitor, and metformin, a biguanide.

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

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions such as lowering both pre-and afterload of the heart and downregulating sympathetic activity.

Metformin HCl
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) *[see Warnings and Precautions (8.5)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

15.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes mellitus, urinary glucose excretion increased immediately following a dose of empagliflozin 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 empagliflozin once daily *[see Clinical Studies (17)]*. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

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 empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

15.3 Pharmacokinetics

JARDIANCE DUO

Administration of 12.5 mg empagliflozin/1,000 mg metformin HCl under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in C_{max} for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and C_{max} decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant.

Empagliflozin

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes mellitus and no clinically relevant differences were noted between the two populations. The steady state mean plasma AUC and C_{max} were 1,870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4,740 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. Empagliflozin does not appear to have time-dependent pharmacokinetic characteristics. Following once-daily dosing, up to 22% accumulation, with respect toplasma AUC, was observed at steady-state.

Absorption

After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose.

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%.

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.

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.

Excretion: 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.

Metformin
Absorption
The absolute bioavailability of a metformin HCl 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower C_{max}, a 25% lower AUC, and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution
The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination
Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism: Intravenous single-dose studies in normal subjects demonstrate that metformin does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion: Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

Specific Populations

Effects of Age, Body Mass Index, Gender, and Race
Empagliflozin: Age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Metformin HCl: No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin HCl in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Patients with Hepatic Impairment
JARDIANCE DUO: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of JARDIANCE DUO in hepatically impaired patients have not been performed *[see Warnings and Precautions (8.1)]*.

Empagliflozin: In adult patients 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.

Metformin HCl: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Patients with Renal Impairment
JARDIANCE DUO: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of Jardiance Duo in renally impaired patients have not been performed.

Empagliflozin: In adult patients with type 2 diabetes mellitus 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 patients on dialysis due to kidney failure, 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 patients with moderate renal impairment and patients on dialysis due to kidney failure, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to patients 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.

Metformin: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased *[see Contraindications (7) and Warnings and Precautions (8.1)]*.

Geriatric
JARDIANCE DUO: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of JARDIANCE DUO in geriatric patients have not been performed *[see Warnings and Precautions (8.2) and Use in Specific Populations (11.5)]*.

Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis *[see Use in Specific Populations (11.5)]*.

Metformin HCl: Limited data from controlled pharmacokinetic studies of metformin HCl in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin or metformin after administration of JARDIANCE DUO in pediatric patients have not been performed.

Drug Interaction Studies

Pharmacokinetic drug interaction studies with JARDIANCE DUO have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin HCl.

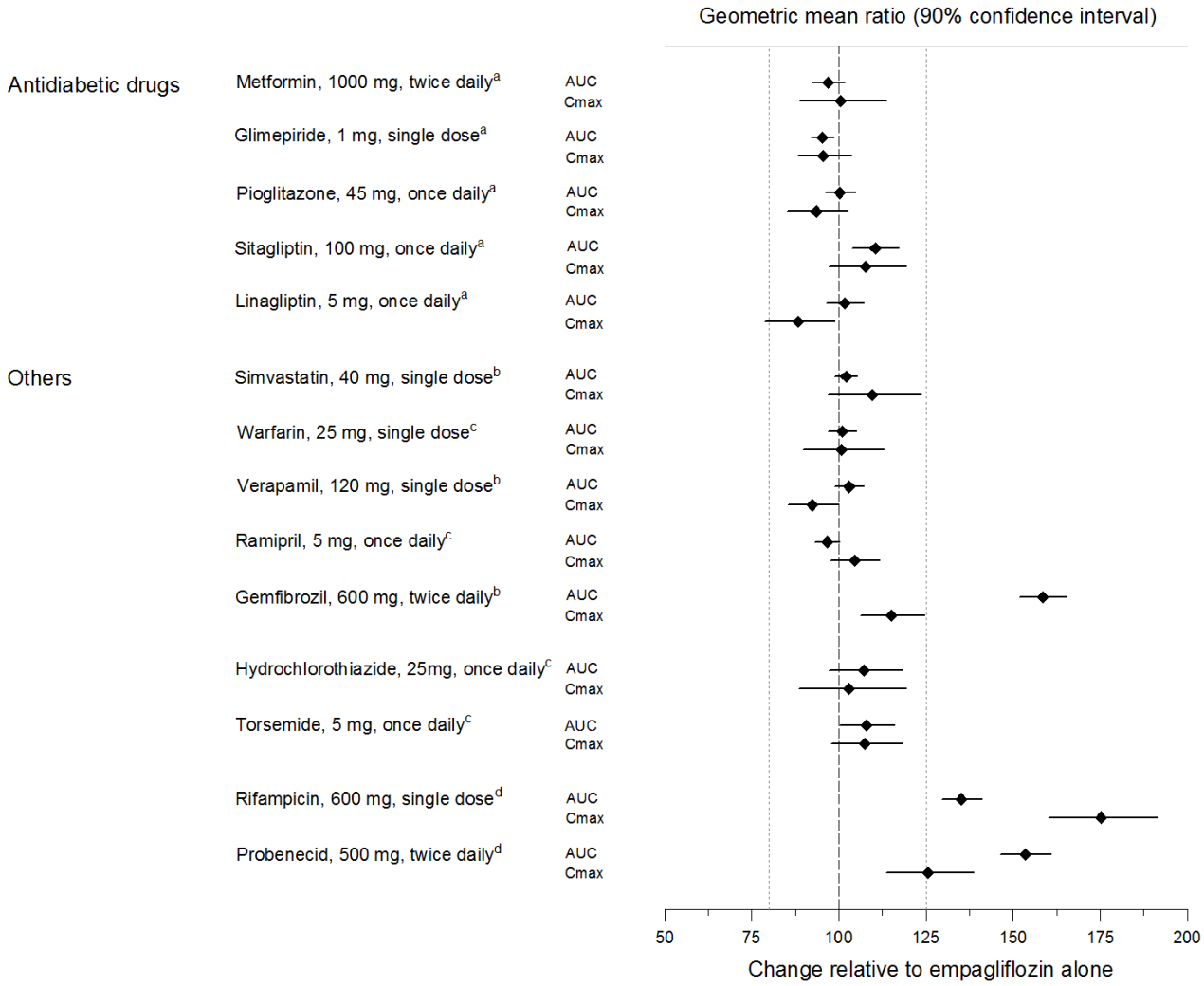
Empagliflozin

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: Empagliflozin pharmacokinetics were similar with and without coadministration of metformin HCl, 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 mellitus (see Figure 1). 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.

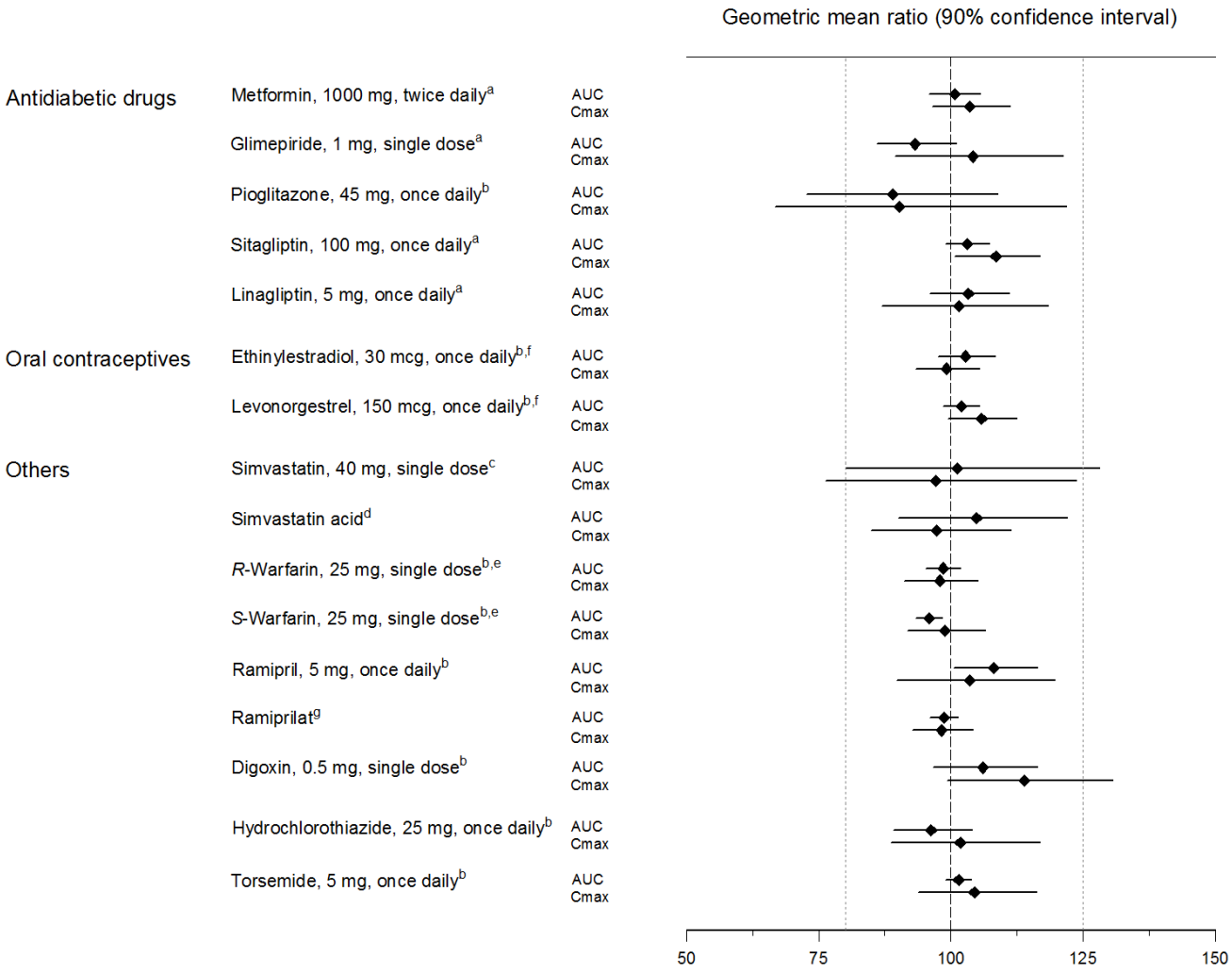
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[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

Metformin HCl

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC†	C_{max}
Glyburide	5 mg	850 mg	metformin	0.91‡	0.93‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination *[see Drug Interactions (10)]*.					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Drug Interactions (10)]*.					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF)
‡ Ratio of arithmetic means
**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC(0-12 hours)

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC†	C_{max}
Glyburide	5 mg	500 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF) unless otherwise noted
‡ Ratio of arithmetic means, p-value of difference <0.05
§ AUC(0-24 hours) reported
¶ Ratio of arithmetic means

16 NONCLINICAL TOXICOLOGY

16.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JARDIANCE DUO

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin and metformin HCl. General toxicity studies in rats up to 13 weeks were performed with the combined components. These studies indicated that no additive toxicity is caused by the combination of empagliflozin and metformin.

Empagliflozin
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 1,000 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 1,000 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.

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.
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).

Metformin HCl
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

17 CLINICAL STUDIES

17.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

In adult patients with type 2 diabetes mellitus, treatment with empagliflozin and metformin produced clinically and statistically significant improvements in HbA1c compared to placebo and metformin. Reductions in HbA1c were observed across subgroups including age, sex, race, and baseline BMI.

Empagliflozin Add-On Combination Therapy with Metformin in Adult Patients with Type 2 Diabetes Mellitus
A total of 637 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of empagliflozin in combination with metformin.

Patients with type 2 diabetes mellitus inadequately controlled on at least 1,500 mg of metformin HCl 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, empagliflozin 10 mg, or empagliflozin 25 mg.

At Week 24, treatment with empagliflozin 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 Trial for Empagliflozin used in Combination with Metformin

	Empagliflozin 10 mg N=217	**Empagliflozin 25 mg N=213**	**Placebo 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 trial (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 empagliflozin 10 mg, empagliflozin 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 empagliflozin 10 mg, n=216, for empagliflozin 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 empagliflozin 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for empagliflozin 25 mg.

Empagliflozin Initial Combination Therapy with Metformin
A total of 1,364 patients with type 2 diabetes mellitus participated in a double-blind, randomized, active-controlled trial to evaluate the efficacy of empagliflozin in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes mellitus 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: empagliflozin 10 mg or 25 mg; metformin HCl 1,000 mg, or 2,000 mg; empagliflozin 10 mg in combination with 1,000 mg or 2,000 mg metformin HCl; or empagliflozin 25 mg in combination with 1,000 mg or 2,000 mg metformin HCl.

At Week 24, initial therapy of empagliflozin in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 8).

Table 8 Glycemic Parameters at 24 Weeks in a Trial Comparing Empagliflozin and Metformin to the Individual Components as Initial Therapy

	Empagliflozin 10 mg + Metformin 1,000 mg[a] N=161	**Empagliflozin 10 mg + Metformin 2,000 mg[a] N=167**	**Empagliflozin 25 mg + Metformin 1,000 mg[a] N=165**	**Empagliflozin 25 mg + Metformin 2,000 mg[a] N=169**	**Empagliflozin 10 mg N=169**	**Empagliflozin 25 mg N=163**	**Metformin 1,000 mg[a] N=167**	**Metformin 2,000 mg[a] N=162**
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	-1.8
Comparison vs empagliflozin (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)	--	--	--	--
Patients [n (%)] achieving HbA1c <7%	96 (63%)	112 (70%)	91 (57%)	111 (68%)	69 (43%)	51 (32%)	63 (38%)	92 (58%)

[a]Metformin HCl 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).

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

Patients with inadequately controlled type 2 diabetes mellitus on at least 1,500 mg per day of metformin HCl 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, empagliflozin 10 mg, or empagliflozin 25 mg.

Treatment with empagliflozin 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 9).

Table 9 Results at Week 24 from a Placebo-Controlled Trial for Empagliflozin in Combination with Metformin and Sulfonylurea

	Empagliflozin 10 mg N=225	Empagliflozin 25 mg N=216	Placebo 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 trial (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 empagliflozin 10 mg, empagliflozin 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 empagliflozin 10 mg, n=225, for empagliflozin 25 mg, n=215, for placebo, n=224

Active-Controlled Trial vs Glimepiride in Combination with Metformin
The efficacy of empagliflozin was evaluated in a double-blind, glimepiride-controlled, trial in 1,545 patients with type 2 diabetes mellitus 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 empagliflozin 25 mg.

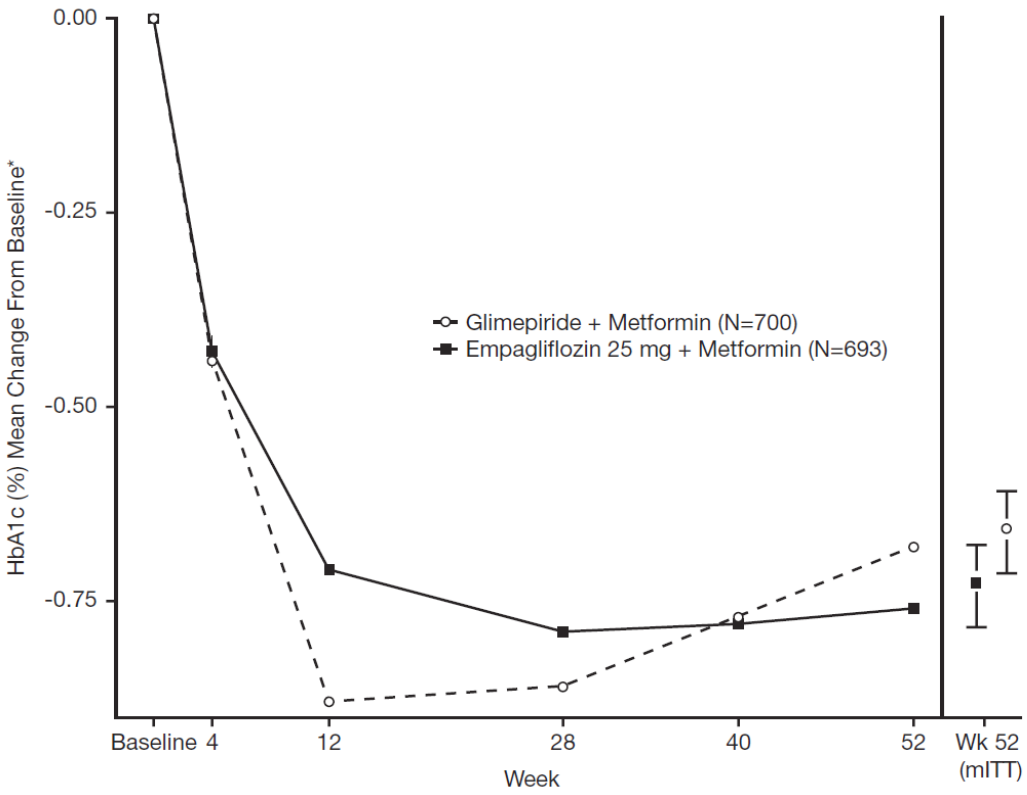
At Week 52, empagliflozin 25 mg and glimepiride lowered HbA1c and FPG (see Table 10, Figure 3). The difference in observed effect size between empagliflozin 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dosage of glimepiride was 2.7 mg and the maximal approved dosage in the United States is 8 mg per day.

Table 10 Results at Week 52 from an Active-Controlled Trial Comparing Empagliflozin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

	Empagliflozin 25 mg N=765	**Glimepiride 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 trial (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 empagliflozin 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 empagliflozin 25 mg, n=764, for glimepiride, n=779

Figure 3 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 empagliflozin 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 dosage of glimepiride was 2.7 mg and the maximal approved dosage 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 empagliflozin 25 mg and 12.9% for glimepiride.

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

17.2 Empagliflozin Cardiovascular Outcome Trial in Adult Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of JARDIANCE DUO on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease has

not been established. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease is presented below.

EMPA-REG OUTCOME was a multicenter, multinational, randomized, double-blind parallel group trial that compared the risk of experiencing a major adverse cardiovascular event (MACE) between empagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Concomitant antidiabetic medications were 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 7,020 patients were treated (empagliflozin 10 mg = 2,345; empagliflozin 25 mg = 2,342; placebo = 2,333) and followed for a median of 3.1 years. Approximately 72% of the trial population was White, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the trial 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 diabetes mellitus 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 non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg dosages 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.

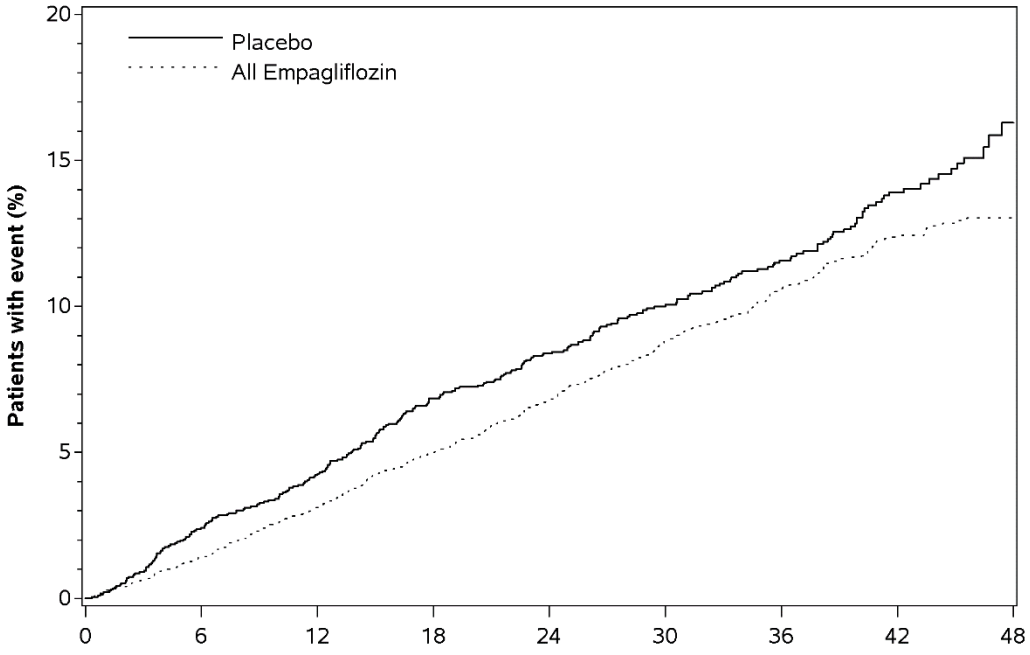
Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects 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 11 and Figures 4 and 5). Results for the 10 mg and 25 mg empagliflozin dosages were consistent with results for the combined dosage groups.

Table 11 Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2,333	**Empagliflozin N=4,687**	**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)

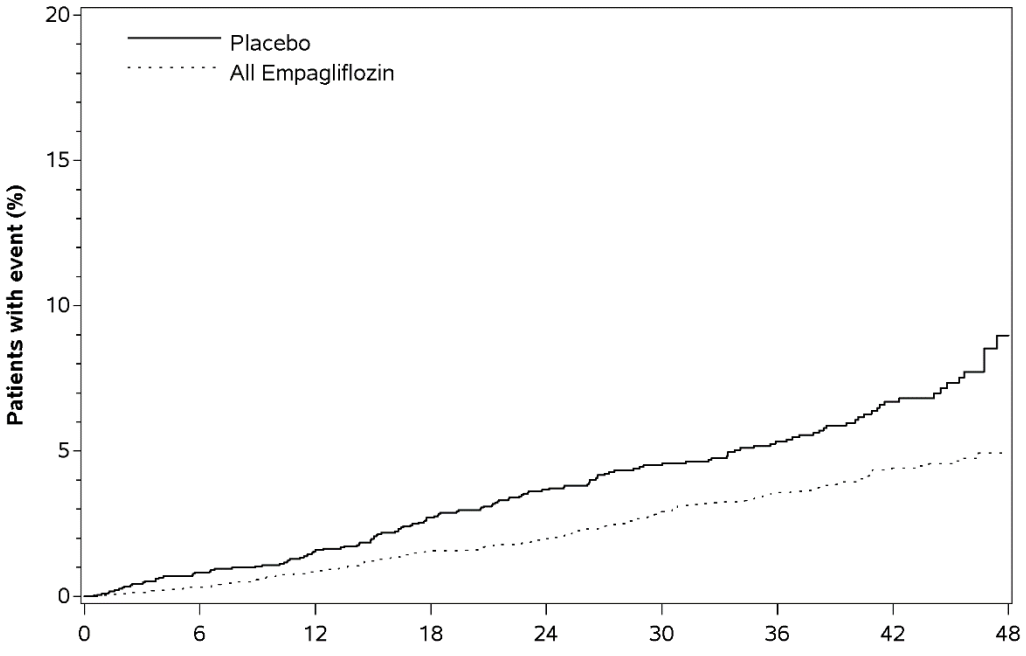
[a]Treated set (patients who had received at least one dose of trial drug)
[b]p−value for superiority (2−sided) 0.04
[c]Total number of events

Figure 4 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 5 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 empagliflozin 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 empagliflozin, and 2.4% of patients treated with placebo).

18 HOW SUPPLIED/STORAGE AND HANDLING

JARDIANCE DUO tablets are available as follows

Tablet Strength	Color/Shape	Tablet Markings	Package Size
5 mg Empagliflozin 850 mg Metformin HCl	yellowish white, oval, biconvex, film coated tablet	Boehringer Ingelheim company symbol and “S5” debossed on one side; the other side is debossed with “850”	Blister of 14, 60,180 Tablets
5 mg Empagliflozin 1,000 mg Metformin HCl	brownish yellow, oval, biconvex, film coated tablet	Boehringer Ingelheim company symbol and “S5” debossed on one side; the other side is debossed with “1000”	Blister of 14, 60,180 Tablets
12.5 mg Empagliflozin 850 mg Metformin HCl	pinkish white, oval, biconvex, film coated tablet	Boehringer Ingelheim company symbol and “S12” debossed on one side; the other side is debossed with “850”	Blister of 14, 60,180 Tablets
12.5 mg Empagliflozin 1,000 mg Metformin HCl	dark brownish purple, oval, biconvex, film coated tablet	Boehringer Ingelheim company symbol and “S12” debossed on one side; the other side is debossed with “1000”	Blister of 14, 60,180 Tablets

Storage
Store below 25°C.
The expiry date of the product is indicated on the packaging materials.

19. MANUFACTURER

Boehringer Ingelheim International GmbH
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

20. LICENSE HOLDER/ IMPORTER

Boehringer Ingelheim Israel LTD
Medinat Ha-Yehudim St. 89, POB 4124,
4676672 Herzliya Pituach
Israel

21. LICENSE NUMBER:

Jardiance Duo 5mg/850 mg:	155-26-34512
Jardiance Duo 5mg/1000 mg:	155-28-34533
Jardiance Duo 12.5mg/850 mg:	155-29-34534
Jardiance Duo 12.5mg/1000 mg:	155-27-34532

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