PRODUCT MONOGRAPH

Pr**JARDIANCE**®

empagliflozin tablets

10 mg and 25 mg

ATC Code: A10BK03
Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Boehringer Ingelheim (Canada) Ltd
5180 South Service Rd
Burlington, ON L7L 5H4

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TABLE OF CONTENTS

[Pr]JARDIANCE®

empagliflozin tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet / 10 mg, 25 mg	Lactose *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Monotherapy: JARDIANCE (empagliflozin) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: JARDIANCE is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control, when metformin used alone does not provide adequate glycemic control, in combination with:

- metformin,
- metformin and a sulfonylurea,
- pioglitazone (alone or with metformin),
- basal or prandial insulin (alone or with metformin),

when the existing therapy, along with diet and exercise, does not provide adequate glycemic control (see CLINICAL TRIALS).

Add-on combination in patients with established cardiovascular disease: JARDIANCE is indicated as an adjunct to diet, exercise and standard care therapy to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease who have inadequate glycemic control (see CLINICAL TRIALS).

Important Limitations of Use: Use of JARDIANCE with insulin mix (regular or analogue mix) has not been studied. Therefore, JARDIANCE should not be used with insulin mix (see CLINICAL TRIALS).

Geriatrics (≥65 years of age): JARDIANCE should be used with caution in geriatric patients. A greater increase in risk of adverse reactions was seen with JARDIANCE in the elderly, compared to younger patients, therefore, JARDIANCE should be used with caution in this population (see WARNINGS AND PRECAUTIONS, Special Populations, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age): JARDIANCE should not be used in pediatric patients. Safety and effectiveness of JARDIANCE have not been studied in patients under 18 years of age.

CONTRAINDICATIONS

JARDIANCE (empagliflozin) is contraindicated in:

- Patients with a history of hypersensitivity reaction to the active substance or to any of the excipients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with severe renal impairment (eGFR less than 30 mL/min/1.73m^2), end-stage renal disease and patients on dialysis.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Diabetic Ketoacidosis

- Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with JARDIANCE and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Some cases of DKA have been fatal. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see ADVERSE REACTIONS).

- Patients should be assessed for diabetic ketoacidosis immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur, regardless of blood glucose level, and JARDIANCE should be **discontinued immediately**.

- JARDIANCE should not be used for the treatment of DKA or in patients with a history of DKA.

- JARDIANCE is not indicated, and should not be used, in patients with type 1 diabetes.

General

JARDIANCE (empagliflozin) is not indicated for use in patients with type 1 diabetes and should not be used for the treatment of diabetic ketoacidosis.

Cardiovascular

Use in Patients at Risk for Volume Depletion, Hypotension and/or Electrolyte Imbalances:
JARDIANCE is not recommended for use in patients who are volume depleted.
Due to its mechanism of action, JARDIANCE causes diuresis that may be associated with decreases in blood pressure (see CLINICAL TRIALS).

Caution should be exercised in patients for whom an empagliflozin induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on antihypertensive therapy (particularly loop diuretics), elderly patients, patients with low systolic blood pressure, or in case of intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness).

Careful monitoring of volume status is recommended. Temporary interruption of JARDIANCE should be considered for patients who develop volume depletion until the depletion is corrected (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

Cerebrovascular Accidents

In the EMPA-REG cardiovascular outcomes trial, JARDIANCE (empagliflozin 10 mg and 25 mg treatment groups combined) was associated with a non-significant trend for a higher risk of fatal/non-fatal stroke compared to the placebo group: HR 1.18 (95% CI 0.89, 1.56) (see CLINICAL TRIALS). A causal relationship between JARDIANCE and stroke has not been established; however, caution should be observed in patients at high risk for cerebrovascular accidents.

Endocrine and Metabolism

Diabetic ketoacidosis: Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus treated with JARDIANCE and other SGLT2 inhibitors. Some cases of DKA have been fatal. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 13.9 mmol/L (250 mg/dL).

JARDIANCE is not indicated, and should not be used, in patients with type 1 diabetes. The diagnosis of type 2 diabetes mellitus should therefore be confirmed before initiating JARDIANCE.

Diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.

If these symptoms occur, regardless of blood glucose level, patients should discontinue JARDIANCE treatment and be assessed for diabetic ketoacidosis immediately.

Interruption of treatment with JARDIANCE should be considered in type 2 diabetes patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illnesses.

SGLT2 inhibitors have been shown to increase blood ketones in clinical trial subjects. Conditions that can precipitate DKA while taking empagliflozin include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), dehydration, high alcohol consumption, and a low beta-cell function reserve. JARDIANCE should be used with caution in these patients. These patients should be monitored closely.

Caution should be taken when reducing the insulin dose in patients requiring insulin (see DOSAGE AND ADMINISTRATION).

Use with Medications Known to Cause Hypoglycemia: Insulin secretagogues and insulin are known to cause hypoglycemia. The use of JARDIANCE in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial (see ADVERSE REACTIONS). 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 (see DOSAGE AND ADMINISTRATION).

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C are seen with JARDIANCE treatment (see ADVERSE REACTIONS). LDL-C levels should be monitored and treated as appropriate.

Genitourinary

Genital Mycotic Infections: JARDIANCE increases the risk of genital mycotic infections, particularly for patients with a history of genital mycotic infections (see ADVERSE REACTIONS). Monitor and treat as appropriate.

Urinary tract infections (including urosepsis and pyelonephritis): JARDIANCE increases the risk for urinary tract infections (see ADVERSE REACTIONS). There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis, some of them requiring hospitalization, in patients receiving SGLT2 inhibitors, including JARDIANCE. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

In the EMPA-REG cardiovascular outcomes trial, the incidence of urosepsis was greater in the empagliflozin groups than in the placebo group (0.3% for empagliflozin 10 mg, 0.5% for empagliflozin 25 mg, and 0.1% for placebo).

Hematologic

Elevated Hemoglobin and Hematocrit: Mean hemoglobin and hematocrit increased in patients administered JARDIANCE, as did the frequency of patients with abnormally elevated values for hemoglobin/hematocrit (see ADVERSE REACTIONS). JARDIANCE should be used with caution in patients with an elevated hematocrit.

Hepatic/Biliary/Pancreatic

Substantial elevations in hepatic transaminases have been reported in empagliflozin treated patients in clinical trials; however a causal relationship with empagliflozin has not been established (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY). Use of empagliflozin is not recommended in patients with severe hepatic impairment.

Immune

Hypersensitivity Reactions: JARDIANCE is contraindicated in patients with a history of hypersensitivity reaction to the active substance or to any of the excipients (see CONTRAINDICATIONS). Serious hypersensitivity reactions, including rash, angioedema and urticaria, have been observed with JARDIANCE in post marketing reports (see ADVERSE REACTIONS). If a hypersensitivity reaction occurs, discontinue JARDIANCE; treat promptly per standard of care, and monitor until signs and symptoms resolve.

Renal

JARDIANCE causes intravascular volume contraction and increases serum creatinine and decreases eGFR in a dose dependent fashion. Renal function abnormalities can occur after initiating JARDIANCE. Patients with hypovolemia are more susceptible to these changes (see ADVERSE REACTIONS).

The glucose-lowering benefit of JARDIANCE decreases with declining renal function and was not demonstrated to be statistically significant in subjects with eGFR less than 30 mL/min/1.73 m^2 (see CLINICAL TRIALS, Use in Patients with Type 2 Diabetes and Renal Impairment [Study 1245.36]).

Renal function should be assessed prior to initiation of JARDIANCE and regularly thereafter.

Use of JARDIANCE is contraindicated in patients with eGFR less than 30 mL/min/1.73m^2.

In patients with eGFR less than 60 mL/min/1.73m^2, more intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended, especially if the eGFR is less than 45 mL/min/1.73 m^2.

Discontinuation of JARDIANCE is recommended if the eGFR falls to less than 30 mL/min/1.73 m^2 during treatment (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors. 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.

Special Populations

Pregnant Women: JARDIANCE must not be used in pregnancy. There are limited data for the use of JARDIANCE (empagliflozin) in pregnant women. When pregnancy is detected, JARDIANCE should be discontinued. Based on results from animal studies, SGLT2 inhibitors may affect renal development and maturation (see TOXICOLOGY).

Nursing Women: JARDIANCE must not be used in nursing women. No data in humans are available on excretion of JARDIANCE into milk. Available animal data have shown excretion of empagliflozin in milk reaching levels up to 5 times higher than that in the maternal plasma (see TOXICOLOGY). As functional maturation of the kidneys in humans continues in the first 2 years of life, there may be a risk to the developing kidney if JARDIANCE is used during breastfeeding.

Pediatrics (<18 years of age): JARDIANCE should not be used in pediatric patients. The safety and efficacy have not been established in pediatric patients.

Geriatrics (≥65 years of age): JARDIANCE should be used with caution in geriatric patients. A total of 2721 (32%) patients treated with empagliflozin were 65 years and over, and 491 (6%) were 75 years and over in the pool of double-blind, controlled clinical safety and efficacy studies of JARDIANCE. Therapeutic experience in patients aged ≥85 years is limited. Initiation of empagliflozin therapy in this population is not recommended.

A greater increase in risk of adverse reactions related to urinary tract infections was seen with JARDIANCE in the elderly, compared to younger patients and increased in patients who were 75 years of age and older. A greater increase in risk of adverse reactions related to volume depletion was seen with JARDIANCE in patients ≥75 years of age. JARDIANCE is expected to have diminished antihyperglycemic efficacy in elderly patients as older patients are more likely to have impaired renal function. Therefore, JARDIANCE should be used with caution in this population (see INDICATIONS AND CLINICAL USE, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Blood Glucose and HbA1c: Response to JARDIANCE treatment should be monitored by periodic measurements of blood glucose and HbA1c levels.

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

Renal Function: JARDIANCE is contraindicated in patients with an eGFR< 30 mL/min/1.73m^2. Renal function should be assessed prior to initiation of JARDIANCE and regularly thereafter, with more frequent monitoring in patients whose eGFR decreases to < 60 mL/min/1.73m^2. (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Reduced Intravascular Volume: JARDIANCE is not recommended for use in patients who are volume depleted (see DOSAGE AND ADMINISTRATION). Before initiating JARDIANCE, assess volume status, particularly in patients at risk (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION), as well as in case of intercurrent conditions that may lead to fluid loss (such as a gastrointestinal illness) for patients already taking JARDIANCE. In these patients, careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum

electrolytes and renal function tests) is recommended. Temporary interruption of treatment with JARDIANCE should be considered until fluid loss is corrected.

LDL-Cholesterol: LDL-cholesterol levels should be measured at baseline and at regular intervals during treatment with JARDIANCE due to dose-dependent increases in LDL-C seen with therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 10 004 patients with type 2 diabetes were treated with JARDIANCE in clinical studies to evaluate the safety of JARDIANCE, alone or in combination with other antidiabetic agents.

Placebo controlled double-blinded trials of 18 to 24 weeks of exposure included 2971 patients, of which 995 were treated with placebo, 999 were treated with JARDIANCE 10 mg and 977 were treated with JARDIANCE 25 mg.

In these trials, the frequency of AEs leading to discontinuation was similar by treatment groups for placebo (5.3%) and JARDIANCE 10 mg (4.8%) and 25 mg (4.9%).

The most frequent adverse drug reaction was hypoglycaemia, which depended on the type of background therapy used in the respective studies (see ADVERSE REACTIONS, Hypoglycemia). The overall incidence of adverse events with JARDIANCE and the frequency of adverse events leading to discontinuation with JARDIANCE were similar to placebo.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a pooled dataset of the five 24-week placebo-controlled clinical trials and 18-week data from the placebo-controlled study as add-on to insulin therapy, adverse events regardless of causality that occurred in ≥1% of patients receiving JARDIANCE and more commonly than in patients given placebo (excluding hypoglycemia), are shown in Table 1.

Table 1 Adverse Events Reported in ≥1% of Patients Treated with JARDIANCE and More Frequently than in Patients Treated with Placebo

System organ class Preferred term	JARDIANCE 10 mg n = 999 N (%)	JARDIANCE 25 mg n = 977 N (%)	Placebo n = 995 N (%)
Gastrointestinal disorders			
Nausea	23 (2.3)	11 (1.1)	14 (1.4)
Constipation	14 (1.4)	8 (0.8)	12 (1.2)
Toothache	10 (1.0)	3 (0.3)	5 (0.5)
Dry mouth	3 (0.3)	10 (1.0)	1 (0.1)
General disorders and administration site conditions			
Fatigue	19 (1.9)	6 (0.6)	11 (1.1)
Thirst	15 (1.5)	12 (1.2)	0 (0)
Infections and infestations			
Urinary tract infection	82 (8.2)	60 (6.1)	58 (5.8)
Upper respiratory tract infection	31 (3.1)	39 (4.0)	38 (3.8)
Vaginal infection[1]	6 (1.4)	4 (1.0)	2 (0.4)
Bronchitis	13 (1.3)	9 (0.9)	10 (1.0)
Gastroenteritis	13 (1.3)	10 (1.0)	9 (0.9)
Sinusitis	11 (1.1)	9 (0.9)	7 (0.7)
Vulvovaginal candidiasis[1]	5 (1.1)	3 (0.7)	0 (0)
Vulvovaginal mycotic infection[1]	4 (0.9)	7 (1.7)	0 (0)
Influenza	9 (0.9)	12 (1.2)	11 (1.1)
Vulvitis[1]	0 (0)	5 (1.2)	0 (0)
Investigations			
Weight decreased	5 (0.5)	14 (1.4)	2 (0.2)
Metabolism and nutrition disorders			
Hypoglycemia	78 (7.8)	79 (8.1)	61 (6.1)
Dyslipidemia	39 (3.9)	28 (2.9)	34 (3.4)
Hyperlipidemia	8 (0.8)	12 (1.2)	8 (0.8)
Musculoskeletal and connective tissue disorders			
Arthralgia	24 (2.4)	22 (2.3)	22 (2.2)
Muscle spasms	9 (0.9)	10 (1.0)	7 (0.7)
Renal and urinary disorders			
Pollakiuria	19 (1.9)	15 (1.5)	5 (0.5)
Polyuria	14 (1.4)	10 (1.0)	1 (0.1)
Reproductive system and breast disorders			
Balanoposthitis[2]	7 (1.3)	1 (0.2)	0 (0)
Vulvovaginal pruritus[1]	11 (2.5)	8 (1.9)	3 (0.6)
Respiratory, thoracic and mediastinal disorders			
Cough	14 (1.4)	12 (1.2)	11 (1.1)

[1]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).
[2]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).

Less common Clinical trial Adverse Drug Reactions (<1%)[a]

Infections and infestations: Balanitis, balanitis candida, candiduria, genital candidiasis, genital infection, genital infection fungal, genitourinary tract infection, penile infection, pyelonephritis, scrotal abscess, urinary tract infection bacterial, urogenital infection fungal, urosepsis, vaginitis bacterial, vulvovaginitis.
Investigations: Blood glucose decreased, blood creatinine increased, glomerular filtration rate decreased, hematocrit increased.

Metabolism and nutrition disorders: Dehydration, hypovolemia.

Renal and urinary disorders: Nocturia, oliguria, renal impairment, renal failure acute, dysuria.

Skin and subcutaneous disorders: Pruritus

Vascular disorders: Hypotension, orthostatic hypotension.

[a]Adverse drug reactions (ADRs) were identified based on a comprehensive assessment of biological plausibility, mechanism of action, dose dependence in incidence rate, time of onset, seriousness and consistency of findings across pivotal Phase 3 clinical studies.

Table 2: Serious and/or unexpected adverse events reported at a higher frequency than placebo during JARDIANCE treatment in the EMPA-REG cardiovascular outcomes trial

MedDRA System organ class/ Preferred term (PT)	**JARDIANCE 10 mg N=2345 n (%)**	**JARDIANCE 25 mg N=2342 n (%)**	**Placebo N=2333 n (%)**
Skin and subcutaneous tissue disorders			
Rash	43 (1.8)	53 (2.3)	34 (1.5)
Musculoskeletal and connective tissue disorders			
Osteoporosis[a]	25 (1.1)	16 (0.7)	13(0.6)
Infections and infestations			
Urosepsis	6 (0.3)	11 (0.5)	3 (0.1)
Pyelonephritis	3 (0.1)	10 (0.4)	4 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Pancreatic neoplasm malignant[a,b]	6 (0.3)	6 (0.3)	2 (0.1)
Hepatobiliary disorders			
Hepatomegaly	5 (0.2)	4 (0.2)	2 (0.1)
Vascular disorders			
Deep vein thrombosis	3 (0.1)	10 (0.4)	5 (0.2)
Metabolism and nutrition disorders			
Diabetic ketoacidosis[a]	3 (0.1)	1 (0.04)	1 (0.04)

a) Based on grouping of terms
b) Up until trial completion

Description of Selected Adverse Reactions

Hypoglycemia: The frequency of hypoglycemia depended on the type of background therapy used in each study (see Table 3). The incidence of hypoglycaemia is increased when JARDIANCE was administered with insulin or a sulfonylurea (see WARNINGS AND PRECAUTIONS).

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

Monotherapy (24 weeks)			
	Placebo (n=229)	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
Background 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
Background 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
Background 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 MDI Insulin (18 weeks)			
	Placebo (n=53)	**JARDIANCE 10 mg (n=58)**	**JARDIANCE 25 mg (n=52)**
Overall (%)	30.2	41.4	40.4
Severe (%)	0	1.7	0
In combination with MDI Insulin + Metformin (18 weeks)			
	Placebo (n=135)	**JARDIANCE 10 mg (n=128)**	**JARDIANCE 25 mg (n=137)**
Overall (%)	40	39.1	41.6
Severe (%)	0.7	0	0.7
Patients with high CV risk (EMPA-REG OUTCOME)			
	Placebo (n=2333)	**JARDIANCE 10 mg (n=2345)**	**JARDIANCE 25 mg (n=2342)**
Overall (%)	27.9	28.0	27.6
Severe (%)	1.5	1.4	1.3

[a]Overall hypoglycaemic events: plasma or capillary glucose of less than or equal to 3.89 mmol/L
[b]Severe hypoglycaemic events: requiring assistance regardless of blood glucose

Genital Mycotic Infections: In a pooled dataset of the five 24-week placebo-controlled clinical trials and 18-week data from the placebo-controlled study as add-on to insulin therapy, the frequency of vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for JARDIANCE 10 mg (4.1%) and JARDIANCE 25 mg (3.7%) compared to placebo (0.9%). Patients with a prior history of genital infections were more likely to experience a genital infection event.

Genital infection events were reported more frequently in female patients (5.4%, 6.4% and 1.5%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively) than in male patients (3.1%, 1.6% and 0.4%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively). Discontinuation from study due to genital infection occurred in 0.2% of patients treated with either JARDIANCE 10 or 25 mg and 0% of placebo treated patients.

In the EMPA-REG cardiovascular outcomes trial, genital infection events were reported more frequently in patients treated with JARDIANCE than placebo, and more frequently in female patients (9.2%, 10.8% and 2.6%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively) than in male patients (5.4%, 4.6% and 1.5%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively).

Phimosis occurred more frequently in patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%) in the pooled 24-week placebo-controlled trials. In the subgroup of male patients in the EMPA-REG cardiovascular outcomes trial, phimosis was reported at an incidence of 0.3% in the empagliflozin 10 mg group, 0.8% in the empagliflozin 25 mg group, and 0.2% in the placebo group.

Increased urination: In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) were reported by 3.4%, 3.2% and 1.0% of patients treated with JARDIANCE 10 mg, 25 mg and placebo, respectively. Nocturia was reported by 0.3%, 0.8%, and 0.4% of patients treated with JARDIANCE 10 mg, 25 mg, and placebo respectively.

Urinary Tract Infections: In a pooled dataset of the five 24-week placebo-controlled clinical trials and 18-week data from the placebo-controlled study as add-on to insulin therapy, the frequency of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) occurred in 9.3%, 7.6%, and 7.6% of patients treated with JARDIANCE 10 mg, 25 mg, and placebo, respectively. Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection.

Urinary tract infection events were reported more frequently in female patients (18.3% and 15.5% for JARDIANCE 10 mg and 25 mg respectively, 12.5% for placebo) than in male patients (2.2% and 1.6% for JARDIANCE 10 mg and 25 mg respectively, 3.1% for placebo). The incidence of pyelonephritis and urosepsis with JARDIANCE was <0.1% and similar to placebo.

In elderly patients the incidence of urinary tract infections with JARDIANCE compared to placebo was greater than in younger patients (see WARNINGS AND PRECAUTIONS).

Volume Depletion and hypotension: Adverse reactions related to volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) were reported for 0.5%, 0.3%, and 0.3% of patients treated with JARDIANCE 10 mg, 25 mg and placebo, respectively. The incidence of volume depletion was increased in patients ≥75 years of age, with adverse events reported for 2.3%, 4.4%, and 2.1% of patients treated with JARDIANCE 10 mg, 25 mg, and placebo, respectively.

Blood creatinine increased and glomerular filtration rate decreased: In placebo-controlled, double-blind studies up to 76 weeks, increases in creatinine (mean change from baseline after 12 weeks: empagliflozin 10 mg 0.02 mg/dL, empagliflozin 25 mg 0.01 mg/dL) and decreases in estimated glomerular filtration rates (mean change from baseline after 12 weeks: empagliflozin 10 mg -1.34 mL/min/1.73m2, empagliflozin 25 mg -1.37 mL/min/1.73m2) have been observed. These changes were reversible in some patients during continuous treatment or after drug discontinuation (see WARNINGS AND PRECAUTIONS, Renal. See Monitoring and Laboratory Tests, Renal Function).

In the EMPA-REG OUTCOME trial, the decrease in eGFR was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes. (see CLINICAL TRIALS)

Patients with renal impairment: JARDIANCE was compared to placebo as add-on to pre-existing antidiabetic therapy over 52 weeks in 741 patients with type 2 diabetes and renal impairment (see CLINICAL TRIALS). The adverse reactions related to renal impairment, volume depletion and urinary tract and genital infections increased with worsening renal function (see WARNINGS AND PRECAUTIONS). Use of JARDIANCE was associated with increases in serum creatinine and decreases in eGFR, and patients with moderate renal impairment at baseline (eGFR 30 to <60 mL/min/1.73m^2), displayed larger mean changes. In patients with moderate renal impairment, decreases in eGFR at Week 24 were -3.2 mL/min/1.73m^2 versus 0.2 mL/min/1.73m^2, for empagliflozin 25 mg and placebo, respectively, compared to the pooled 24 week clinical trial population, where eGFR decreased -1.4 mL/min/1.73m^2 and -0.3 mL/min/1.73m^2, for empagliflozin 25 mg and placebo, respectively.

Diabetic ketoacidosis: Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes treated with JARDIANCE, and other SGLT2 inhibitors. Some cases of DKA have been fatal. JARDIANCE is not indicated, and should not be used, in patients with type 1 diabetes. In some cases, the presentation of the condition was atypical, with blood glucose levels only moderately elevated (<13.9 mmol/L (250 mg/dL)) (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

In the EMPA-REG cardiovascular outcomes trial, serious adverse events of diabetic ketoacidosis occurred at a rate of 0.05/100 pt. yrs in the empagliflozin 10 mg group and 0.02/100 pt. yrs in the empagliflozin 25 mg group. One patient (0.02/100 pt. yrs with a non-serious ketoacidosis event was reported in the placebo group.

Abnormal Hematologic and Clinical Chemistry Findings

Increases in serum creatinine and decreases in eGFR: In a pool of four-placebo-controlled trials, the mean change from baseline for eGFR (mL/min/1.73 m^2) at week 24 was -0.55, -1.41 and -0.32, for JARDIANCE 10 mg, 25 mg and placebo respectively. The mean change from baseline for creatinine (µmol/L) was 0.66, 1.28 and 0.35 for JARDIANCE 10 mg, 25 mg and placebo, respectively.

In the EMPA-REG cardiovascular outcomes trial, mean eGFR in the JARDIANCE 10 mg and 25 mg groups showed an initial decrease, and then stabilized, whereas mean eGFR in the placebo group showed a progressive decline (see Figure 1).

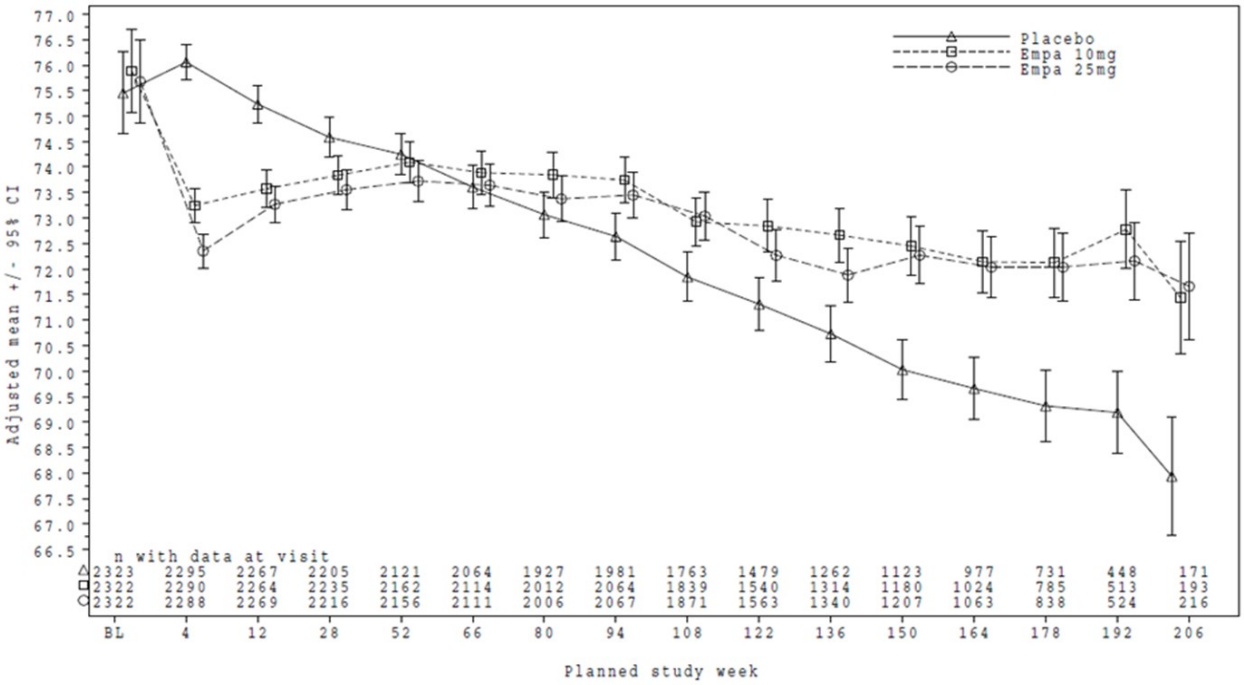


Figure 1: Time profile plot adjusted mean eGFR, individual empagliflozin doses vs placebo

Electrolytes: The following statistically significant changes from baseline in serum electrolytes were observed during JARDIANCE treatment (see Table 4).

Table 4 Placebo-Adjusted Mean Changes from Baseline in Electrolytes at Week 12 in EMPA-REG

Analyte [normal range, unit]	Baseline, mean (SE)	Placebo-corrected change from baseline at Week 12, mean (95% CI)	p-value
Sodium [135 – 145 mmol/L]			
JARDIANCE 10 mg	141.04 (0.06)	0.46 (0.32, 0.60)	<0.0001
JARDIANCE 25 mg	141.12 (0.07)	0.55 (0.41, 0.69)	<0.0001
Potassium [3.5 – 5.0 mmol/L]			
JARDIANCE 10 mg	4.54 (0.01)	−0.02 (−0.04, 0.00)	0.1034
JARDIANCE 25 mg	4.54 (0.01)	−0.03 (−0.05, 0.00)	0.0370
Magnesium [0.75 – 0.95 mmol/L]			
JARDIANCE 10 mg	0.77 (0.00)	0.07 (0.07, 0.08)	<0.0001
JARDIANCE 25 mg	0.78 (0.00)	0.08 (0.08, 0.08)	<0.0001
Bicarbonate [24 – 30 mmol/L]			
JARDIANCE 10 mg	25.72 (0.07)	−0.35 (−0.50, −0.19)	<0.0001
JARDIANCE 25 mg	25.76 (0.07)	−0.48 (−0.64, −0.33)	<0.0001
Phosphate [0.80 – 1.50 mmol/L]			
JARDIANCE 10 mg	1.16 (0.00)	0.06 (0.05, 0.07)	<0.0001
JARDIANCE 25 mg	1.16 (0.00)	0.07 (0.06, 0.08)	<0.0001

SE = standard error
ANCOVA for Week 12 includes baseline electrolyte and baseline HbA_{1c} as linear covariates and baseline eGFR category, baseline BMI category, geographical region, and treatment as fixed effects.

The following shifts from normal range at baseline to below or above the normal range at worst value on treatment were reported in the treated set in EMPA-REG:

- Increases in serum sodium above the upper limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (6.8%, 6.7%, and 4.4% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

- Decreases in serum potassium below the lower limit of normal occurred slightly more frequently in patients receiving JARDIANCE than in those receiving placebo (4.8%, 4.4%, and 3.9% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

- Decreases in serum magnesium below the lower limit of normal occurred more frequently in patients receiving placebo (13.8%, 11.7%, and 35.0% for JARDIANCE 10 mg, 25 mg, and placebo, respectively), whilst increases in serum magnesium above the upper limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (2.0%, 2.7%, and 0.8% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

- Decreases of serum bicarbonate below the lower limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (43.0%, 44.2%, and 34.7% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

- Increases of serum phosphate above the upper limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (11.8%, 12.6% and 9.7% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

Elevations of serum phosphate above the normal range occurred more frequently in patients receiving empagliflozin than in those receiving placebo (1.5%, 1.9% and 0.4% for JARDIANCE 10 mg, 25 mg, and placebo, respectively) in a pool of four placebo-controlled trials.

Low density lipoprotein Cholesterol (LDL-C): In a pool of four placebo-controlled studies, LDL-C increases with JARDIANCE were observed. Placebo-corrected mean changes from baseline in LDL-C were 2.3 mg/dL (3.5%) for JARDIANCE 10 mg and 3.3 mg/dL (4.6%) for JARDIANCE 25 mg.

Uric Acid: In the EMPA-REG cardiovascular outcomes trial, statistically significant reductions in uric acid were observed at most time points during empagliflozin treatment. At week 12, the placebo-adjusted mean change from baseline was -0.36 mg/dL in both the empagliflozin 10 mg and 25 mg treatment groups ($p<0.0001$).

Hematocrit: In a pool of four placebo-controlled studies, hematocrit increases with JARDIANCE were observed. Mean changes from baseline in hematocrit were 2.3%, 2.6% and -0.8% for JARDIANCE 10 mg, 25 mg and placebo respectively. Elevations of hematocrit or hemoglobin above the normal ranges occurred more frequently in patients receiving empagliflozin than in those receiving placebo (2.5%, 3.2% and 0.5% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

In the EMPA-REG cardiovascular outcomes trial, statistically significant ($p<0.0001$) differences from placebo in mean change from baseline in hematocrit were observed from week 12 to week 206, inclusive (2.21% in the empagliflozin 10 mg group and 2.56% in the empagliflozin 25 mg group at week 12).

Post-Market Adverse Drug Reactions

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

Metabolism: diabetic ketoacidosis

Skin and subcutaneous tissue disorders: Allergic skin reactions (e.g., rash, angioedema and urticaria)

DRUG INTERACTIONS

Overview

In vitro assessment of interactions

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. The relative contribution of each isoform to empagliflozin clearance has not been determined.

Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1. The effect of UGT induction 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, JARDIANCE 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. JARDIANCE does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations therefore, no effect of JARDIANCE is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

Drug-Drug Interactions

Pharmacokinetic interactions

Effects of other co-administered drugs on JARDIANCE

In clinical studies, JARDIANCE pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin (CYP2C9 substrate), verapamil (P-gp inhibitor), ramipril, and simvastatin (CYP3A4, OATP1B1, OATP1B3 substrate) in healthy volunteers (see Table 5). Torasemide and hydrochlorothiazide had no clinically relevant effect on the pharmacokinetics of JARDIANCE in T2DM patients.

JARDIANCE overall exposure (AUC) increased by 59%, 35% and 53%, when co-administered with gemfibrozil (CYP2C8 and OATP1B1 inhibitor), rifampicin (OATP1B1 and 1B3 inhibitor) and probenecid (UGT, OAT3 inhibitor) respectively and were not considered clinically relevant. In subjects with normal renal function, co-administration of JARDIANCE with probenecid resulted in a 30% decrease in the fraction of JARDIANCE excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

Table 5 Effect of Other Co-Administered Drugs on Pharmacokinetics of JARDIANCE

Co-administered drug	Dose of co-administered drug	Dose of JARDIANCE	Geometric Mean ratio (Ratio with/without co-administered drug) No effect=1.0		Clinical comment
			AUC (90% CI)	C_{max} (90% CI)	
Metformin	1000 mg, bid, 5 days	50 mg, qd, 5 days	0.97 (0.92; 1.02)	1.00 (0.89; 1.14)	No dose adjustment of JARDIANCE required
Glimepiride	1 mg, single dose	50 mg, qd, 6 days	0.95 (0.92; 0.99)	0.96 (0.88; 1.03)	No dose adjustment of JARDIANCE required
Pioglitazone	45 mg, q.d., 7 days	50 mg, qd, 7 days	1.00 (0.96; 1.05)	0.93 (0.85; 1.03)	No dose adjustment of JARDIANCE required
Warfarin	25 mg, single dose	25 mg, qd, 7 days	1.01 (0.97; 1.05)	1.01 (0.90; 1.13)	No dose adjustment of JARDIANCE required
Sitagliptin	100 mg, qd, 5 days	50 mg, qd, 5 days	1.10 (1.04; 1.17)	1.08 (0.97; 1.19)	No dose adjustment of JARDIANCE required
Linagliptin	5 mg, qd, 7 days	50 mg, qd, 7 days	1.02 (0.97; 1.07)	0.88 (0.79; 0.99)	No dose adjustment of JARDIANCE required
Hydrochloro-thiazide	25 mg, qd, 5 days	25 mg, qd, 5 days	1.07 (0.97; 1.18)	1.03 (0.89; 1.19)	No dose adjustment of JARDIANCE required
Torasemide	5 mg, qd, 5 days	25 mg, qd, 5 days	1.08 (1.00; 1.16)	1.08 (0.98; 1.18)	No dose adjustment of JARDIANCE required
Verapamil	120 mg, single dose	25 mg, single dose	1.03 (0.99; 1.07)	0.92 (0.85; 1.00)	No dose adjustment of JARDIANCE required
Ramipril	5 mg, qd, 5 days	25 mg, qd, 5 days	0.97 (0.93; 1.00)	1.04 (0.98; 1.12)	No dose adjustment of JARDIANCE required
Gemfibrozil	600 mg, bid, 5 days	25 mg, single dose	1.59 (1.52; 1.66)	1.15 (1.06; 1.25)	No dose adjustment of JARDIANCE required
Simvastatin	40 mg, single dose	25 mg, single dose	1.02 (0.99; 1.05)	1.09 (0.97; 1.24)	No dose adjustment of JARDIANCE required
Rifampicin	600 mg, single dose	10 mg, single dose	1.35 (1.30; 1.41)	1.75 (1.60; 1.92)	No dose adjustment of JARDIANCE required
Probenecid	500 mg, bid, 4 days	10 mg, single dose	1.53 (1.46; 1.61)	1.26 (1.14; 1.39)	No dose adjustment of JARDIANCE required

For single dose, AUC is $AUC_{0-\infty}$; for multiple dose, AUC is $AUC_{\tau,ss}$

Effects of JARDIANCE on other co-administered drugs

In clinical studies, JARDIANCE had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin (CYP2C9 substrate), digoxin (P-gp substrate), ramipril, simvastatin (CYP3A4, OATP1B1, OATP1B3 substrate), and oral contraceptives ethinyl estradiol and norgestrel (CYP3A4 substrate) when co-administered in healthy volunteers. JARDIANCE had no clinically relevant effect on the pharmacokinetics of torasemide and hydrochlorothiazide in patients with T2DM (see Table 6).

Table 6 Effect of JARDIANCE on Pharmacokinetics of Other Co-Administered Drugs Co-administered drug

	Dose of co-administered drug	Dose of JARDIANCE	Geometric Mean ratio (Ratio with/without co-administered drug) No effect=1.0		Clinical comment
			AUC (90% CI)	Cmax (90% CI)	
Metformin	1000 mg, bid, 5 days	50 mg, qd, 5 days	1.01 (0.96; 1.06)	1.04 (0.97; 1.11)	No dose adjustment required for metformin
Glimepiride	1 mg, single dose	50 mg, qd, 6 days	0.93 (0.86; 1.01)	1.04 (0.89; 1.21)	No dose adjustment required for glimepiride
Pioglitazone	45 mg, q.d., 7 days	50 mg, qd, 7 days	1.58 (1.48; 1.69)	1.88 (1.66; 2.12)	No dose adjustment required for pioglitazone
	45 mg, q.d., 7 days	10 mg, q.d., 9d	0.90 (0.78; 1.04)	0.88 (0.74; 1.04)	
	45 mg, q.d., 7 days	25 mg, q.d., 9d	0.89 (0.73; 1.09)	0.90 (0.67; 1.22)	
	45 mg, q.d., 7 days	50 mg, q.d., 9d	0.91 (0.77; 1.07)	0.90 (0.71; 1.14)	
Warfarin (R-warfarin)	25 mg, single dose	25 mg, qd, 7 days	0.98 (0.95; 1.02)	0.98 (0.91; 1.05)	No dose adjustment required for warfarin
(S-warfarin)			0.96 (0.93; 0.98)	0.99 (0.92; 1.06)	
Sitagliptin	100 mg, qd, 5 days	50 mg, qd, 5 days	1.03 (0.99; 1.07)	1.08 (1.01; 1.17)	No dose adjustment required for sitagliptin
Linagliptin	5 mg, qd, 7 days	50 mg, qd, 7 days	1.03 (0.96; 1.11)	1.01 (0.87; 1.19)	No dose adjustment required for linagliptin
Digoxin	0.5 mg, single dose	25 mg, qd, 8 days	1.06 (0.97; 1.16)	1.14 (0.99; 1.31)	No dose adjustment required for digoxin
Microgynon® tablet	ethinylestradiol, 30 µg, qd, 7 days	25 mg, q.d., 7 days	1.03 (0.98; 1.08)	0.99 (0.93; 1.05)	No dose adjustment required for oral contraceptives
	levonorgestrel 150 µg, qd, 7 days		1.02 (0.99; 1.05)	1.06 (0.99; 1.13)	
Hydrochloro-	25 mg,	25 mg, qd,	0.96	1.02	No dose

thiazide	qd, 5 days	5 days	(0.89; 1.04)		(0.89; 1.17)	adjustment required for hydrochlorothiazide
Torasemide	5 mg, qd, 5 days	25 mg, qd, 5 days	1.01 (0.99; 1.04)		1.04 (0.94; 1.16)	No dose adjustment required for torasemide
			M1 meta-bolite	1.04 (1.00; 1.09)	1.03 (0.94; 1.12)	
			M3 meta-bolite	1.03 (0.96; 1.11)	1.02 (0.98; 1.07)	
Ramipril	5 mg, qd, 5 days	25 mg, qd, 5 days	1.08 (1.01; 1.16)		1.04 (0.90; 1.20)	No dose adjustment required for ramipril
			Rami-prilat	0.99 (0.96; 1.01)	0.98 (0.93; 1.04)	
Simvastatin	40 mg, single dose	25 mg, single dose	1.01 (0.80; 1.28)		0.97 (0.76; 1.24)	No dose adjustment required for simvastatin
			Simvastatin acid	1.05 (0.90; 1.22)	0.97 (0.85; 1.11)	

For single dose, AUC is $AUC_{0-\infty}$; for multiple dose, AUC is $AUC_{\tau,ss}$

Pharmacodynamic interactions

Diuretics: JARDIANCE may add to the diuretic effect of loop diuretics and may increase the risk of dehydration and hypotension. Caution is recommended when JARDIANCE is co-administered with diuretics; particularly loop diuretics (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Drug-Food Interactions

Interactions with food have not been established (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Due to its mechanism of action, patients taking JARDIANCE will test positive for glucose in their urine. Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Drug-Lifestyle Interactions

The effects of smoking, diet, and alcohol use on the pharmacokinetics of JARDIANCE have not been specifically studied.

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be alerted to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural hypotension, and to the risk of hypoglycemia when JARDIANCE is used in combination with insulin or an insulin secretagogue.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Concomitant Use with Insulin or an Insulin Secretagogue (e.g. sulfonylurea): When JARDIANCE is used as add-on therapy with insulin or an insulin secretagogue a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Diuretics: JARDIANCE should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events due to volume depletion during co-administration.

Recommended Dose and Dosage Adjustment

The recommended starting dose of JARDIANCE is 10 mg once daily at any time of the day with or without food. In patients tolerating JARDIANCE 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily.

In patients with evidence of volume depletion, this condition should be corrected prior to initiation of JARDIANCE (see WARNINGS AND PRECAUTIONS).

Hepatic Impairment: No dosage adjustment for JARDIANCE is necessary for patients with mild or moderate hepatic impairment. JARDIANCE exposure is increased in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Experience in patients with severe hepatic impairment is limited. Therefore, JARDIANCE is not recommended for use in this population.

Renal Impairment: The glucose lowering efficacy of JARDIANCE declines with decreasing renal function (see CLINICAL TRIALS, Use in Patients with Type 2 Diabetes and Renal Impairment [Study 1245.36]). Renal function must be assessed prior to initiation of JARDIANCE therapy and periodically thereafter. JARDIANCE is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease or patients on dialysis (see CONTRAINDICATIONS). No dosage adjustment for JARDIANCE is necessary in patients with mild to moderate renal impairment.

More intensive monitoring of glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended if JARDIANCE is used in patients with an eGFR <60 mL/min/1.73 m^2, especially if the eGFR is less than 45 mL/min/1.73 m^2.

JARDIANCE should be discontinued if the eGFR fall to a level persistently less than 30 mL/min/1.73m^2. (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and CLINICAL TRIALS).

Pediatrics (<18 years of age): The safety and efficacy of JARDIANCE in pediatric and adolescent patients have not been established. Therefore, JARDIANCE should not be used in this population.

Geriatrics (≥65 years of age): No dose adjustment for JARDIANCE is required based on age; however renal function and risk of volume depletion should be taken into account. Initiation of JARDIANCE therapy is not recommenced in patients aged ≥85 years as therapeutic experience is limited in this population (see WARNINGS AND PRECAUTIONS, Geriatrics).

Missed Dose

If a dose is missed, it should be taken as soon as the patient remembers. A double dose of JARDIANCE should not be taken on the same day.

OVERDOSAGE

It is reasonable to employ 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. The removal of JARDIANCE by haemodialysis has not been studied.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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.

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.

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 treatment.

Cardiac Electrophysiology: In a randomized, double-blind, 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 recommended dose), moxifloxacin, and placebo. The empagliflozin 25 mg and 200 mg treatments were not observed to affect the QTc interval, the QRS duration, the PR interval, or heart rate.

Pharmacokinetics

Table 7 Summary[a] of JARDIANCE's Pharmacokinetic Parameters in T2DM Patients

Single dose mean	$C_{max,ss}$ (nmol/L) mean (% CV)	$T_{max,ss}$ (h) (% CV)	$AUC_{\tau,ss}$ (nmol.h/L) (% CV)	CL/F_{ss} (ml/min) (% CV)
25 mg qd	687 (18.4)	1.5 (49.9)	4740 (21.2)	203 (21.4)
10 mg qd	259 (24.8)	1.72 (42.5)	1870 (15.9)	202 (15.9)

a parameters after oral administration of multiple doses of empagliflozin (Day 28)

Absorption: After oral administration in patients with T2DM, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median Tmax 1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal elimination phase. The steady state mean plasma AUC and Cmax 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. Population pharmacokinetic analysis results suggested that empagliflozin exposure (AUC) in T2DM patients is approximately 33% higher for doses less than 400 mg compared to healthy volunteers.

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 Cmax 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 [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%, mainly to albumin. Protein binding is independent of plasma empagliflozin concentration. There were no relevant changes in protein binding of empagliflozin due to renal or hepatic impairment.

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: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent

drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Dose proportionality, accumulation and steady state pharmacokinetics: Systemic exposure of multiple dose empagliflozin in male and female diabetic patients increased in a dose-proportional manner between the doses of 2.5 mg to 100 mg q.d. for both AUC and Cmax. The single-dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time.

With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 23% accumulation with respect to plasma AUC, was observed at steady state.

Special Populations and Conditions

Pediatrics (<18 years of age): Studies characterizing the pharmacokinetics of empagliflozin in pediatric patients have not been performed.

Geriatrics (≥65 years of age): Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. The changes in AUCτ,ss were decreased by 8.06% for patients 35 years of age and increased by 6.43%, and 10.1% for patients 65 and 75 years of age, respectively, compared to patients with an age of 50 years and assuming normal renal function (eGFR 100 mL/min/1.73 m^2).

Body Mass Index: BMI had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. The changes in AUCτ,ss were increased by 7.48% for patients with BMI of 20 kg/m^2 and decreased by 5.82%, 10.4%, and 17.3% for patients with BMI of 30, 35 and 40 kg/m^2, respectively, compared to patients with a BMI of 25 kg/m^2.

Gender: Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. AUCτ,ss in females was 12.8% higher compared to males.

Race: Based on the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asian patients with a BMI of 25 kg/m^2 compared to non-Asian patients with a BMI of 25 kg/m^2. These changes are not considered clinically meaningful.

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

Renal Insufficiency: In patients with mild (eGFR: 60 - <90 mL/min/1.73m^2), moderate (eGFR: 30 - <60 mL/min/1.73m^2), severe (eGFR: <30 mL/min/1.73m^2) renal impairment and patients with kidney failure/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 (see DOSAGE AND ADMINISTRATION).

Genetic Polymorphism: The influence of UGT1A9 and other UGT genetic polymorphisms on the pharmacokinetics of JARDIANCE have not been evaluated.

STORAGE AND STABILITY

Store at room temperature (15-30°C).

SPECIAL HANDLING INSTRUCTIONS

Store in a safe place and out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each film-coated tablet of JARDIANCE contains 10 mg or 25 mg of empagliflozin free base.

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

25 mg film-coated tablets are pale yellow, oval, biconvex and debossed with "S25" on one side and the Boehringer Ingelheim logo on the other.

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, macrogol, microcrystalline cellulose, titanium dioxide, talc, and yellow ferric oxide.

PVC/aluminium unit dose blisters in cartons containing 10 x 1 blister card (physician sample for the patients), or 3 x 10, or 9 x 10 (commercial presentation).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

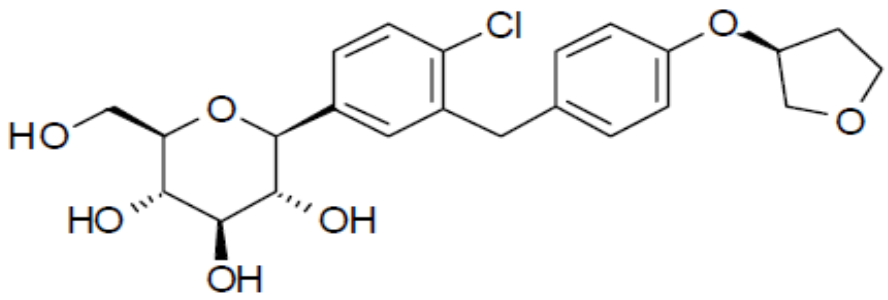
Common name: empagliflozin

Chemical name: (1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3 yloxy]benzyl}phenyl)-D-glucitol

Molecular formula: $C_{23}H_{27}ClO_7$

Molecular mass: 450.91 g/mol

Structural formula:



Empagliflozin is a white to yellowish, not hygroscopic solid powder, very slightly soluble in water (0.28 mg/mL), sparingly soluble in methanol (33.4 mg/mL), slightly soluble in ethanol (8.0 mg/mL), slightly soluble in acetonitrile (2.6 mg/mL), slightly soluble in 50% methanol in water (6.4 mg/mL), soluble in 50% acetonitrile in water (68 mg/mL), and practically insoluble in toluene (<0.001 mg/mL).

Solubility data of empagliflozin in aqueous media at room temperature: Water (pH 8.6) 0.28 mg/mL; 0.1N HCl (pH 1.1) 0.30 mg/mL; McIlvaine buffer pH 4.0 (pH 4.1) 0.21 mg/mL; McIlvaine buffer pH 7.4 (pH 7.5) 0.14 mg/mL.

CLINICAL TRIALS

JARDIANCE (empagliflozin) was studied as monotherapy and in combination with other antidiabetic medications, including metformin, metformin and sulfonylurea, pioglitazone, or basal or prandial insulin (with or without metformin) (see Table 8). JARDIANCE was also studied in patients with type 2 diabetes and cardiovascular disease and in patients with different degrees of renal impairment.

Treatment with JARDIANCE as monotherapy and in combination with metformin, glimepiride, pioglitazone, basal and prandial insulin (with or without metformin) produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c, fasting plasma glucose (FPG), blood pressure and 2-hour post-prandial glucose (where measured), compared to placebo or control. In the double-blind placebo-controlled extension of these studies, reductions of HbA1c and body weight were sustained up to Week 76. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, baseline BMI and patients with high baseline HbA1c >10%.

Study Demographics and Trial Design

Table 8 Summary of patient demographics for clinical trials in specific indication

Study No.	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomised / treated	Mean age years (SD)	Gender (%M/F)
Monotherapy					
1245.20	Randomised, multicentre, double-blind, active and placebo-controlled parallel group	Empagliflozin 10 mg or 25 mg vs placebo or vs Sitagliptin 100 mg Tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomised treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total: 986/986 Empagliflozin: 10 mg: 224/224 25 mg: 224/224 Placebo: 228/228 Sitagliptin: 223/223	 Empagliflozin: 10 mg: 56.2 (11.6) 25 mg: 53.8 (11.6) Placebo: 54.6 (10.9) Sitagliptin: 55.1 (9.9)	 Empagliflozin: 10 mg: 63/37 25 mg: 65/35 Placebo: 54/46 Sitagliptin: 63/37
Add-on Combination Therapy with Metformin					
1245.23	Randomised, multicentre, double-blind, placebo-controlled, parallel group	Empagliflozin 10 mg, 25 mg , placebo tablets, Tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomised Treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total: 707/706 Empagliflozin: 10 mg: 217/217 25 mg: 214/213 Placebo: 207/207	 Empagliflozin: 10 mg: 55.5 (9.9) 25 mg: 55.6 (10.2) Placebo: 56.0 (9.7)	 Empagliflozin: 10 mg: 58/42 25 mg: 56/44 Placebo: 56/44
1245.28	Randomised, multicentre, double blind, active-controlled, parallel-group	Empagliflozin 25 mg Glimepiride (Amaryl®):1 to 4 mg Placebo (run-in period) tablets, oral, once daily Run-in: 2 weeks	Total: 1549/1545 (until interim database lock) Empagliflozin: 25 mg: 769/765	 Empagliflozin: 25 mg: 56.2 (10.3)	 Empagliflozin: 25 mg: 56/43

Study No.	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomised / treated	Mean age years (SD)	Gender (%M/F)
		Treatment: 104 weeks Extension: 104 weeks Follow-up: 4 weeks	Glimepiride 1 to 4 mg: 780/780	Glimepiride: 55.7 (10.4)	Glimepiride: 54/46
Add-on Combination Therapy with Metformin and a Sulfonylurea					
1245.23+	Randomised, multicentre, double-blind, placebo-controlled, parallel group	Empagliflozin 10 mg, 25 mg , placebo tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomised treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total: 669/666 Empagliflozin: 10 mg: 226/225 25 mg: 218/216 Placebo: 225/225	Empagliflozin: 10 mg: 57.0 (9.2) 25 mg: 57.4 (9.3) Placebo: 56.9 (9.2)	Empagliflozin: 10 mg: 50/50 25 mg: 53/47 Placebo: 50/50
Add-on Combination Therapy with Pioglitazone					
1245.19	Randomised, multicentre, double-blind, placebo-controlled parallel group	Empagliflozin 10mg or 25 mg vs placebo Tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomised treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total 499/498 patients Empagliflozin 10 mg: 165/165 25 mg: 168/168 Placebo: 166/165	Empagliflozin: 10 mg: 54.7 (9.9) 25 mg: 54.2 (8.9) Placebo: 54.6 (10.5)	Empagliflozin: 10 mg: 50/50 25 mg: 50/50 Placebo: 44/56
Add-on Combination Therapy with MDI of Basal and Prandial Insulin (with or without Metformin)					
1245.49	Randomized, multicentre, double-blind, placebo-controlled, parallel group	E 10mg, 25 mg Placebo tablets, oral, once daily Randomised treatment: 52 weeks Week 1-18 &41-52 - stable insulin dose Week 19-40, treat-to-target insulin dose	Total: 566/563 Empagliflozin: 10 mg: 187/186 25 mg: 190/189 Placebo: 189/188	Empagliflozin: 10 mg: 56.7 (8.7) 25 mg: 58.0 (9.4) Placebo: 55.3 (10.1)	Empagliflozin: 10 mg: 52/48 25 mg: 44/56 Placebo: 40/60
Patients With Type 2 Diabetes and Established Cardiovascular Disease					
1245.25	Randomized, multicentre, double-blind, placebo-controlled	E 10mg, 25 mg Placebo tablets, oral, once daily + standard of care treatment: event-driven follow up: about 3 years	Total: 7028/7020 Empagliflozin: 10 mg: 2347/2345 25 mg: 2344/2342 Placebo: 2337/2333	Empagliflozin: 10 mg: 63.0 (8.6) 25 mg: 63.2 (8.6) Placebo: 63.2 (8.8)	Empagliflozin: 10 mg: 70/30 25 mg: 72/28 Placebo: 72/28

Study results

Monotherapy (Study 1245.20)

The efficacy and safety of JARDIANCE as monotherapy was evaluated in a double-blind, placebo- and active-controlled study of 24 weeks duration in treatment-naïve patients. As shown in Table 9, statistically significant reductions ($p<0.0001$) in HbA1c and body weight relative to placebo were observed with JARDIANCE 10 mg and 25 mg at Week 24. Statistically significant changes from baseline in systolic blood pressure (SBP, mmHg) of -2.9, -3.7, and -0.3 were observed for JARDIANCE 10 mg, 25 mg, and placebo, respectively.

Table 9 Results at Week 24 (LOCF) in a Placebo-Controlled Study of JARDIANCE Monotherapy in Patients with Type 2 Diabetes

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg	Sitagliptin[a]
N	228	224	224	223
HbA1c (%)				
Baseline (mean)	7.91	7.87	7.86	7.85
Change from baseline[1]	0.08	-0.66	-0.78	-0.66
Difference from placebo[1] (97.5% CI)		-0.74* (-0.90, -0.57)	-0.85* (-1.01, -0.69)	-0.73 (-0.88, -0.59)[2]
N	208	204	202	200
Patients[3] (%) achieving HbA1c <7%	15.4	39.3	46.0	41.7
N	228	224	224	223
Body Weight (kg)				
Baseline (mean)	78.23	78.35	77.80	79.31
Change from baseline[1]	-0.33	-2.26	-2.48	0.18
Difference from placebo[1] (97.5% CI)		-1.93* (-2.48, -1.38)	-2.15* (-2.70,-1.60)	0.52 (-0.04, 1.00)[2]

a Sitagliptin 100 mg per day
1 mean adjusted for baseline value
2 95% CI
3 The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.
*<0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.5% and -0.55% respectively; $p<0.0001$) which were sustained over time.

Add-on Therapy with Metformin (Study 1245.23)

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of JARDIANCE in patients not sufficiently treated with metformin. As shown in Table 10, statistically significant ($p<0.0001$) reductions in HbA1c, FPG and body weight relative to placebo were observed with JARDIANCE 10 mg and 25 mg at Week 24.

Table 10 Results of a 24-Week (LOCF) Placebo-Controlled Study of JARDIANCE in Add-on Combination with Metformin

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	207	217	213
HbA1c (%)			
Baseline (mean)	7.90	7.94	7.86
Change from baseline[1]	-0.13	-0.70	-0.77
Difference from placebo[1] (97.5% CI)		-0.57* (-0.72, -0.42)	-0.64* (-0.79, -0.48)
N	184	199	191
Patients[2] (%) achieving HbA1c <7%	16.4	40.6	40.8
N	207	216	213
FPG (mmol/L)			
Baseline (mean)	8.66	8.58	8.29
Change from baseline[1]	0.35	-1.11	-1.24
Difference from placebo[1] (95% CI)		-1.47 (-1.74, -1.20)	-1.59 (-1.86, -1.32)
N	207	217	213
Body Weight (kg)			
Baseline (mean)	79.73	81.59	82.21
Change from baseline[1]	-0.45	-2.08	-2.46
Difference from placebo[1](97.5% CI)		-1.63* (-2.17, -1.08)	-2.01* (-2.56, -1.46)

1 mean adjusted for baseline value
2 The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.
*p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.46% and -0.51% respectively; p<0.0001) which were sustained over time.

Add-on Therapy with Metformin - Active-Controlled Study versus Glimepiride (Study 1245.28)
In a study comparing the efficacy and safety of JARDIANCE 25 mg versus glimepiride (4 mg) in patients with inadequate glycemic control on metformin alone, as shown in Table 11, JARDIANCE daily resulted in a statistically significant (p<0.0001) reduction in HbA1c, FPG and body weight at Week 104. Systolic blood pressure (SBP, mmHg) change from baseline was -3.1, and 2.5 for JARDIANCE 25 mg, and glimepiride respectively.

Treatment with JARDIANCE resulted in statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for JARDIANCE 25 mg, 24.2% for glimepiride, p<0.0001).

Table 11 Results at 104-Week (LOCF) in an Active-Controlled Study Comparing JARDIANCE to Glimepiride as Add-on to Metformin

Efficacy Parameter	JARDIANCE 25 mg	Glimepiride
N	765	780
HbA1c (%)		
Baseline (mean)	7.92	7.92
Change from baseline[1]	-0.66	-0.55
Difference from glimepiride[1] (97.5% CI)	-0.11*(-0.20, -0.01)	
N	690	715
Patients[2] (%) achieving HbA1c <7%	37.5	32.6
N	764	779
FPG (mmol/L)		
Baseline (mean)	8.33	8.32
Change from baseline[1]	-0.85	-0.17
Difference from glimepiride[1] (95% CI)	-0.69 (-0.86, -0.52)	
N	765	780
Body Weight (kg)		
Baseline (mean)	82.52	83.03
Change from baseline[1]	-3.12	1.34
Difference from glimepiride[1] (97.5% CI)	-4.46** (-4.87, -4.05)	

1 mean adjusted for baseline value
2 The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.
* p<0.0001 for non-inferiority, p<0.0153 for superiority
** p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 4 and resulted in reductions in HbA1c with JARDIANCE 25 mg and glimepiride vs baseline (-0.41% and -0.43% respectively) which were sustained over time.

Add-on Therapy with Metformin and Sulfonylurea (Study 1245.23+)

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of JARDIANCE in patients not sufficiently treated with a combination of metformin and a sulphonylurea. As shown in Table 12, treatment with JARDIANCE resulted in statistically significant (p<0.0001) reductions in HbA1c and body weight, and clinically meaningful reductions in FPG compared to placebo at Week 24.

Table 12 Results of a 24-Week (LOCF) Placebo-Controlled Study of JARDIANCE as Add-on Therapy to Metformin with a Sulfonylurea

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	225	225	216
HbA1c (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.17	-0.82	-0.77
Difference from placebo[1] (97.5% CI)		-0.64* (-0.79, -0.49)	-0.59* (-0.74, -0.44)
N	216	209	202
Patients[2] (%) achieving HbA1c <7%	11.1	31.1	34.3
N	224	225	215
FPG (mmol/L)			
Baseline (mean)	8.42	8.38	8.68
Change from baseline[1]	0.31	-1.29	-1.29
Difference from placebo[1] (95% CI)		-1.60 (-1.90, -1.30)	-1.60 (-1.90, -1.29)
N	225	225	216
Body Weight (kg)			
Baseline (mean)	76.23	77.08	77.50
Change from baseline[1]	-0.39	-2.16	-2.39
Difference from placebo[1](97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)

1 mean adjusted for baseline value
2 The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.
*p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.58% and -0.6% respectively; p<0.0001) which were sustained over time.

Add-on Therapy with Pioglitazone (with or without Metformin, Study 1245.19)

The efficacy and safety of JARDIANCE were evaluated in a double-blind, placebo-controlled study of 24 weeks duration in patients not sufficiently treated with a combination of metformin and pioglitazone or pioglitazone alone. As shown in Table 13, JARDIANCE in combination with pioglitazone (mean dose ≥30 mg) with or without metformin resulted in statistically significant (p<0.0001) reductions in HbA1c, fasting plasma glucose, and body weight compared to placebo at Week 24.

Table 13 Results of a 24-Week (LOCF) Placebo-Controlled Study of JARDIANCE as Add-on to Pioglitazone

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	165	165	168
HbA1c (%)			
Baseline (mean)	8.16	8.07	8.06
Change from baseline[1]	-0.11	-0.59	-0.72
Difference from placebo[1] (97.5% CI)		-0.48* (-0.69, -0.27)	-0.61* (-0.82, -0.40)
N	155	151	160
Patients[2] (%) achieving HbA1c <7%	9.7	27.9	31.5
N	165	163	168
FPG (mmol/L)			
Baseline (mean)	8.43	8.44	8.43
Change from baseline[1]	0.37	-0.94	-1.23
Difference from placebo[1] (97.5% CI)		-1.32 (-1.72, -0.91)	-1.61 (-2.01, -1.21)
N	165	165	168
Body Weight (kg)			
Baseline (mean)	78.1	77.97	78.93
Change from baseline[1]	0.34	-1.62	-1.47
Difference from placebo[1] (97.5% CI)		-1.95* (-2.64, -1.27)	-1.81* (-2.49, -1.13)

1 mean adjusted for baseline value
2 The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.
*p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.4% and -0.51% respectively; p<0.0001) which were sustained over time.

Add-on Therapy with MDI of Basal and Prandial Insulin (with or without Metformin) (Study 1245.49)

The efficacy and safety of JARDIANCE as add on to multiple daily injections of basal and prandial insulin with or without metformin were evaluated at Week 18 and Week 52 in a randomized, double-blind, placebo-controlled study of empagliflozin 10 mg and 25 mg. From Week 1 to Week 18, patients were to maintain a stable insulin dose. From Week 19 to 40, treat-to-target insulin dose adjustments were to be made as needed in order to achieve glucose treat-to-target values (pre-prandial 5.5 mmol/L and post-prandial 7.8 mmol/L). From Week 41 to Week 52, patients were to maintain a stable insulin dose, and adjustments were to be made for safety reasons only. Insulin mix, regular and/or analogue mix, have not been studied.

The primary endpoint was the change from baseline in HbA1c after 18 weeks of treatment, analyzed on the full analysis set (FAS-18). As shown in Table 14, statistically significant reduction in HbA1c relative to placebo was observed with JARDIANCE 10 mg and 25 mg at Week 18.

Table 14 Results of 18-Week Placebo-Controlled Study- FAS (LOCF−18) of JARDIANCE in Combination with Insulin alone or with Metformin

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
All patients, N	188	186	189
Insulin only, N (%)	53 (28.2)	58 (31.2)	52 (27.5)
HbA1c (%)			
Baseline[2] (mean) (SE)	8.44 (0.10)	8.32 (0.10)	8.31 (0.11)
Change from baseline[1] mean (SE) (at Week 18)	-0.33 (0.10)	-0.79 (0.10)	-0.96 (0.10)
Difference from placebo[1] 97.5% confidence interval	--	-0.46 (-0.78, -0.14)	-0.62 (-0.95, -0.29)
p-value	--	0.0016	<0.0001
Insulin+metformin, N (%)	135 (71.8)	128 (68.8)	137 (72.5)
HbA1c (%)			
Baseline[2] (mean) (SE)	8.29 (0.06)	8.42 (0.06)	8.29 (0.06)
Change from baseline[1] mean (SE) (at Week 18)	-0.58 (0.06)	-0.99 (0.06)	-1.03 (0.06)
Difference from placebo[1] 97.5% confidence interval	--	-0.41 (-0.61, -0.21)	-0.45 (-0.65, -0.25)
p-value	--	<0.0001	<0.0001

During the first 18 weeks of treatment, the background insulin dose was not to be changed.
SE= standard error
1 adjusted mean for baseline HbA1c, eGFR and geographical region
2 Model included baseline HbA1c (p<0.0001) as a linear covariate, baseline eGFR (MDRD) (p=0.7812), treatment (p<0.0001), baseline background medication (p=0.0541), and treatment by baseline background medication interaction (p=0.3254) as fixed effects.

Blood pressure

The effects of JARDIANCE on blood pressure were evaluated in a double-blind, placebo-controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic and up to 2 antihypertensive therapies. Treatment with JARDIANCE once daily resulted in statistically significant reduction in 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (see Table 15).

Treatment with JARDIANCE also provided reductions in seated SBP (change from baseline of -0.67 mmHg for placebo -4.60 mmHg for empagliflozin 10 mg and -5.47 mmHg for empagliflozin 25 mg) and seated DBP (change from baseline of -1.13 mmHg for placebo and -3.06 mmHg for empagliflozin 10 mg and -3.02 mmHg for empagliflozin 25 mg) at week 12.

Table 15 24-Hour Ambulatory Blood Pressure Results at 12 week (LOCF) in a placebo-controlled study of JARDIANCE in patients with type 2 diabetes and uncontrolled blood pressure[#] (Full Analysis Set)

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	271	276	276
24 hour SBP at week 12			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[1]	0.48	-2.95	-3.68
Difference from placebo[1] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour DBP at week 12			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[1]	0.32	-1.04	-1.40
Difference from placebo[1] (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

[a] completer analysis
Patients with mean seated SBP 130 to 159 mmHg and DBP 80 to 99 mmHg at screening
[1] mean adjusted for baseline value
*p-value <0.0001
**p-value=0.0008

Use in Patients with Type 2 Diabetes and Established Cardiovascular Disease (EMPA-REG OUTCOME; study 1245.25)

The EMPA-REG OUTCOME study is a multi-centre, multi-national, randomized, double-blind, placebo-controlled, parallel-group, event-driven trial, investigating the effect of JARDIANCE as adjunct to standard care therapy in reducing cardiovascular events in patients with type 2 diabetes and one or more of the following established cardiovascular diseases: coronary artery disease, peripheral artery disease, history of myocardial infarction (MI), and history of stroke.

The study was conducted in patients with an eGFR ≥30 mL/min/1.73m^2.

The primary endpoint was the time to first event in the composite of CV death, nonfatal MI, or nonfatal stroke (Major Adverse Cardiovascular Events [MACE-3]). The key secondary composite outcome was MACE-4 (i.e., MACE-3 plus hospitalization for unstable angina). Additional pre-specified, adjudicated endpoints included CV death, fatal/nonfatal myocardial infarction, fatal/non-fatal stroke, hospitalization for heart failure, and all-cause mortality. Patients without events were considered censored at the end of their individual observation periods.

A total of 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) for a median duration of 2.6 years and followed for a median of 3.1 years. Baseline demographic and other characteristics, including background medications for diabetes and cardiovascular disease, were balanced across the treatment groups.

The population was 72.4% Caucasian, 21.6% Asian, and 5.1% Black. The mean age was 63 years (9.3% patients at least 75 years old) and 71.5% were male.

At randomisation, 75.6% of patients had coronary artery disease (including 46.6% with a history of myocardial infarction), 23.3% had a history of stroke, and 20.8% had peripheral artery disease. In total, 80.3% of patients had only 1 of these 3 factors reported at baseline, while 17.3% had 2 of the 3 factors and 1.6% had all 3 high-risk factors. A history of heart failure was reported for 10% of the patients.

At baseline, approximately 81% of patients were being treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 89% with anticoagulants, and 81% with lipid-lowering medication. Approximately 74% of patients were being treated with metformin at baseline, 48% with insulin, and 43% with sulphonylurea.

At baseline 52.2% of patients had an eGFR of 60-90 ml/min/1.73 m^2, 17.8% had an eGFR of 45-60 ml/min/1.73 m^2 and 7.7% had eGFR of 30-45 ml/min/1.73 m^2.

Mean systolic BP was 135 mmHg, diastolic BP 77 mmHg, LDL 2.22 mmol/L, and HDL 1.14 mmol/L at baseline.

Primary MACE Composite Endpoint: The primary analysis of MACE-3 was based on the treated set (TS), considering all events up to individual trial completion. According to hierarchical testing for non-inferiority and superiority, the pooled empagliflozin 10 and 25 mg treatment group (all empagliflozin) was found to be:

- Non-inferior to placebo, since the upper bound of the 95.02% CI was below 1.3, and
- Superior to placebo, since the upper bound of the 95.02% CI was also below 1.0

Table 16 Cox regression for time to first 3-point MACE, all JARDIANCE vs. placebo – TS

	Placebo	All JARDIANCE
Analysed patients, N (100%)	2333	4687
Patients with event, N (%)	282 (12.1)	490 (10.5)
Incidence rate per 1000 years at risk	43.9	37.4
Hazard ratio vs. placebo	--	0.86
(95.02% CI) [1]		(0.74, 0.99)
(95% CI)		(0.74, 0.99)
p−value for HR≥1.3 (1-sided)		<0.0001
p−value for HR≥1.0 (1-sided)		0.0191
p−value (2-sided)		0.0382

[1] Based on the reduced alpha level of 0.0249 resulting from the interim analysis

The treatment effect reflected a significant reduction in cardiovascular death with no significant change in non-fatal MI, or non-fatal stroke

Results for the MACE-4 composite endpoint, including hospitalization for unstable angina, were non-inferior, but not superior, to placebo.

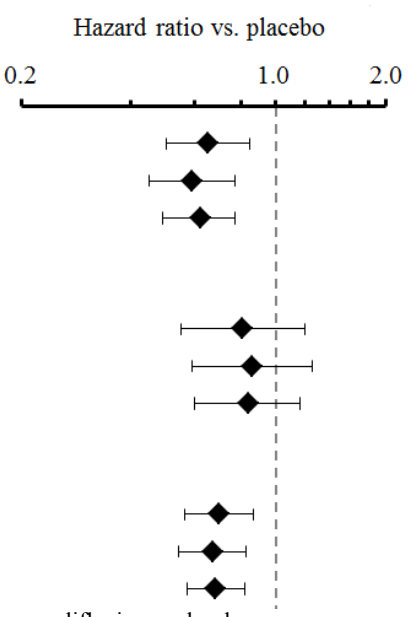
Other Adjudicated Cardiovascular Endpoints

Mortality Endpoints

JARDIANCE decreased all-cause mortality which was driven by a reduction in cardiovascular death. There was no statistically significant difference between JARDIANCE and placebo in non-cardiovascular mortality.

Table 17 Summary of endpoints of death - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
CV death						
Placebo	137 (5.9)	20.2	--	--	--	--
Empa 10 mg	90 (3.8)	13.0	0.65	0.50	0.85	0.0016
Empa 25 mg	82 (3.5)	11.8	0.59	0.45	0.77	0.0001
All empa	172 (3.7)	12.4	0.62	0.49	0.77	<0.0001
Non-CV death						
Placebo	57 (2.4)	8.4	--	--	--	--
Empa 10 mg	47 (2.0)	6.8	0.81	0.55	1.20	0.2909
Empa 25 mg	50 (2.1)	7.2	0.86	0.59	1.26	0.4400
All empa	97 (2.1)	7.0	0.84	0.60	1.16	0.2852
All-cause mortality						
Placebo	194 (8.3)	28.6	--	--	--	--
Empa 10 mg	137 (5.8)	19.8	0.70	0.56	0.87	0.0013
Empa 25 mg	132 (5.6)	19.0	0.67	0.54	0.83	0.0003
All empa	269 (5.7)	19.4	0.68	0.57	0.82	<0.0001



For the graph: the diamond indicates the HR and the bars 95% CIs for the HR of empagliflozin vs. placebo

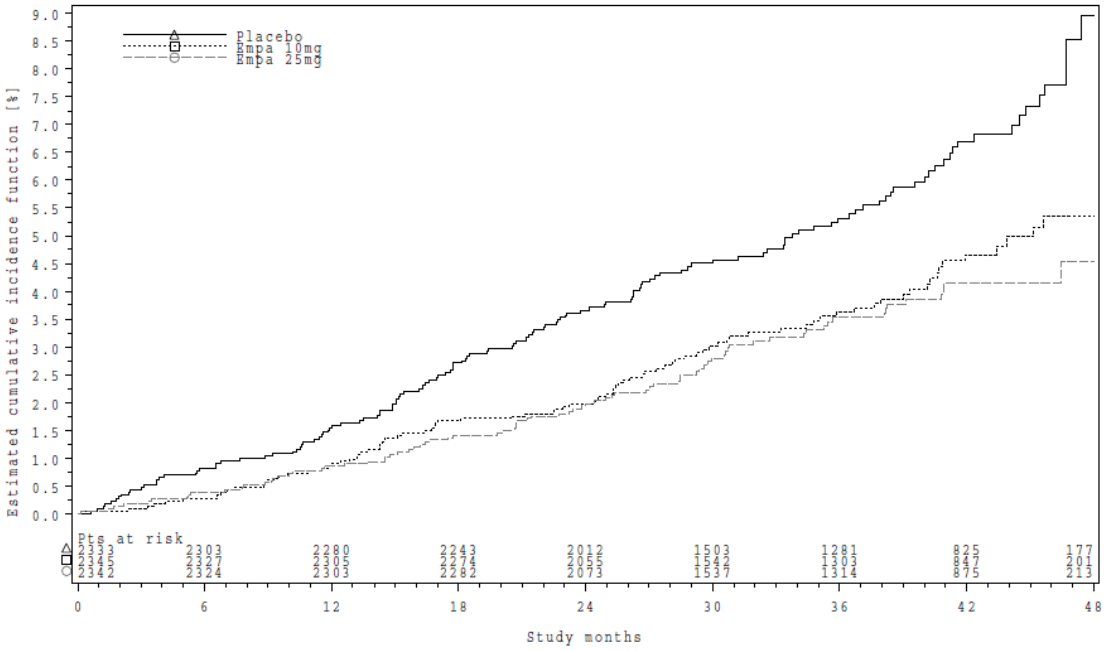


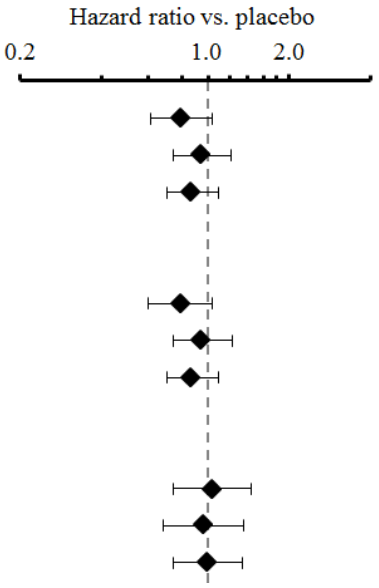
Figure 2 Estimated cumulative incidence function for time to CV death, individual empagliflozin doses vs placebo - treated set

Myocardial Infarction (MI) and Hospitalization for Unstable Angina

No statistically significant difference was observed between JARDIANCE and placebo for fatal/non-fatal MI, non-fatal MI, or hospitalization for unstable angina.

Table 18 Summary of MI-related endpoints - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
MI (fatal/non-fatal)						
Placebo	126 (5.4)	19.3	--	--	--	--
Empa 10 mg	101 (4.3)	15.2	0.79	0.61	1.03	0.0852
Empa 25 mg	122 (5.2)	18.3	0.95	0.74	1.22	0.7141
All empa	223 (4.8)	16.8	0.87	0.70	1.09	0.2302
Non-fatal MI						
Placebo	121 (5.2)	18.5	--	--	--	--
Empa 10 mg	96 (4.1)	14.4	0.79	0.60	1.03	0.0769
Empa 25 mg	117 (5.0)	17.6	0.95	0.74	1.23	0.7114
All empa	213 (4.5)	16.0	0.87	0.70	1.09	0.2189
Hospitalization for unstable angina						
Placebo	66 (2.8)	10.0	--	--	--	--
Empa 10 mg	69 (2.9)	10.4	1.03	0.74	1.45	0.8509
Empa 25 mg	64 (2.7)	9.5	0.96	0.68	1.35	0.7981
All empa	133 (2.8)	10.0	0.99	0.74	1.34	0.9706

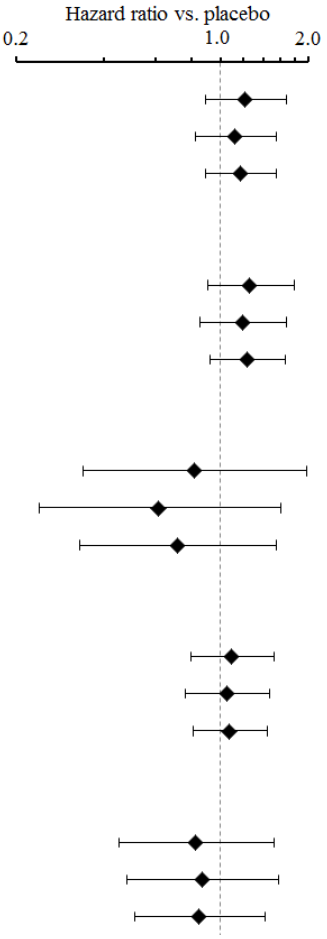


Stroke

For the endpoints fatal/non-fatal stroke and non-fatal stroke, non-significant unfavourable trends were observed in the empagliflozin groups. Much of this imbalance was driven by events that occurred off-treatment (more than 90 days after stop of treatment). For transient ischemic attacks, a non-significant favourable trend was observed. The majority of the stroke events were ischemic (149 of 164 for empagliflozin, 62 of 69 for placebo).

Table 19 Summary of cerebrovascular disease-related endpoints - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
Stroke (fatal/non-fatal)						
Placebo	69 (3.0)	10.5	--	--	--	--
Empa 10 mg	85 (3.6)	12.7	1.22	0.89	1.68	0.2119
Empa 25 mg	79 (3.4)	11.8	1.13	0.82	1.56	0.4594
All empa	164 (3.5)	12.3	1.18	0.89	1.56	0.2567
Non-fatal stroke						
Placebo	60 (2.6)	9.1	--	--	--	--
Empa 10 mg	77 (3.3)	11.5	1.27	0.91	1.79	0.1593
Empa 25 mg	73 (3.1)	10.9	1.20	0.85	1.69	0.2954
All empa	150 (3.2)	11.2	1.24	0.92	1.67	0.1638
Fatal stroke						
Placebo	11 (0.5)	1.6	--	--	--	--
Empa 10 mg	9 (0.4)	1.3	0.82	0.34	1.98	0.6572
Empa 25 mg	7 (0.3)	1.0	0.62	0.24	1.61	0.3275
All empa	16 (0.3)	1.2	0.72	0.33	1.55	0.4015
Treatment-emergent stroke (fatal/non-fatal)*						
Placebo	66 (2.8)	11.1	--	--	--	--
Empa 10 mg	74 (3.2)	12.0	1.10	0.79	1.53	0.5773
Empa 25 mg	72 (3.1)	11.6	1.06	0.76	1.48	0.7229
All empa	146 (3.1)	11.8	1.08	0.81	1.45	0.6014
Transient ischaemic attack (TIA)						
Placebo	23 (1.0)	3.5	--	--	--	--
Empa 10 mg	19 (0.8)	2.8	0.83	0.45	1.53	0.5603
Empa 25 mg	20 (0.9)	2.9	0.87	0.48	1.58	0.6357
All empa	39 (0.8)	2.9	0.85	0.51	1.42	0.5368



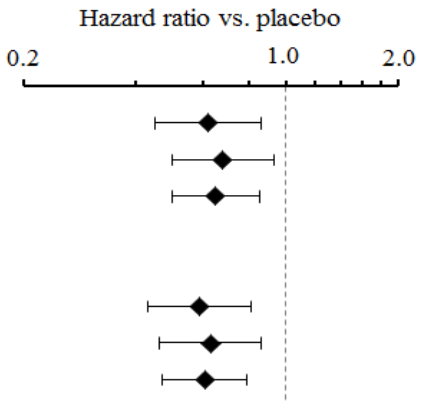
* Including all events up to 90 days after stop of treatment

Reductions in risk of heart failure requiring hospitalization or death from heart failure

JARDIANCE significantly reduced the risk of heart failure requiring hospitalization and heart failure requiring hospitalization or death from heart failure compared with placebo.

Table 20 Summary of heart failure-related endpoints - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
Heart failure requiring hospitalization						
Placebo	95 (4.1)	14.5	--	--	--	--
Empa 10 mg	60 (2.6)	8.9	0.62	0.45	0.86	0.0044
Empa 25 mg	66 (2.8)	9.8	0.68	0.50	0.93	0.0166
All empa	126 (2.7)	9.4	0.65	0.50	0.85	0.0017
Heart failure requiring hospitalization or death from heart failure						
Placebo	104 (4.5)	15.8	--	--	--	--
Empa 10 mg	62 (2.6)	9.2	0.59	0.43	0.81	0.0010
Empa 25 mg	67 (2.9)	9.9	0.63	0.46	0.86	0.0034
All empa	129 (2.8)	9.6	0.61	0.47	0.79	0.0002



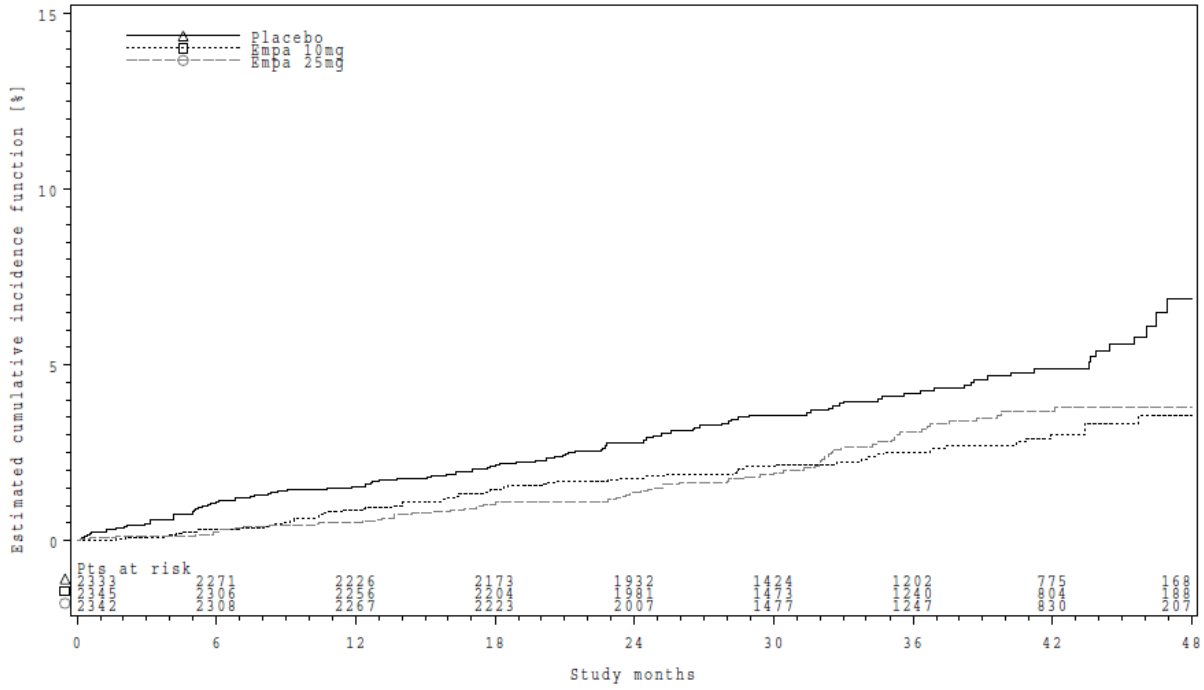


Figure 3 Estimated cumulative incidence function for time to first hospitalization for heart failure (HF) or death from worsening of heart failure, individual empagliflozin vs placebo - treated set

Other

Use in Patients with Type 2 Diabetes and Renal Impairment (Study 1245.36)
The efficacy and safety of JARDIANCE as add-on to antidiabetic therapy were evaluated in patients with type 2 diabetes and different degrees of renal impairment. A total of 738 patients with a baseline eGFR less than 90 mL/min/1.73 m^2 participated in a 52-week randomized, double-blind, placebo-controlled, parallel-group study.

In patients with mild renal impairment, treatment with JARDIANCE 10 mg and 25 mg led to statistically significant reduction of HbA1c at Week 24 compared to placebo. Although the 10 mg dose is the recommended starting dose of JARDIANCE, this dose was only studied in patients with mild renal impairment. For patients with type 2 diabetes with moderate or severe renal impairment, the 25 mg dose of JARDIANCE was used. The glucose lowering efficacy of JARDIANCE 25 mg decreased with decreasing renal function (see Table 21). In patients with severe renal impairment, JARDIANCE 25 mg did not reduce HbA1c at Week 24 and more adverse events were noted.

Table 21 Results at 24-Week (LOCF) in a Placebo-Controlled Study of JARDIANCE in Renally Impaired Type 2 Diabetes Patients (Full Analysis Set)

Efficacy Parameter	Placebo	JARDIANCE		Placebo	JARDIANCE 25 mg	Placebo	JARDIANCE 25 mg
		10 mg	25 mg				
	Mild (eGFR ≥60 to <90 mL/min/1.73m²)			Moderate 3A (eGFR ≥45 to <60 mL/min/1.73m²		Moderate 3B (eGFR ≥30 to <45 mL/min/1.73m²)	
N (%)	95 (12.9)	98 (13.3)	97 (13.1)	89 (12.1)	91 (12.3)	98 (13.3)	96 (13.0)
HbA1c (%)							
Baseline (mean)	8.09	8.02	7.96	8.08	8.12	8.01	7.95
Change from baseline[1]	0.06	-0.46	-0.63	-0.09	-0.54	0.17	-0.21
Difference from placebo[1] (95% CI)		-0.52* (-0.72, -0.32)	-0.68* (-0.88,-0.49)		-0.46* (-0.66, -0.27)		-0.39* (-0.58, -0.19)

1 mean adjusted for baseline value
* p<0.0001

DETAILED PHARMACOLOGY

Empagliflozin demonstrated good *in vitro* potency towards inhibition of human (IC50 of 1.3 nM) and rat (IC50 of 1.7 nM) renal SGLT2 transporters. The three major human metabolites of empagliflozin, all glucuronides, exhibited very weak activity toward the SGLT2 transporter *in vitro*, with IC50 values ranging from 860 – 1435 nM. Oral doses of empagliflozin increased urinary glucose excretion in diabetic rodents and normoglycemic dogs. This triggered the lowering of blood glucose in diabetic rodents after single oral dosing, as well as after chronic treatment.

TOXICOLOGY

Acute Toxicity
Empagliflozin demonstrated low acute toxicity. The single lethal oral dose of empagliflozin was greater than 2000 mg/kg in mice and rats.

Sub-chronic and Chronic Toxicity
Repeat-dose oral toxicity studies were conducted in mice, rats and monkeys for up to 13, 26, and 52 weeks, respectively. Signs of toxicity were generally observed at exposures greater than or equal to 10 times the human exposure (AUC) at the maximum recommended dose of 25 mg. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and included decreased body weight and body fat, increased food consumption, diarrhea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism, gluconeogenesis and electrolyte imbalances, urinary changes such as polyuria and glycosuria. Increases in liver weight, elevated hepatic enzyme activities (e.g., AST and ALT) and hepatocellular vacuolation were observed in mice, rats and dogs. These changes in the liver may be related to gluconeogenesis and/or mobilization of lipid for energy production. The main target organ of empagliflozin toxicity was the kidney. Microscopic changes in the kidney were observed across species and included tubular karyomegaly, single cell necrosis, cystic hyperplasia and hypertrophy (mouse), renal mineralization and cortical tubular vacuolation (rat), and tubular nephropathy and interstitial nephritis (dog).

In a 2-year study in mice, mortality associated with urinary tract lesions was dose-dependently increased for males given empagliflozin at oral doses of ≥100 mg/kg/day (≥4 times the clinical dose of 25 mg based on AUC comparisons).

Carcinogenicity
The carcinogenic potential of empagliflozin was evaluated in 2-year studies in mice and rats. Empagliflozin did not increase the incidence of tumors in female rats up to the highest dose of 700 mg/kg/day (up to 72 times the clinical dose of 25 mg based on AUC comparisons). In male rats, treatment-related benign vascular proliferative lesions (hemangiomas) of the mesenteric lymph node were observed at 700 mg/kg/day (approximately 42 times the clinical dose of 25 mg based on AUC comparisons), but not at 300 mg/kg/day which corresponds to approximately 26 times the clinical exposure from 25 mg dose. These tumors are common in rats and the incidence (18%) was within literature historical control (0-26%). No vascular lesions were seen in the mouse and dog. Empagliflozin did not increase the incidence of tumors in female mice at doses up to 1000 mg/kg/day (up to, approximately 62 times the clinical dose of 25 mg based on AUC

comparisons). Renal tumors were observed in male mice at 1000 mg/kg/day (approximately 45 times the clinical dose of 25 mg based on AUC comparisons), but not at 300 mg/kg/day which corresponds to approximately 11 times the clinical exposure from a 25 mg dose. The mode of action for these tumors may be dependent on the natural predisposition of the male mouse to renal pathology which is exacerbated by a male mouse kidney-specific cytotoxic oxidative metabolite. Therefore the renal tumors found in mice may not be relevant to patients given clinical doses of empagliflozin.

Genotoxicity
Empagliflozin was not genotoxic in the Ames bacterial mutagenesis test, the L5178/tk+/-mouse lymphoma assay, or the *in vivo* rat micronucleus test.

Reproductive Toxicity
In a study of fertility and early embryonic development in rats, empagliflozin had no effects on mating and fertility in males or females or early embryonic development up to the highest dose of 700 mg/kg/day (approximately 50 times the clinical dose of 25 mg based on AUC comparisons).Empagliflozin administered during the period of organogenesis was not teratogenic at doses up to 300 mg/kg/day in the rat or rabbit, which corresponds to approximately 48 times or 128 times the clinical dose of 25 mg based on AUC comparisons, respectively. Doses of empagliflozin causing maternal toxicity in the rat also caused the malformation of bent limb bones at exposures approximately 155 times the clinical exposure from a 25 mg dose. Maternally toxic doses in the rabbit also caused increased embryofetal loss at doses approximately 139 times the clinical dose of 25 mg based on AUC comparisons.
In a pre- and postnatal toxicity study in rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at 10, 30 and 100 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. There was no evidence of maternal toxicity up to the high dose of 100 mg/kg/day; however, a reduction in F1 pup body weight gains, mainly during lactation, was observed at doses of ≥30 mg/kg/day (≥4 times the clinical dose of 25 mg based on AUC comparisons). The F1 male pups also had learning and memory deficits at 100 mg/kg (approximately 16 times the clinical dose of 25 mg based on AUC comparisons) on postnatal day (PND) 22, but not on PND 62. These neurobehavioral effects were likely to be secondary to the retarded growth rates of the F1 male pups. The NOAEL for F1 neonatal toxicity was 10 mg/kg/day (approximately 1.4 times the clinical dose of 25 mg based on AUC comparisons).

In a juvenile toxicity study, empagliflozin was administered directly to young rats from post-natal day 21 until postnatal day 90 at oral doses of 1, 10, 30 and 100 mg/kg/day. Increases in kidney weights were observed in males at ≥ 10 mg/kg/day (≥ 0.7 times the clinical dose of 25 mg based on AUC comparisons) and in females at ≥ 30 mg/kg/day (≥ 4 times the clinical dose of 25 mg based on AUC comparisons). Minimal to mild renal tubular and pelvic dilation was seen at 100 mg/kg/day, which approximates 11-times the clinical dose of 25 mg based on AUC comparisons. These findings were absent after a 13-week, drug-free recovery period.

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PART III: CONSUMER INFORMATION

Pr Jardiance®

empagliflozin tablets

This leaflet is part III of a three-part "Product Monograph" published when JARDIANCE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JARDIANCE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
JARDIANCE is used along with diet and exercise to improve blood sugar levels in adults with type 2 diabetes. JARDIANCE can be used:
- alone, if you cannot take metformin;
- with metformin;
- with metformin and a sulfonylurea;
- with pioglitazone (with or without metformin);
- with basal or prandial insulin (with or without metformin).

If you have type 2 diabetes and an increased cardiovascular risk (health problems due to your heart and blood vessels), JARDIANCE can be used along with diet and exercise to lower your risk of dying from events related to your heart or blood vessels.

What it does:
JARDIANCE removes excess glucose from the body through the urine.

When it should not be used:
Do not take JARDIANCE if you:
- have type 1 diabetes (a disease in which your body does not produce any insulin);
- have diabetic ketoacidosis (DKA, a complication of diabetes) or a history of DKA;
- have severe kidney problems or you are on dialysis;
- have severe liver disease;
- are pregnant or planning to become pregnant; it is not known if JARDIANCE will harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant;
- are breast-feeding or plan to breast-feed; it is not known if JARDIANCE will pass into your breast milk. Talk to your doctor if you would like to breast-feed;
- are allergic to empagliflozin or any of the other ingredients listed below.

What the medicinal ingredient is:
Empagliflozin

What the non-medicinal ingredients are:
Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, macrogol, microcrystalline cellulose, titanium dioxide, talc, and yellow ferric oxide**.**

What dosage forms it comes in:
Tablets 10 mg and 25 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Diabetic ketoacidosis (DKA) is a serious and life-threatening condition that requires urgent hospitalization. DKA has been reported in patients with type 2 diabetes mellitus (T2DM), with normal or high blood sugar levels, who are treated with JARDIANCE and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Some cases of DKA have led to death.
- Seek medical attention right away **and stop taking JARDIANCE immediately** if you have any of the following symptoms (even if your blood sugar levels are normal): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, feeling very thirsty, feeling unusually tired, a sweet smell to the breath, a sweet or metallic taste in the mouth or a different odour to urine or sweat.
- JARDIANCE should not be used in patients with type 1 diabetes.
- JARDIANCE should not be used to treat DKA or if you have a history of DKA.

BEFORE you use JARDIANCE talk to your doctor or pharmacist if you:

- are older than 65 years of age;
- have type 1 diabetes (your body does not produce insulin). JARDIANCE should not be used in patients with type 1 diabetes;
- have or have had any kidney problems;
- have or have had any cases of liver disease;
- have heart disease or low blood pressure;
- are taking a medicine for high blood pressure or taking a water pill (used to remove excess water from the body);
- are taking medicines to lower your blood sugar such as glyburide, gliclazide or glimepiride (sulfonylureas) or insulin. Taking JARDIANCE with any of these medicines can increase the risk of having low blood sugar (hypoglycemia);
- have intolerance to some milk sugars. JARDIANCE tablets contain lactose;
- are 85 years old or older as you should not start taking JARDIANCE;
- have an increased chance of developing DKA, including if you:
  - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
  - are on a very low carbohydrate diet;

- drink a lot of alcohol;
- have/have had problems with your pancreas, including pancreatitis or surgery on your pancreas;
- are hospitalized for major surgery, serious infection or serious medical illnesses;
- have a history of diabetic ketoacidosis (DKA).

JARDIANCE is not recommended for use in patients under 18 years of age.

JARDIANCE will cause your urine to test positive for sugar (glucose).

JARDIANCE may cause changes in the amount of cholesterol or fats in your blood.

JARDIANCE may cause abnormal kidney function. Your doctor will do blood tests to monitor how well your kidneys are working while you are taking JARDIANCE.

JARDIANCE increases the chance of getting a yeast infection of the penis or vagina. This is more likely in people who have had yeast infections in the past.

Driving and using machines: JARDIANCE may cause dizziness or lightheadedness. Do not drive or use machines until you know how the medicine affects you.

INTERACTIONS WITH THIS MEDICATION

Talk to your doctor or pharmacist about all the drugs you take. This includes prescription drugs, as well as those you buy yourself, and herbal supplements.

Drugs that may interact with JARDIANCE include: medicines you take for diabetes, especially sulfonylurea medications or insulin. Low blood sugar (hypoglycemia) may occur if you already take another medication to treat diabetes. Discuss with your doctor how much of each medicine to take.

PROPER USE OF THIS MEDICATION

Follow the directions given to you by your doctor.

Take JARDIANCE:
- once a day;
- at any time of the day;
- by mouth;
- with or without food.

Swallow whole. Do NOT cut or divide tablets.

Usual Adult dose:
Recommended starting dose: one 10 mg tablet a day.
Your doctor may increase your dose to one 25 mg tablet, if needed to further control your blood sugar level.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Do not take a double dose of JARDIANCE.

If it is 12 hours or more until your next dose, take JARDIANCE as soon as you remember. Then take your next dose at the usual time.

If it is less than 12 hours until your next dose, skip the missed dose. Then take your next dose at the usual time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- dehydration;
- unusual thirst;
- passing more urine than usual or needing to pass more often;
- itching;
- rash;
- straining or pain when emptying the bladder.

If any of these affects you severely, tell your doctor or pharmacist.

JARDIANCE can cause abnormal blood test results. Your doctor will decide when to perform blood tests. They may check kidney function, blood fat levels and amount of red blood cells in your blood (hematocrit).

Diabetic Ketoacidosis (DKA) is a serious medical condition with normal or high blood glucose levels. Get immediate medical help if you have any of the symptoms described in the table below under DKA, even if your blood glucose levels are normal.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Get immediate medical help
		Only if severe	In all cases	
Very Common	**Low blood sugar (hypoglycaemia):** shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood.		✓	
Common	**Urinary tract infection:** burning sensation when passing urine, pain in the pelvis, or mid-back pain, or increased need to urinate.		✓	
	Genital infections: Vaginal yeast infection: severe itching, burning, soreness, irritation, and a whitish-gray cottage cheese-like discharge. Yeast infection of the penis: red, swollen, itchy, head of penis, thick, lumpy discharge under foreskin, unpleasant odour, difficulty retracting foreskin, pain passing urine or during sex.	✓		
	Volume depletion (loss of needed fluids from the body, dehydration, especially in patients older than 75 years of age): dry or sticky mouth, headache, dizziness or urinating less often than normal.			✓
	Allergic skin reactions: rash, hives, swelling of your lips, face, throat or tongue that may cause difficulty in breathing or swallowing.			✓
Uncommon	**Low Blood Pressure:** dizziness, fainting, lightheadedness. May occur when you go from lying to sitting to standing up.		✓	
	Kidney problems: any change in the amount, frequency or colour (pale or dark) of urine.		✓	
	Severe infection that spreads from urinary tract throughout body (sepsis): fever or low body temperature, chills, rapid breathing, rapid heartbeat, pain with urination, difficulty urinating, frequent urination.			✓
	Acute kidney infection: painful, urgent or frequent urination, lower back (flank) pain, fever or chills, cloudy or foul smelling urine, blood in your urine.			✓
Rare	**Diabetic Ketoacidosis (DKA):** difficulty breathing, feeling very thirsty, vomiting, stomach pain, nausea, loss of appetite, confusion, unusual tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.			✓

This is not a complete list of side effects. For any unexpected effects while taking JARDIANCE, contact your doctor or pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Store at room temperature (15 – 30°C).

Keep in a safe place out of reach from children.

MORE INFORMATION

If you want more information about JARDIANCE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website (http://www.boehringer-ingelheim.ca), or by calling the manufacturer, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, extension 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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Boehringer Ingelheim (Canada) Ltd.,
Burlington, ON, Canada L7L 5H4

Co-promoted with:
Eli Lilly Canada Inc.,
Toronto, ON, Canada M1N 2E8