PRODUCT MONOGRAPH

Pr JARDIANCE™

empagliflozin tablets

10 mg and 25 mg

ATC Code: A10BX12
Other blood glucose lowering drugs, excl. insulins

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TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION....3
SUMMARY PRODUCT INFORMATION....3
INDICATIONS AND CLINICAL USE....3
CONTRAINDICATIONS....4
WARNINGS AND PRECAUTIONS....4
ADVERSE REACTIONS....7
DRUG INTERACTIONS....13
DOSAGE AND ADMINISTRATION....18
OVERDOSAGE....19
ACTION AND CLINICAL PHARMACOLOGY....19
STORAGE AND STABILITY....22
SPECIAL HANDLING INSTRUCTIONS....22
DOSAGE FORMS, COMPOSITION AND PACKAGING....22

PART II: SCIENTIFIC INFORMATION....23
PHARMACEUTICAL INFORMATION....23
CLINICAL TRIALS....24
DETAILED PHARMACOLOGY....32
TOXICOLOGY....32
REFERENCES....35

PART III: CONSUMER INFORMATION....37

[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).

Important Limitations of Use: In combination therapy, 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 is expected to have diminished efficacy in elderly patients as older patients are more likely to have impaired renal function. 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.
- Renally impaired patients with eGFR less than 45 mL/min/1.73m^2, severe renal impairment, end-stage renal disease and patients on dialysis.

WARNINGS AND PRECAUTIONS

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.

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).

Endocrine and Metabolism

Diabetic ketoacidosis: Cases of diabetic ketoacidosis (DKA) have been reported in patients treated with empagliflozin and other SGLT2 inhibitors. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).

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.

Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. Discontinuation or temporary interruption of JARDIANCE should be considered.

Patients at higher risk of DKA while taking empagliflozin include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), dehydrated patients, and patients with a history of ketoacidosis or who are known to have a low beta-cell function reserve. JARDIANCE should be used with caution in these patients. 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.

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).

Urinary tract infections: JARDIANCE increases the risk for urinary tract infections (see ADVERSE REACTIONS).

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.

Renal

JARDIANCE 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).

Renal function should be assessed prior to initiation of JARDIANCE and regularly thereafter. JARDIANCE should not be initiated in patients with an eGFR <60 mL/min/1.73m^2, and must be discontinued if eGFR falls below 45 mL/min/1.73m^2 (see CONTRAINDICATIONS). It is not expected to be effective in these patients and adverse reactions are more frequent (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY). In patients with moderate impairment and eGFR ≥45 mL/min/1.73m^2 to 60 mL/min/1.73m^2, close monitoring of renal function is recommended (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

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, SGLT-2 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): The safety and efficacy have not been established in pediatric patients; therefore JARDIANCE should not be used in this population.

Geriatrics (≥65 years of age): 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.

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 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). Therapeutic experience in patients aged ≥85 years is limited. Initiation of empagliflozin therapy in this population is not recommended.

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: 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. JARDIANCE is contraindicated in patients with an eGFR <45 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 8400 patients with type 2 diabetes were treated with JARDIANCE in clinical studies to evaluate the safety of JARDIANCE, alone or in combination with metformin, a sulfonylurea, a PPARγ agonist, DPP4 inhibitors, or insulin. In clinical trials 2856 patients received treatment

with JARDIANCE 10 mg and 3738 patients received treatment with JARDIANCE 25 mg for at least 24 weeks; 601 were treated with JARDIANCE 10 mg and 881 patients were treated with JARDIANCE 25 mg for at least 76 weeks.

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%).

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.

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)

System organ class Preferred term	JARDIANCE 10 mg n = 999 N (%)	JARDIANCE 25 mg n = 977 N (%)	Placebo n = 995 N (%)
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.

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.

Description of Selected Adverse Reactions

Hypoglycemia: The frequency of hypoglycemia depended on the type of background therapy used in each study (see Table 2). The incidence of hypoglycaemia is increased when JARDIANCE was administered with insulin or a sulfonylurea (see WARNINGS AND PRECAUTIONS).

Table 2 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

[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.

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

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.

Patients with renal impairment: JARDIANCE was compared to placebo as add-on to preexisting 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.

Cardiovascular safety: In a prospective meta-analysis of independently adjudicated cardiovascular events from 7 phase II and III clinical studies involving 8247 patients with type 2 diabetes (placebo N=2816, empagliflozin 10 mg N=2614, and empagliflozin 25 mg N=2817), empagliflozin did not increase cardiovascular risk as measured by a composite endpoint based on time to first occurrence of CV death (including fatal stroke and fatal myocardial infarction), non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina.

Diabetic ketoacidosis: Post-marketing cases of diabetic ketoacidosis (DKA) have been reported in patients treated with empagliflozin and other SGLT2 inhibitors (see WARNINGS AND PRECAUTIONS). In some cases, the presentation of the condition was atypical, with blood glucose values only moderately elevated (below 14 mmol/L (250 mg/dL)). 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 be assessed for ketoacidosis immediately, and discontinuation or temporary interruption of JARDIANCE should be considered.

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.

Increases in serum phosphate: There was no difference from baseline in mean serum phosphate, compared to placebo, however, 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).

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.

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).

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, simvastatin (CYP3A4, OATP1B1, OATP1B3 substrate), torasemide and hydrochlorothiazide in healthy volunteers (see Table 3). JARDIANCE overall exposure (AUC) increased by 59%, 35% and 53%, when co-administered with gemfibrozil (CYP2C8 and OATP1B1 inhibitor), rifampicin (OATP1B1 and 1B3inhibitor) 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 3 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)	Cmax (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

Hydrochlorothiazide	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), hydrochlorthiazide, torasemide and oral contraceptives ethinyl estradiol and norgestrel (CYP3A4 substrate) when co-administered in healthy volunteers (see Table 4).

Table 4 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)	
Hydrochlorothiazide	25 mg, qd, 5 days	25 mg, qd, 5 days	0.96 (0.89; 1.04)	1.02 (0.89; 1.17)	No dose 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 metabolite: 1.04 (1.00; 1.09)	1.03 (0.94; 1.12)	

			M3 metabolite	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
			Simva statin 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 efficacy of JARDIANCE is dependent on renal function. Renal function must be assessed prior to initiation of JARDIANCE therapy and periodically thereafter. No dosage adjustment for JARDIANCE is indicated in patients with mild renal impairment (eGFR ≥60 mL/min/1.73m^2).

JARDIANCE should not be initiated in patients with an eGFR <60 mL/min/1.73m^2. JARDIANCE should be discontinued if eGFR falls below 45 mL/min/1.73m^2 (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY). In patients with moderate impairment and eGFR ≥45 mL/min/1.73m^2, close monitoring of renal function is recommended (see WARNINGS AND PRECAUTIONS).

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 5 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 $AUC_{\tau,ss}$ 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 $AUC_{\tau,ss}$ 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. $AUC_{\tau,ss}$ 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

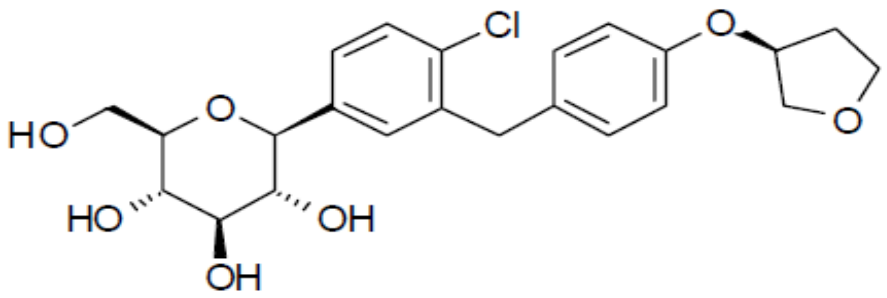
Common name: empagliflozin

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 6). 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, or 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 6 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: 1week	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: 1week	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,	Empagliflozin 25 mg Glimepiride (Amaryl®):1	Total: 1549/1545 (until interim database		

Study No.	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomised / treated	Mean age years (SD)	Gender (%M/F)
	double blind, active-controlled, parallel-group	to 4 mg Placebo (run-in period) tablets, oral, once daily Run-in: 2 weeks Treatment: 104 weeks Extension: 104 weeks Follow-up: 4 weeks	lock) Empagliflozin: 25 mg: 769/765 Glimepiride 1 to 4 mg: 780/780	 Empagliflozin: 25 mg: 56.2 (10.3) Glimepiride: 55.7 (10.4)	 Empagliflozin: 25 mg: 56/43 Glimepiride: 54/46
Add-on Combination Therapy with Metformin and a Sulfonylurea					
1245.23+	Randomised, multicentre, double-blind, placebo-controlled, parallel group	Empagliflozin10 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: 1week	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: 1week	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

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 7, 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 7 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 8, 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 8 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 9, 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 9 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 10, 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 10 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 (%)			

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
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 11, 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 11 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)

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
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 12, statistically significant reduction in HbA1c relative to placebo was observed with JARDIANCE 10 mg and 25 mg at Week 18.

Table 12 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.

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 13). In patients with severe renal impairment, JARDIANCE 25 mg did not reduce HbA1c at Week 24 and more adverse events were noted.

Table 13 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)

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg	Placebo	JARDIANCE 25 mg	Placebo	JARDIANCE 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)	
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 glucosuria. 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).

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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).

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 (a complication of diabetes with high blood sugar, rapid weight loss, nausea, or vomiting);
- 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

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

- are older than 65 years of age;
- 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;
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
- are on a very low carbohydrate diet;
- 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 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.

Rare cases of diabetic ketoacidosis (DKA) have been reported in patients treated with JARDIANCE. Symptoms of ketoacidosis include difficulty breathing, feeling very thirsty, vomiting, stomach pain, nausea, loss of appetite, confusion, and unusual tiredness. Get immediate medical help if you think you have these symptoms.

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 sulphonylurea 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 health care 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;
- straining or pain when empting 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).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	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.		✓	
Common	**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.	✓		
Common	**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.			✓
Uncommon	**Low Blood Pressure:** dizziness, fainting, lightheadedness. May occur when you go from lying to sitting to standing up.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	Symptom / effect	Talk with your doctor or pharmacist		Get immediate medical help
		Only if severe	In all cases	
Rare	**Diabetic Ketoacidosis (DKA):** difficulty breathing, feeling very thirsty, vomiting, stomach pain, nausea, loss of appetite, confusion, and unusual tiredness.			✓

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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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^{0}C).

Keep in a safe place out of reach from children.

MORE INFORMATION

The most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: http://www.boehringer-ingelheim.ca or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, ext. 84633 (Medical Information).

Please visit our website to see if more up-to-date information has been posted.

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