Jardiance®
Empagliflozin

DESCRIPTION
Jardiance 10 mg film-coated tablets :
Pale yellow, round, biconvex, bevel-edged film-coated tablets. Debossed on one side with Boehringer Ingelheim company symbol and "S10" on other side.
Jardiance 25 mg film-coated tablets :
Pale yellow, oval, biconvex, film-coated tablets. Debossed on one side with Boehringer Ingelheim company symbol and "S25" on other side.

COMPOSITION
JARDIANCE film-coated tablets contain 10 or 25 mg D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3- furanyl]oxy]phenyl]methyl]phenyl]-, (1S) (= empagliflozin)

Excipients:
Lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, talc, macrogol 400, iron oxide yellow.

INDICATIONS
Type 2 diabetes mellitus
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,
- metformin and pioglitazone,

When the existing therapy, along with diet and exercise, does not provide adequate glycemic control

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections Special warnings and precautions for use, Interaction with other medicinal products and other forms of interactions, and Pharmacodynamic properties

Heart failure
Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure.

Chronic kidney disease
Jardiance is indicated in adults for the treatment of chronic kidney disease (eGFR 20 – 90 ml/min/1.73 m^2) in reducing the time to the first occurrence of kidney disease progression.

DOSAGE AND ADMINISTRATION
Type 2 diabetes mellitus
Recommended dose and dosage adjustment:
The recommended starting dose of JARDIANCE is 10 mg once daily. In patients tolerating

empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73m^2 and requiring additional glycemic control, the dose can be increased to 25 mg once daily. JARDIANCE can be taken with or without food. The maximum daily dose is 25 mg.

Heart failure
The recommended dose is 10 mg empagliflozin once daily.

Chronic kidney disease
The recommended dose is 10 mg empagliflozin once daily.

Patients with renal impairment
JARDIANCE should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in these patients.

Type 2 diabetes mellitus
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 ≥ 60mL/min/1.73m^2).

JARDIANCE should not be initiated in patients with an eGFR <60mL/min/1.73m^2. JARDIANCE should be discontinued if eGFR falls below 45mL/min/1.73m^2. In patients with moderate impairment and eGFR ≥45mL/min/1.73m^2, close monitoring of renal function is recommended.

Heart failure
Treatment of patients with heart failure (with or without type 2 diabetes mellitus) :
For patients with an eGFR ≥ 20mL/min/1.73m^2, the recommended daily dose is 10 mg empagliflozin. JARDIANCE is not recommended for use in patients with eGFR <20 ml/min/1.73m^2 (see Special warnings and precautions). There are insufficient data to support use in these patients

Chronic kidney disease
Treatment of patients with chronic kidney disease (with or without type 2 diabetes mellitus):
For patients with an eGFR greater than or equal to 20 mL/min/1.73 m^2, the recommended daily dose is 10 mg empagliflozin.

JARDIANCE is not recommended for use in patients with eGFR < 20 mL/min/1.73 m^2 (see Special warnings and precautions). There are insufficient data to support use in these patients.

Patients with hepatic insufficiency
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. Experience in patients with severe hepatic impairment is limited. Therefore, JARDIANCE is not recommended for use in this population.

Elderly patients
No dose adjustment for JARDIANCE is required based on age; In patients 75 years and older, an increased risk for volume depletion should be taken into account.

Concomitant Use with sulfonylurea
When JARDIANCE is used as add-on therapy with a sulfonylurea, a lower dose of the sulfonylurea may be considered to reduce the risk of hypoglycemia

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.

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

CONTRAINDICATIONS
- Hypersensitivity to empagliflozin or any of the excipients in Jardiance.
- Severe renal impairment (eGFR <20 ml/min/1.73m^2), end-stage renal disease and patient on dialysis for the treatment of heart failure.
- Renally impaired patients with eGFR less than 45 mL/min/1.73m^2 for treatment of type 2 diabetes mellitus. The efficacy of Jardiance is dependent on renal function (see special warning and precautions).
- In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated. The 10 mg tablet contains 162.5 mg of lactose and the 25 mg tablet contains 113 mg of lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

SPECIAL WARNINGS AND PRECAUTIONS
General
JARDIANCE should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Ketoacidosis
Cases of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with diabetes mellitus treated with empagliflozin, including fatal cases. 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). Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients.
The risk of 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. If ketoacidosis is suspected, JARDIANCE should be discontinued, patient should be evaluated, and prompt treatment should be instituted.
Patients who may be at higher risk of ketoacidosis while taking JARDIANCE include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration, and patients with a history of ketoacidosis.

Ketoacidosis and glucosuria may be prolonged after discontinuation of JARDIANCE in some patients, i.e. it may last longer than expected from 5 plasma half-lives of empagliflozin (see section Pharmacokinetics)

JARDIANCE should be used with caution in these patients. When reducing the insulin dose (see Dosage and Administration), caution should be taken. In patients treated with JARDIANCE consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to acute illness or surgery).
In these situations, consider monitoring of ketones, even if Jardiance treatment has been interrupted.

Necrotizing fasciitis of the perineum (Fournier's gangrene)
Cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in female and male patients treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with JARDIANCE who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotizing fasciitis. If suspected, JARDIANCE should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Use in patients with renal impairment
Type 2 diabetes mellitus
JARDIANCE should not be initiated in patients with an eGFR <60ml/min/1.73m^2. Jardiance should be discontinued if eGFR falls below 45ml/min/1.73m^2. In patients with moderate renal impairment and eGFR ≥45ml/min/1.73m^2, close monitoring of renal function is recommended.
JARDIANCE should not be used in patients with ESRD or in patients on dialysis as it is not expected to be effective in these patients (see section dosage and administration and pharmacokinetics).

Heart failure
JARDIANCE is not recommended in patients with eGFR <20 ml/min/1.73m^2.

Chronic kidney disease
JARDIANCE is not recommended for use in patients with eGFR < 20 mL/min/1.73 m^2 (see Special warnings and precautions).

Monitoring of renal function
Assessment of renal function is recommended as follows:
- Prior to JARDIANCE initiation and periodically during treatment, i.e. at least yearly (see section Dosage and Administration and Pharmacokinetics).
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

Hepatic injury
Cases of hepatic injury have been reported with JARDIANCE in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established.

Use in patients at risk for volume depletion
Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying glucosuria may lead to a modest decrease in blood pressure (see section Pharmacodynamic Properties). Therefore, 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 anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.
In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with JARDIANCE should be considered until the fluid loss is corrected.

Complicated urinary tract infections
Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin (see Side Effect). Temporary interruption of JARDIANCE should be considered in patients with complicated urinary tract infections.

Elderly patients
The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with JARDIANCE had adverse reactions related to volume depletion as compared to placebo (see section Side Effects).
Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).

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

Lactose
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet.

USE IN SPECIFIC POPULATION
Fertility, Pregnancy and Lactation
Pregnancy
There are no data from the use of empagliflozin in pregnant women. Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development (see section Reproduction Toxicity). As a precautionary measure, it is preferable to avoid the use of JARDIANCE during early pregnancy. JARDIANCE is not recommended during the second and third trimester of pregnancy.

Lactation
No data in humans are available on excretion of empagliflozin into milk. Available toxicological data in animals have shown excretion of empagliflozin in milk. A risk to the newborns/infants cannot be

excluded. JARDIANCE should not be used during breast-feeding.

Fertility
No studies on the effect on human fertility have been conducted for JARDIANCE. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section Reproduction Toxicity)

Effects on ability to drive and use machines
JARDIANCE has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when JARDIANCE is used in combination with a sulfonylurea

INTERACTIONS

Pharmacodynamic Interactions

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section Special Warnings and Precautions for Use).

Insulin secretagogues

Insulin secretagogues, such as sulfonylurea, may increase the risk of hypoglycaemia. Therefore, a lower dose of an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin (see sections Dosage and Administration and Side Effects).

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5- AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Pharmacokinetic Interactions

Lithium

Concomitant use of SGLT2 inhibitors, including empagliflozin, with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with empagliflozin initiation or following dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

***In vitro* assessment of drug interactions**

Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. At therapeutic doses, the potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 and UGT isoforms is remote. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

***In vivo* assessment of drug interactions**

No clinically meaningful pharmacokinetic interactions were observed when empagliflozin was coadministered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of JARDIANCE is recommended when co- administered with commonly prescribed medicinal products.

Empagliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, in healthy volunteers and with or without co-administration of torasemide and hydrochlorothiazide in

patients with T2DM. Increases in overall exposure (AUC) of empagliflozin were seen following co-administration with gemfibrozil (59%), rifampicin (35%), or probenecid (53%). These changes were not considered to be clinically meaningful. Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

SIDE EFFECTS

Type 2 diabetes mellitus

A total of 15,582 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin, of which 10,004 patients were treated with empagliflozin, either alone or in combination with metformin, a sulfonylurea, a PPARγ agonist, DPP4 inhibitors, or insulin. This pool includes the EMPA-REG OUTCOME study involving 7,020 patients at high cardiovascular risk (mean age 63.1 years, 9.3% patients at least 75 years old, 28.5% women) treated with JARDIANCE 10 mg/ day (n=2345), JARDIANCE 25 mg/ day (n=2342), or placebo (n=2333) up to 4.5 years. The overall safety profile of empagliflozin in this study was comparable to the previously known safety profile.
In the above described trials, the frequency of AEs leading to discontinuation was similar by treatment groups for placebo (5.6%), JARDIANCE 10 mg (5.0%) and JARDIANCE 25 mg (5.3%). Placebo-controlled double-blind trials of 18 to 24 weeks of exposure included 3534 patients, of which 1183 were treated with placebo, 1185 were treated with JARDIANCE 10 mg and 1166 were treated with JARDIANCE 25 mg (Table 1).
The most frequent adverse drug reaction was hypoglycaemia, which depended on the type of background therapy used in the respective studies (Table 2).

Heart failure

The EMPEROR studies included patients with heart failure and either reduced ejection fraction (N=3 726) or preserved ejection fraction (N=5 985) treated with empagliflozin 10 mg or placebo. Approximately half of the patients had type 2 diabetes mellitus. The most frequent adverse reaction of the pooled EMPEROR-Reduced and EMPEROR-Preserved studies was volume depletion (empagliflozin 10 mg: 11.4%. placebo: 9.7%).

Chronic kidney disease

The EMPA-KIDNEY study included patients with chronic kidney disease (N = 6 609) treated with 10 mg empagliflozin or placebo. About 44% of the patients had type 2 diabetes mellitus. The most frequent adverse events in the EMPA-KIDNEY study were gout (empagliflozin 7.0% vs placebo 8.0%), and acute kidney injury (empagliflozin 2.8% vs placebo 3.5%) which were more frequently reported in patients on placebo.
The overall safety profile of empagliflozin was generally consistent across the studied indications.

Table 1 Side effects reported in patients who received JARDIANCE in placebo controlled double-blind studies of 18 to 24 weeks, classified by MedDRA System organ class and MedDRA Preferred terms

	Placebo n=1183 %	**Empagliflozin 10 mg n=1185 %**	**Empagliflozin 25 mg n=1166 %**
System Organ Class Adverse reaction			
Infection and infestations			
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections*	1.0	4.0	3.9
Urinary tract infections*	7.2	8.8	7.0
Metabolism and nutrition disorders			
Hypoglycaemia		Refer to Table 2	
Gastrointestinal Disorder			
Constipation	1.1	1.4	0.9
Skin and subcutaneous tissue disorders			
Pruritus	0.7	0.9	0.7
Vascular disorders			
Volume depletion	0.3	0.6	0.4
Renal and urinary disorders			
Increased urination	1.4	3.5	3.3
Dysuria	0.3	0.3	0.4
General disorders and administration site conditions			
Thirst	0	1.4	1.5
Investigations			
Glomerular filtration rate decreased[c]	0.3	0.1	0
Blood creatinine increased[c]	0.5	0.6	0.1
Haematocrit increased[#, c]	0	<0.1	0.1
Serum lipids increased[c]	4.9	5.7	5.1

* based on prespecified list of preferred terms;
[#] frequency of the preferred term in the broad safety data pool
[a] frequency from add on to metformin and sulfonylurea study
[b] frequency from add on to basal insulin study after 18 weeks of treatment
[c] see subsections below

Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for JARDIANCE and placebo as monotherapy, as add-on to metformin, as add-on to pioglitazone +/- metformin, and as add-on with linagliptin + metformin.

The frequency of patients with hypoglycaemia was increased in patients treated with JARDIANCE compared to placebo when given as add-on to metformin plus sulfonylurea, and as add-on to insulin +/- metformin and +/-sulfonylurea. (Table 2)

Major hypoglycaemia (events requiring assistance)

The frequency of patients with major hypoglycaemic events was low (<1%) and similar for JARDIANCE and placebo as monotherapy, as add-on to metformin +/-sulfonylurea, as add on to pioglitazone +/- metformin. The frequency of patients with major hypoglycaemic events was increased in patients treated with JARDIANCE compared to placebo when given as add- on to insulin +/- metformin and +/-sulfonylurea.

Table 2 Frequency of patients with confirmed hypoglycaemic events per trial (1245.19, 1245.20, $1245.23_{(met)}$, $1245.23_{(met+SU)}$, 1245.33, 1245.49, $1275.9_{(lina+met)}$ and 1245.25 – Treated Set_1)

	Placebo	**Empagliflozin 10 mg**	**25 mg**
Monotherapy (1245.20) (24 weeks)	n=229	n=224	n=223
Overall confirmed (%)	0.4%	0.4%	0.4%
Major (%)	0%	0%	0%
In combination with metformin (1245.23*(met)*) (24 weeks)	n=206	n=217	n=214
Overall confirmed (%)	0.5%	1.8%	1.4%
Major (%)	0%	0%	0%
In combination with metformin + sulfonylurea (1245.23 *(met + SU)*) (24 weeks)	n=225	n=224	n=217
Overall confirmed (%)	8.4%	16.1%	11.5%
Major (%)	0%	0%	0%
In combination with pioglitazone +/- metformin (1245.19) (24 weeks)	n=165	n=165	n=168
Overall confirmed (%)	1.8%	1.2%	2.4%
Major (%)	0%	0%	0%
In combination with basal insulin (1245.33) (18 weeks$_2$ / 78 weeks)	n=170	n=169	n=155
Overall confirmed (%)	20.6%/35.3%	19.5%/36.1%	28.4%/36.1%
Major (%)	0%/0%	0%/0%	1.3%/1.3%
In combination with MDI insulin +/- metformin (1245.49) (18 weeks$_2$ / 52 weeks)	n=188	n=186	n=189
Overall confirmed (%)	37.2%/58.0%	39.8%/51.1%	41.3%/57.7%
Major (%)	0.5%/1.6%	0.5%/1.6%	0.5%/0.5%
In combination with metformin and linagliptin (1275.9) (24 weeks)$_3$	n=110	n=112	n=110

Overall confirmed (%)	0.9%	0.0%	2.7%
Major (%)	0%	0%	0.9%
EMPA-REG OUTCOME (1245.25)	n=2333	n=2345	n=2342
Overall confirmed (%)	27.9%	28%	27.6%
Major (%)	1.5%	1.4%	1.3%

Confirmed: blood glucose ≤3.9 mmol/L or required assistance Major: required assistance

[1] i.e. patients who had received at least one dose of study drug

[2] The dose of insulin as background medication was to be stable for the first 18 weeks

[3] This was a fixed-dose combination of empagliflozin with linagliptin 5 mg with a background treatment with metformin MDI = multiple daily injections

Urinary tract infection

The overall frequency of urinary tract infection adverse events was similar in patients treated with JARDIANCE 25 mg and placebo (7.0% and 7.2%), and higher in patients treated with JARDIANCE 10 mg (8.8%). Similar to placebo, urinary tract infection was reported more frequently for JARDIANCE in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections was similar to placebo for mild, moderate, and severe intensity reports. Urinary tract infection events were reported more frequently for empagliflozin compared to placebo in female patients, but not in male patients.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for JARDIANCE 10 mg (4.0%) and JARDIANCE 25 mg (3.9%) compared to placebo (1.0%). These adverse events were reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe in intensity.

Cases of phimosis/acquired phimosis have been reported concurrent with genital infections.

Increased urination

As expected via its mechanism of action, increased urination (as assessed by PT search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with JARDIANCE 10 mg (3.5%) and JARDIANCE 25 mg (3.3%) compared to placebo (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and JARDIANCE (<1%).

Volume depletion

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was similar to placebo (JARDIANCE 10 mg 0.6%, JARDIANCE 25 mg 0.4% and placebo 0.3%,). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients aged 75 years and older. In patients ≥75 years of age (pooling of all patients with diabetes, n=13,402) the frequency of volume depletion events was similar for JARDIANCE10 mg (2.3%) compared to placebo (2.1%), but it increased with JARDIANCE 25 mg (4.3%).

Blood creatinine increased and glomerular filtration rate decreased
The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between empagliflozin and placebo (blood creatinine increased : JARDIANCE 10 mg 0.6%, JARDIANCE 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%).
In placebo-controlled, double-blind studies up to 76 weeks, initial transient increases in creatinine (mean change from baseline after 12 weeks: JARDIANCE 10 mg 0.0011 mmol/L, JARDIANCE 25 mg 0.0006 mmol/L) and initial transient decreases in estimated glomerular filtration rates (mean change from baseline after 12 weeks: JARDIANCE 10 mg - 1.34mL/min/1.73m^2, JARDIANCE 25 mg - 1.37mL/min/1.73m^2) have been observed. These changes were generally reversible during continuous treatment or after drug discontinuation (see CLINICAL TRIALS - Cardiovascular outcome - Figure 4 for the eGFR course in the EMPA- REG OUTCOME study).

Laboratory parameters
Haematocrit increased
In a pooled safety analysis (pooling of all patients with diabetes, n=13,402), mean changes from baseline in haematocrit were 3.4% and 3.6% for empagliflozin 10 mg and 25 mg, respectively, compared to -0.1% for placebo. In the EMPA-REG OUTCOME study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

Serum lipids increased
In a pooled safety analysis (pooling of all patients with diabetes, n=13,402), mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 4.9% and 5.7% versus 3.5%; HDL-cholesterol 3.3% and 3.6% versus 0.4%; LDL-cholesterol 9.5% and 10.0% versus 7.5%; triglycerides 9.2% and 9.9% versus 10.5%.

Marketing experience
Ketoacidosis, Urosepsis, Pyelonephritis, Allergic skin reactions (e.g. rash, urticaria), Angioedema. Infections and infestations : Necrotizing fasciitis of the perineum (Fournier´s gangrene)*.
*Observed in patients with diabetes mellitus

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via following contact: Telephone: +62 21 21684084 Or Email: IDsafety@zuelligpharma.com

OVERDOSE
Symptoms
During controlled clinical trials in healthy subjects, single doses of up to 800 mg empagliflozin, were well tolerated.

Therapy
In the event of an overdose, supportive treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03.

Mode of Action

Empagliflozin is a reversible competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC_{50} of 6278 nM), responsible for glucose absorption in the gut.

SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR. Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine. In patients with T2DM, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24-hour dosing interval. Increased urinary glucose excretion was maintained at the end of 4-week treatment period, averaging approximately 78 g/day with empagliflozin 25 mg once daily. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with T2DM. Empagliflozin (10 mg and 25 mg) improves both fasting and post-prandial plasma glucose levels.

There is no direct effect on changes in β cell function and insulin secretion / action, and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-B (HOMA-β) and proinsulin to insulin ratio were noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction.

The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure.

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart, downregulating sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodeling, filling pressures and diastolic function as well as preserving kidney structure and function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial cardiac and renal effects.

Clinical Trials

<u>Type 2 diabetes mellitus</u>

A total of 17331 patients with type 2 diabetes were evaluated in 15 double-blind, placebo- and active-controlled clinical studies, of which 4603 patients received empagliflozin 10 mg and 5567 received empagliflozin 25 mg. Six studies had a treatment duration of 24 weeks; in extensions of applicable studies, and other trials, patients were exposed to JARDIANCE for up to 102 weeks.

Treatment with empagliflozin (10 mg and 25 mg) as monotherapy and in combination with metformin, pioglitazone, and sulfonylurea lead to clinically relevant improvements in HbA1c, fasting

plasma glucose (FPG), body weight, systolic and diastolic blood pressure (SBP and DBP, respectively). Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving an HbA1c goal of < 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. There was a clinically meaningful improvement in HbA1c in all subgroups of gender, race, geographic region, time since diagnosis of T2DM, body mass index, insulin resistance based on HOMA-IR, and beta cell function based on HOMA-β. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Clinically meaningful HbA1c reduction was seen in patients with eGFR >45mL/min/1.73m² (see Dosage AND Administration – Patients with Renal Impairment). In patients aged 75 years and older, reduced efficacy of JARDIANCE was observed.

Empagliflozin as add on to metformin therapy

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients with type 2 diabetes not controlled on metformin. The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment.

Treatment with JARDIANCE resulted in statistically significant improvements in HbA1c and body weight, and clinically meaningful reductions in FPG and blood pressure compared to placebo (Table 3).

In the double-blind placebo-controlled extension of this study, reductions of HbA1c (change from baseline of -0.62% for empagliflozin 10 mg, -0.74% for empagliflozin 25 mg and -0.01% for placebo), body weight (change from baseline of -2.39 kg for empagliflozin 10 mg, -2.65 kg for empagliflozin 25 mg and -0.46 kg for placebo) and blood pressure (SBP: change from baseline of -5.2 mmHg for empagliflozin 10 mg, -4.5 mmHg for empagliflozin 25 mg and 0.8 mmHg for placebo, DBP: change from baseline of -2.5 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg and -0.5 mmHg for placebo) were sustained up to 76 weeks of treatment.

Table 3 Results of a 24-week (LOCF)[3] placebo-controlled study of JARDIANCE as add-on to metformin (Full Analysis Set)

JARDIANCE as add-on to metformin therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 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 (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	12.5	37.7	38.7
N	207	216	213
Fasting plasma glucose (mmol/L)[2]			
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)
N	207	217	213
Patients (%) achieving weight loss of >5%[2]	4.8	21.2	23.0
N	207	217	213
SBP (mmHg)[2]			
Baseline (mean)	128.6	129.6	130.0
Change from baseline[1]	-0.4	-4.5	-5.2
Difference from placebo[1] (95% CI)		-4.1* (-6.2, -2.1)	-4.8* (-6.9, -2.7)

[1] mean adjusted for baseline value and stratification
[2] not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[3] Last observation (prior to glycaemic rescue) carried forward (LOCF)
*p-value <0.0001

Empagliflozin as add on to a combination of metformin and sulfonylurea therapy

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients with type 2 diabetes not sufficiently treated with a combination of metformin and a sulfonylurea. The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment. Treatment with JARDIANCE resulted in statistically significant improvements in HbA1c and body weight and clinically meaningful reductions in FPG and blood pressure compared to placebo (Table 4).

In the double-blind, placebo-controlled extension of this study, reductions of HbA1c (change from baseline of -0.74% for empagliflozin 10 mg, -0.72% for empagliflozin 25 mg and -0.03% for placebo), body weight (change from baseline of -2.44 kg for empagliflozin 10 mg, -2.28 kg for empagliflozin 25 mg and -0.63 kg for placebo) and blood pressure (SBP: change from baseline of -3.8 mmHg for empagliflozin 10 mg, -3.7 mmHg for empagliflozin 25 mg and -1.6 mmHg for placebo, DBP: change from baseline of -2.6 mmHg for empagliflozin 10 mg, -2.3 mmHg for empagliflozin 25 mg and -1.4 mmHg for placebo) were sustained up to 76 weeks of treatment.

Table 4 Results of a 24-week (LOCF)[3] placebo-controlled study of empagliflozin as add-on to metformin and a sulfonylurea (Full Analysis Set)

JARDIANCE as add-on to metformin and a sulfonylurea therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 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 (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	9.3	26.3	32.2
N	224	225	215
Fasting plasma glucose (mmol/L)[2]			
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)
N	225	225	216
Patients (%) achieving weight loss of >5%[2]	5.8	27.6	23.6
N	225	225	216
Systolic blood pressure (mmHg)[2]			
Baseline (mean)	128.8	128.7	129.3
Change from baseline[1]	-1.4	-4.1	-3.5
Difference from placebo[1] (95% CI)		-2.7# (-4.6, -0.8)	-2.1# (-4.0, -0.2)

[1] mean adjusted for baseline value and stratification
[2] not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[3] Last observation (prior to glycaemic rescue) carried forward (LOCF)
*p-value <0.0001, #p-value <0.05

2 hour post-prandial glucose

Treatment with empagliflozin (10 mg or 25 mg) as add-on to metformin or metformin plus sulfonylurea resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin, placebo (n=57) +5.9 mg/dL, empagliflozin 10 mg (n=52): -46.0 mg/dl, empagliflozin 25 mg (n=58): -44.6 mg/dL; add-on to metformin plus sulfonylurea, placebo (n=35): -2.3 mg/dL, empagliflozin 10 mg (n=44): - 35.7 mg/dl, empagliflozin 25 mg (n=46): -36.6 mg/dL).

Empagliflozin as add on to a combination of metformin and pioglitazone therapy

The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo-controlled study of 24 weeks duration in patients with type 2 diabetes not controlled on a combination of metformin and pioglitazone. The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in FPG and body weight after 24 weeks of treatment.

Empagliflozin in combination with pioglitazone (dose ≥30 mg) with metformin resulted in statistically significant reductions in HbA1c, FPG, and body weight and clinically meaningful

reductions in blood pressure compared to placebo (Table 5).

In the double-blind, placebo-controlled extension of this study, reductions of HbA1c (change from baseline of -0.61% for empagliflozin 10 mg, -0.70% for empagliflozin 25 mg and -0.01% for placebo), body weight (change from baseline of -1.47 kg for empagliflozin 10 mg, -1.21 kg for empagliflozin 25 mg and +0.50 kg for placebo) and blood pressure (SBP: change from baseline of -1.7 mmHg for empagliflozin 10 mg, -3.4 mmHg for empagliflozin 25 mg and +0.3 mmHg for placebo, DBP: change from baseline of -1.3 mmHg for empagliflozin 10 mg, -2.0 mmHg for empagliflozin 25 mg and +0.2 mmHg for placebo) were sustained up to 76 weeks of treatment.

Table 5 Results of a 24 week (LOCF)3 placebo-controlled study of JARDIANCE as add-on to metformin and pioglitazone (Full Analysis Set)

JARDIANCE as add-on to metformin and pioglitazone therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 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 (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	7.7	23.8	30.0
N	165	163	168
Fasting plasma glucose (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)		-1.30* (-1.72, -0.91)	-1.58* (-2.04, -1.12)
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)
N	165	165	168
Patients(%) achieving weight loss of >5%[3]	5.5	18.8	13.7
N	165	165	168
SBP (mmHg) [2]			
Baseline (mean)	125.7	126.5	125.9
Change from baseline[1]	0.7	-3.1	-4.0
Difference from placebo[1] (95% CI)		-3.9 (-6.2, -1.5)	-4.7 (-7.1, -2.4)

[1] mean adjusted for baseline value and stratification
[2] not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[3] Last observation (prior to glycaemic rescue) carried forward (LOCF)
*p-value <0.0001

Empagliflozin 2-year data, as add on to metformin in comparison to glimepiride

In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (4 mg) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin 25 mg daily resulted in superior reduction in HbA1c, and a clinically meaningful reduction in FPG,

compared to glimepiride (Table 6). Empagliflozin 25 mg daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure (change from baseline in DBP of -1.8 mmHg for empagliflozin and +0.9 mmHg for glimepiride, p<0.0001).
Treatment with empagliflozin 25 mg daily resulted in statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin 25 mg, 24.2% for glimepiride, p<0.0001).

Table 6 Results at 104 weeks (LOCF)[4] in an active-controlled study comparing empagliflozin to glimepiride as add on to metformin (Full Analysis Set)

Empagliflozin as add-on to metformin therapy in comparison to glimepiride	**Empagliflozin 25 mg**	**Glimepiride (up to 4 mg)**
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 (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	33.6	30.9
N	764	779
Fasting Plasma Glucose [mmol/L] [2]		
Baseline (mean)	150.00	149.82
Change from baseline[1]	-15.36	-2.98
Difference from glimepiride[1] (95% CI)	-12.37 (-15.47,-9.27)	
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)	
N	765	780
Patients(%) achieving weight loss of >5%[2]	27.5	3.8
N	765	780
SBP (mmHg)[3]		
Baseline (mean)	133.4	133.5
Change from baseline[1]	-3.1	2.5
Difference from glimepiride[1] (97.5% CI)	-5.6** (-7.0,-4.2)	
N	765	780
Diastolic blood pressure (mmHg)[3]		
Baseline (mean)	79.5	79.4
Change from baseline[1]	-1.8	0.9
Difference from glimepiride[1] (97.5% CI)	-2.7** (-3.5,-1.8)	

[1] mean adjusted for baseline value and stratification
[2] not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[3] Last observation (prior glycemic rescue or to antihypertensive rescue) carried forward (LOCF)
[4] Last observation (prior to glycemic rescue) carried forward (LOCF)
* p-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority
** p-value <0.0001

Patients with renal impairment, 52-week placebo-controlled data

The efficacy and safety of empagliflozin as add on to antidiabetic therapy was evaluated in patients with mild and moderate renal impairment in a double-blind, placebo-controlled study for 52 weeks. Treatment with JARDIANCE led to statistically significant reduction of HbA1c and clinically meaningful improvement in FPG, body weight and BP compared to placebo at Week 24 (Table 7). The improvement in HbA1c, FPG, body weight, and blood pressure was sustained up to 52 weeks.

Table 7 Results at 24 weeks (LOCF) in a placebo-controlled study of JARDIANCE in renally impaired type 2 diabetes patients (Full Analysis Set)

	eGFR ≥60 to <90mL/min/1.73m²			**eGFR ≥45 to <60mL/min/1.73m²**	
	Placebo	**Empagliflozin**		**Placebo**	**Empagliflozin 25 mg**
		10 mg	**25 mg**		
N	95	98	97	89	91
HbA1c (%)					
Baseline (mean)	8.09	8.02	7.96	8.08	8.12
Change from baseline[1]	0.06	-0.46	-0.63	-0.08	-0.54
Difference from placebo[1] (95% CI)		-0.52* (-0.72, -0.32)	-0.68* (-0.88, -0.49)		-0.46* (-0.66, -0.27)
N	89	94	91	84	86
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	6.7	17.0	24.2	10.7	15.1
N	95	98	97	89	90
Fasting plasma glucose (mmol/L)					
Baseline (mean)	8.04	8.10	8.24	8.55	8.02
Change from baseline[1]	0.31	-0.77	-1.00	0.37	-0.82
Difference from placebo[1] (95% CI)		-1.09 (-1.62, -0.55)	-1.32 (-1.86, -0.78)		-1.19 (-1.77, -0.60)
N	95	98	97	89	91
Body Weight (kg)[2]					
Baseline (mean)	86.00	92.05	88.06	83.20	84.90
Change from baseline[1]	-0.33	-1.76	-2.33	-0.25	-0.98
Difference from placebo[1] (95% CI)		-1.43 (-2.09, -0.77)	-2.00 (-2.66, -1.34)		-0.74 (-1.50, 0.03)
N	95	98	97	89	91
Systolic blood pressure (mmHg)[2]					
Baseline (mean)	134.69	137.37	133.68	137.29	135.04
Change from baseline[1]	0.65	-2.92	-4.47	0.37	-5.69
Difference from placebo[1] (95% CI)		-3.57 (-6.86, -0.29)	-5.12 (-8.41, -1.82)		-6.07 (-9.79, -2.34)

[1] mean adjusted for baseline value and stratification
[2] not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
* p<0.0001

Patients with high baseline HbA1c >10%

In a pre-specified pooled analysis of three phase 3 studies, treatment with open-label empagliflozin 25 mg in patients with severe hyperglycaemia (N=184 mean baseline HbA1c 11.15%) resulted in a clinically meaningful reduction in HbA1c from baseline (-3.27%) at week 24.

Body weight
In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin resulted in body weight reduction compared to placebo at week 24 (-2.04 kg for empagliflozin 10 mg, -2.26 kg for empagliflozin 25 mg and -0.24 kg for placebo) that was maintained up to week 52 (-1.96 kg for empagliflozin 10 mg, -2.25 kg for empagliflozin 25 mg and -0.16 kg for placebo).

Waist circumference
At 24 weeks, treatment with empagliflozin as monotherapy or as add-on to metformin, pioglitazone, or metformin plus sulfonylurea resulted in sustained reduction of waist circumference over the duration of studies in a range of -1.7 cm to -0.9 cm for empagliflozin and -0.5 cm to +0.2 cm for placebo

Blood pressure
The efficacy and safety of empagliflozin (10 mg and 25 mg) was evaluated in a double-blind, placebo controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different oral antidiabetic drugs and up to 2 antihypertensive therapies (Table 8). Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c, 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring. Treatment with empagliflozin 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, -3.06 mmHg for empagliflozin 10 mg and -3.02 mmHg for empagliflozin 25 mg).

Table 8 Results at 12 weeks (LOCF)3 in a placebo-controlled study of JARDIANCE in patients with type 2 diabetes and uncontrolled blood pressure (Full Analysis Set)

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	271	276	276
HbA1c (%) at week 12			
Baseline (mean)	7.90	7.87	7.92
Change from baseline[1]	0.03	-0.59	-0.62
Difference from placebo[1] (95% CI)		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour SBP at week 12[2]			
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[2]			
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)

[1] mean adjusted for baseline value and stratification
[2] Last observation (prior to antihypertensive rescue) carried forward (LOCF)
[3] Last observation (prior to glycaemic rescue) carried forward (LOCF)
*p-value <0.0001
** p-value =0.0008

In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin resulted in a reduction in systolic blood pressure (empagliflozin 10 mg -3.9 mmHg, empagliflozin 25 mg -4.3 mmHg) compared with placebo (-0.5 mmHg), and in diastolic blood

pressure (empagliflozin 10 mg -1.8 mmHg, empagliflozin 25 mg -2.0 mmHg) compared with placebo (-0.5 mmHg), at week 24, that were maintained up to week 52.

Cardiovascular outcome

The EMPA-REG OUTCOME study is a multi-centre, multi-national, randomized, double-blind, placebo-controlled 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 cardiovascular risk factors, including coronary artery disease, peripheral artery disease, history of myocardial infarction (MI), or history of stroke. The primary endpoint was the time to first event in the composite of CV death, nonfatal MI, or non-fatal stroke (Major Adverse Cardiovascular Events (MACE-3)). Additional pre-specified endpoints addressing clinically relevant outcomes tested in an exploratory manner included CV death, the composite of heart failure requiring hospitalisation or CV death, all-cause mortality and the composite of new or worsening nephropathy.

A total of 7020 patients were treated with JARDIANCE (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years.

The population was 72.4% Caucasian, 21.6% Asian, and 5.1% Black. The mean age was 63 years and 71.5% were male. 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 sulfonylurea. The baseline HbA1c was <7% in 6.0% of the patients, 7 to <8% in 43.7% of the patients, 8 to <9% in 33.2% of the patients, and ≥9% in 17.0% of the patients. The time since diagnosis of diabetes was ≤5 years for 18.0% of the patients, >5 to 10 years for 24.9% of the patients, and
>10 years for 57.1% of the patients.

About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73m^2, 17.8% of 45-60 ml/min/1.73 m^2 and 7.7% of 30-45 ml/min/1.73m^2. Mean systolic BP was 136 mmHg, diastolic BP 76 mmHg, LDL 86 mg/dL, and HDL 44 mg/dL. The urinary albumin to creatinine ratio (UACR) was normal in 59.4% of the patients, 28.7% had microalbuminuria, and 11% had macroalbuminuria.

Reductions in risk of CV death and all-cause mortality

JARDIANCE was superior in reducing the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke compared to placebo. The incidence rate was 37.1 for JARDIANCE (10 and 25 mg, pooled) compared to 43.9 with placebo. The treatment effect reflected a significant reduction in cardiovascular death with no significant change in non- fatal MI, or non-fatal stroke (Table 9 and Figure 1).

JARDIANCE also improved all-cause mortality (Table 9), which was driven by a reduction in cardiovascular death with JARDIANCE. There was no statistically significant difference between empagliflozin and placebo in non-cardiovascular mortality.

Table 9 Treatment effect for the primary composite endpoint, its components and mortality (Treated Set*)

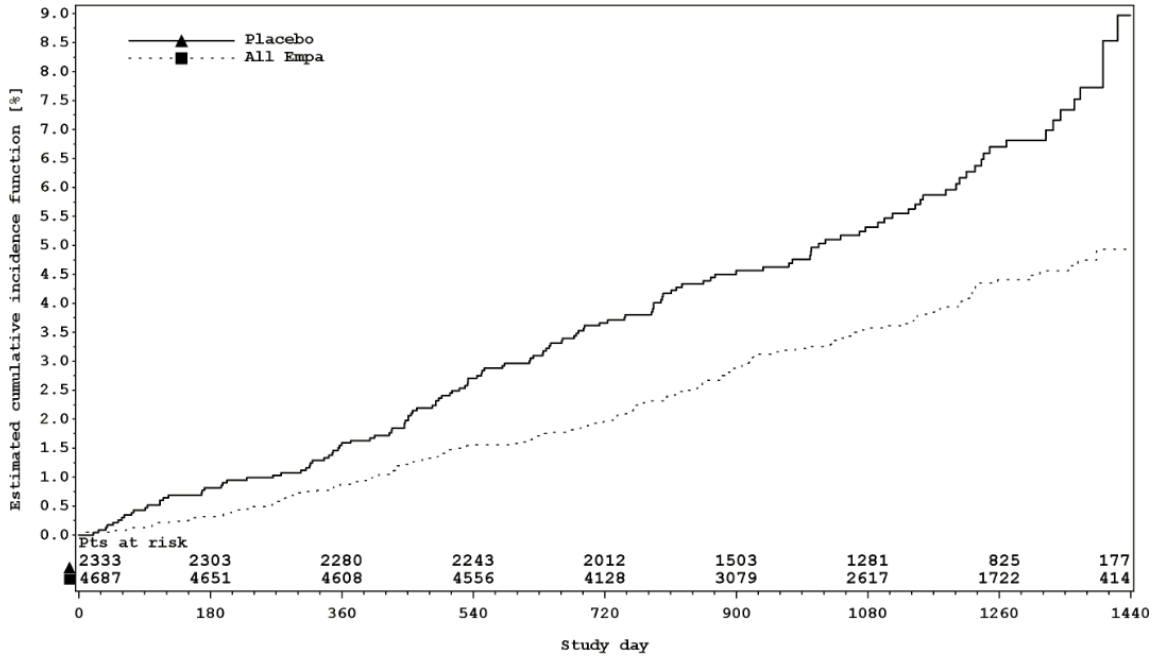
	Placebo	**Empagliflozin (10 and 25 mg, pooled)**
N	2333	4687
Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke N (%)	282 (12.1)	490 (10.5)
Hazard ratio vs. placebo (95.02% CI)**		0.86 (0.74, 0.99)
p–value for superiority		0.0382
CV Death N (%)	137 (5.9)	172 (3.7)

Hazard ratio vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		<0.0001
Non-fatal MI N (%)	121 (5.2)	213 (4.5)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.09)
p−value		0.2189
Non-fatal stroke N (%)	60 (2.6)	150 (3.2)
Hazard ratio vs. placebo (95% CI)		1.24 (0.92, 1.67)
p−value		0.1638
All-cause mortality N (%)	194 (8.3)	269 (5.7)
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
Non-CV mortality N (%)	57 (2.4)	97 (2.1)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.16)

* i.e. patients who had received at least one dose of study drug

** Since data from the trial were included in an interim analysis, a two-sided 95.02% confidence interval applied which corresponds to a p- value of less than 0.0498 for significance.

Figure 1 Time to occurrence of CV death



Reductions in risk of heart failure requiring hospitalization or CV death

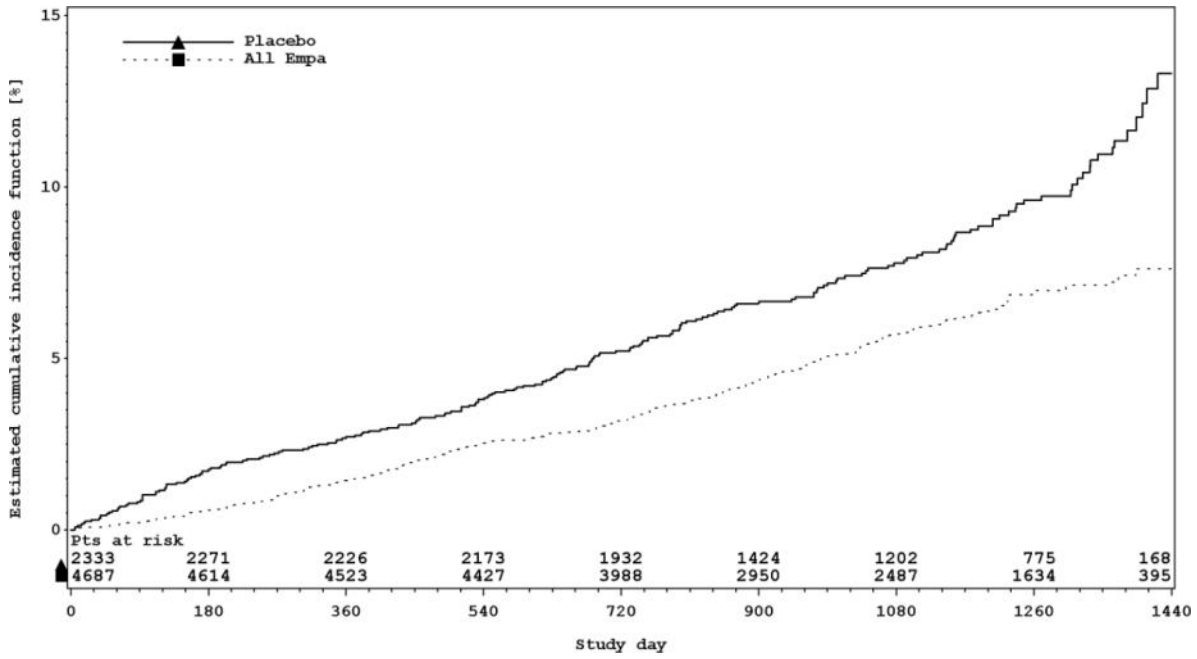
JARDIANCE significantly reduced the risk of hospitalization for heart failure and cardiovascular death or hospitalization for heart failure compared with placebo (Table 10 and Figure 2).

Table 10 Treatment effect for hospitalization for heart failure or cardiovascular death (excluding fatal stroke) (Treated Set*)

	Placebo	**Empagliflozin** (10 and 25 mg, pooled)**
N	2333	4687
Heart failure requiring hospitalisation or CV death (excluding fatal stroke) N (%)***	198 (8.5)	265 (5.7)
HR (95% CI)		0.66 (0.55, 0.79)
p−value		<0.0001
Heart failure requiring hospitalization N (%)	95 (4.1)	126 (2.7)
HR (95% CI)		0.65 (0.50, 0.85)
p−value		0.0017
CV death (excluding fatal stroke) N (%)	126 (5.4)	156 (3.3)
HR (95% CI)		0.61 (048, 0.77)
p−value		<0.0001

*i.e. patients who had received at least one dose of study drug
**empagliflozin 10 mg and 25 mg showed consistent results
*** time to first event

Figure 2 Time to first occurrence of first heart failure hospitalization or CV death*



*Estimated cumulative incidence function for time to first occurrence of first heart failure hospitalization or CV death, pooled empagliflozin vs placebo – treated set

The cardiovascular benefits (CV death and hospitalisation for heart failure or CV death) of JARDIANCE observed were consistent across major demographic and disease subgroups.

Diabetic kidney disease

In the EMPA-REG OUTCOME study population, the risk of new or worsening nephropathy (defined as onset of macroalbuminuria, doubling of serum creatinine, and initiation of renal replacement therapy (i.e. hemodialysis)) was significantly reduced in empagliflozin group compared to placebo (Table 11 and Figure 3).

JARDIANCE compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria (HR 1.82, 95% CI 1.40, 2.37).

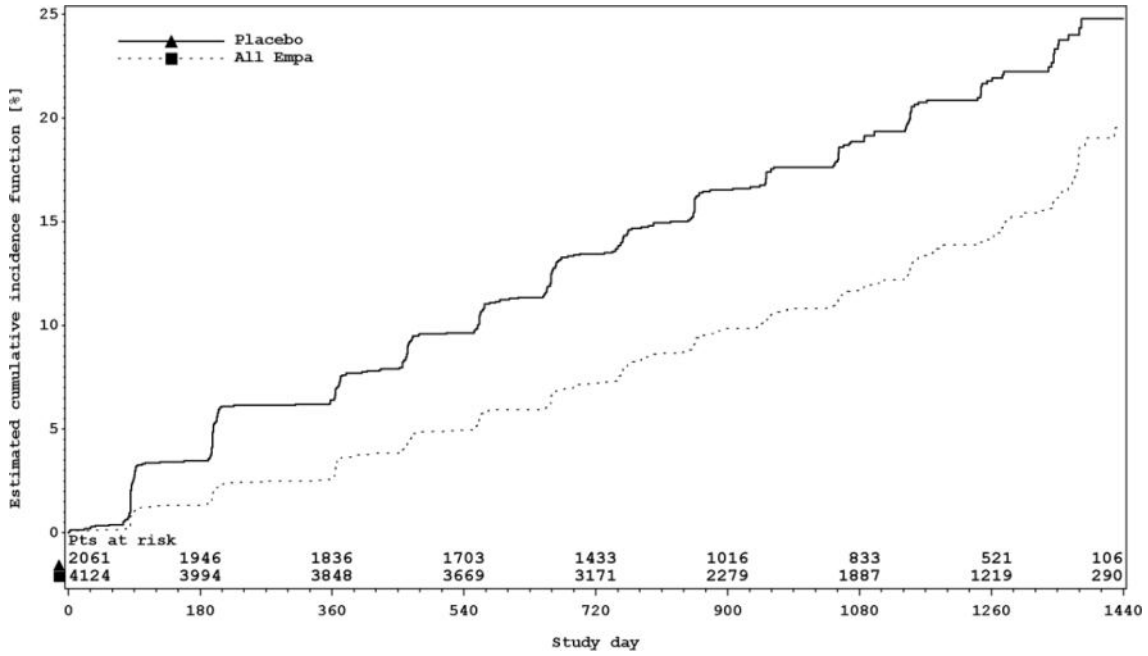
Table 11 Time to first new or worsening of nephropathy (Treated Set*)

	Placebo	**Empagliflozin (10 and 25 mg, pooled)**
N	2061	4124
New or worsening nephropathy N (%)	388 (18.8)	525 (12.7)
HR (95% CI)		0.61 (0.53, 0.70)
p−value		<0.0001
N	2323	4645
Doubling of serum creatinine levelN (%)**	60 (2.6)	70 (1.5)
HR (95% CI)		0.56 (0.39, 0.79)
p−value		0.0009
N	2033	4091
New onset of macroalbuminuria* N (%)**	330 (16.2)	459 (11.2)
HR (95% CI)		0.62 (0.54, 0.72)
p−value		<0.0001
N	2333	4687
Initiation of continuous renal replacement therapy N (%)	14 (0.6)	13 (0.3)
HR (95% CI)		0.45 (0.21, 0.97)

p−value		0.0409
N	2333	4687
Death due to renal disease N (%)[****]	0	3 (0.1)

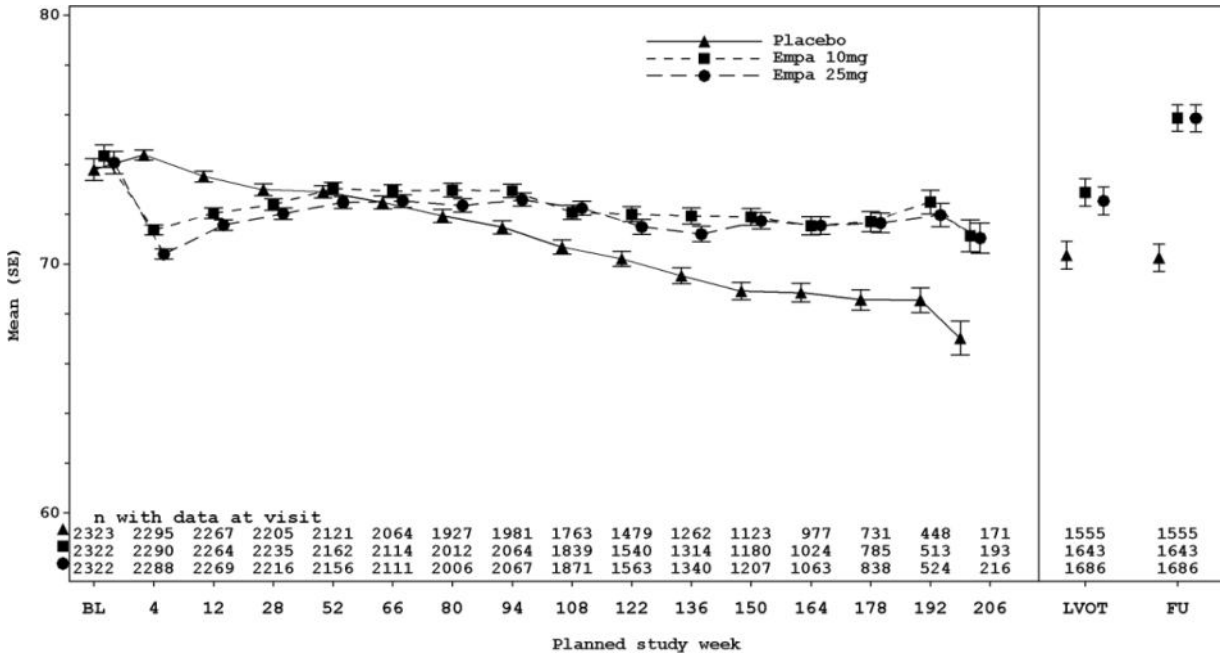
*i.e. patients who had received at least one dose of study drug
[**]Accompanied by an eGFR ≤45 mL/min/1.73m^2
[***]Urine Albumin Creatinine Ratio >300 mg/g
[****]Due to low event rate, HR not calculated

Figure 3 Time to first new or worsening of nephropathy



Treatment with empagliflozin preserved eGFR and eGFR increased during the post treatment 4-week follow up. However, the placebo group showed a gradual decline in GFR during the course of the study with no further change during 4-week follow up. (see Figure 4)

Figure 4 eGFR over time*



*eGFR (MDRD) (mL/min/1.73m^2) MMRM results over time, unadjusted last value on treatment and follow-up value - treated set – right side based on patients with available last value on treatment (LVOT) and follow-up (FU).

Thorough QTc study

In a randomized, placebo-controlled, active-comparator, crossover study of 30 healthy subjects, no increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Heart failure

A randomized, double-blind, placebo-controlled study (EMPEROR-Reduced) was conducted in 3730 patients with chronic heart failure (New York Heart Association [NYHA] II-IV) and reduced ejection fraction (LVEF $\leqslant$40 %) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care heart failure therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent) and eGFR(CKD-EPI)$_{cr}$ slope of change from baseline were included in the confirmatory testing. Heart Failure therapy at baseline included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (88.3%), beta blockers (94.7%), mineralocorticoid receptor antagonists (71.3%) and diuretics (95.0%).

A total of 1863 patients were randomized to empagliflozin 10 mg (placebo: 1867) and followed for a median of 15.7 months. The study population consisted of 76.1% men and 23.9% women with a mean age of 66.8 years (range: 25-94 years), 26.8% were 75 years of age or older. 70.5% of the study population were White, 18.0% Asian and 6.9% Black/African American. At randomization, 75.1% of patients were NYHA class II, 24.4% were class III and 0.5% were class IV. The mean LVEF was 27.5%. At baseline, the mean eGFR was 62.0 ml/min/1.73m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. About half of the patients (51.7%) had an eGFR of $\geqslant$60 ml/min/1.73m^2, 24.1% of 45 to <60 ml/min/1.73m^2, 18.6% of 30 to <45 ml/min/1.73m^2 and 5.3% 20 to

<30 ml/min/1.73m^2.

Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline (Table 12; Figure 5 and 6).

Table 12: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

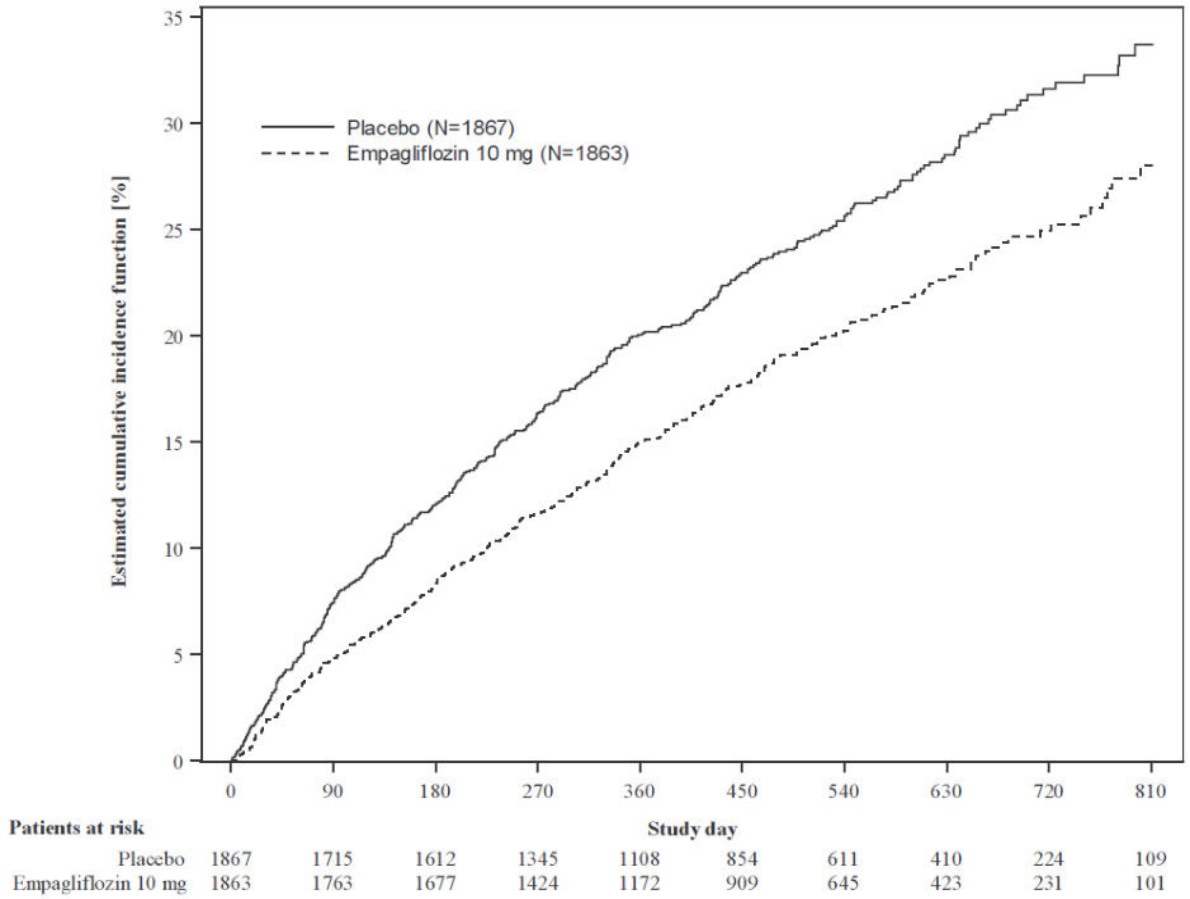
	Placebo	**Empagliflozin 10 mg**
N	1867	1863
Time to first event of CV death or HHF, N (%)	462 (24.7)	361 (19.4)
Hazard ratio vs. placebo (95% CI)*		0.75 (0.65, 0.86)
p−value for superiority		<0.0001
CV Death, N (%)	202 (10.8)	187 (10.0)
Hazard ratio vs. placebo (95% CI)		0.92 (0.75, 1.12)
HHF (first occurrence), N (%)	342 (18.3)	246 (13.2)
Hazard ratio vs. placebo (95% CI)		0.69 (0.59, 0.81)
HHF (first and recurrent), N of events	553	388
Hazard ratio vs. placebo (95% CI)*		0.70 (0.58, 0.85)
p−value		0.0003
eGFR (CKD EPI)cr slope, Rate of decline (ml/min/1.73m^2/year)**	-2.28	-0.55
Treatment difference vs. placebo (95% CI)		1.73 (1.10, 2.37)
p-value		p< 0.0001

CV = cardiovascular, HHF = hospitalization for heart failure, eGFR = Estimated glomerular filtration rate, CKD EPI = Chronic kidney disease epidemiology collaboration equation

* CV death and HHF events were adjudicated by an independent clinical event committee and analysed based on the randomized set.

**eGFR slope was analysed based on the treated set. Intercept is -0.95 ml/min/1.73m^2 for placebo and -3.02 ml/min/1.73m^2 for empagliflozin. The intercept represents the acute effect on eGFR while the slope represents the long-term effect.

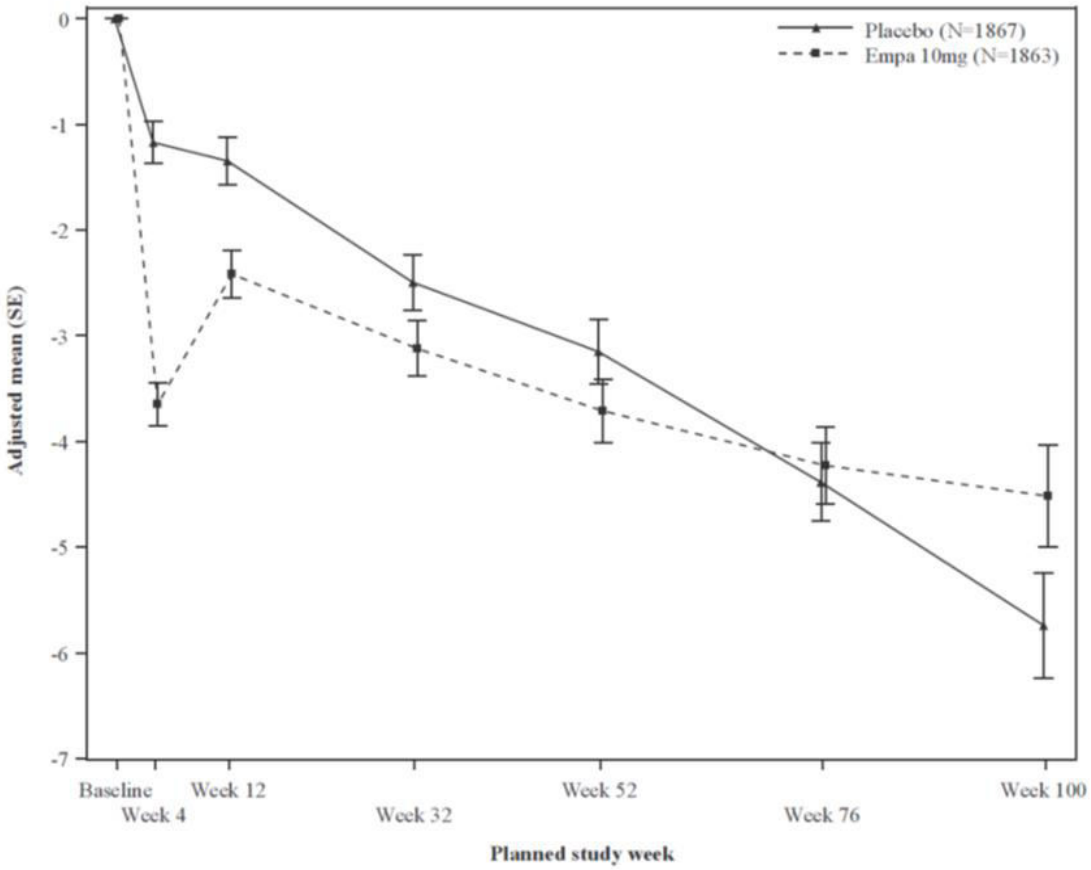
Figure 5 Time to first event of adjudicated CV death or HHF



The results of the primary composite endpoint were generally consistent with a hazard ratio (HR) below 1 across the pre-specified subgroups, including patients with heart failure, with or without type 2 diabetes mellitus and with or without renal impairment (down to an eGFR of 20 ml/min/1.73m^2).

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (Figure 6). Treatment with empagliflozin 10 mg significantly reduced the rate of eGFR decline (Table 12) and the effect was consistent across all pre-specified subgroups. Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

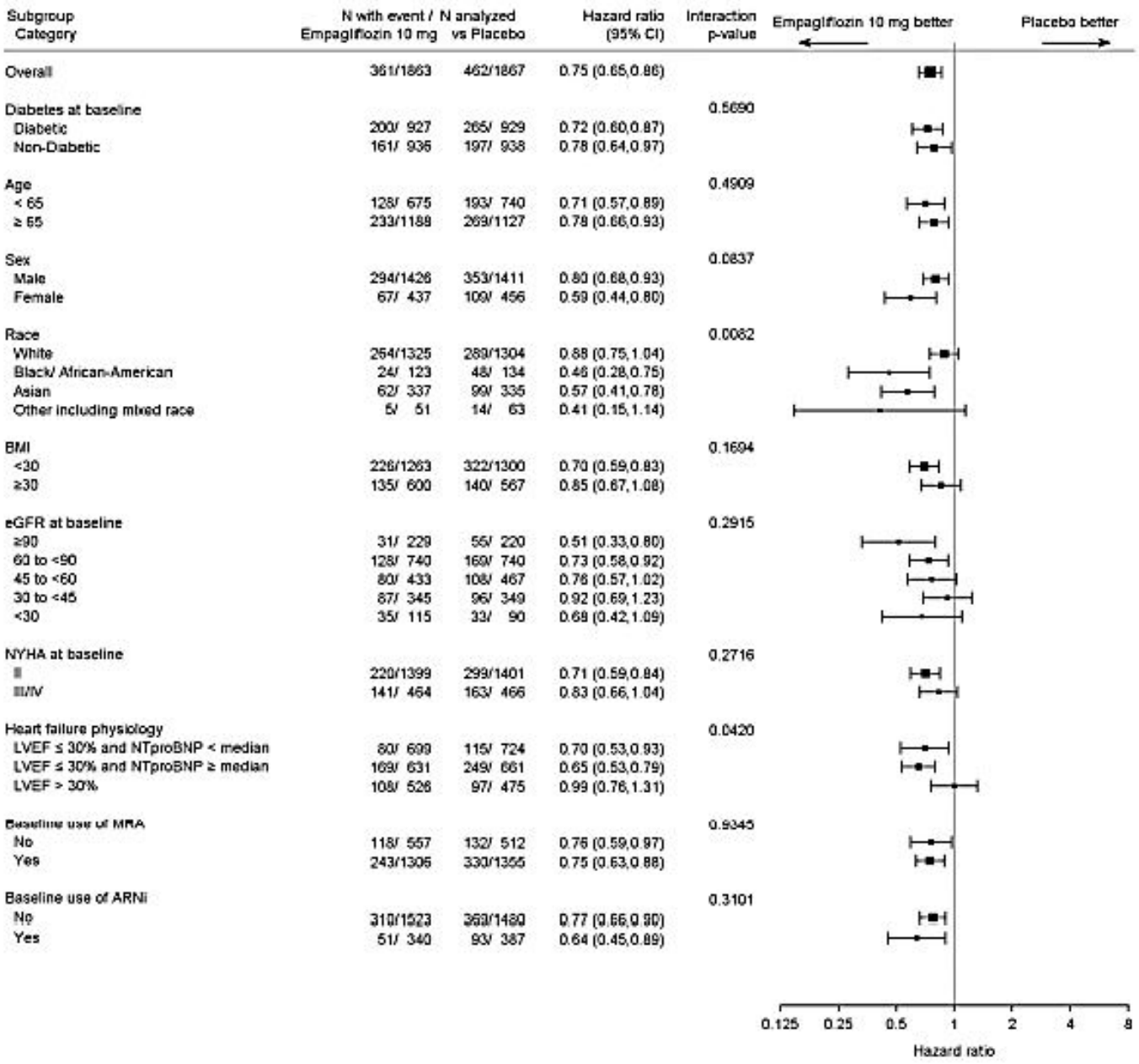
Figure 6 Change in eGFR over time*



*eGFR (CKD-EPI) (mL/min/1.73m^2) MMRM results over time - randomized set.

The results of the primary composite were generally consistent across the pre-specified subgroups, including heart failure patients with and without type 2 diabetes mellitus (see Figure 7).

Figure 7 Subgroup analyses for the time to the first event of adjudicated of CV death or HHF



LVEF >30%: Includes both above and below the median NTproBNP. To be eligible for inclusion, patients with an LVEF >30% were required to meet a higher NTproBNP threshold than those with LVEF ⩽30%, unless they additionally had a history of HHF within the past 12 months.

Empagliflozin in patients with heart failure and preserved ejection fraction

A randomised, double-blind, placebo-controlled study (EMPEROR-Preserved) was conducted in 5 988 patients with chronic heart failure (NYHA II-IV) and preserved ejection fraction (LVEF >40%) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent), and eGFR (CKD-EPI)cr slope of change from baseline were included in the confirmatory testing. Baseline therapy included ACE inhibitors/angiotensin receptor blockers/angiotensin

receptorneprilysin inhibitor (80.7%), beta blockers (86.3%), mineralocorticoid receptor antagonists (37.5%) and diuretics (86.2%).

A total of 2 997 patients were randomised to empagliflozin 10 mg (placebo: 2 991) and followed for a median of 26.2 months. The study population consisted of 55.3% men and 44.7% women with a mean age of 71.9 years (range: 22-100 years), 43.0% were 75 years of age or older. 75.9% of the study population were White, 13.8% Asian and 4.3% Black/African American. At randomisation, 81.5% of patients were NYHA class II, 18.1% were class III and 0.3% were class IV. The EMPEROR-Preserved study population included patients with a LVEF <50% (33.1%), with a LVEF 50 to <60% (34.4%) and a LVEF ≥60% (32.5%). At baseline, the mean eGFR was 60.6 ml/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 21 mg/g. About half of the patients (50.1%) had an eGFR of ≥60 ml/min/1.73 m^2, 26.1% of 45 to <60 ml/min/1.73 m^2, 18.6% of 30 to <45 ml/min/1.73 m^2 and 4.9% 20 to <30 ml/min/1.73 m^2.

Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline (Table 13, Figure 8 and 9)

Table 13: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

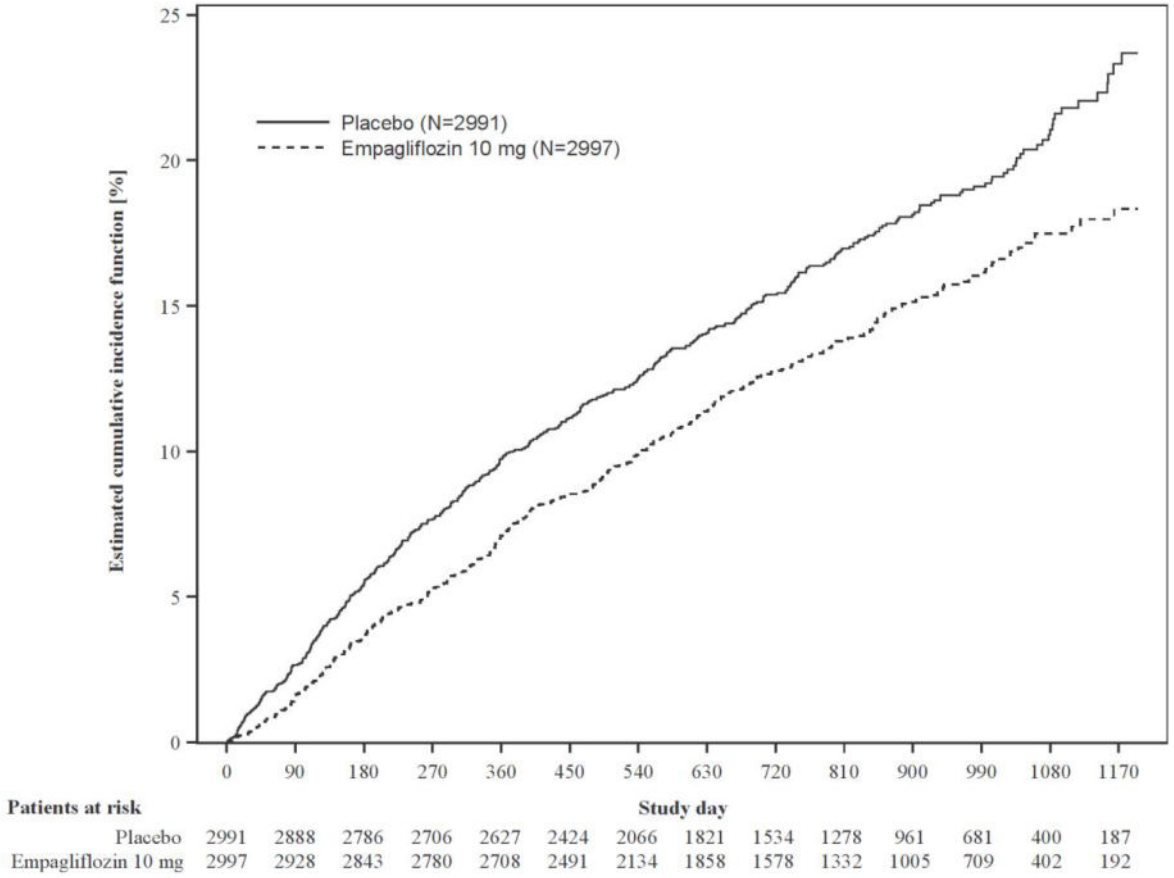
	Placebo	**Empagliflozin 10 mg**
N	2991	2997
Time to first event of CV death or HHF, N (%)	511 (17.1)	415 (13.8)
Hazard ratio vs. placebo (95.03% CI)**		0.79 (0.69, 0.90)
p−value for superiority		0.0003
CV Death, N (%)*	244 (8.2)	219 (7.3)
Hazard ratio vs. placebo (95% CI)		0.91 (0.76, 1.09)
p-value		0.2951
HHF (first occurrence), N (%)*	352 (11.8)	259 (8.6)
Hazard ratio vs. placebo (95% CI)		0.71 (0.60, 0.83)
p−value		<0.0001
HHF (first and recurrent), N of events	541	407
Hazard ratio vs. placebo (95.03% CI)**		0.73 (0.61, 0.88)
p−value		0.0009
eGFR (CKD EPI)cr slope, Rate of decline (ml/min/1.73m²/year)	−2.62	−1.25
Treatment difference vs. placebo (99.9% CI)***		1.36 (0.86, 1.87)
p-value		<0.0001

CV = cardiovascular, HHF = hospitalization for heart failure, eGFR = Estimated glomerular filtration rate, CKD EPI = Chronic kidney disease epidemiology collaboration equation

* CV death and HHF events were adjudicated by an independent clinical event committee and analysed based on the randomised set.

**eGFR slope was analysed based on the treated set. Intercept is -0.18 ml/min/1.73 m^2 for placebo and -3.02 ml/min/1.73 m^2 for empagliflozin. The intercept represents the acute effect on eGFR while the slope represents the long-term effect.

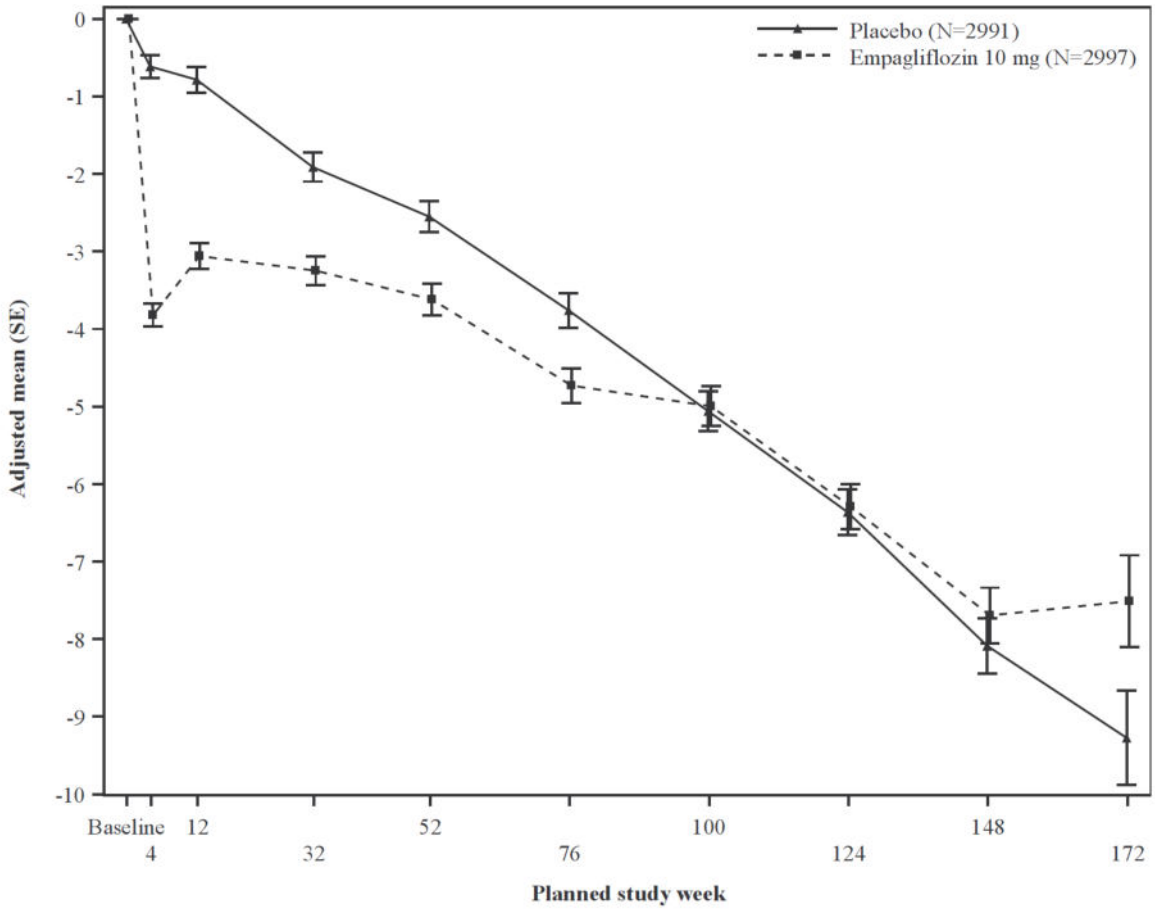
Figure 8 Time to first event of adjudicated CV death or HHF



The results of the primary composite endpoint were consistent across each of the pre-specified subgroups categorized by e.g., LVEF, diabetes status or renal function (down to an eGFR of 20 ml/min/1.73 m^2).

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (see Figure 9). Treatment with empagliflozin 10 mg significantly reduced the rate of eGFR decline and the effect was consistent across all pre-specified subgroups (see Table 13). Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

Figure 9 Change in eGFR over time*



*eGFR (CKD-EPI) (mL/min/1.73m^2) MMRM results over time - randomised set

For heart failure indication, the finding of reduced occurrence of HHF or CV death is an important benefit. It is, however, important to point out that this finding seems mainly due to the effect on HHF, as no relevant reduction in CV death was observed. With the current indication, the beneficial effect on HFF or CV death results in a positive benefit-risk ratio, especially as no new major safety issues have been observed.

Chronic kidney disease

A randomised, double-blind, placebo-controlled study of empagliflozin 10 mg once daily (EMPA-KIDNEY) was conducted in 6609 patients with chronic kidney disease (eGFR ≥20 - <45 ml/min/1.73 m^2; or eGFR ≥45 - <90 ml/min/1.73 m^2 with an urine albumin-to-creatinine ratio [UACR] ≥200 mg/g*)* to assess cardio-renal outcomes as adjunct to standard of care therapy. The primary endpoint was the time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomisation, sustained eGFR <10 ml/min/1.73 m^2, end-stage kidney disease, or renal death) or CV death. All-cause hospitalisation (first and recurrent), first occurrence of hospitalisation for heart failure or CV death, and all-cause mortality were included in the confirmatory testing. Baseline therapy included an appropriate use of a RAS-inhibitor (85.2% ACE inhibitor or angiotensin receptor blocker).

A total of 3304 patients were randomised to empagliflozin 10 mg (placebo: 3305) and followed for a median of 24.3 months. The study population consisted of 66.8% men and 33.2% women with a mean age of 63.3 years (range: 18-94 years), 23.0% were 75 years of age or older. 58.4% of the study population were White, 36.2% Asian and 4.0% Black/ African American.

At baseline, the mean eGFR was 37.3 ml/min/1.73 m^2, 21.2% patients had an eGFR of ≥45 ml/min/1.73 m^2, 44.3% of 30 to <45 ml/min/1.73 m^2 and 34.5% <30 ml/min/1.73 m^2 including 254 patients with an eGFR <20 ml/min/1.73 m^2. The median UACR was 329 mg/g, 20.1% patients had an UACR <30 mg/g, 28.2% had an UACR 30 to ≤300mg/g and 51.7% had an UACR >300 mg/g; 41.1% of patients had an UACR <200 mg/g. Primary causes of chronic kidney disease were diabetic nephropathy/diabetic kidney disease (31%), glomerular disease (25%), hypertensive/renovascular disease (22%) and other/unknown (22%).

Empagliflozin was superior in reducing the risk of the primary composite endpoint of kidney disease progression or CV death compared with placebo. Additionally, empagliflozin significantly reduced the risk of all-cause hospitalisation (first and recurrent). (see Table 14)

Table 14 Treatment effect for the primary composite and key secondary endpoints included in the pre-specified confirmatory testing and its components

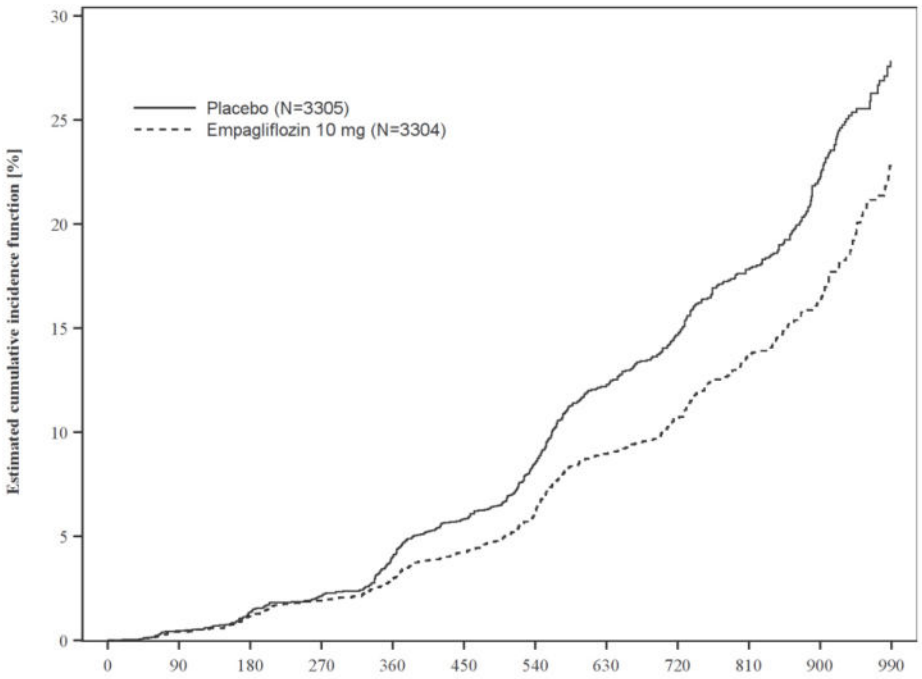
	Placebo	**Empagliflozin 10 mg**
N	3305	3304
Time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomisation, sustained eGFR <10 ml/min/1.73 m², end-stage kidney disease* (ESKD), or renal death) or CV death, N (%)	558 (16.9)	432 (13.1)
Hazard ratio vs. placebo (99.83% CI)		0.72 (0.59, 0.89)
p−value for superiority		<0.0001
Sustained ≥40% eGFR decline from randomisation, N (%)	474 (14.3)	359 (10.9)
Hazard ratio vs. placebo (95% CI)		0.70 (0.61, 0.81)
p-value		<0.0001
ESKD*or sustained eGFR <10 ml/min/1.73 m², N (%)	222 (6.7)	157 (4.8)
Hazard ratio vs. placebo (95% CI)		0.68 (0.55, 0.84)
p-value		0.0002
Renal death, N (%)**	4 (0.1)	4 (0.1)
Hazard ratio vs. placebo (95% CI)		
p-value		
CV Death, N (%)	70 (2.1)	59 (1.8)
Hazard ratio vs. placebo (95% CI)		0.83 (0.59, 1.17)
p-value		0.2932
Occurrence of all-cause hospitalisation (first and recurrent), N of events	1895	1612
Hazard ratio vs. placebo (99.03% CI)		0.86 (0.76, 0.98)
p-value		0.0022

CV = cardiovascular, HHF = hospitalisation for heart failure, eGFR = estimated glomerular filtration rate

* End-stage kidney disease (ESKD) is defined as the initiation of maintenance dialysis or receipt of a kidney transplant.

** There were too few events of renal death to compute a reliable hazard ratio.

Figure 10 Time to first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function



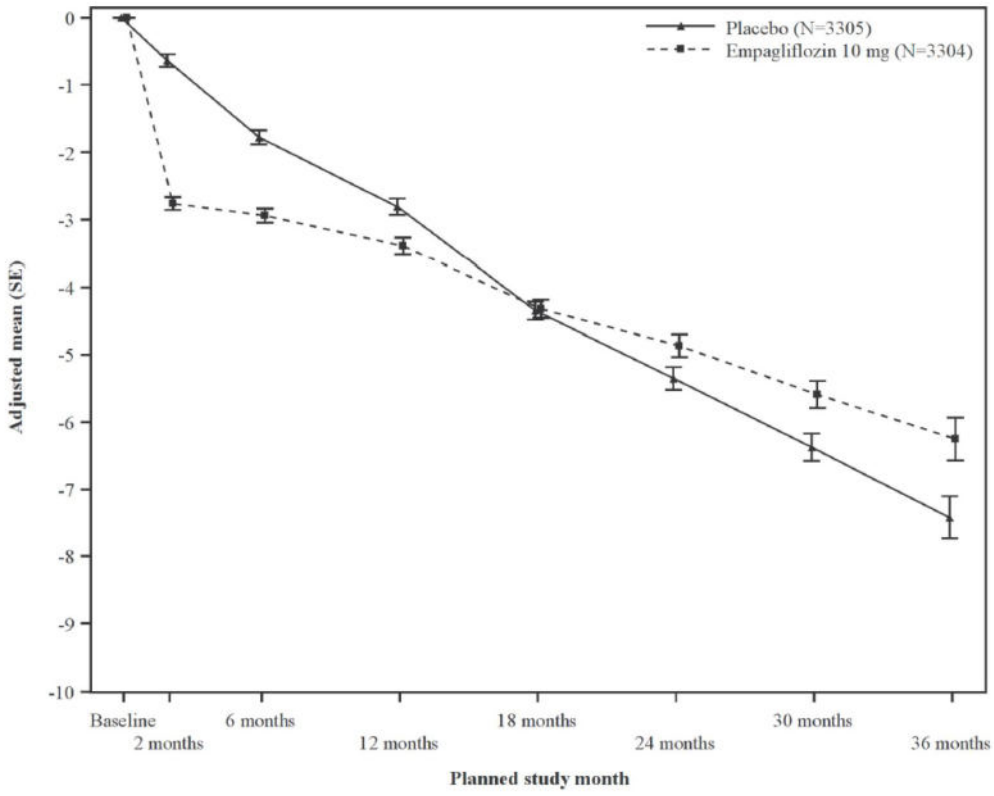
Patients at risk

Placebo	3305	3290	3256	3220	3146	2885	2361	1804	1562	1203	681	283
Empagliflozin 10 mg	3304	3289	3256	3220	3176	2926	2398	1851	1610	1255	726	295

The results of the primary composite endpoint were generally consistent across the pre-specified subgroups, including eGFR categories, underlying cause of renal disease, diabetes status, or background use of RAS inhibitors. Treatment benefits were more clearly evident in patients with higher levels of albuminuria.

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (Figure 11). Empagliflozin slowed the annual rate of eGFR decline compared to placebo by 1.38 ml/min/1.73 m2 /year (95% CI 1.16, 1.59), based on a pre-specified analysis of all eGFR measurements taken from the 2-month visit to the final follow-up visit. Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation as demonstrated in several of the empagliflozin studies, supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

Figure 11 Change in eGFR over time*



*eGFR (CKD-EPI) (ml/min/1.73 m2) MMRM results over time - randomised set.

Pharmacokinetics

Absorption

The pharmacokinetics of empagliflozin have been extensively characterized in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations (C_{max}) with a median time to reach C_{max} (t_{max}) of 1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively

slow terminal phase. The steady state mean plasma AUC was 4740 nmol.h/L and C_{max} was 687 nmol/L with 25 mg empagliflozin once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single- dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with T2DM.

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

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

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

Elimination
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [^{14}C]- 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.

Specific Populations
Renal Impairment
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/ESKD 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/ESKD 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. In line with the Phase I study, the population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. Based on pharmacokinetics, no dosage adjustment is recommended in patients with renal insufficiency.

However, due to the mechanism of action, the efficacy of JARDIANCE is dependent on renal function, and therefore JARDIANCE is contraindicated for use in patients with persistent eGFR <45mL/min/1.73m^2 (see Contraindications, Special Warnings and Precautions, and Dosage AND Administration).

Hepatic Impairment
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. Based on pharmacokinetics, no dosage adjustment is recommended in patients with hepatic impairment.

Body Mass Index (BMI)
No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Gender
No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race
No dosage adjustment is necessary based on 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.

Geriatric
Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

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

TOXICOLOGY
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.
In long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Carcinogenicity
In a 2 year carcinogenicity study, empagliflozin did not increase the incidence of tumours in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72- times the maximal clinical AUC exposure to empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumours in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both tumours are common in rats and are unlikely to be relevant to humans. Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

Genotoxicity
Empagliflozin is not genotoxic.

Reproduction Toxicity
At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.
In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.
In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period.

Only on doctor's prescription
Harus dengan resep dokter

Availability :
Film coated tablet 10 mg
Box, 3 blisters @ 10 film coated tablet — Reg. No: DKI2324200617A1

Film coated tablet 25 mg
Box, 3 blisters @ 10 film coated tablet — Reg. No: DKI2324200617B1

Storage conditions :
Store below 30°C
Store in a safe place, out of the reach of children

Manufactured by :
Rottendorf Pharma GmbH
Ennigerloh, Germany

For :
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Imported by :
PT Tunggal Idaman Abdi
Jakarta, Indonesia

DISETUJUI OLEH BPOM: 27/10/2025

ID: EREG10015512500138
& EREG10015512500139

Produk Informasi untuk Pasien

Jardiance®

(Empagliflozin)

Tablet Salut Selaput

Bacalah seluruh leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisikan informasi yang penting bagi Anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya kembali.
- Bila Anda memiliki pertanyaan lebih lanjut, bertanyalah kepada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda saja. Jangan berikan kepada orang lain. Hal ini dapat membahayakan mereka, walau tanda-tanda penyakit mereka sama dengan Anda.
- Bila Anda mengalami efek samping apapun, bicarakan kepada dokter, apoteker atau perawat Anda, termasuk efek samping yang belum tertulis dalam leaflet ini.

Apakah yang terdapat dalam leaflet ini?

1. Apakah JARDIANCE dan digunakan untuk apakah obat ini

Zat aktif yang terkandung dalam JARDIANCE yaitu empagliflozin

Jardiance merupakan anggota dari kelompok obat yang bekerja menghambat protein dalam ginjal yang disebut *sodium-glucose co-transporter 2* (SGLT2).

Dokter Anda meresepkan obat ini untuk :

A. Membantu menurunkan kadar gula darah Anda.
   - JARDIANCE digunakan untuk mengobati diabetes tipe 2 pada pasien dewasa (usia 18 tahun atau lebih).
   - JARDIANCE digunakan bila diabetes Anda tidak dapat dikontrol dengan diet dan olah raga serta dengan obat lain untuk diabetes. Pemberian JARDIANCE dikombinasikan dengan obat lain yaitu metformin, metformin dan sulfonilurea, atau metformin dan pioglitazone

SGLT2 mencegah glukosa diekskresikan melalui urin dengan menyerap glukosa kembali ke dalam aliran darah pada saat darah sedang disaring oleh ginjal. Dengan penghambatan protein ini, JARDIANCE menyebabkan pengeluaran glukosa (gula darah) melalui urin sehingga kadar gula darah yang tinggi, karena diabetes tipe 2 yang Anda alami, menjadi turun.

Obat ini juga dapat membantu mencegah penyakit jantung pada penderita diabetes melitus tipe 2. Penting bagi Anda untuk melanjutkan rencana diet dan olah raga Anda seperti yang telah dianjurkan oleh dokter, apoteker, atau perawat Anda.

Gagal jantung

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• Jardiance digunakan untuk mengobati gagal jantung pada pasien dewasa dengan gejala akibat fungsi pompa jantung yang lemah.

Gagal ginjal kronis
• Jardiance digunakan untuk mengobati gagal ginjal kronis pada pasien dewasa (eGFR 20 – 90 ml/min/1.73 m^2) untuk memperlambat waktu terjadinya perburukan penyakit ginjal

Apakah diabetes tipe 2?
Diabetes tipe 2 adalah suatu penyakit yang berasal dari gen dan gaya hidup Anda. Bila Anda memiliki diabetes tipe 2, berarti pankreas Anda tidak menghasilkan insulin dalam jumlah yang cukup untuk mengontrol kadar glukosa dalam darah Anda, dan tubuh Anda tidak dapat menggunakan insulinnya sendiri secara efektif. Kadar gula darah yang tinggi dalam darah dapat menyebabkan masalah kesehatan seperti penyakit jantung, penyakit ginjal, kebutaan, dan sirkulasi darah yang buruk pada anggota tubuh sehingga dapat menyebabkan amputasi

Apa itu gagal jantung?
Jenis gagal jantung ini terjadi ketika jantung lemah dan tidak dapat memompa cukup darah ke paru-paru dan ke seluruh tubuh. Hal ini dapat menyebabkan masalah medis yang serius dan membutuhkan perawatan di rumah sakit. Gejala gagal jantung yang paling umum adalah merasa sesak napas, merasa lelah atau sangat lelah sepanjang waktu, dan bengkak pada pergelangan kaki.

Jardiance membantu melindungi jantung Anda agar tidak semakin lemah dan memperbaiki gejala Anda.

Apa itu gagal ginjal kronis?
Gagal ginjal kronis merupakan kondisi jangka panjang. Hal ini mungkin disebabkan oleh penyakit lain seperti diabetes dan tekanan darah tinggi atau bahkan karena sistem kekebalan tubuh yang menyerang ginjal Anda. Ketika Anda menderita penyakit ginjal kronis, ginjal Anda mungkin secara bertahap kehilangan kemampuannya untuk membersihkan dan menyaring darah dengan baik. Hal ini dapat menyebabkan masalah kesehatan yang serius seperti kaki bengkak, gagal jantung, atau perlunya perawatan di rumah sakit.

Jardiance membantu melindungi ginjal Anda dari kehilangan fungsinya

2. Apa yang perlu Anda ketahui sebelum Anda minum JARDIANCE

Jangan minum JARDIANCE:

- Bila Anda alergi terhadap empagliflozin atau bahan lainnya dalam obat ini (tertulis dalam bab 6).
- Pasien dengan gangguan ginjal berat (eGFR <20 ml/min/1.73m^2), gangguan ginjal stadium akhir dan pasien yang menjalani dialisis/cuci darah untuk pengobatan gagal jantung
- Pasien gangguan ginjal dengan eGFR kurang dari 45mL/menit/1,73m^2, untuk pengobatan diabetes melitus tipe 2.
- Pasien dengan kondisi bawaan yang langka dari intoleransi / alergi terhadap gula dengan jenis galaktosa (misalnya galaktosemia) tidak boleh minum obat ini.

Peringatan dan perhatian
Bicarakan dengan dokter, apoteker, atau perawat Anda sebelum minum obat ini dan selama pengobatan:

- Tentang hal-hal yang dapat Anda lakukan untuk mencegah dehidrasi.
- Bila Anda mengidap diabetes tipe 1. Tipe ini biasanya diidap sejak Anda masih kecil dan badan Anda tidak memproduksi insulin sama sekali.
- Bila Anda mengalami penurunan berat badan yang cepat, merasa mual atau muntah, nyeri perut, rasa haus yang berlebihan, nafas cepat dan berat, bingung, ngantuk atau kelelahan yang tidak biasa, nafas berbau manis, rasa manis atau rasa logam pada mulut, atau bau urin atau keringat yang berbeda, segera hubungi dokter atau rumah sakit terdekat segera. Gejala tersebut disebut gejala "*ketoacidosis*" yaitu masalah yang timbul karena adanya peningkatan kadar badan keton di dalam urin atau darah berdasarkan hasil pengujian laboratorium. Risiko terjadinya *ketoacidosis* dapat meningkat seiring dengan puasa yang berkepanjangan, terlalu banyak minum minuman keras, dehidrasi, penurunan dosis insulin yang mendadak, atau semakin tingginya kebutuhan insulin karena menjalani operasi besar atau mengalami penyakit berat.
- Bila Anda mengidap masalah ginjal serius – dokter Anda mungkin akan membatasi dosis Anda menjadi 10 mg sekali sehari atau meresepkan Anda obat yang lain.
- Bila Anda mengidap masalah hati serius – dokter Anda mungkin meresepkan Anda obat yang lain.
- Bila Anda berusia 75 tahun atau lebih tua, karena peningkatan berkemih yang disebabkan oleh obat ini dapat mempengaruhi keseimbangan cairan pada tubuh Anda dan meningkatkan risiko dehidrasi. Gejala-gejalanya dapat dilihat pada bagian 4. Kemungkinan Efek Samping – Dehidrasi.
- Bila Anda merasa mual, mengalami diare atau demam, atau bila Anda tidak dapat makan atau minum. Kondisi ini dapat menyebabkan dehidrasi. Dokter Anda mungkin akan meminta Anda untuk berhenti minum JARDIANCE hingga Anda membaik untuk mencegah kehilangan cairan tubuh yang terlalu banyak.
- Bila Anda mengalami infeksi serius pada ginjal atau saluran kemih yang disertai dengan demam. Dokter Anda mungkin akan meminta Anda untuk berhenti minum JARDIANCE hingga Anda membaik.
- Perawatan kaki
  Seperti pasien diabetes lainnya, sangat penting untuk dilakukan pemeriksaan kaki secara berkala dan ikuti saran perawatan kaki lainnya yang disarankan oleh tenaga kesehatan Anda.

Glukosa urin
Karena aksi kerja JARDIANCE maka tes urin Anda akan positif untuk gula ketika Anda minum obat ini.

Anak dan remaja
JARDIANCE tidak direkomendasikan untuk anak dan remaja usia dibawah 18 tahun, karena obat ini belum diteliti pada populasi pasien ini.

Obat-obatan lainnya dan JARDIANCE
Beritahukan kepada dokter atau apoteker Anda bila Anda sedang minum, akhir-akhir ini minum, atau mungkin minum obat-obatan lainnya.
- Bila Anda minum obat yang mengurangi cairan tubuh (diuretik). Dokter Anda mungkin meminta Anda untuk berhenti minum JARDIANCE. Gejala-gejala yang mungkin muncul karena kehilangan cairan dapat dilihat pada bagian 4. Kemungkinan Efek Samping – Dehidrasi.

- Bila anda minum obat lainnya yang dapat menurunkan kadar gula dalam darah anda seperti obat “sulfonilurea”. Dokter anda mungkin akan menurunkan dosis obat tersebut untuk mencegah kadar gula menjadi terlalu rendah (hipoglikemia).
- Bila anda mengonsumsi Lithium, karena Jardiance dapat menurunkan kadar lithium dalam darah anda.

Kehamilan dan menyusui
Bila Anda hamil atau menyusui, berpikir bahwa kemungkinan Anda hamil atau merencanakan untuk memiliki bayi, mintalah saran kepada dokter atau apoteker Anda sebelum minum obat ini.
Lebih baik Anda menghindari menggunakan JARDIANCE bila Anda hamil. Belum diketahui apakah JARDIANCE berbahaya bagi janin. Jangan menggunakan JARDIANCE bila Anda sedang menyusui. Belum diketahui apakah JARDIANCE dapat masuk kedalam air susu ibu.

Mengemudi dan mengoperasikan mesin
JARDIANCE sedikit mempengaruhi kemampuan mengemudi dan mengoperasikan mesin.
Apabila minum obat ini yang dikombinasikan dengan obat sulfonilurea dapat menyebabkan kadar gula darah turun menjadi terlalu rendah (hipoglikemia), yang dapat menyebabkan gejala seperti gemetar, berkeringat dan perubahan penglihatan, yang dapat mempengaruhi kemampuan Anda dalam mengemudi dan mengoperasikan mesin. Jangan mengemudi atau mengoperasikan mesin, bila Anda merasa pusing ketika minum JARDIANCE.

JARDIANCE mengandung laktosa
JARDIANCE mengandung laktosa. Bila Anda telah diberitahukan oleh dokter Anda bahwa Anda mengalami intoleransi terhadap beberapa jenis gula, hubungi dokter Anda sebelum minum obat ini.

3. Bagaimana cara minum JARDIANCE

Selalu minum obat ini sesuai dengan instruksi dokter Anda. Tanyakan kepada dokter atau apoteker Anda bila Anda merasa tidak yakin.

Berapa banyak yang diminum
- Dosis awal JARDIANCE adalah satu tablet 10 mg sekali sehari. Dokter Anda akan menentukan apakah dosis Anda akan ditingkatkan menjadi 25 mg sekali sehari.
- Dokter Anda mungkin akan membatasi dosis Anda menjadi 10 mg sekali sehari apabila Anda mengalami gangguan ginjal.
- Dokter Anda akan meresepkan dosis yang tepat untuk Anda. Jangan ganti dosis Anda kecuali atas anjuran dokter Anda.

Cara minum obat ini
- Telan seluruh tablet dengan air
- Anda dapat minum tablet ini dengan atau tanpa makanan
- Anda dapat minum tablet kapan saja, akan tetapi cobalah untuk selalu minum diwaktu yang sama setiap harinya. Hal ini akan membantu Anda untuk mengingat untuk meminumnya.

Dokter Anda mungkin meresepkan JARDIANCE bersama dengan obat antidiabetik oral lainnya. Ingatlah untuk meminum semua obat sesuai dengan instruksi yang diberikan oleh dokter Anda agar dapat dicapai hasil terbaik bagi kesehatan Anda.

Diet dan olah raga dapat membantu tubuh anda agar menggunakan gula darah Anda sendiri secara lebih baik. Penting bagi Anda untuk tetap menjaga program diet dan olah raga sesuai yang direkomendasikan oleh dokter ketika Anda minum JARDIANCE.

Bila Anda minum JARDIANCE lebih banyak dari seharusnya
Bila Anda minum JARDIANCE lebih banyak dari seharusnya, Anda harus beritahukan dokter Anda segera atau pergi ke rumah sakit segera. Bawalah obat tersebut beserta kemasannya bersama Anda.

Yang perlu Anda lakukan apabila terlupa minum satu tablet, tergantung kepada berapa lama waktu hingga dosis berikutnya.

- Bila waktunya 12 jam atau lebih hingga dosis Anda yang berikutnya, segera minum JARDIANCE segera saat Anda ingat. Kemudian minum obat Anda berikutnya pada waktu yang biasa.
- Bila waktunya kurang dari 12 jam hingga dosis yang berikutnya, maka sebaiknya Anda lewati dosis yang terlupakan tersebut. Kemudian minum obat Anda berikutnya pada waktu yang biasa.
- Jangan minum dosis ganda untuk menggantikan dosis yang terlupa.

Bila Anda berhenti minum JARDIANCE
Jangan berhenti minum JARDIANCE tanpa berkonsultasi terlebih dahulu dengan dokter Anda. Kadar gula darah akan dapat meningkat ketika Anda berhenti minum JARDIANCE.
Bila Anda memiliki pertanyaan lebih lanjut mengenai cara menggunakan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda

4. Kemungkinan efek samping

Sebagaimana obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Hubungi dokter Anda atau rumah sakit terdekat segera bila Anda mengalami salah satu efek samping berikut ini:

*Ketoacidosi*s, jarang terjadi (dapat dialami hingga 1 dari 1.000 orang)
Berikut ini merupakan gejala-gejala *ketoacidosis* (lihat juga bagian 2. Apa yang perlu Anda ketahui sebelum Anda minum JARDIANCE)

- Peningkatan “badan keton” pada urin atau darah Anda
- Penurunan berat badan yang cepat
- Merasa mual atau muntah
- Rasa haus yang berlebihan
- Nafas cepat dan berat
- Merasa bingung
- Mengantuk atau kelelahan yang tidak biasa
- Rasa manis pada nafas Anda, rasa manis atau rasa besi pada mulut Anda, atau bau yang berbeda pada urin atau keringat.

Hal ini dapat terjadi pada berapa pun kadar gula darah Anda. Dokter Anda dapat memutuskan untuk menghentikan pemberian obat JARDIANCE secara sementara atau permanen.

Hubungi dokter Anda segera apabila Anda melihat salah satu efek samping berikut ini:

Gula darah Anda rendah (hipoglikemia) sangat sering terjadi (dapat dialami lebih dari 1 dari 10 orang)
Bila Anda minum JARDIANCE bersama dengan obat lainnya yang dapat menyebabkan gula darah rendah, seperti sulfonilurea, maka Anda memiliki risiko lebih tinggi untuk mengalami gula darah rendah. Gejala-gejala gula darah rendah adalah:

- gemetar, berkeringat, merasa sangat cemas atau bingung, detak jantung cepat
- sangat lapar, sakit kepala

Dokter Anda akan memberitahukan kepada Anda bagaimana menangani kadar gula darah rendah. Bila Anda mengalami gejala gula darah rendah, makan tablet glukosa, makanan ringan tinggi gula atau minum jus buah. Ukur gula darah Anda jika memungkinkan dan beristirahatlah.

Infeksi saluran kemih sering terjadi (dapat dialami hingga 1 dari 10 orang). Gejala-gejala infeksi saluran kemih adalah:

- rasa terbakar ketika berkemih
- urin tampak keruh
- nyeri pada panggul atau nyeri punggung (ketika ginjal Anda terinfeksi)

Tanda seperti ingin berkemih atau lebih sering berkemih kemungkinan disebabkan mekanisme aksi JARDIANCE, akan tetapi dapat juga merupakan gejala infeksi saluran kemih. Bila Anda melihat terdapat peningkatan gejala-gejala tersebut di atas, Anda sebaiknya segera menghubungi dokter Anda.

Dehidrasi, tidak sering terjadi (dapat dialami hingga 1 dari 100 orang)
Gejala-gejala dehidrasi tidaklah spesifik, tetapi dapat meliputi:

- Rasa haus yang tidak biasa
- Kepala terasa ringan atau pusing saat berdiri
- Pingsan atau kehilangan kesadaran

Efek samping lain yang dialami ketika minum JARDIANCE:
Sering

- Infeksi jamur kelamin (sariawan pada alat kelamin)
- Berkemih lebih sering dari biasanya atau lebih sering merasa ingin berkemih
- Gatal-gatal
- Kehausan
- Hasil tes darah menunjukkan adanya perubahan kadar lemak (kolesterol) di dalam darah
- Konstipasi

Tidak sering

- Sulit atau nyeri ketika berkemih
- Hasil tes darah menunjukkan perubahan fungsi ginjal (kreatinin atau urea)
- Hasil tes darah menunjukkan peningkatan jumlah sel darah merah di dalam darah (hematokrit)

Pelaporan efek samping
Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk efek samping yang mungkin terjadi yang belum tercantum di leaflet ini. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut: Telepon: +62 21 21684084 atau Email IDsafety@zuelligpharma.com

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5. Bagaimana cara menyimpan JARDIANCE

Simpanlah obat ini jauh dari pandangan dan jangkauan anak-anak.
Jangan gunakan obat ini setelah tanggal kadaluarsa yang tertulis pada blister dan karton setelah tulisan 'EXP'. Tanggal kadaluarsa merujuk kepada hari terakhir pada bulan tersebut.
Obat ini tidak memerlukan kondisi penyimpanan khusus.

Jangan gunakan JARDIANCE bila paket rusak atau menunjukkan tanda-tanda rusak.

Jangan membuang obat apapun melalui pembuangan limbah air atau limbah rumah tangga. Bertanyalah kepada apoteker Anda bagaimana cara membuang obat-obatan yang tidak Anda gunakan lagi. Tindakan ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya

Apakah bahan yang terkandung dalam JARDIANCE
Zat aktifnya adalah empagliflozin. Setiap tablet mengandung empagliflozin 10 mg.
Zat aktifnya adalah empagliflozin. Setiap tablet mengandung empagliflozin 25 mg.
Bahan lainnya adalah:

inti tablet: laktosa monohidrat, selulosa mikrokristalin, hidroksipropilselulosa, natrium kroskarmelosa, koloidal anhidrosa silika, magnesium stearat
penyalut tablet: hipromelosa, titanium dioksida , talk, makrogol 400, iron oxide yellow

Seperti apakah tampilan dan isi paket JARDIANCE
Tablet salut selaput JARDIANCE 10 mg berbentuk bulat, bikonveks dan berwarna kuning pucat. Tablet ini bertuliskan "S10" pada satu sisi dan logo Boehringer Ingelheim pada sisi lainnya.

Tablet salut selaput JARDIANCE 25 mg berbentuk oval, bikonveks dan berwarna kuning pucat. Tablet ini bertuliskan "S25" pada satu sisi dan logo Boehringer Ingelheim pada sisi lainnya.

Tablet JARDIANCE tersedia dalam blister *unit dose* yang terbuat dari PVC/aluminium yang dapat dikoyak. Ukuran paket adalah 30x1, tablet salut selaput.

Jardiance 10mg Reg. No: DKI2324200617A1
Jardiance 25mg Reg. No: DKI2324200617B1

Harus dengan resep dokter

Kondisi penyimpanan :
Simpan di bawah suhu 30°C
SImpan di tempat yang aman, jauhkan dari jangkauan anak-anak

Diproduksi oleh :
Rottendorf Pharma GmbH
Ennigerloh, Germany

Untuk :
Boehringer Ingelheim International GmbH

Ingelheim am Rhein, Jerman

Diimpor oleh :
PT Tunggal Idaman Abdi
Jakarta, Indonesia