Jardiance®
Empagliflozin

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
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, effects on glycaemic control and cardiovascular 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

DOSAGE AND ADMINISTRATION
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.

Patients with renal impairment
The efficacy of JARDIANCE is dependent on renal function. Renal function must be assessed prior to initiation of JARDIANCE therapy and periodically thereafter. No dosage adjustment for JARDIANCE is indicated in patients with mild renal impairment (eGFR ≥ 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.
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.

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

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.
Renally impaired patients with eGFR less than 45 mL/min/1.73m^2, severe renal impairment, end-stage renal disease and patients on dialysis.
The efficacy of JARDIANCE is dependent on renal function (see SPECIAL WARNINGS 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.

Diabetic ketoacidosis
Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients 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).

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.
Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. 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. 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)
Postmarketing 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 with diabetes mellitus 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

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. 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).

Monitoring of renal function
Due to the mechanism of action, the efficacy of JARDIANCE is dependent on renal function. Therefore 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 therapeutic 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.

Urinary tract infections
In the pooled placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was higher than placebo in patients treated with empagliflozin 10 mg and similar to placebo in patients treated with empagliflozin 25 mg (see Side effects). Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. 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).
Therapeutic experience in patients aged 85 years and older is limited. Initiation of JARDIANCE therapy in this population is not recommended (see section Dosage and Administration).

Cardiac failure
Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with JARDIANCE in NYHA class III-IV.

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
***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
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).

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.

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%.

Postmarketing experience
Ketoacidosis, Urosepsis, Pyelonephritis, Allergic skin reactions (e.g. rash, urticaria), Angioedema. Infections and infestations : Necrotizing fasciitis of the perineum (Fournier´s gangrene)

OVERDOSE
During controlled clinical trials in healthy subjects, single doses of up to 800 mg empagliflozin, equivalent to 32 times the maximum recommended daily dose, 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. Throughinhibition 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.

Clinical Trials
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/1.73 m^2, 17.8% of 45-60 ml/min/1.73 m^2 and 7.7% of 30-45 ml/min/1.73 m^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.

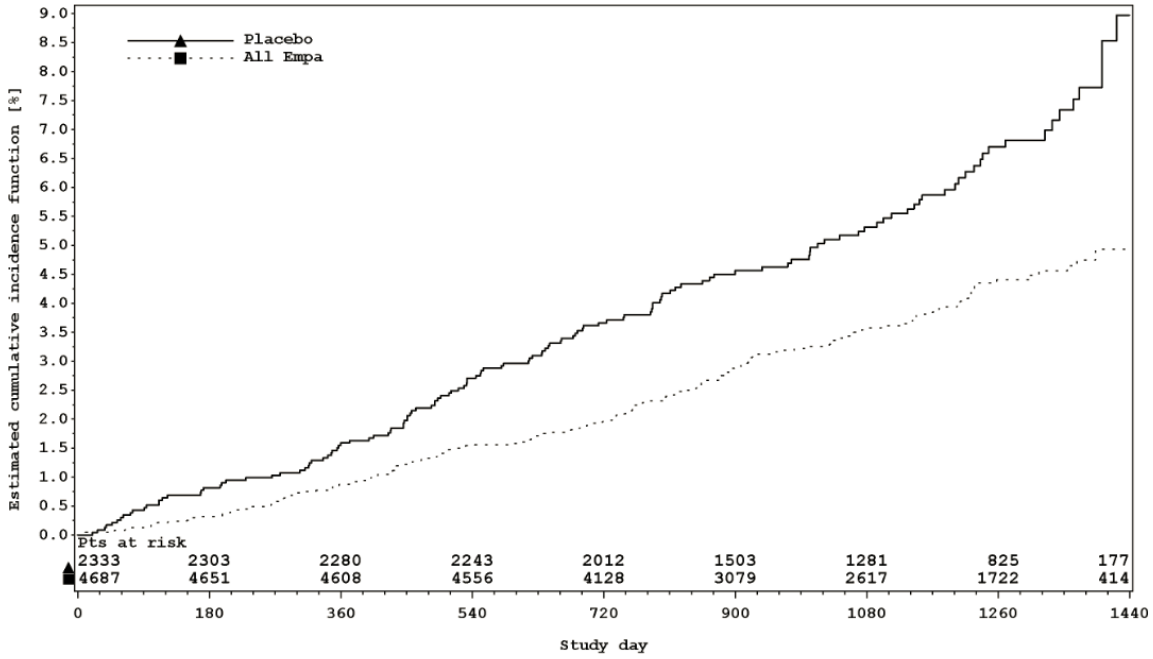
Reductions in risk of CV death and all-cause mortality
JARDIANCE was superior in reducing the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke compared to placebo. The incidence rate was 37.1 for JARDIANCE (10 and 25 mg, pooled) compared to 43.9 with placebo. The 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

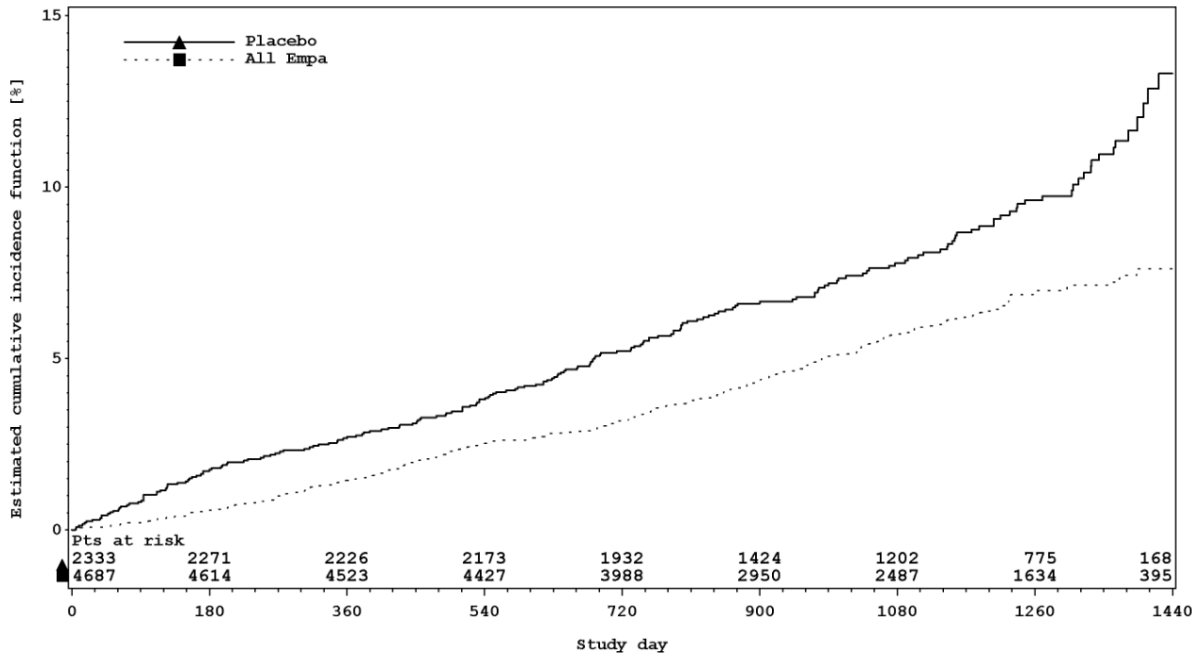
JARDIANCE significantly reduced the risk of hospitalization for heart failure and cardiovascular death or hospitalization for heart failure compared with placebo (Table 10 and Figure 2).

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).

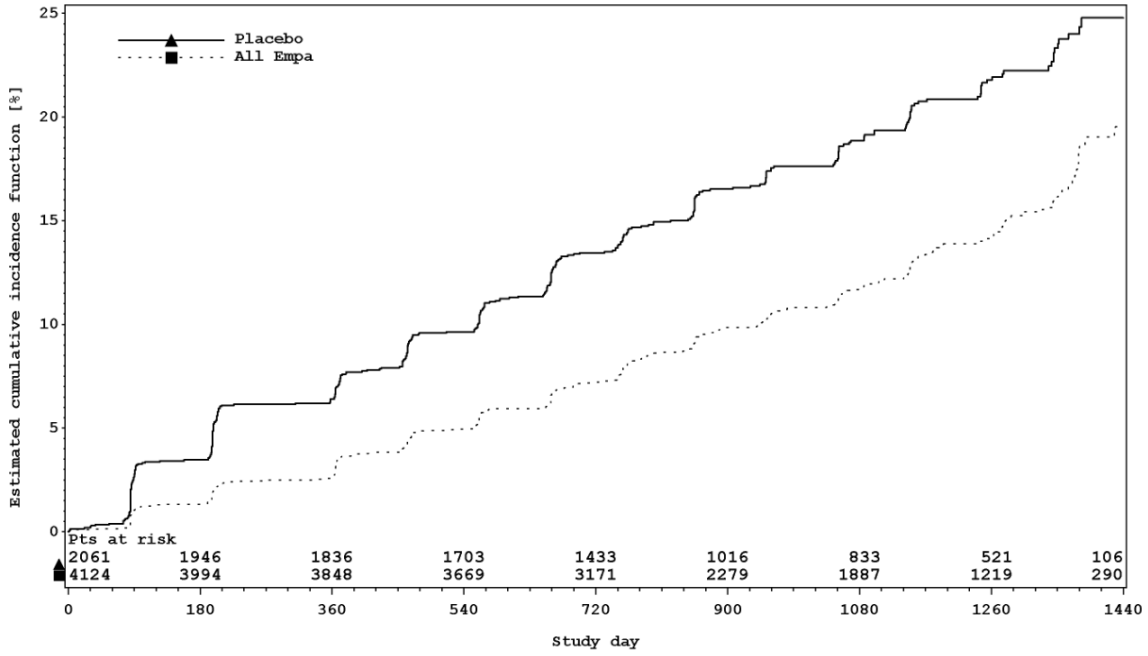
JARDIANCE compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria (HR 1.82, 95% CI 1.40, 2.37).

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)

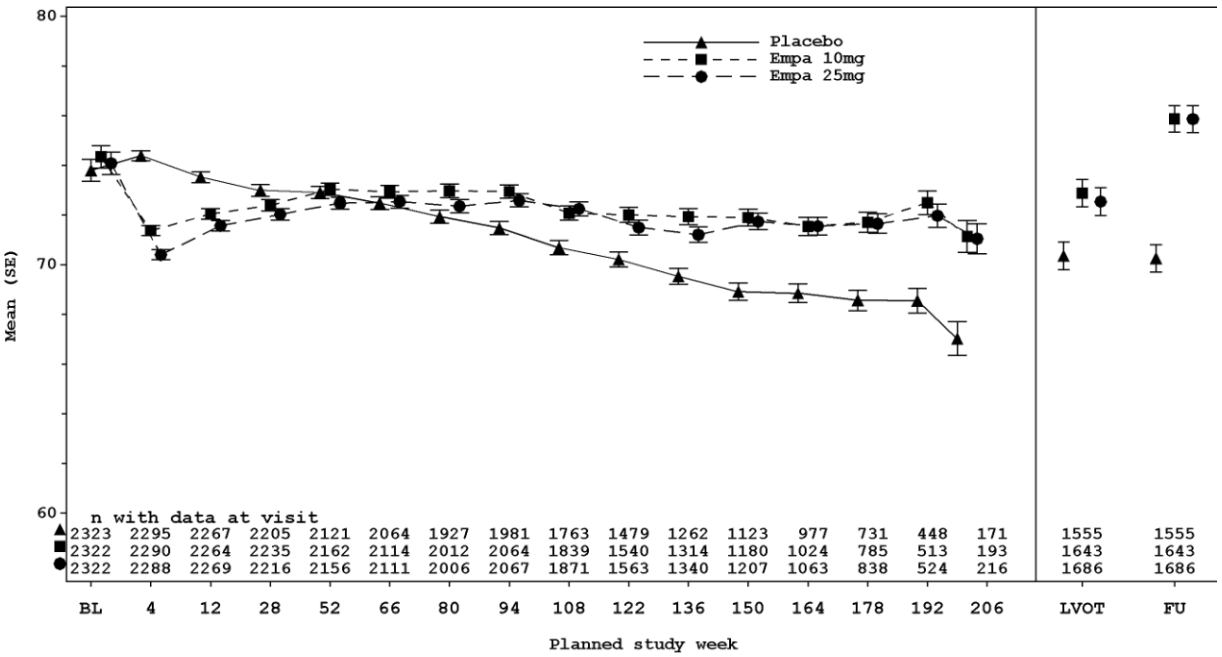
*i.e. patients who had received at least one dose of study drug
*Accompanied by an eGFR ≤45 mL/min/1.73m²
**Urine Albumin Creatinine Ratio >300 mg/g
***Due to low event rate, HR not calculated

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.

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 (Cmax) with a median time to reach Cmax (tmax) 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/1.73 m^2), moderate (eGFR: 30 - <60 mL/min/1.73 m^2), severe (eGFR: <30 mL/min/1.73 m^2) renal impairment and patients with kidney failure/ESRD patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. 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: DKI2124200417A1

Film coated tablet 25 mg
Box, 3 blisters @ 10 film coated tablet — Reg. No: DKI2124200417B1

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

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