For the use only of Registered Medical Practitioner

1. Generic Name & Brand Name

Empagliflozin Tablets 10 mg
Empexel™ 10

Empagliflozin Tablets 25 mg
Empexel™ 25

2. Qualitative and Quantitative Composition:

Empexel 10

Each Film Coated Tablet Contains:
Empagliflozin.…….10 mg
Excipients …….. q.s.
Colour: Ferric Oxide USP-NF Yellow

Empexel 25

Each Film Coated Tablet Contains:
Empagliflozin.…….25 mg
Excipients …….. q.s.
Colour: Ferric Oxide USP-NF Yellow.

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication

1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes Mellitus.
2. To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.
3. To reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction.

4.2 Posology and method of administration

Posology

Testing Prior to Initiation of Empagliflozin Tablets

- Assess renal function before initiating Empagliflozin Tablets and as clinically indicated.
- Use for glycemic control is not recommended in patients with an eGFR less than 30 mL/min/1.73 m^2.
- Empagliflozin Tablets is contraindicated in patients on dialysis.
- Assess volume status in patients with volume depletion and correct this condition before initiating Empagliflozin Tablets.

Method of Administration:

Table presents the recommended dosage of Empagliflozin Tablets in adult:

Population	*Indication*	*Recommended Dosage*

Adults	Reduce the risk of cardiovascular death and hospitalization in patients with heart failure	• 10 mg orally once daily in the morning, taken with or without food. • Data are insufficient to provide a dosage recommendation in patients who have: o type 2 diabetes mellitus and established cardiovascular disease with an eGFR less than 30 mL/min/1.73 m^2, or o heart failure with an eGFR less than 20 mL/min/1.73 m^2.
	Reduce the risk of cardiovascular death in patients with type 2 diabetes mellitus with established cardiovascular disease	
	Glycemic control in type 2 diabetes mellitus	• 10 mg orally once daily in the morning, taken with or without food. • For additional glycemic control, may increase to 25 mg orally once daily in patients tolerating 10 mg once daily.

Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible
- Do not double up the next dose

4.3 Contraindications

Empagliflozin Tablets is contraindicated in patients:

- with a hypersensitivity to empagliflozin or any of the excipients in Empagliflozin Tablets, reactions such as angioedema have occurred.
- on dialysis.

4.4 Special warnings and precautions for use

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and post marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including Empagliflozin Tablet. Fatal cases of ketoacidosis have been reported in patients taking Empagliflozin Tablet. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Empagliflozin Tablet is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Empagliflozin Tablet who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with Empagliflozin Tablet may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Empagliflozin Tablet should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the post marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic

acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.
Before initiating Empagliflozin Tablet, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing Empagliflozin Tablet for at least 3 days prior to surgery.
Consider monitoring for ketoacidosis and temporarily discontinuing Empagliflozin Tablet in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Empagliflozin Tablet.
Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Empagliflozin Tablet and seek medical attention immediately if signs and symptoms occur.

Volume Depletion
Empagliflozin Tablet can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including Empagliflozin Tablet. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Empagliflozin Tablet in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin Tablet. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Urosepsis and Pyelonephritis
There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving Empagliflozin Tablet. Treatment with Empagliflozin Tablet increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia
Insulin and insulin secretagogues are known to cause hypoglycemia. In adult patients, the risk of hypoglycemia may be increased when Empagliflozin Tablet is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. In pediatric patients aged 10 years and older, the risk of hypoglycemia was higher with Empagliflozin Tablet regardless of insulin use.
The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

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

Patients treated with Empagliflozin Tablet presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Empagliflozin Tablet, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

Empagliflozin Tablet increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Hypersensitivity Reactions

There have been post marketing reports of serious hypersensitivity reactions (e.g., angioedema) in patients treated with Empagliflozin Tablet. If a hypersensitivity reaction occurs, discontinue Empagliflozin Tablet; treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin Tablet is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in Empagliflozin Tablet.

4.5 Drug Interactions

Table Clinically Relevant Interactions with Empagliflozin Tablet

Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating Empagliflozin Tablet, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin Tablet. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when Empagliflozin Tablet is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of Empagliflozin Tablet with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during Empagliflozin Tablet initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.

Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, Empagliflozin Tablet is not recommended during the second and third trimesters of pregnancy.

The limited available data with Empagliflozin Tablet in pregnant women are not sufficient to determine a drug associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30, and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week, drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

Lactation

Risk Summary

There is limited information regarding the presence of Empagliflozin Tablet in human milk, the effects of Empagliflozin Tablet on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats [see Data]. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of Empagliflozin Tablet is not recommended while breastfeeding.

Data

Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5 and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use

The safety and effectiveness of Empagliflozin Tablet as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older. Use of Empagliflozin Tablet for this indication is supported by evidence from a 26-week double-blind, placebo-controlled clinical trial, with a double-blind active treatment safety extension period of up to 52 weeks in 157 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus and a pediatric pharmacokinetic study. The safety profile of pediatric patients treated with Empagliflozin Tablet was similar to that observed in adults with type 2 diabetes mellitus, with the exception of hypoglycemia risk which was higher in pediatric patients treated with Empagliflozin Tablet regardless of concomitant insulin use.

The safety and effectiveness of Empagliflozin Tablet have not been established in pediatric patients less than 10 years of age.

Geriatric Use

In glycemic control trials in patients with type 2 diabetes mellitus, a total of 2,721 (32%) patients treated with Empagliflozin Tablet were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin Tablet is expected to have diminished glycemic efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, Empagliflozin Tablet 10 mg, and Empagliflozin Tablet 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, Empagliflozin Tablet 10 mg, and Empagliflozin Tablet 25 mg, respectively.

In heart failure trials, EMPEROR-Reduced included 1,188 (64%) patients treated with Empagliflozin Tablet 65 years of age and older, and 503 (27%) patients 75 years of age and older. EMPEROR-Preserved included 2,402 (80%) patients treated with Empagliflozin Tablet 65 years of age and older, and 1,281 (43%) patients 75 years of age and older. No overall differences in safety and effectiveness have been observed between patients 65 years of age and older and younger adult patients.

Renal Impairment
The efficacy and safety of Empagliflozin Tablet for glycemic control were evaluated in a study of adult patients with type 2 diabetes mellitus with mild and moderate renal impairment (eGFR 30 to less than 90 mL/min/1.73 m^2) [see Clinical Studies (14)]. In this study, 195 adult patients exposed to Empagliflozin Tablet had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 adult patients exposed to Empagliflozin Tablet had an eGFR between 45 and 60 mL/min/1.73 m^2, and 97 patients exposed to Empagliflozin Tablet had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of Empagliflozin Tablet 25 mg decreased in adult patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. Use of Empagliflozin Tablet for glycemic control in patients without established cardiovascular disease or cardiovascular risk factors is not recommended when eGFR is less than 30 mL/min/1.73 m^2.
In a large cardiovascular outcomes study of adult patients with type 2 diabetes mellitus and established cardiovascular disease, there were 1819 patients with eGFR below 60 mL/min/1.73 m^2. The cardiovascular death findings in this subgroup were consistent with the overall findings.
Studies of adult patients with heart failure [see Clinical Studies (14)] enrolled patients with eGFR equal to or above 20 mL/min/1.73 m^2. No dosage adjustment is recommended for these patients. There are insufficient data to support a dosing recommendation in patients with eGFR below 20 mL/min/1.73 m^2.
Efficacy and safety trials with Empagliflozin Tablet did not enroll adult patients with an eGFR less than 20 mL/min/1.73 m^2. Empagliflozin Tablet is contraindicated in patients on dialysis.
In the trial of pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, patients with an eGFR less than 60 mL/min/1.73 m^2 were not enrolled.

Hepatic Impairment
Empagliflozin Tablet may be used in patients with hepatic impairment.

4.7 Effects on ability to drive and use machines
Empagliflozin Tablet 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 Empagliflozin Tablet is used in combination with a Sulphonylureas and/or insulin.

4.8 Undesirable effects
Summary of the safety profile
Type 2 diabetes mellitus
A total of 15582 patients with type 2 diabetes were included in clinical studies to evaluate the safety of empagliflozin, of which 10004 patients received empagliflozin, either alone or in combination with metformin, a Sulphonylureas, pioglitazone, DPP-4 inhibitors, or insulin.
In 6 placebo-controlled trials of 18 to 24 weeks duration, 3534 patients were included of which 1183 were treated with placebo and 2351 with empagliflozin. The overall incidence of adverse events in patients treated with empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycaemia when used with Sulphonylureas or insulin.
Heart failure
The EMPEROR studies included patients with heart failure and either reduced ejection fraction (N=3726) or preserved ejection fraction (N=5985) 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%).
The overall safety profile of empagliflozin was generally consistent across the studied indications.
Tabulated list of adverse reactions

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received empagliflozin in placebo-controlled studies are presented in the table below
The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), or very rare (<1/10 000), and not known (cannot be estimated from the available data).
Table Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled studies and from post-marketing experience

System organ class	Very common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[a] Urinary tract infection (including pyelonephritis and urosepsis)[a]		Necrotising fasciitis of the perineum (Fournier's gangrene)*	
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[a]	Thirst	Diabetic ketoacidosis*		
Gastrointestinal disorders		Constipation			
Skin and subcutaneous tissue disorders		Pruritus (generalised) Rash	Urticaria Angioedema		
Vascular disorders	Volume depletion[a]				
Renal and urinary disorders		Increased urination[a]	Dysuria		Tubulo-interstitial nephritis
Investigations		Serum lipids increased[a]	Blood creatinine increased/ Glomerular filtration rate decreased[a] Haematocrit increased[a]		

[a] see subsection below for additional information
* see section 4.4

Description of selected adverse reactions

Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as monotherapy, add-on to metformin, add-on to pioglitazone with or without metformin, as add-on to linagliptin and metformin, and as adjunct to standard care therapy and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to metformin and a Sulphonylureas (empagliflozin 10 mg: 16.1%, empagliflozin 25 mg: 11.5%, placebo: 8.4%), add-on to basal insulin with or without metformin and with or without a Sulphonylureas (empagliflozin 10 mg: 19.5%, empagliflozin 25 mg: 28.4%, placebo: 20.6% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg and 25 mg: 36.1%, placebo 35.3% over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 39.8%, empagliflozin 25 mg: 41.3%, placebo: 37.2% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 51.1%, empagliflozin 25 mg: 57.7%, placebo: 58% over the 52-week trial).
In the EMPEROR heart failure studies, similar frequency of hypoglycaemia was noted when used add-on to Sulphonylureas or insulin (empagliflozin 10 mg: 6.5%, placebo: 6.7%).

Major hypoglycaemia (events requiring assistance)

No increase in major hypoglycaemia was observed with empagliflozin compared to placebo as monotherapy, add-on to metformin, add-on to metformin and a Sulphonylureas, add-on to pioglitazone with or without metformin, add-on to linagliptin and metformin, as adjunct to standard care therapy and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to basal insulin with or without metformin and with or without a Sulphonylureas (empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo: 0% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo 0% over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 0.5%, empagliflozin 25 mg: 0.5%, placebo: 0.5% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 1.6%, empagliflozin 25 mg: 0.5%, placebo: 1.6% over the 52-week trial).
In the EMPEROR heart failure studies, major hypoglycaemia was observed at similar frequencies in patients with diabetes mellitus when treated with empagliflozin and placebo as add-on to Sulphonylureas or insulin (empagliflozin 10 mg: 2.2%, placebo: 1.9%).

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in patients treated with empagliflozin (empagliflozin 10 mg: 4.0%, empagliflozin 25 mg: 3.9%) compared to placebo (1.0%). These infections were reported more frequently in females treated with empagliflozin compared to placebo, and the difference in frequency was less pronounced in males. The genital tract infections were mild or moderate in intensity.
In the EMPEROR heart failure studies, the frequency of these infections was more pronounced in patients with diabetes mellitus (empagliflozin 10 mg: 2.3%; placebo: 0.8%) than in patients without diabetes mellitus (empagliflozin 10 mg: 1.7%; placebo: 0.7%) when treated with empagliflozin compared to placebo.

Increased urination

Increased urination (including the predefined terms pollakiuria, polyuria, and nocturia) was observed at higher frequencies in patients treated with empagliflozin (empagliflozin 10 mg: 3.5%, empagliflozin 25 mg: 3.3%) compared to placebo (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was similar for placebo and empagliflozin (<1%).
In the EMPEROR heart failure studies, increased urination was observed at similar frequencies in patients treated with empagliflozin and placebo (empagliflozin 10 mg: 0.9%, placebo 0.5%).

Urinary tract infection
The overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo (7.0% and 7.2%) and higher in empagliflozin 10 mg (8.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity (mild, moderate, severe) of urinary tract infection was similar in patients treated with empagliflozin and placebo. Urinary tract infection was reported more frequently in females treated with empagliflozin compared to placebo; there was no difference in males.
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 in patients treated with empagliflozin (empagliflozin 10 mg: 0.6%, empagliflozin 25 mg: 0.4%) and placebo (0.3%). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2.3%) or empagliflozin 25 mg (4.3%) compared to placebo (2.1%).
Blood creatinine increased/Glomerular filtration rate decreased
The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%).
Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with empagliflozin were generally transient during continuous treatment or reversible after drug discontinuation of treatment.
Consistently, in the EMPA-REG OUTCOME study, patients treated with empagliflozin experienced an initial fall in eGFR (mean: 3 ml/min/1.73 m^2). Thereafter, eGFR was maintained during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting acute hemodynamic changes may play a role in these renal function changes.
Serum lipids increased
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%.
Haematocrit increased
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.

4.9 Overdose
Symptoms
In controlled clinical studies single doses of up to 800 mg empagliflozin in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg in humans.
Therapy
In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied.

5. Pharmacological properties

5.1 Mechanism of action

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

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

5.2 Pharmacodynamic Properties

Urinary Glucose Excretion

In patients with type 2 diabetes mellitus, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily [see Clinical Studies (14)]. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

5.3 Pharmacokinetic properties

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median tmax of 1.5 hours 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 and Cmax were 1 870 nmol·h/l and 259 nmol/l with empagliflozin 10 mg and 4 740 nmol·h/l and 687 nmol/l with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic 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 type 2 diabetes.

Administration of empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax 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 the population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Biotransformation

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-, 3-, 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

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour. 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 the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady state. Following administration of an oral [14C]-empagliflozin solution to healthy volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). 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.

Special populations

Renal impairment

In patients with mild, moderate or severe renal impairment (eGFR <30 - <90 ml/min/1.73 m2) and patients with kidney failure/end stage renal disease (ESRD), 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. 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.

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 Cmax by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Body Mass Index

Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. In this analysis, AUC was estimated to be 5.82%, 10.4%, and 17.3% lower in subjects with BMI of 30, 35, and 45 kg/m2, respectively, compared to subjects with a body mass index of 25 kg/m2.

Gender

Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race

In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25 kg/m2 compared to non-Asians with a body mass index of 25 kg/m2.

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

Paediatric population
A paediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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 mineralization 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 mineralization at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic.
In a 2-year carcinogenicity study, empagliflozin did not increase the incidence of tumors 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 (hemangiomas) 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 tumors 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 tumors are common in rats and are unlikely to be relevant to humans.
Empagliflozin did not increase the incidence of tumors in female mice at doses up to 1 000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumors in male mice at 1 000 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 tumors 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 tumors are considered not relevant to humans.
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 week drug-free recovery period.

7. Description

Empexel 10 : Empexel 10 is supplied for oral administration as a film coated tablet of Empagliflozin. Each Empexel 10 tablet contains Empagliflozin 10 mg.
Empexel 25 : Empexel 25 is supplied for oral administration as a film coated tablet of Empagliflozin. Each Empexel 25 tablet contains Empagliflozin 25 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

NA.

8.2 Shelf Life

Refer pack.

8.3 Packaging Information

Refer pack

8.4 Storage condition & Handling instructions

Refer pack

9. Patient Counseling Information

1. What is the most important information I should know about Empagliflozin Tablet?

- Empagliflozin Tablet can cause serious side effects, including:
  Ketoacidosis (increased ketones in your blood or urine). Ketoacidosis has happened in people who have type 1 diabetes or type 2 diabetes, during treatment with Empagliflozin Tablet. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with Empagliflozin Tablet. Ketoacidosis is a serious condition, which needs to be treated in a hospital. Ketoacidosis may lead to death. Ketoacidosis can happen with Empagliflozin Tablet even if your blood sugar is less than 250 mg/dL. Stop taking Empagliflozin Tablet and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms:
  i. Nausea
  ii. tiredness
  iii. vomiting
  iv. trouble breathing
  v. stomach-area (abdominal) pain
  If you get any of these symptoms during treatment with Empagliflozin Tablet, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- Dehydration. Empagliflozin Tablet can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden worsening of kidney function in people who are taking Empagliflozin Tablet. You may be at higher risk of dehydration if you:
  i. take medicines to lower your blood pressure, including diuretics (water pills)

ii. are on low sodium (salt) diet
iii. have kidney problems
iv. are 65 years of age or older

Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Talk to your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you are sick or cannot eat, or start to lose liquids from your body, for example from vomiting, diarrhea or being in the sun too long.

2. What is Empagliflozin Tablet?

Empagliflozin Tablet is a prescription medicine used to:

- reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, when the heart cannot pump enough blood to the rest of your body.
- reduce the risk of cardiovascular death in adults with type 2 diabetes and who also have known cardiovascular disease.
- lower blood sugar along with diet and exercise in adults and children who are 10 years of age and older with type 2 diabetes.

Empagliflozin Tablet is not for people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in blood or urine).

Empagliflozin Tablet is not for use to lower blood sugar in adults with type 2 diabetes who have severe kidney problems, because it may not work.

It is not known if Empagliflozin Tablet is safe and effective in children under 10 years of age.

3. Who should not take Empagliflozin Tablet?

Do not take Empagliflozin Tablet if you:

- are allergic to empagliflozin or any of the ingredients in Empagliflozin Tablet. See the end of this Medication Guide for a complete list of ingredients in Empagliflozin Tablet. Symptoms of a serious allergic reaction to Empagliflozin Tablet may include:
  - swelling of your face, lips, throat, and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking Empagliflozin Tablet and call your healthcare provider right away or go to the nearest hospital emergency room.
- are on dialysis.

4. What should I tell my healthcare provider before taking Empagliflozin Tablet?

Before taking Empagliflozin Tablet, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have liver problems.
- have a history of infection of the vagina or penis.
- have a history of urinary tract infections or problems with urination.
- are going to have surgery. Your healthcare provider may stop your Empagliflozin Tablet before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking Empagliflozin Tablet and when to start it again.
- are eating less, or there is a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often or drink a lot of alcohol in the short term ("binge" drinking).
- have type 1 diabetes. Empagliflozin Tablet should not be used to treat people with type 1 diabetes.

- are pregnant or plan to become pregnant. Empagliflozin Tablet may harm your unborn baby. If you become pregnant while taking Empagliflozin Tablet, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. Empagliflozin Tablet may pass into your breast milk and may harm your baby.

Talk with your healthcare provider about the best way to feed your baby if you are taking Empagliflozin Tablet. Do not breastfeed while taking Empagliflozin Tablet.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Empagliflozin Tablet may affect the way other medicines work, and other medicines may affect how Empagliflozin Tablet works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

5. How should I take Empagliflozin Tablet?

- Take Empagliflozin Tablet exactly as your healthcare provider tells you to take it.
- Take Empagliflozin Tablet by mouth 1 time in the morning each day, with or without food.
- Your healthcare provider may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of Empagliflozin Tablet at the same time. Talk with your healthcare provider if you have questions about a missed dose.
- Your healthcare provider may tell you to take Empagliflozin Tablet along with other diabetes medicines. Low blood sugar can happen more often when Empagliflozin Tablet is taken with certain other diabetes medicines.
- If you take too much Empagliflozin Tablet, call your healthcare provider or go to the nearest hospital emergency room right away.
- When taking Empagliflozin Tablet, you may have sugar in your urine, which will show up on a urine test.
- Your healthcare provider may do blood tests to check how well your kidneys are working before and during your treatment with Empagliflozin Tablet.

6. What are the possible side effects of Empagliflozin Tablet?

Empagliflozin Tablet may cause serious side effects, including:

- See "What is the most important information I should know about Empagliflozin Tablet?"
- Serious urinary tract infections. Serious urinary tract infections that may lead to hospitalization have happened in people who are taking Empagliflozin Tablet. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- Low blood sugar (hypoglycemia). In adults, if you take Empagliflozin Tablet with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. In children 10 years of age and older, the risk for low blood sugar may be higher with Empagliflozin Tablet regardless of use with another medicine that can also lower blood sugar. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take Empagliflozin Tablet.
- Signs and symptoms of low blood sugar may include:
    a) Headache
    b) Irritability

c) Confusion
d) dizziness
e) drowsiness
f) hunger
g) shaking or feeling jittery
h) sweating
i) weakness
j) fast heartbeat

- A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum). Necrotizing fasciitis of the perineum has happened in women and men who take Empagliflozin Tablet. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:
    a) pain or tenderness
    b) swelling
    c) redness of skin (erythema)
- Vaginal yeast infection. Symptoms of a vaginal yeast infection include:
    a) vaginal odor
    b) white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
    c) vaginal itching
- Yeast infection of the penis (balanitis or balanoposthitis). Swelling of an uncircumcised penis may develop that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
    a) redness, itching, or swelling of the penis
    b) rash of the penis
    c) foul smelling discharge from the penis
    d) pain in the skin around the penis

  Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.
- Allergic (hypersensitivity) reactions. Serious allergic reactions have happened in people who are taking Empagliflozin Tablet. Symptoms may include:
    a) swelling of your face, lips, throat and other areas of your skin
    b) difficulty with swallowing or breathing.
    c) raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking Empagliflozin Tablet and call your healthcare provider right away or go to the nearest hospital emergency room.
  The most common side effects of Empagliflozin Tablet include:
    a) urinary tract infections
    b) yeast infections in females

  These are not all the possible side effects of Empagliflozin Tablet. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effect

10. Details of manufacturer

Refer Pack for manufacturer details

11. Details of permission or licence number
Refer Pack for Permission/License details

12. Date of revision
Version 1.0, dated 14/11/2024

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