PATIENT INFORMATION LEAFLET

For the use of a Registered Medical Practitioner, or a Hospital, or a Laboratory only

Empagliflozin Tablets 25 mg

AMERICAN Empafox 25 Tablets
एम्पाफॉक्स २५

1. GENERIC NAME

Empagliflozin Tablets 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Empagliflozin 25 mg

Excipients q.s.

Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Oral dosage form (Tablets),

Empagliflozin 25 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes Mellitus.

4.2 Posology and method of administration

Testing Prior to Initiation of Empagliflozin

- Assess renal function before initiating Empagliflozin 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
- Assess volume status. In patients with volume depletion, correct this condition before initiating Empagliflozin.

Recommended Dosage

Table 1 presents the recommended dosage of Empagliflozin in adult and pediatric patients aged 10 years and older.

Table 1 Recommended Dosage of Empagliflozin

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.
	Reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression.	
	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.
Pediatric patients aged 10 years and older	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.

Temporary Interruption for Surgery

Withhold Empagliflozin for at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume Empagliflozin when the patient is clinically stable and has resumed oral intake.

4.3 Contraindications

Empagliflozin is contraindicated in patients:

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

4.4 Special warnings and precautions for use

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, Empagliflozin significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose co-transporter 2 (SGLT2) inhibitors compared to patients who received placebo and fatal ketoacidosis has occurred with Empagliflozin. Empagliflozin is not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including Empagliflozin.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing Empagliflozin however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients with type 1 diabetes mellitus and consider ketone monitoring in others at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue Empagliflozin, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting Empagliflozin.

Withhold Empagliflozin, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume Empagliflozin when the patient is clinically stable and has resumed oral intake.

Educate all patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Empagliflozin and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

Empagliflozin 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. 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 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. 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. Treatment with Empagliflozin 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 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 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. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Empagliflozin 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, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

Empagliflozin 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.

Lower Limb Amputation

In some clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. Across four Empagliflozin outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the Empagliflozin 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95 % CI) (0.81, 1.36).

In a long-term cardio-renal outcome trial, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1000 patient years in the placebo, and Empagliflozin 10 mg treatment arms, respectively.

Amputation of the toe and mid-foot were most frequent (21 out of 28 Empagliflozin 10 mg treated patients with lower limb amputations), and some involving above and below the knee. Some patients had multiple amputations.

Peripheral artery disease, and diabetic foot infection (including osteomyelitis), were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of diabetic foot, peripheral artery disease (including previous amputation) or diabetes.

Counsel patients about the importance of routine preventative foot care. Monitor patients receiving Empagliflozin for signs and symptoms of diabetic foot infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

Hypersensitivity Reactions

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

4.5 Drug Interactions

Table 2 Clinically Relevant Interactions with Empagliflozin

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, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin. 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 is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of Empagliflozin 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 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

Risk Summary

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

The limited available data with Empagliflozin 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 48- times (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 in human milk, the effects of Empagliflozin on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats. 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 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 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 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 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 regardless of concomitant insulin use

The safety and effectiveness of Empagliflozin have not been established in pediatric patients less than 10 years of age as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus.

The safety and effectiveness of Empagliflozin have not been established in pediatric patients to reduce the risk of:

cardiovascular death and hospitalization for heart failure in patients with heart failure.

sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalization in patients with chronic kidney disease at risk of progression.

cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease.

Geriatric Use

In glycemic control trials in patients with type 2 diabetes mellitus, a total of 2,721 (32%) patients treated with Empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin 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 10 mg, and Empagliflozin 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 10 mg, and Empagliflozin 25 mg, respectively.

In the EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-KIDNEY trials, no overall differences in safety and effectiveness have been observed between patients 65 years of age and older and younger adult patients. EMPEROR-Reduced included 1,188 (64%) patients treated with Empagliflozin 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 65 years of age and older, and 1,281 (43%) patients 75 years of age and older. EMPA-KIDNEY included 2,089 (32%) patients treated with Empagliflozin 65 years of age and older, and 1,518 (23%) patients 75 years of age and older.

Renal Impairment

The efficacy and safety of Empagliflozin for glycemic control were evaluated in a trial 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). In this trial, 195 adult patients exposed to Empagliflozin had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 adult patients exposed to Empagliflozin had an eGFR between 45 and 60 mL/min/1.73 m^2, and 97 patients exposed to Empagliflozin had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of Empagliflozin 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 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.

Empagliflozin was evaluated in 7,020 adult patients with type 2 diabetes and established cardiovascular disease (eGFR greater than or equal to 30 mL/min/1.73 m^2) in the EMPA-REG OUTCOME trial, in a total of 9,718 patients with heart failure (eGFR greater than or equal to 20 mL/min/1.73 m^2) in the EMPEROR-Reduced and EMPEROR-Preserved trials, and in 6,609 adult patients with chronic kidney disease (eGFR 20 to 90 mL/min/1.73 m^2) in the EMPA-KIDNEY study. The safety profile across eGFR subgroups in these trials was consistent with the known safety profile.

Efficacy and safety trials with Empagliflozin did not enroll adult patients with an eGFR less than 20 mL/min/1.73 m^2 or on dialysis. Once enrolled, adult patients in the EMPA-REG OUTCOME, EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-KIDNEY trials were not required to discontinue therapy for worsening of eGFR to less than 20 mL/min/1.73 m^2 or initiation of dialysis.

Hepatic Impairment

Empagliflozin may be used in patients with hepatic impairment.

4.7 Effects on ability to drive and use machines

Empagliflozin 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 sulphonylurea and/or insulin.

4.8 Undesirable effects

The following important adverse reactions are described below and elsewhere in the labeling:

- ***Genital Pruritus***
- ***Diabetic ketoacidosis and Urinary Tract Infection Warning-Cases of a rare but serious infection of the genitals and area around the genitals have been reported with this class of type 2 diabetes medicines ie., Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fascitis of the perineum, is also referred to as Fournier's gangrene.***
- Volume Depletion
- Urosepsis and Pyelonephritis
- Hypoglycemia
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections
- Hypersensitivity Reactions

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Empagliflozin has been evaluated in clinical trials in adult and pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, in adults with heart failure, and in adults with chronic kidney disease. The overall safety profile of Empagliflozin was generally consistent across the studied indications.

Clinical Trials in Adults with Type 2 Diabetes Mellitus

The data are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin in adult patients with type 2 diabetes mellitus. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials.

These data reflect exposure of 1,976 adult patients to Empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), Empagliflozin 10 mg (N=999), or Empagliflozin 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes mellitus more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes mellitus at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m^2).

Table 3 shows adverse reactions (excluding hypoglycemia) that were not present at baseline, occurred more commonly in Empagliflozin-treated patients than on placebo and occurred in greater than or equal to 2% Empagliflozin-treated patients.

Table 3: Adverse Reactions Reported in ≥2% of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Trials of Empagliflozin Monotherapy or Combination Therapy

Adverse Reactions	Placebo (%) N=995	Empagliflozin 10 mg (%) N=999	Empagliflozin 25 mg (%) N=977
Urinary tract infection[a]	7.6	9.3	7.6
Female genital mycotic infections[b]	1.5	5.4	6.4
Upper respiratory tract infection	3.8	3.1	4.0
Increased urination[c]	1.0	3.4	3.2
Dyslipidemia	3.4	3.9	2.9
Arthralgia	2.2	2.4	2.3
Male genital mycotic infections[d]	0.4	3.1	1.6
Nausea	1.4	2.3	1.1

[a] Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

[b] Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), Empagliflozin 10 mg (N=443), Empagliflozin 25 mg (N=420).

[c] Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia

[d] Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), Empagliflozin 10 mg (N=556), Empagliflozin 25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg, respectively.

Volume Depletion

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials in adults, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction

Increased Urination

In the pool of five placebo-controlled clinical trials in adults, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on Empagliflozin than on placebo. Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg, respectively.

Hypoglycemia in Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus

The incidence of hypoglycemia in adults by trial is shown in Table 4. The incidence of hypoglycemia increased when Empagliflozin was administered with insulin or sulfonylurea.

Table 4: Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus[c]

Monotherapy (24 weeks)	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**Empagliflozin 10 mg + Metformin (n=217)**	**Empagliflozin 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)**	**Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)**	**Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin (18 weeks[d])	**Placebo (n=170)**	**Empagliflozin 10 mg (n=169)**	**Empagliflozin 25 mg (n=155)**
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/- Metformin (18 weeks[d])	**Placebo (n=188)**	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

[a] Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL

[b] Severe hypoglycemic events: requiring assistance regardless of blood glucose

[c] Treated set (patients who had received at least one dosage of trial drug)
[d] Insulin dosage could not be adjusted during the initial 18-week treatment period

Other Adverse Reactions in Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus

Genital Mycotic Infections: In the pool of five placebo-controlled clinical trials in adults, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with Empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg, respectively. Discontinuation from trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either Empagliflozin 10 mg or 25 mg.
Genital mycotic infections occurred more frequently in female than male patients.
Phimosis occurred more frequently in male patients treated with Empagliflozin 10 mg (less than 0.1%) and Empagliflozin 25 mg (0.1%) than placebo (0%).

Urinary Tract Infections: In the pool of five placebo-controlled clinical trials in adults, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with Empagliflozin compared to placebo. Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg, respectively.
Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively

Clinical Trial in Pediatric Patients Aged 10 to 17 Years with Type 2 Diabetes Mellitus

Empagliflozin was administered to 52 patients in a trial of 157 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus with a mean exposure to Empagliflozin of 23.8 weeks. Background therapies as adjunct to diet and exercise included metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). The mean HbA1c at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2.1 years. The mean age was 14.5 years (range: 10-17 years) and 51.6% were aged 15 years and older. Approximately, 50% were White, 6% were Asian, 31% were Black or African American, and 38% were of Hispanic or Latino ethnicity. The mean BMI was 36.0 kg/m^2 and mean BMI Z score was 3.0. Approximately 25% of the trial population had microalbuminuria or macroalbuminuria.
The risk of hypoglycemia was higher in pediatric patients treated with Empagliflozin regardless of concomitant insulin use. Hypoglycemia, defined as a blood glucose < 54 mg/dL, occurred in 10 (19.2%) patients and in 4 (7.5%) patients treated with Empagliflozin and placebo, respectively. No severe hypoglycemic events occurred (severe hypoglycemia was defined as an event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions).

Clinical Trials in Adults with Heart Failure

No new adverse reactions were identified in EMPEROR-Reduced or EMPEROR-Preserved heart failure trials.

Clinical Trial in Adults with Chronic Kidney Disease

The safety profile in patients with chronic kidney disease was generally consistent with that observed across the studied indications. In a long-term cardio-renal outcome, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and Empagliflozin 10 mg treatment arms, respectively.

Laboratory Test Abnormalities in Clinical Trials

Increases in Serum Creatinine and Decreases in eGFR

Initiation of Empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a trial of adults with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with Empagliflozin.

Increase in Low-Density Lipoprotein Cholesterol (LDL-C)

Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in adults treated with Empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit

In a pool of four placebo-controlled trials in adults, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in Empagliflozin 10 mg and 2.8% in Empagliflozin 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg, respectively.

Postmarketing Experience

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

Gastrointestinal Disorders: Constipation
Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis
Metabolism and Nutrition Disorders: Ketoacidosis
Renal and Urinary Disorders: Acute kidney injury
Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

4.9 Overdose

In the event of an overdose with Empagliflozin consider contacting medical toxicologist for additional overdosage management recommendations. Removal of empagliflozin by hemodialysis 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 including, but not restricted to, increasing tubuloglomerular feedback and reducing intraglomerular pressure, 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. 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

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes mellitus and no clinically relevant differences were noted between the two populations. The steadystate mean plasma AUC and C_{max} were 1,870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4,740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. Empagliflozin does not appear to have time-dependent pharmacokinetic characteristics. Following once daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state.

Absorption

After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. 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 [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

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.

Metabolism

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

Excretion

Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug

Specific Populations

Pediatric Patients

The pharmacokinetics and pharmacodynamics of empagliflozin were investigated in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus. Oral administration of empagliflozin at 10 mg and 25 mg resulted in exposure within the range observed in adult patients.

Effects of Age, Body Mass Index, Gender, and Race

Age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Patients with Hepatic Impairment

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

Patients with Renal Impairment

In adult patients with type 2 diabetes mellitus with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and patients on dialysis due to kidney failure, 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 patients with moderate renal impairment and patients on dialysis due to kidney failure compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to patients with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Drug Interaction Studies

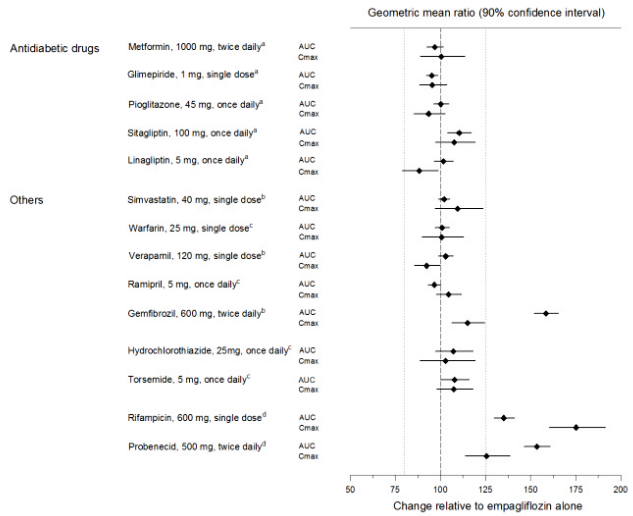
In vitro Assessment of Drug Interactions

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'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.
Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, 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, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes mellitus. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown. Figure 1:

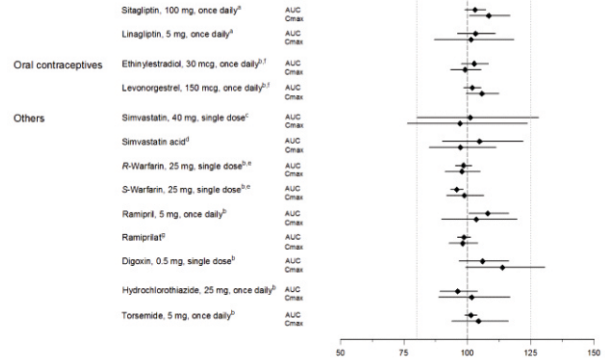
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (Figure 2).
[a]empagliflozin, 50 mg, once daily;[b]empagliflozin, 25 mg, once daily; [c] empagliflozin, 25 mg, single dose;[d] administered

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



as simvastatin; [e]administered as warfarin racemic mixture; [f] administered as Microgynon®; [g]administered as ramipril

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Carcinogenesis

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1,000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1,000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Mutagenesis

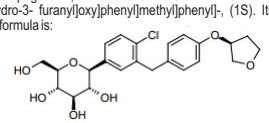
Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y tk+/- mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Impairment of Fertility

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

7. DESCRIPTION

Empagliflozin tablets for oral use contain empagliflozin, an inhibitor of the SGLT2. The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3- furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
NA
8.2 Shelf life
Please refer details on blister/carton.
8.3 Packaging information
Blister Pack of 10 Tablets.
8.4 Storage & Handling Instructions
Store in a cool and dry place, at a temperature not exceeding 25°C.

9. PATIENT COUNSELLING INFORMATION

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor, pharmacist or nurse.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *If you get any side effects gets serious, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.*

What are Empagliflozin Tablets?

Empagliflozin is an SGLT2 inhibitor used to manage type 2 diabetes mellitus, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones.

Who should not take Empagliflozin Tablets?

Do not take Empagliflozin Tablets if you are allergic to any of its ingredients or excipients used in the Tablets.

What you need to know before you take Empagliflozin Tablets?

Do not take Empagliflozin Tablets

- have type 1 diabetes or have had diabetic ketoacidosis.
- have a decrease in your insulin dose.
- have a serious infection.
- have a history of infection of the vagina or penis.
- have a history of amputation.
- have kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems with urination.
- are on a low sodium (salt) diet. Your healthcare provider may change your diet or your dose.
- are going to have surgery. Your healthcare provider may stop your Empagliflozin Tablets before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking Empagliflozin Tablets and when to start it again.
- are eating less, or there is a change in your diet.
- are dehydrated.
- 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 ever had an allergic reaction to Empagliflozin Tablets.
- are pregnant or plan to become pregnant. Empagliflozin Tablets may harm your unborn baby. If you become pregnant while taking Empagliflozin Tablets, 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 Tablets 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 Tablets. Do not breastfeed while taking Empagliflozin Tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Empagliflozin Tablets may affect the way other medicines work, and other medicines may affect how Empagliflozin Tablets works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Empagliflozin Tablets?

- Take Empagliflozin Tablets exactly as your healthcare provider tells you to take it.
- Take Empagliflozin Tablets by mouth 1 time in the morning each day, with or without food.
- Your healthcare provider will tell you how much Empagliflozin Tablets to take and when to take it. Your healthcare provider may change your dose if needed.
- Your healthcare provider may tell you to take Empagliflozin Tablets along with other diabetes medicines. Low blood sugar can happen more often when Empagliflozin Tablets is taken with certain other diabetes medicines.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take two doses of Empagliflozin Tablets at the same time.
- Talk with your healthcare provider if you have questions about a missed dose.
- When taking Empagliflozin Tablets, you may have sugar in your urine, which will show up on a urine test.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.
- Your healthcare provider may do certain blood tests before you start Empagliflozin Tablets and during treatment as needed.

What are the possible side effects of Empagliflozin Tablets?

- urinary tract infections
- yeast infections in females
- Serious urinary tract infections. Serious urinary tract infections that may lead to hospitalization have happened in people who are taking Empagliflozin Tablets. 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 Tablets 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 is higher with Empagliflozin Tablets even if you do not use 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 Tablets. Signs and symptoms of low blood sugar may include:
  - headache
  - irritability
  - confusion
  - dizziness
  - drowsiness
  - hunger
  - shaking or feeling jittery
  - sweating
  - weakness
  - 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 people who take Empagliflozin Tablets. 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:
  - pain or tenderness
  - swelling
  - redness of skin (erythema)
- Amputations. SGLT2 inhibitors may increase your risk of lower limb amputations. You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - have had blocked or narrowed blood vessels, usually in your leg
  - have had diabetic foot infection, ulcers or sores

Call your healthcare provider right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Talk to your healthcare provider about proper foot care.

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