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EMPAGLIFLOZIN

EMPAZ 10®

10 mg Film coated tablet
Antidiabetic Agent

PRODUCT DESCRIPTION:
Yellow, round, biconvex film-coated tablet with breakline on one side.

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Empagliflozin.....10 mg

INDICATIONS:

Type 2 diabetes mellitus
Empaz is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

Heart failure
Empaz is indicated in adults for the treatment of symptomatic chronic heart failure.
Chronic kidney disease
Empaz is indicated in adults for the treatment of chronic kidney disease

DOSAGE AND ADMINSTRATION:

Type 2 diabetes mellitus
The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg.

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

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

All indications
When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same day.

Special populations
Renal impairment
Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 m2.
In patients with an eGFR <60 ml/min/1.73 m2 the daily dose of empagliflozin is 10 mg.
In patients with type 2 diabetes mellitus, the glucose lowering efficacy of empagliflozin is reduced in patients with an eGFR <45 ml/min/1.73 m2 and likely absent in patients with an eGFR <30 ml/min/1.73 m2. Therefore, if eGFR falls below 45 ml/min/1.73 m2, additional glucose lowering treatment should be considered if needed.
Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population (see section
5.2).
Elderly
No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be considered
Pediatric population
The recommended starting dose is 10 mg empagliflozin once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily (see sections 5.1 and 5.2). No data are available for children with eGFR <60 ml/min/1.73 m^2 and children below 10 years of age.

The safety and efficacy of empagliflozin for the treatment of heart failure or for the treatment of chronic kidney disease in children under 18 years of age have not been established. No data are available.
Method of administration
The tablets can be taken with or without food, swallowed whole with water

CONTRAINDICATIONS:
Hypersensitivity to the active ingredient or any excipients

SPECIAL WARNING AND PRECAUTIONS:
General
Empagliflozin should not be used in patients with type 1 diabetes mellitus.
Ketoacidosis
In patients where ketoacidosis is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.
Renal impairment
Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 m2
Risk for volume depletion
Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom an empagliflozin-induced decrease in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.
In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including hematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.
Elderly
The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).
Urinary tract infections
Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin (see section 4.8). Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

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

Lactation
No data in humans are available on excretion of empagliflozin into milk. Available toxicological data in animals have shown excretion of empagliflozin in milk. A risk to the newborns/infants cannot be excluded. Empaz should not be used during breast-feeding.

Fertility
No studies on the effect on human fertility have been conducted for Jardiance. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

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

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%).

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 were 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%).

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.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

The insulin independent mechanism of action of empagliflozin contributes to a low risk of hypoglycaemia. The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure.

Pharmacokinetic properties:

Absorption

After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median tmax 1.5 h post-dose. Plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Systemic exposure increased in a dose proportional manner for single-dose and steady-state suggesting linear pharmacokinetics with respect to time. A high-fat, high calorie meal prior to intake of 25 mg empagliflozin resulted in slightly lower exposure compared to fasted condition. The effect 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%.

Biotransformation

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-Oglucuronide). Systemic exposure of each metabolite was less than 10% of total drugrelated material. In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphosphoglucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. Consistent with 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 subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

STORAGE CONDITION:

Store at or below 30°C

AVAILABILITY:

Blister pack x 10's (Box of 120's)

MANUFACTURED BY:

Quest Pharmaceuticals Pvt. Ltd.
Chhatapipara, Bara, Nepal

MARKETING AUTHORIZATION HOLDER:

Quest Pharmaceuticals Pvt. Ltd.
Daan Sadan, Teku, Kathmandu, Nepal