EMPOLI® Tablets
(Empagliflozin)

DESCRIPTION
EMPOLI® tablets contain empagliflozin, an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2). The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91.

QUALITATIVE AND QUANTITATIVE COMPOSITION
EMPOLI® Tablets 10mg
Each film coated tablet contains:
Empagliflozin MS..... 10mg

EMPOLI® Tablets 25mg
Each film coated tablet contains:
Empagliflozin MS..... 25mg

PHARMACEUTICAL FORM
Tablets

CLINICAL PARTICULARS
THERAPEUTIC INDICATION:
EMPOLI® is indicated:

- For the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.
  - As mono therapy when metformin is considered inappropriate due to intolerance.
  - In addition to other medicinal products for the treatment of diabetes.

POSOLOGY AND METHOD OF ADMINISTRATION:
The recommended starting dose is 10mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10mg once daily who have an eGFR • 60ml/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25mg once daily. The maximum daily dose is 25mg.
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

SPECIAL POPULATIONS:
Renal impairment: Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. No dose adjustment is required for patients with an eGFR • 60ml/min/1.73 m^2 or CrCl • 60ml/min.
Empagliflozin should not be initiated in patients with an eGFR <60ml/min/1.73m^2 or CrCl <60ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60ml/min/1.73m^2 or CrCl below 60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45ml/min/1.73m^2 or CrCl persistently below 45ml/min.
Empagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in these patients.

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

Elderly: No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

Paediatric population: The safety and efficacy of empagliflozin in children and adolescents has not yet been established. No data are available.

CONTRAINDICATIONS:
Empagliflozin is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNING & PRECAUTIONS FOR USE:
Diabetic ketoacidosis: Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250mg/dl). It is not known if DKA is more likely to occur with higher doses of empagliflozin.
The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.
Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Renal impairment: Empagliflozin should not be initiated in patients with an eGFR below 60ml/min/1.73m^2 or CrCl <60ml/min. In patients tolerating empagliflozin whose eGFR is persistently below 60ml/min/1.73m^2 or CrCl <60ml/min, the dose of empagliflozin should be adjusted to or maintained at 10mg once daily.
Empagliflozin should be discontinued when eGFR is persistently below 45ml/min/1.73 m^2 or CrCl persistently below 45ml/min. Empagliflozin should not be used in patients with ESRD or in patients on dialysis as it is not expected to be effective in these patients.
Monitoring of renal function
Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. Therefore assessment of renal function is recommended as follows:

- Prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly.
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function

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

Elevated haematocrit: Haematocrit increase was observed with empagliflozin treatment.

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 drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.
In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with 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. 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). Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended.

Urinary tract infections: Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene): Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, empagliflozin should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Lower limb amputations: An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

Cardiac failure: Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. In the EMPA-REG OUTCOME study, 10.1% of the patients were reported with cardiac failure at baseline. The reduction of cardiovascular death in these patients was consistent with the overall study population.

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

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

INTERACTION WITH OTHER MEDICINAL PRODUCTS & OTHER FORMS OF INTERACTION:
Pharmacodynamic Interactions
Diuretics: Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

210 mm

120 mm

Insulin and insulin secretagogues: Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin.

Pharmacokinetic Interactions
Effects of other medicinal products on empagliflozin: Co-treatment with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy. Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Effects of empagliflozin on other medicinal products: Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely. Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

FERTILITY, PREGNANCY & LACTATION:
Fertility: No studies on the effect on human fertility have been conducted.

Pregnancy: There are no data from the use of empagliflozin in pregnant women. As a precautionary measure, it is preferable to avoid the use during pregnancy.

Breast-feeding: No data in humans are available on excretion of empagliflozin into milk. Empagliflozin should not be used during breast-feeding.

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 used in combination with a sulphonylurea and/or insulin.

UNDESIRABLE EFFECTS:
Very common: Hypoglycaemia (when used with sulphonylurea or insulin)

Common: Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection. Urinary tract infection (including pyelonephritis and urosepsis). Thirst, pruritus (generalized), rashes, increased urination, increased serum lipids.

Uncommon: Urticaria, volume depletion, dysuria, increased blood creatinine, decreased glomerular filtration rate, increased hematocrit.

Rare: Diabetic ketoacidosis.

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

PHARMACOLOGICAL PROPERTIES

MECHANISM OF ACTION:
Empagliflozin is a reversible, highly potent selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). 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.

PHARMACOKINETICS
Absorption: The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes. After oral administration, peak plasma concentrations of empagliflozin were reached at 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 1870nmol.h/L and 259nmol/L, respectively, with 10mg empagliflozin once daily treatment, and 4740nmol·h/L and 687nmol/L, respectively, with 25mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.
Administration of 25mg 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%.

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

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. 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%).

SPECIAL POPULATIONS:
Renal impairment: In patients with mild, moderate or severe renal impairment (eGFR <30 - <90 ml/min/1.73 m^2) 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. 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.

Race: In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25kg/m^2 compared to non-Asians with a body mass index of 25kg/m^2.

STABILITY
See expiry on the pack

AVAILABILITY
EMPOLI® tablets 10mg in a pack of 14's.
EMPOLI® tablets 25mg in a pack of 14's.

INSTRUCTIONS
Dosage as advised by the physician.
To be sold on the prescription of registered medical practitioner.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Store in the original package in order to protect from moisture.

Please read the contents carefully before use.
This package insert is regularly reviewed and updated.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
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اِمپولی ٹیبلٹ

(امپیگلیفلوزن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں
ورنہ دوا خراب ہو جائیگی۔
دوا کو نمی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔

R.N-01/HA/03/2020

210 mm

120 mm