28-05-2021
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210mm

EMPOLI® Plus Tablet
(Empagliflozin + Metformin HCl)

WARNING: LACTIC ACIDOSIS

Lactic acidosis resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Litre), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/ml. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. If metformin-associated lactic acidosis is suspected, immediately discontinue and institute in a hospital setting.

QUALITATIVE AND QUANTITATIVE COMPOSITION

EMPOLI® Plus Tablet 5 + 850mg
Each film coated tablet contains:
Empagliflozin MS..... 5mg
Metformin HCl BP.....850mg

EMPOLI® Plus Tablet 5 + 1000mg
Each film coated tablet contains:
Empagliflozin MS..... 5mg
Metformin HCl BP.....1000mg

EMPOLI® Plus Tablet 12.5 + 500mg
Each film coated tablet contains:
Empagliflozin MS..... 12.5mg
Metformin HCl BP.....500mg

EMPOLI® Plus Tablet 12.5 + 850mg
Each film coated tablet contains:
Empagliflozin MS..... 12.5mg
Metformin HCl BP.....850mg

EMPOLI® Plus Tablet 12.5 + 1000mg
Each film coated tablet contains:
Empagliflozin MS..... 12.5mg
Metformin HCl BP.....1000mg

PHARMACEUTICAL FORM
Tablet

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS:

EMPOLI® Plus tablet is indicated for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise:

- In patients insufficiently controlled on their maximally tolerated dose of metformin alone.
- In combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products.
- In patients already being treated with the combination of empagliflozin and metformin as separate tablets.
- Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitations of Use: **EMPOLI® Plus** is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Adults with normal renal function (GFR ≥90 ml/min): The recommended dose is one tablet twice daily. The dosage should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of 10mg or 25mg of empagliflozin, while not exceeding the maximum recommended daily dose of metformin.
For patients insufficiently controlled on metformin (either alone or in combination with other medicinal products for the treatment of diabetes): In patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes, the recommended starting dose should provide empagliflozin 5mg twice daily (10mg daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating a total daily dose of empagliflozin 10mg and who need tighter glycaemic control, the dose can be increased to a total daily dose of empagliflozin 25mg. When used in combination a lower dose of sulphonylurea and/or insulin may be required to reduce the risk of hypoglycemia.
For patients switching from separate tablets of empagliflozin and metformin: Patients switching from separate tablets of empagliflozin and metformin to **EMPOLI® Plus** should receive the same daily dose of empagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.
Missed dose: 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 time. The missed dose should be skipped.
Special Populations:
Renal impairment: No dose adjustment is recommended for patients with mild renal impairment. A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR ml/min	Metformin	Empagliflozin
60-89	Maximum daily dose is 3000mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 25mg.
45-59	Maximum daily dose is 2000mg. The starting dose is at most half of the maximum dose.	Empagliflozin should not be initiated. The dose should be adjusted to or maintained at a maximum daily dose of 10mg.
30-44	Maximum daily dose is 1000mg. The starting dose is at most half of the maximum dose.	Empagliflozin is not recommended
<30	Metformin is contraindicated.	Empagliflozin is not recommended.

Hepatic impairment: This medicinal product must not be used in patients with hepatic impairment.
Elderly: **EMPOLI® Plus** tablet should be used with caution in these patients.
Paediatric population: The safety and efficacy in children and adolescents aged 0 to 18 years has not been established. No data are available.

Method of administration: Tablet should be taken with meals to reduce the GI adverse reactions associated with metformin. The tablets should be swallowed whole with water.

CONTRAINDICATIONS:

- Hypersensitivity to the active substances or to any of the excipients.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure (GFR <30 ml/min). Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic impairment, acute alcohol intoxication, alcoholism.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Lactic acidosis: A very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of dehydration metformin should be temporarily discontinued and consult with doctor.
Diabetic ketoacidosis: Patients should be assessed for ketoacidosis immediately if symptoms occur, regardless of blood glucose level. Treatment with empagliflozin should be discontinued immediately.
Administration of iodinated contrast agent: Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours.
Renal function: **EMPOLI® Plus** tablet is contraindicated in patients with GFR<30 ml/min.
Cardiac function: In patients with stable chronic heart failure, **EMPOLI® Plus** tablet may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure and cardiac failure it is contraindicated due to the metformin component.
Surgery: Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia.
Risk for volume depletion: Caution should be exercised in patients for whom a empagliflozin-induced drop in blood pressure in patients with known cardiovascular disease, on anti-hypertensive therapy, history of hypotension or patients aged 75 years and older.
Elderly: The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status.
Urinary tract infections: Temporary interruption of treatment should be considered in patients with complicated urinary tract infections.
Necrotising fasciitis of the perineum (Fournier's gangrene): 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. **EMPOLI® Plus** tablet should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

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Lower Limb Amputations: Lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor.
Hepatic injury: Cases have been reported with empagliflozin in clinical trials. A causal relationship has not been established.
Elevated haematocrit: Haematocrit increase was observed with empagliflozin treatment.
Urine laboratory assessments: Patients taking **EMPOLI® Plus** tablet will test positive for glucose in their urine.
Interference with 1,5-anhydroglucitol (1,5-AG) assay: Use of alternative methods to monitor glycaemic control is advised.

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

Metformin Concomitant use not recommended: ***Alcohol:*** Alcohol intoxication is associated with an increased risk of lactic acidosis.
Organic cation transporters (OCT): Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with verapamil may reduce efficacy of metformin. Rifampicin may increase GI absorption and efficacy of metformin. Cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole may decrease the renal elimination of metformin. Crizotinib, olaparib may alter efficacy and renal elimination of metformin. Caution is advised, especially in renal impairment, when these drugs are co-administered with metformin.
Combination requiring precautions for use: Some medicinal products may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. Close monitoring of renal function is necessary.
Glucocorticoids Frequent blood glucose monitoring performed, especially at the beginning of treatment.
Insulin and insulin secretagogues: Such as sulphonylureas, may increase the risk of hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with metformin.

FERTILITY, PREGNANCY AND LACTATION:
Fertility: No studies on the effect on human fertility have been conducted for this medicinal product or empagliflozin.
Pregnancy: There are no data from the use of this medicinal product or empagliflozin in pregnant women.
Lactation: Metformin is excreted into human milk. No effects have been shown in breastfed newborns/infants of treated women. This medicinal product should not be used during breast feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: EMPOLI® Plus 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 used in combination with a sulfonylurea and/or insulin.

UNDESIRABLE EFFECTS:
The most commonly reported adverse reactions in clinical trials were hypoglycaemia in combination with insulin and/or sulfonylurea, and gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain and loss of appetite). ***Common:*** Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection (including pyelonephritis and urosepsis), thirst, taste disturbance, pruritus (generalised), rash, increased urination, serum lipids increased. ***Uncommon:*** Volume depletion, urticaria, dysuria, blood creatinine increased/glomerular filtration rate decreased, haematocrit increase. ***Rare:*** Lactic acidosis, vitamin B12 deficiency, liver function tests abnormalities hepatitis, erythema. ***Not known:*** Necrotising fasciitis of the perineum (Fournier's gangrene), angioedema.

Description of selected adverse reactions
Hypoglycaemia: The incidence of hypoglycaemia increased when empagliflozin was administered with insulin or sulfonylurea. The overall frequency of patients with major hypoglycaemic events was low (<1%).
Urinary tract infection: Urinary tract infections occurred more frequently in female patients.
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection: Genital mycotic infections occurred more frequently in female than male patients.
Increased urination: Adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin.
Volume depletion: Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion.
Blood creatinine increased/Glomerular filtration rate decreased: Treatment with empagliflozin was associated with increases in serum creatinine and decreases in eGFR.

OVERDOSE:
Empagliflozin increased urine glucose excretion leading to an increase in urine volume. In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The most effective method to remove lactate and metformin is haemodialysis. The removal of empagliflozin by haemodialysis has not been studied.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs. **ATC code:** A10BD20.

MECHANISM OF ACTION: EMPOLI® Plus tablet combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes:
Empagliflozin: An inhibitor of Sodium-glucose co-transporter 2 (SGLT2). By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.
Metformin hydrochloride: An anti-hyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

PHARMACOKINETIC PROPERTIES:
Empagliflozin:
Absorption: After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median tmax of 1.5 hours post-dose.
Distribution: The apparent steady-state volume of distribution was estimated to be 73.8 L based on the population pharmacokinetic analysis.
Biotransformation: No major metabolites of empagliflozin were detected in human plasma, as defined by at least 10% of total drug-related material,
Elimination: 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 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.
Metformin:
Absorption: After an oral dose of metformin, tmax is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects.
Distribution: Plasma protein binding is negligible. The mean volume of distribution (Vd) ranged between 63 - 276 l.
Biotransformation: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination: Renal clearance of metformin is >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
EMPOLI® Plus tablet 5 + 850mg in a pack of 14's
EMPOLI® Plus tablet 5 + 1000mg in a pack of 14's
EMPOLI® Plus tablet 12.5 + 500mg in a pack of 14's
EMPOLI® Plus tablet 12.5 + 850mg in a pack of 14's
EMPOLI® Plus tablet 12.5 + 1000mg in a pack of 14's

INSTRUCTIONS
Dosage: As advised by the physician. To be sold on the prescription of registered medical practitioner only.
Keep out of the 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.

Full Prescribing Information available on www.samipharmapk.com

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg Lic. No. 000072

امپولی پلس ٹیبلٹ
(امپیگلیفلوزن + میٹ فورمن ہائیڈروکلورائیڈ)

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 گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری
سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

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