

EMPAVID FILM-COATED TABLETS

eVIEMPxx-09 (MY)

COMPOSITION

Empavid 10mg Film-Coated Tablets
Each Empavid 10mg Film-Coated Tablets contains empagliflozin 10mg.

Excipient with known effect:

Each tablet contains the following amount of lactose monohydrate:
Empavid 10mg Film-Coated Tablets contains 42.96mg of lactose monohydrate.

DESCRIPTION

Empavid 10mg Film-Coated Tablets
Pale yellow, round, biconvex film-coated tablets debossed with "10" on one side and "A" on other side. Should be free from physical defects.

INDICATION

Heart failure
Empavid is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV).

Chronic kidney disease
Empavid is indicated in adults for the treatment of chronic kidney disease.

RECOMMENDED DOSE

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

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

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
Patients with renal impairment
Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73m².

Patients with 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 patients
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.

Paediatric population
Heart failure
Safety and effectiveness of Empavid for the treatment of heart failure in children under 18 years of age have not been established.

Chronic kidney disease
Safety and effectiveness of Empavid for the treatment of CKD in children under 18 years of age have not been established.

ROUTE OF ADMINISTRATION

Oral

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

General
Empavid should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Ketoacidosis
Cases of ketoacidosis, a serious life-threatening condition requiring urgent hospitalisation, have been reported in patients with diabetes mellitus treated with empagliflozin, including fatal cases. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl). Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients.

The risk of 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. If ketoacidosis is suspected, Empavid should be discontinued, patients should be evaluated and prompt treatment should be instituted.

Patients who may be at higher risk of ketoacidosis while taking Empavid include patients with a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g. type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration and patient with a history of ketoacidosis. Empavid should be used with caution in these patients. When reducing the insulin dose, caution should be taken. In patients treated with Empavid, consider monitoring for ketoacidosis and temporarily discontinuing Empavid in clinical situations known to predispose to ketoacidosis (e.g. prolong fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if Empavid treatment has been interrupted.

Necrotizing fasciitis of the perineum (Fournier's gangrene)
Cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Empavid who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotizing fasciitis. If suspected, Empavid should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Use in patients with renal impairment
Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73m².

The glucose lowering efficacy of empagliflozin is dependent on renal function, and is reduced in patients with an eGFR <45 ml/min/1.73m² and is likely absent in patients with an eGFR <30 ml/min/1.73m².

Monitoring of renal function
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.

Elderly patients
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. 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).

Use in patients at risk for volume depletion
Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying 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.

Complicated urinary tract infections
Cases of complicated urinary tract infections including pyelonephritis or urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

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 prevention foot-care.

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

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

INTERACTIONS WITH OTHER

MEDICAMENTS

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.

Interference with 1, 5-anhydroglucitol (1, 5-AG) Assay
Monitoring glycaemic control with 1, 5-AG assay is not recommended as measurements of 1, 5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.

Pharmacokinetic interactions
Lithium
Concomitant use of SGLT2 inhibitors, including empagliflozin, with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with empagliflozin initiation or following dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

Effects of other medicinal products on empagliflozin
In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9 and UGT2B7. Empagliflozin is a substrate of the human transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in increase in peak empagliflozin plasma concentrations (C_{max}) and a increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

The effect of UGT induction on empagliflozin had not been studied. Co-medication with known inducers of UGT enzymes should be avoided due to potential risk of decreased efficacy.

An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C_{max} increased and AUC increased following co-administration. These changes were not considered to be clinically meaningful.

Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in an increase in C_{max} and an increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin.

Interaction studies suggested 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
Based on in vitro studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 isoforms or UGT with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in an increase in AUC and an increase in C_{max} of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 in vitro at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are 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.

Paediatric population
Interaction studies have only been performed in adults.

PREGNANCY AND LACTATION

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 Empavid during early pregnancy. Empavid is not recommended during the second and third trimester of pregnancy.

Breast-feeding
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. Empavid should not be used during breast-feeding.

Fertility

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Empavid 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 Empavid is used in combination with a sulphonylurea and/or insulin.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received empagliflozin are presented in the table below:

Frequency are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000) or very rare (< 1/10,000) and unknown (cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon	Rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection Urinary tract infection (including pyelonephritis and urosepsis)		Necrotizing fasciitis of the perineum (Fournier's gangrene)*
Metabolism and nutrition disorders	Hypoglycaemia (When used with sulphonylurea or insulin)	Thirst	Ketoacidosis*	
Gastrointestinal disorders		Constipation		
Skin and subcutaneous tissue disorders		Pruritus (generalised), Allergic skin reactions (rash, urticaria)	Angioedema	
Vascular disorders	Volume depletion			
Renal and urinary disorders		Increased urination	Dysuria	
Investigations		Serum lipids increased	Blood creatinine increased/ Glomerular filtration rate decreased, Haematocrit increased	

*see Warnings and Precautions

Paediatric population

Overall, the safety profile in children was similar to the safety profile in adults with T2DM.

OVERDOSE AND TREATMENT

Symptoms

Multiple daily doses of up to 10mg empagliflozin (equivalent to 4 times the highest recommended daily dose) 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.

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.

PHARMACODYNAMICS

Pharmacotherapeutic group: Sodium-glucose co-transporter 2 (SGLT2) inhibitors. ATC code: A10BK03.

Mechanism of action

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). 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, downregulating of sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodeling, filling pressures and diastolic function as well as preserving kidney structure and function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial cardiac and renal effects.

PHARMACOKINETICS

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes.

Administration of empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure. 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 73.8L based on the population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

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Metabolism

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

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [14C]-empagliflozin solution to healthy volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). The majority of drug-related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Special populations

Renal impairment

In patients with mild (eGFR: 60 - < 90 ml/min/1.73m²), moderate (eGFR: 30 - < 60 ml/min/1.73m²) or severe renal impairment (eGFR <30 ml/min/1.73m²) and patients with kidney failure/end stage kidney disease (ESKD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESKD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. Based on pharmacokinetics, no dosage adjustment is recommended in patients with renal insufficiency (see section recommended dosage).

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 C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Body Mass Index

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

Gender

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

Race

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

Elderly patients

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

Paediatric patients

Pharmacokinetics and pharmacodynamics of a single dose of empagliflozin 5mg, 10mg and 25mg were investigated in children and adolescents 10 to 17 years of age with T2DM. The observed pharmacokinetics and the pharmacokinetics-pharmacodynamics (urinary glucose excretion) relationship of adult and paediatric patients was comparable after accounting for significant covariates.

Pharmacokinetics and pharmacodynamics (HbA1c change from baseline) of empagliflozin 10mg with a possible dose-increase to 25mg were investigated in children and adolescents 10 to 17 years of age with T2DM. The observed exposure-response relationship was overall comparable in adults and children and adolescents. Oral administration of empagliflozin resulted in an exposure within the range observed in adult patients. The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration at steady state were 26.6 nmol/L and 308 nmol/L with empagliflozin 10mg once daily and 67.0 nmol/L and 525 nmol/L with empagliflozin 25mg once daily.

Storage Condition: Store below 30°C.

Presentation/Packing: Blister pack (peel-push lidding foil) of 3 x 10's

Product Registration Holder (Malaysia)/
Marketing Authorisation Holder/ Product Owner: **HOVID Berhad**
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500100 India.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

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