EMRENE FILM-COATED TABLETS 25MG (EMPAGLIFLOZIN FILM-COATED TABLETS 25MG)
EMRENE FILM-COATED TABLETS 10MG (EMPAGLIFLOZIN FILM-COATED TABLETS 10MG)

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1. NAME OF MEDICINAL PRODUCT

Emrene Film-Coated Tablets 25mg
Emrene Film-Coated Tablets 10mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Emrene Film-Coated Tablets 25 mg: Contains 25 mg of empagliflozin and 174.50 mg of lactose monohydrate.
Emrene Film-Coated Tablets 10 mg: Contains 10 mg of empagliflozin and 69.80 mg of lactose monohydrate.

3. PHARMACEUTICAL FORM

Film-coated tablet

3.1 Product Description

Emrene Film-Coated Tablets 25 mg: 9 mm round, pale yellow, biconvex, plain on both sides, film coated tablets
Emrene Film-Coated Tablets 10 mg: 6.5 mm round, pale yellow, biconvex, plain on both sides, film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of cardiovascular death
Emrene is indicated in adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death.

To prevent cardiovascular deaths, *Emrene* should be used in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care.

Heart failure
Emrene 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
Emrene is indicated in adults for the treatment of chronic kidney disease.

4.2 Posology and method of administration

Posology

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
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/1.73 m2.

If eGFR falls below 30 ml/min/1.73 m2, the recommended dose of empagliflozin is limited to 10 mg and additional treatment should be considered if needed.

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

Heart failure:
Safety and effectiveness of *Emrene* for the treatment of heart failure in children under 18 years of age have not been established.

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

Method of administration
The tablets can be taken with or without food, swallowed whole with water.

Route of administration
Oral

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General
Emrene 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, *Emrene* should be discontinued, patients should be evaluated and prompt treatment should be instituted.

Ketoacidosis and glucosuria may be prolonged after discontinuation of *Emrene* in some patients, i.e. it may last longer than expected from 5 plasma half-lives of empagliflozin

Patients who may be at higher risk of ketoacidosis while taking *Emrene* 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. *Emrene* should be used with caution in these patients. When reducing the insulin dose, caution should be taken. In patients treated with *Emrene*, consider monitoring for ketoacidosis and temporarily discontinuing *Emrene* 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 *Emrene* 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 treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with *Emrene* who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotizing fasciitis. If suspected, *Emrene* 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/1.73 m2.

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 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).

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 *Emrene* 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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions	**Pharmacokinetic 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	*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. *Effect 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 uptake 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 a 26% increase in peak empagliflozin plasma concentrations (Cmax) and a 53% 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 has not been studied. Co-medication with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy.
	An interaction study with gemfibrozil, an *in vitro* inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin Cmax increased by 15% and AUC increased by 59% following co-administration. These changes were not considered to be clinically meaningful. Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in Cmax and a 35% 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 a 6% increase in AUC and 14% increase in Cmax 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, ramipiril, digoxin, diuretics and oral contraceptives. *Paediatric population* Interaction studies have only been performed in adults.

4.6 Fertility, 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 *Emrene* during early pregnancy. *Emrene* 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. *Emrene* should not be used during breast-feeding.

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

4.7 Effect on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received empagliflozin in placebo-controlled studies are presented in the table below (Table 1).

The adverse reactions are listed by absolute frequency. Frequencies 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 not known (cannot be estimated from the available data).

Table 1: Adverse reactions reported in placebo-controlled studies

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

4.9 Overdose

Symptoms

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.

5. PHARMACOLOGICAL PROPERTIES

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

Mechanism of action
Empagliflozin is a reversible, highly potent (IC_{50} 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 5000 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.

The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure. 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 tubuleglomerular 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.

5.2 Pharmacokinetic properties
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. The steady state mean plasma AUC and C_{max} were 1870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. 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; AUC decreased by approximately 16% and C_{max} 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 the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

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. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. 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 [^{14}C]-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/1.73m^2), moderate (eGFR: 30 - < 60 ml/min/1.73m^2) or severe renal impairment (eGFR <30 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. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD 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.

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. In this analysis, AUC was estimated to be 5.82%, 10.4%, and 17.3% lower in subjects with BMI of 30, 35, and 45 kg/m_2, respectively, compared to subjects with a body mass index of 25 kg/m^2.

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/m^2 compared to non-Asians with a body mass index of 25 kg/m^2.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core: Lactose monohydrate, Microcrystalline cellulose, Hydroxypropyl cellulose, Croscarmellose Sodium, Magnesium stearate, Purified Water
Film coating (Opadry Yellow 02B38190): Hypromellose, Titanium dioxide, Talc, Macrogol, Yellow Iron Oxide

6.2 Shelf Life
Refer foil/label

6.3 Special precautions for storage
Store in a dry place below 30°C

6.4 Nature and contents of container
Emrene Film-Coated Tablets 25 mg: 3 x 10's
Emrene Film-Coated Tablets 10 mg: 3 x 10's

7 PRODUCT REGISTRATION HOLDER
Duopharma Manufacturing (Bangi) Sdn. Bhd.
Lot No. 2, 4, 6, 8 & 10, Jalan P/7, Seksyen 13, Kawasan Perusahaan Bandar Baru Bangi, 43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.

8 MANUFACTURER
Duopharma Manufacturing (Bangi) Sdn. Bhd.
Lot No. 2 & 4, Jalan P/7, Seksyen 13, Kawasan Perusahaan Bandar Baru Bangi, 43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.

9 DATE OF REVISION
Feb 2026

Remarks: Leaflet is preliminary drafted in Times New Roman with Font size of 10 which subject to change to any equivalent font and readable font size.