SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Empator 10 mg tablets
Empator 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Empator 10 mg film-coated tablets
Each tablet contains 10 mg empagliflozin.

Empator 25 mg film-coated tablets
Each tablet contains 25 mg empagliflozin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Empator is indicated for the treatment of adults with 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

4.2 Posology and method of administration

Posology
The recommended starting dose is 10 mg Empator once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating Empator 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg (see below and section 4.4).
When Empator 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 (see sections 4.5 and 4.8).

Special populations

Renal impairment
Due to the mechanism of action, the glycaemic efficacy of Empator is dependent on renal function. No dose adjustment is required for patients with an eGFR ≥60 ml/min/1.73 m^2 or CrCl ≥60 ml/min.
Empator should not be initiated in patients with an eGFR <60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 or CrCl below 60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empator

should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl persistently below 45 ml/min (see sections 4.4, 4.8, 5.1, and 5.2).

Empator 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 (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment. Empator 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 taken into account (see sections 4.4 and 4.8). In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience (see section 4.4).

Paediatric population

The safety and efficacy of Empator in children and adolescents has not yet been established. No data are available.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and 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 (250 mg/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.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.
Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.
Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT-2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.
The safety and efficacy of empagliflozin in patients with type 1 diabetes have not been established and empagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Renal impairment

Empagliflozin should not be initiated in patients with an eGFR below 60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR is persistently below 60 ml/min/1.73 m^2 or CrCl <60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl persistently below 45 ml/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 (see sections 4.2 and 5.2).

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 (see sections 4.2, 5.1 and 5.2).
- 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 (see section 4.8).

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 (see section 5.1). 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. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo (see section 4.8). 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 (see section 4.2).

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.

4.5 Interaction with other medicinal products and 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 (see section 4.4).

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 (see sections 4.2 and 4.8).

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

Known 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 (C_{max}) 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-treatment 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 C_{max} 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 C_{max} 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 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

Based on known 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 and UGT isoforms 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 active substances 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 individuals 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.

4.6 Fertility, pregnancy and lactation

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

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

Fertility
No studies on the effect on human fertility have been conducted for Empagliflozin. (see section 5.3).

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

4.8 Undesirable effects

Tabulated list of adverse reactions
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: Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled studies and from post-marketing experience.

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection Urinary tract infection (including pyelonephritis and urosepsis)			Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)	Thirst		Diabetic ketoacidosis	
Skin and subcutaneous tissue disorders		Pruritus (generalised) 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		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the email productsafety@martindow.com.

4.9 Overdose

Symptoms

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy individuals and multiple daily doses of up to 100 mg 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. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Other blood glucose lowering drugs, excl. insulins, 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 improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. Empagliflozin improves both fasting and post-prandial plasma glucose levels. 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 diuresis which may contribute to sustained and moderate reduction of blood pressure. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetics of empagliflozin have been extensively characterised in healthy individuals and patients with type 2 diabetes. After oral administration, empagliflozin is known to be rapidly absorbed with peak plasma concentrations occurring at a median tmax 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 Cmax are known to be 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 individuals and patients with type 2 diabetes.

The effect of food on empagliflozin pharmacokinetics may not be considered clinically relevant and empagliflozin may be administered with or without food.

Distribution
The apparent steady-state volume of distribution is known to be estimated 73.8L based on the population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy

individuals, the red blood cell partitioning is known to be approximately 37% and plasma protein binding is 86%.

Biotransformation

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.

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozinis known to be estimated 12.4 hours and apparent oral clearance is known to be 10.6 l/hour. With once-daily dosing, steady-state plasma concentrations of empagliflozin are known to be 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 individuals, approximately 96% of the drug-related radioactivity is known to be 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 is unchanged parent drug.

Special populations

Renal impairment

In individuals with mild, moderate, and severe renal impairment and individuals with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin may increase by approximately 18%, 20%, 66%, and 48%, respectively, compared to individuals with normal renal function. Peak plasma levels of empagliflozin is known to be similar in individuals with moderate renal impairment and kidney failure/ESRD compared to individuals with normal renal function. Peak plasma levels of empagliflozin roughly known are 20% higher in individuals with mild and severe renal impairment as compared to individuals with normal renal function. The apparent oral clearance of empagliflozin may
decrease with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that excreted unchanged in urine, and urinary glucose excretion, may decline with decrease in eGFR.

Hepatic impairment

In individuals with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin is known to be increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to individuals with normal hepatic function.

Body Mass Index

Body mass index may have no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. In this analysis, AUC is known to be estimated to be 5.82%, 10.4%, and 17.3% lower in individuals with BMI of 30, 35, and 45 kg/m^2, respectively, compared to individuals with a body mass index of 25 kg/m^2.

Gender

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

Race
In the population pharmacokinetic analysis, AUC is known to be 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
Age impact on the pharmacokinetics of empagliflozin is not known.

Paediatric population
Pharmacokinetics of empagliflozin in pediatric patients is not known .

5.3 Preclinical safety data

Non-clinical known data reveal any special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients for Empator 10mg & 25mg are:

- Lactose Powder
- Microcrystalline Cellulose M 101
- Klucel LF Pharm Hydroxy Propyl Cellulose
- Sodium Croscarmellose Type A
- Colloidal Anhydrous Silica V200
- Magnesium Stearate
- Sheffcoat White 5Y00065
- Iron Oxide Yellow (AR. Y 300407)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- Nature of the container:
  Alu/Alu blister

- Contents of the container:

Empator is supplied in following dosage form, strengths and pack size:

Tablets	10mg	14's
Tablets	25mg	14's

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Martin Dow Limited
Plot 37, Sector 19,
Korangi Industrial Area,
Karachi-74900, Pakistan.

8. MARKETING AUTHORISATION NUMBER(S)

For Empator Tablet 10mg:
098822
For Empator Tablet 25mg:
098823

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/10/2019