PROFESSIONAL INFORMATION
EMAPGLIFLOZIN PD RANGE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EMPAGLIFLOZIN 10 mg PD film coated tablets

EMPAGLIFLOZIN 25 mg PD film coated tablets

EMPAGLIFLOZIN PD IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES.

EMPAGLIFLOZIN PD IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES.

There have been reports of metabolic acidosis, including ketoacidosis which were serious, life threatening or fatal, in patients taking empagliflozin.

Cases of ketoacidosis have also been reported in patients without diabetes mellitus.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 11 mmol/L. EMPAGLIFLOZIN PD should be discontinued and the patient should be promptly evaluated and managed accordingly.

Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with EMPAGLIFLOZIN.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. EMPAGLIFLOZIN PD is contraindicated in these patients.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EMPAGLIFLOZIN 10 mg PD: Each film coated tablet contains empagliflozin 10 mg.

EMPAGLIFLOZIN 25 mg PD: Each film coated tablet contains empagliflozin 25 mg.

EMPAGLIFLOZIN PD contains sugar (lactose monohydrate 45,2 mg per 10 mg tablet and 113 mg per 25 mg tablet).

Essentially 'sodium free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

EMPAGLIFLOZIN 10 mg PD: Pale yellow, round, debossed with "L75" on one side and the other side plain, film coated tablets.

EMPAGLIFLOZIN 25 mg PD: Pale yellow, oval, debossed with 'LU' on one side and 'E65' on the other side, film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus (T2DM)

Glycaemic control:

EMPAGLIFLOZIN PD tablets are indicated as an adjunct to diet and exercise to improve glycaemic control, in adults with type 2 diabetes mellitus.

Prevention of cardiovascular events:

EMPAGLIFLOZIN PD is indicated in patients with type 2 diabetes mellitus and high cardiovascular risk* to reduce the risk of:

- cardiovascular death due to myocardial infarction
- cardiovascular death or hospitalisation for heart failure.

*e.g. previous myocardial infarction, multi vessel coronary artery disease, previous coronary revitalisation, single vessel coronary disease, at least 50 % narrowing of coronary artery lumen.

Heart failure (HF):

EMPAGLIFLOZIN PD is indicated in adult patients with heart failure (New York Heart Association (NYHA) class II-IV) independent of left ventricular ejection fraction, with or without type 2 diabetes mellitus:

- to reduce the risk of cardiovascular death and hospitalisation for heart failure
- to slow kidney function decline.

Chronic kidney disease (CKD):

EMPAGLIFLOZIN PD is indicated in adult patients with chronic kidney disease to reduce the risk of:

- kidney disease progression (sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or renal death) or cardiovascular death
- all-cause hospitalisation.

4.2 Posology and method of administration

Prior to initiating therapy with EMPAGLIFLOZIN PD, hydration status and renal function should be assessed.

Do not initiate treatment if the estimated glomerular filtration rate (eGFR) < 60 mL/min/1,73 m^2 (or creatinine clearance < 60 mL/min) and/or in patients who are volume-depleted or acidotic (see section 4.4).

Posology

Type 2 diabetes mellitus (T2DM) indications

The recommended starting dose of EMPAGLIFLOZIN PD is 10 mg once daily.

In patients tolerating EMPAGLIFLOZIN PD, 10 mg once daily who have an eGFR ≥30 mL/min/1,73 m^2 and requiring additional glycaemic control, the dose may be increased to 25 mg once daily.

Heart failure (HF) indication

The recommended dose of EMPAGLIFLOZIN PD is 10 mg once daily.

Chronic kidney disease (CKD) indication

The recommended dose of EMPAGLIFLOZIN PD is 10 mg once daily.

Special populations

Patients with renal insufficiency:

Empagliflozin 10 mg can be used regardless of renal function. However, due to limited experience, it is not recommended to initiate treatment with EMPAGLIFLOZIN PD in patients on dialysis. Glycaemic efficacy of empagliflozin is dependent on renal function and likely absent in patients with severe renal impairment. If eGFR falls below 30 mL/min/1,73 m^2 the recommended dose of EMPAGLIFLOZIN PD is limited to 10 mg and additional glucose lowering treatment should be considered if needed (see section 4.4).

Patients with hepatic insufficiency:

In patients with severe hepatic impairment dose adjustments may be necessary.

Elderly patients:

If the creatinine clearance is ≥ 60 mL/min, no dose adjustment based on age is recommended. Therapeutic experience in patients aged 85 years and older is limited. Initiation of EMPAGLIFLOZIN PD therapy in this population is not recommended (see section 4.4).

Paediatric population

Safety and effectiveness of EMPAGLIFLOZIN PD in children under 18 years of age have not been established.

Method of administration

EMPAGLIFLOZIN PD should be swallowed whole, with water and can be taken with or without food.

Missed dose:

Medical practitioners should advise patients who forget to take EMPAGLIFLOZIN PD to take a dose

as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

EMPAGLIFLOZIN PD is contraindicated in:

- hypersensitivity to empagliflozin or to any of the ingredients of EMPAGLIFLOZIN PD (see section 6.1)
- treatment of type 1 diabetes mellitus
- treatment of ketoacidosis
- pregnancy and lactation.

4.4 Special warnings and precautions for use

EMPAGLIFLOZIN PD should not be used in patients with type 1 diabetes.

Ketoacidosis with atypical presentation:

Cases of ketoacidosis, which may be serious, life-threatening or fatal, have been reported in patients treated with empagliflozin as in EMPAGLIFLOZIN PD. Such cases require hospitalisation.

The presentation of ketoacidosis is frequently atypical with either euglycaemia or with blood glucose values mildly or moderately increased below 11 mmol/L (196 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.

Regardless of blood glucose level, patients should be assessed for ketoacidosis immediately should these symptoms occur. Treatment with EMPAGLIFLOZIN PD is to be discontinued immediately in such cases and treatment instituted which, amongst others, may require fluids, carbohydrate and insulin.

The risk of developing ketoacidosis during therapy with EMPAGLIFLOZIN PD, is increased in patients with a reduced fluid and food intake, those on a very low carbohydrate diet, those who are severely

dehydrated, insulin dose reduction in patients also requiring insulin, patients with a history of ketoacidosis or who are known to have a low beta-cell function reserve, or any pancreatic disease/disorder with or without an insulin deficiency, or in patients with alcohol abuse or misusing alcohol.

Progressive increases in blood and urine ketones as well as a progressive increase in metabolic acidosis may be indicative of the development of ketoacidosis irrespective of blood glucose levels.

Regular monitoring of blood and urine ketones as well as blood pH is recommended.

In clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to an acute illness or surgery) the treatment with EMPAGLIFLOZIN PD should be temporarily discontinued.

In these situations, consider monitoring of ketones, even if EMPAGLIFLOZIN PD treatment has been interrupted.

Treatment should be interrupted in patients who are hospitalised for acute serious medical illnesses.

The underlying mechanism for sodium-glucose co-transporter 2 (SGLT2) inhibition-associated ketoacidosis has not been established.

Atypical metabolic acidosis (no ketone bodies) may present in a very similar manner to ketoacidosis.

Haemoconcentration:

An increase in the haematocrit of patients on EMPAGLIFLOZIN PD therapy is to be expected**.**

Use in patients with renal impairment:

As the efficacy of EMPAGLIFLOZIN PD is dependent on renal function, assessment of renal function is recommended prior to EMPAGLIFLOZIN PD initiation and periodically during treatment, i.e. at least 6-monthly.

EMPAGLIFLOZIN PD should not be used in patients with end-stage renal disease (ESRD) or in patients on dialysis. There are insufficient data to support use in these patients (see sections 4.2, 5.1 and 5.2)

Glycaemic efficacy of EMPAGLIFLOZIN PD is dependent on renal function and likely absent in patients with an eGFR<30 mL/min/1,73 m^2 (see section 4.2).

Monitoring of renal function:

Assessment of renal function is recommended prior to EMPAGLIFLOZIN PD initiation and periodically during treatment, i.e. at least 6-monthly.

Hepatic injury:

Cases of hepatic injury have been reported during empagliflozin therapy.

Use in patients at risk for volume depletion:

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glycosuria may lead to intravascular volume contraction with a 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 antihypertensive therapy and/or diuretics, and with a history of hypotension, or the elderly especially patients aged 75 years and older.

Should conditions that may lead to fluid loss, such as gastrointestinal illness, arise, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving EMPAGLIFLOZIN PD.

Temporary interruption of treatment with EMPAGLIFLOZIN PD should be considered until the fluid loss is corrected.

Urinary tract infections and genital infections:

Studies show that patients treated with empagliflozin showed an overall increase in frequency of urinary tract infection, and/or genital infection than those treated with placebo (see section 4.8), especially mycotic infections in females. Genital infections occurred more frequently in females than in males. Balanoposthitis in males may result in phimosis.

Urosepsis and pyelonephritis:

Patients with a history of chronic or recurrent urinary tract infection (UTI) were more likely to experience UTI.

Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with EMPAGLIFLOZIN PD (see section 4.8).

Temporary interruption of EMPAGLIFLOZIN PD should be considered in patients with complicated urinary tract infections.

Heart failure:

EMPAGLIFLOZIN PD is not recommended in patients with eGFR <20 ml/min/1,73 m^2.

Necrotising fasciitis of the perineum (Fournier's gangrene):

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

Serious outcomes have included hospitalisation, multiple surgeries, and death.

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 urogenital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, EMPAGLIFLOZIN PD 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.

Urine laboratory assessments:

Due to its mechanism of action, patients taking EMPAGLIFLOZIN PD will test positive for glucose in their urine.

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 of alternative methods to monitor glycaemic control is advised.

Additional information on special populations:

Elderly patients:

Elderly patients (aged 75 years and older) are at increased risk of volume depletion. EMPAGLIFLOZIN PD should therefore be prescribed with caution in these patients (see section 4.8). Therapeutic experience in patients aged 85 years and older is limited. Initiation of EMPAGLIFLOZIN PD therapy in this population is not recommended.

Excipients:

EMPAGLIFLOZIN PD contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take EMPAGLIFLOZIN PD.

EMPAGLIFLOZIN PD contains less than 1 mmol sodium (0,023 g) per dose, that is to say essentially ‘sodium-free’.

Paediatric population

EMPAGLIFLOZIN PD is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

4.5 Interaction with other medicines and other forms of interaction

Effects on laboratory tests: Interference with 1,5-anhydroglucitol (1,5-AG) Assay:

Monitoring of glycaemic control cannot be done by urine glucose monitoring or with a 1,5 AG blood assay, as SGLT2 inhibitors interfere with the assay.

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 medical practitioner in order to monitor serum concentration of lithium.

Effects of EMPAGLIFLOZIN PD on other medicines

***In vitro* assessment of medicine interactions:**

EMPAGLIFLOZIN PD does not inhibit, inactivate, or induce CYP450 isoforms.

4.6 Fertility, pregnancy and lactation

EMPAGLIFLOZIN PD is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

Animal studies showed that empagliflozin as contained in EMPAGLIFLOZIN PD crosses the placenta.

Breastfeeding

EMPAGLIFLOZIN PD is contraindicated when breastfeeding (see section 4.3).
Animal studies have shown excretion of empagliflozin in milk of animals, therefore a risk to human newborns/infants cannot be excluded.

Fertility

There is no data on fertility with EMPAGLIFLOZIN PD.

4.7 Effects on ability to drive and use machines

EMPAGLIFLOZIN PD is expected to have influence on the ability to drive and use machines. Hypoglycaemia may impair driving and machinery use capabilities. Patients should be advised to avoid the onset of hypoglycaemia, and act appropriately.

4.8 Undesirable effects

a. Summary of the safety profile

Type 2 diabetes:

Patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin (as in EMPAGLIFLOZIN PD), of which 64 % of the patients were treated with empagliflozin. In further clinical trials, some patients received treatment with empagliflozin 10 mg and others received treatment with empagliflozin 25 mg for periods of at least 24 weeks and at least 76 weeks.
In these trials, the frequency of adverse effects leading to discontinuation was similar in all treatment groups: for placebo (5,3 %), empagliflozin 10 mg (4,8 %) and empagliflozin 25 mg (4,9 %).
The most frequent adverse effect reported was hypoglycaemia, which depended on the type of background therapy used in the respective studies.

Heart failure:

The EMPEROR-Reduced study included 3730 patients with heart failure and reduced ejection fraction treated with empagliflozin 10 mg (as in EMPAGLIFLOZIN PD) or placebo. Approximately half of the patients had type 2 diabetes mellitus. The most frequent adverse reaction was volume depletion (empagliflozin 10 mg: 10,6 %. placebo: 9,9 %). Major hypoglycaemia (events requiring assistance) was observed only in patients with diabetes mellitus.
No new adverse reactions were identified in the EMPEROR-Reduced heart failure study.

Chronic Kidney Disease Indication:

The EMPA-KIDNEY study included patients with chronic kidney disease (N = 6 609) treated with 10 mg empagliflozin or placebo. About 44 % of the patients had type 2 diabetes mellitus.
No new adverse reactions were identified in the EMPA-KIDNEY study.
The overall safety profile of empagliflozin was generally consistent across the studied indications.

b. Tabulated list of adverse effects

The frequencies of adverse events are ranked according to the following:

Frequent = (≥ 1/100 to < 1/10).

Less frequent = Infrequent (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (<1/10,000).

Frequency not known = cannot be estimated from the available data.

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, urinary tract infection (including urosepsis and pyelonephritis)
	Less frequent	Necrotising fasciitis of the perineum (Fournier's gangrene) in in heart failure
	Frequency unknown	Necrotising fasciitis of the perineum (Fournier's gangrene) in T2DM
Metabolism and nutrition disorders	Frequent	Weight loss, serum lipids increased
	Frequency unknown	Diabetic ketoacidosis
Vascular disorders	Frequent	Volume depletion (hypotension and dehydration)
	Less frequent	Volume depletion (hypotension and dehydration) in T2DM

Gastrointestinal disorders	Frequent Less Frequent	Thirst (10mg, 25 mg tablet) , constipation (10 mg tablet) in T2DM Constipation (25 mg tablet) in T2DM, thirst in heart failure
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, rash Urticaria, angioedema
Renal and urinary disorders	Frequent Less frequent	Glycosuria, increased urination in T2DM Glycosuria and increased urination in Heart failure, dysuria, ketonuria, fluid volume depletion/dehydration, increased blood creatinine, decreased GFR (glomerular filtration rate) in T2DM and heart failure
Reproductive system and breast disorders	Frequency unknown	Phimosis*
Investigations	Less frequent	Increased haematocrit (haemoconcentration)

*Post marketing experience

c. Description of selected adverse reactions

Volume depletion:

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) of empagliflozin (as in EMPAGLIFLOZIN PD) was similar to

placebo (empagliflozin 10 mg - 0,5 %, empagliflozin 25 mg - 0,3 % and placebo - 0,3 %). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older or those otherwise at risk. In patients 75 ≥ years of age the frequency of volume depletion events was similar for empagliflozin 10 mg (2,3 %) compared to placebo (2,1 %), but it increased with empagliflozin 25 mg (4,4 %).

Blood creatinine increased and glomerular filtration rate decreased:

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between empagliflozin and placebo. In placebo controlled, double-blind studies up to 76 weeks, initial transient increases in creatinine and initial transient decreases in estimated glomerular filtration rates have been observed. These changes were generally reversible during continuous treatment or after medicine discontinuation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

The risk and severity of side effects may be increased (see section 4.8).

Management of overdose:

In the event of an overdose, symptomatic and supportive 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, sodium-glucose co-transporter 2 (SGLT2) inhibitors

ATC code: A10BK03

Pharmacological classification: A 21.2 Oral hypoglycaemics

Mechanism of action

Empagliflozin is a reversible inhibitor of SGLT2 (sodium-glucose co-transporter 2) with an IC50 of 1,3 nM. It has a 5 000-fold selectivity over human SGLT1 (IC50 of 6 278 nM), responsible for glucose absorption in the gut. Furthermore, high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues.

SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR.

Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

The effect of empagliflozin in lowering blood glucose is independent of beta-cell function and insulin pathway. Urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction.

The glycosuria 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 tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of

the heart, downregulating sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodelling, 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 T2DM. After oral administration, empagliflozin was absorbed with peak plasma concentrations occurring at a median t_{max} 1,5 h post-dose.

Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. For single doses of 10 mg and 25 mg, the terminal phase half-life is 13,1 ± 4,0 h and 10,2 ± 2,1 h, respectively. The steady-state mean plasma AUC was 4 740 nmol.h/L and C_{max} was 687 nmol/L with 25 mg empagliflozin once daily (qd). Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetics 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 mellitus.

Administration of 25 mg empagliflozin after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16 % and C_{max} decreased by approximately 37 %, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution:

The apparent steady-state volume of distribution was estimated to be 73,8 L, based on a population pharmacokinetic analysis.

Following administration of an oral [14c]-empagliflozin solution to healthy participants, the red

blood cell partitioning was approximately 36,8 % and plasma protein binding was 86,2 %.

Biotransformation:

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide).
Systemic exposure of each metabolite was less than 10 % of total drug-related material. *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:

The apparent terminal elimination half-life of empagliflozin was estimated to be 12,4 h and apparent oral clearance was 10,6 L/h based on the population pharmacokinetic analysis. 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 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 participants, approximately 95,6 % of the medicine related radioactivity was eliminated in faeces (41,2 %) or urine (54,4 %). The majority of medicine related radioactivity recovered in faeces was unchanged parent medicine and approximately half of medicine related radioactivity excreted in urine was unchanged parent medicine.

Pharmacokinetics in special patient groups

Renal insufficiency:

In patients with mild (eGFR: 60 - < 90 mL/min/1,73 m$^{2)}$, moderate (eGFR: 30 - < 60 mL/min/1,73 m^2), renal impairment and severe (eGFR: < 30 mL/min/1,73 m$^{2)}$ patients with kidney failure/ESRD (end stage renal disease) patients, AUC of empagliflozin increased by approximately 18 %, 20 %, 66 %, and 48 %, respectively, compared to patients with normal renal function.

Hepatic Insufficiency:

In patients 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 patients with normal hepatic function. Based on pharmacokinetics, dosage adjustment may be necessary in patients with severe hepatic impairment.

Body mass index (BMI):

No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Gender:

No dosage adjustment is necessary based on gender.

Elderly patients:

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

Paediatric population

Studies characterising the pharmacokinetics of empagliflozin in paediatric patients have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Croscarmellose sodium

Colloidal silicon dioxide

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose.

Film coating (Opadry Yellow)

HPMC (hypromellose)

Iron Oxide Yellow

Macrogol /PEG

Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep container well closed. Protect from light and moisture.

6.5 Nature and contents of container

EMPAGLIFLOZIN 10 mg PD:

30, 60 and 90 tablets: 50 ml round opaque white, 33 mm neck HDPE bottles, with a child resistant cap and printed heat-seal liner containing 30, 60 or 90 tablets in a printed cardboard carton.
500 tablets: 60 ml round opaque white, 33 mm neck HDPE bottles, with a child resistant cap and printed heat-seal liner containing 500 tablets. Not all pack sizes are marketed.

EMPAGLIFLOZIN 25 mg PD:

30, 60 and 90 tablets: 50 mL round opaque white, 33 mm neck HDPE bottles, with a child resistant cap and printed heat-seal liner containing 30, 60 or 90 tablets in a printed cardboard cartons.

500 tablets: 150 mL round opaque white, 38 mm neck HDPE bottles, with a child resistant cap and printed heat-seal liner containing 500 tablets. Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, 7945

Cape Town, South Africa

Tel.: +27 21 707 7000

or 0860-PHARMA (742 762)

8. REGISTRATION NUMBER(S)

EMPAGLIFLOZIN 10 mg PD: A56/21.2/0973

EMPAGLIFLOZIN 25 mg PD: A56/21.2/0974

9. DATE OF FIRST AUTHORISATION

15 April 2025

10. DATE OF REVISION OF THE TEXT