SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medical Product

EMPADIL 10/25 (Empagliflozin Tablets 10 mg/25 mg)

1.1 Strength:

EMPADIL 10 (Empagliflozin Tablets 10 mg)

Each film coated tablet contains:

Empagliflozin …… 10 mg

Excipients……q.s

Colors: Titanium Dioxide and Yellow Iron Oxide

EMPADIL 25 Empagliflozin Tablets 25 mg)

Each film coated tablet contains:

Empagliflozin …… 25 mg

Excipients……q.s

Colors: Titanium Dioxide and Yellow Iron Oxide

1.2 Pharmaceutical Dosage Form:

Tablets

2. Qualitative & Quantitative Composition:

2.1 Qualitative declaration

Film coated tablets contain API Empagliflozin

2.2 Quantitative declaration

EMPADIL 10: Each film coated tablet contains Empagliflozin 10 mg

Excipient with known effect

Each film coated tablet contains 116.900 mg of Mannitol.

EMPADIL 25: Each film coated tablet contains Empagliflozin 10 mg

Excipient with known effect

Each film coated tablet contains 101.900 mg of Mannitol.

For a full list of excipients, see section 6.1 of SmPC

Excipient Specific Warning:

Mannitol:

May have mild laxative effect.

3. Pharmaceutical Form:

Film coated tablets

EMPADIL 10: Pale yellow, round, biconvex and bevel-edged, film-coated debossed with E10 on one side and plain on the other side.

EMPADIL 25: Pale yellow, oval, biconvex, film-coated tablets debossed with E25 on one side and plain on the other side.

4. Clinical Particulars

4.1. Therapeutic Indications:

Type 2 diabetes mellitus

Empagliflozin 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

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Heart failure

Empagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

4.2. Posology and Method of administration:

Posology

Type 2 diabetes mellitus

The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and addon combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 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.

Heart failure

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

Renal impairment

In patients with type 2 diabetes mellitus, the glycaemic efficacy of empagliflozin is dependent on renal function. For cardiovascular risk reduction as add on to standard of care, a dose of 10 mg empagliflozin once daily should be used in patients with an eGFR below 60 ml/min/1.73 m^2 (see Table 1). Because the glycaemic lowering efficacy of empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered. For dose adjustment, recommendations according to eGFR or CrCL refer to Table 1.

Table 1: Dose adjustment recommendations [a]

Indication

Type 2 diabetes mellitus with eGFR [ml/ min/ 1.73 m^2] or CrCL [ml/ min] ≥60 Total daily dose: Initiate with 10 mg empagliflozin. In patients tolerating 10 mg empagliflozin additional glycaemic control, the dose calculation to 25 mg empagliflozin.

Type 2 diabetes mellitus with eGFR [ml/ min/ 1.73 m^2] or CrCL [ml/ min] 45 to <60 Total daily dose: Initiate with 10 mg empagliflozin[b]. Continue with 10 mg empagliflozin in patients taking Empagliflozin.

Type 2 diabetes mellitus with eGFR [ml/ min/ 1.73 m^2] or CrCL [ml/ min]

30 to <45[b] Total daily dose: Initiate with 10 mg empagliflozin. Continue with 10 mg empagliflozin in patients taking Empagliflozin.

Type 2 diabetes mellitus with eGFR [ml/ min/ 1.73 m^2] or CrCL [ml/ min] <30 Empagliflozin is not recommended.

In Heart failure (with or without type 2 diabetes mellitus) with eGFR [ml/ min/ 1.73 m^2] or CrCL [ml/ min] ≥20 Total daily dose Recommended is 10 mg empa

In Heart failure (with or without type 2 diabetes mellitus) with eGFR [ml/ min/ 1.73 m^2] or CrCL [ml/ min] <20 Empagliflozin is not recommended.

[a] See sections 4.4, 4.8, 5.1 and 5.2 [b] patients with type 2 diabetes mellitus and established cardiovascular disease

For treatment of heart failure in patients with or without type 2 diabetes mellitus, empagliflozin 10 mg may be initiated or continued down to an eGFR of 20-ml/min/1.73m^2 or CrCl of 20 ml/min.

Empagliflozin 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

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

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. In patients, aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

Paediatric population

The safety and efficacy of empagliflozin 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.

4.3. Contraindications:

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

4.4. Special warning and precautions for use:

Ketoacidosis

Rare cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes mellitus treated with SGLT 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 ketoacidosis is more likely to occur with higher doses of empagliflozin.

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.

In patients where ketoacidosis 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 ketoacidosis 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 ketoacidosis while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Empagliflozin should not be used for treatment of patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased ketoacidosis occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.

Renal impairment

For the indication of type 2 diabetes mellitus, in patients with an eGFR below 60 ml/min/1.73 m^2 or CrCl <60 ml/min the daily dose of empagliflozin is limited to 10 mg (see section 4.2). Empagliflozin is not recommended when eGFR is below 30 ml/min/1.73 m^2 or CrCl below 30 ml/min.

For the indication of heart failure, Empagliflozin is not recommended in patients with eGFR <20 ml/min/1.73 m^2.

Empagliflozin should not be used in patients with ESRD or in patients on dialysis. There are insufficient data to support use in these patients.

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.

Risk for volume depletion

Based on the mode of action of SGLT-2 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.

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. 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.

Complicated urinary tract infections

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)

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.

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.

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.

Chronic kidney disease

There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease (eGFR ≥30 mL/min/1.73 m^2) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin.

Urine laboratory assessments

Due to its mechanism of action, patients taking Empagliflozin 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.

4.5. Interactions with other medicinal products and other forms of Interactions :

Pharmacodynamic interactions

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin.

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

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) and a max 53% increase in area under the concentration-

time curve (AUC). These changes were not considered to be clinically meaningful.

The effect of UGT induction (e.g. induction by rifampicin or phenytoin) on empagliflozin has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Empagliflozin is appropriate.

An interaction study with gemfibrozil, an *in vitro* inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C increased by 15% and AUC increased by 59% max 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 and a 35% increase in AUC of empagliflozin. These changes were not max considered to be clinically meaningful.

Empagliflozin exposure was similar with and without co-administration with verapamil, a Pgp 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 *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 Pgp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in C of digoxin. These changes were not max 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.

4.6. 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 Empagliflozin during 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. Empagliflozin should not be used during breastfeeding.

Fertility

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

4.7. Effects on ability to drive and use machine:

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:

Summary of the safety profile

Type 2 diabetes mellitus

The most frequently reported adverse reaction was hypoglycaemia when used with sulphonylurea or insulin (see description of selected adverse reactions).

Heart failure

The published EMPEROR-Reduced study included 3730 patients with heart failure and reduced ejection fraction treated with empagliflozin 10 mg 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.

The overall safety profile of empagliflozin was generally consistent across the studied indications. No new adverse reactions were identified in the published EMPEROR-Reduced heart failure study.

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 2).

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

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**
Infections and infestations		Vaginal moniliasis, Vulvovaginitis balanitis and other genital infection[a] Urinary tract infection (including pyelonephritis and urosepsis)a		Necrotising fasciitis of the perineum (Fournier'sgangrene)b, *
Metabolism and nutrition disorders	Hypoglycaemia (whenused with sulphonylurea or insulin)[a]	Thirst		Diabetic ketoacidosis*
Gastrointestinal disorders		Constipation		
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	increaseda Blood creatinine increased/ Glomerular filtration rate decreased[a] Haematocrit increased	

Infections and Vaginal moniliasis, Necrot *infestations* vulvovaginitis, ising balanitis and other fasciiti genital infection[a] s of the

Urinary tract perine infection (including um pyelonephritis and (Fourn urosepsis)[a] ier's gangre ne)[b,*]

Metabolism and Hypoglycaemia Thirst Diabetic *nutrition disorders* (when used with ketoacidosis* sulphonylurea or insulin)[a]

Gastrointestinal Constipation

disorders

Skin and Pruritus Urticaria *subcutaneous tissue* (generalised) Angioedema *disorders* Rash

Vascular disorders Volume depletion[a]

Renal and urinary Increased urination[a] Dysuria

disorders

Investigations Serum lipids Blood increased[a] creatinine increased/

Glomerular filtration rate decreased[a]

Haematocrit increased[a] [a] see subsections below for additional information [b] In the EMPEROR-Reduced heart failure study, one case (<0.1%) of necrotising fasciitis of the perineum (Fournier´s gangrene) was observed in a patient with heart failure and diabetes mellitus treated with empagliflozin.

Reporting of suspected adverse reactions

Health care professionals are asked to report any suspected adverse reactions via the https://pv.pharmacyboardkenya.org

4.9. Overdosage:

Symptoms

In published controlled clinical studies single doses of up to 800 mg empagliflozin in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin 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 dosedependent 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 Category: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors

ATC Code: A10BK03

Mechanism of Action

Empagliflozin is a reversible, highly potent (IC 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. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed. Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24 hour dosing interval. Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78 g/day. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

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. 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, and downregulating of sympathetic activity.

5.2 Pharmacokinetics 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 of 1.5 hours max 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 were 1870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/l max 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 by max

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%.

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. *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 halflife 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.

5.3. Preclinical Safety data:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.

In published long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic.

In a published 2 year carcinogenicity study, empagliflozin did not increase the incidence of tumours in female rats up to the highest dose of 700 mg/kg/day, which corresponds to

approximately 72-times the maximal clinical AUC exposure to empagliflozin. In male rats,

treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumours in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both tumours are common in rats and are unlikely to be relevant to humans.

Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to

empagliflozin. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.

In published pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.

In a published juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period.

6. Pharmaceutical particulars

6.1. List of Excipients:

EMPADIL 10 (Empagliflozin Tablets 10 mg)

Mannitol, Pregelatinised Starch, Crospovidone, Talc, Magnesium Stearate, Opadry 03F82335 Yellow (Hypromellose, Titanium Dioxide [E171], Macrogol, Talc and Iron Oxide Yellow [E172]) and Purified Water.

EMPADIL 25 (Empagliflozin Tablets 25 mg)

Mannitol, Pregelatinised Starch, Crospovidone, Talc, Magnesium Stearate, Opadry 03F82335 Yellow (Hypromellose, Titanium Dioxide [E171], Macrogol, Talc and Iron Oxide Yellow [E172]) and Purified Water.

6.2 Incompatibilities: Not applicable

6.3 Shelf life: 24 months

6.4 Special Precautions for storage: Store below 30°C.

6.5. Nature and contents of container:

10 tablets in Alu-Alu blister pack, 3 such blisters in a printed carton along with Patient

Information Leaflet.

6.6 Special precautions for disposal:

Not applicable

7. MARKETING AUTHORISATION HOLDER

Ajanta Pharma Limited

Ajanta House,

Charkop, Kandivli (West) Mumbai-400 067

India.

Manufacturing Site Address:

Ajanta Pharma Limited Z/103/A,

Dahej SEZ II, Bharuch – 392 130. Gujarat State, Regd./ Corp. Off. : Ajanta House, Charkop, Kandivli (W), Mumbai 400 067.

8. MARKETING AUTHORISATION NUMBER(S)

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