Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Empaflo-L 25/5 mg Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:
Empagliftozin 25mg and Linagliptin 5mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablet
Light red circular biconvex shaped film coated tablet plain on both sides
Alu-Alu blister packed in a unit box with a literature insert included.

4. Clinical particulars

4.1 Therapeutic indications

Empaflo-L 25/5 mg Tablets, fixed dose combination of empagliflozin and linagliptin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- To improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Empaflo-L do not provide adequate glycaemic control
- when already being treated with the free combination of empagliflozin and linagliptin

4.2 Posology and method of administration

Oral use.

Posology

The recommended starting dose is one film-coated tablet of Empaflo-L 25mg/5 mg (25 mg empagliflozin plus 5 mg linagliptin) once daily.
In patients who tolerate this starting dose and require additional glycaemic control, the dose can be increased to one film-coated tablet of Empaflo-L 25 mg/5 mg (25 mg empagliflozin plus 5 mg linagliptin) once daily.
When Empaflo-L is used in combination with metformin, the metformin dose should be continued. When Empaflo-L 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 .

Patients switching from empagliflozin (either 10 mg or 25 mg daily dose) and linagliptin (5 mg daily dose) to Empaflo-L should receive the same daily dose of empagliflozin and linagliptin in the fixed dose combination as in separate tablets.

Missed doses

If a dose is missed, and it is 12 hours or more until the next dose, the dose should be taken as soon as the patient remembers. The next dose should be taken at the usual time. If a dose is missed, and it is less than 12 hours until the next dose, the dose should be skipped and the next dose should be taken at the usual time. A double dose should not be taken to compensate for a forgotten dose.

Special populations

Renal impairment

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 . 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.

eGFR [ml/min/1.73 m²] or CrCL [ml/min]	Empagliflozin	Linagliptin
≥60	Initiate with 10 mg. In patients tolerating 10 mg and requiring additional glycaemic control, the dose can be increased to 25 mg.	5 mg No dose adjustment for lir required.
45 to <60	Initiate with 10 mg.[b] Continue with 10 mg in patients already taking empagliflozin.	
30 to <45	Initiate with 10 mg.[b] Continue with 10 mg in patients already taking empagliflozin. [b]	
<30	Empagliflozin is not recommended.	

Table 1: Dose adjustment recommendations[a]

Empaflo-L should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis, as there are insufficient data on empagliflozin to support use in these patients.

Hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment.
Empagliflozin exposure is increased in patients with severe hepatic impairment and therapeutic experience in such patients is limited. Therefore, Empaflo-L is not recommended for use in this population.

Elderly
No dose adjustment based on age is required. However, renal function and risk of volume depletion should be taken into account in elderly patients. Based on very limited experience in patients 75 years and older, initiation of Empaflo-L therapy is not recommended in this population.

Pediatric population
Safety and efficacy of Empaflo-L in paediatric patients below 18 years of age have not been established. No data are available.

Method of administration
Empaflo-L tablets are for oral use and can be taken with or without a meal at any time of the day at regular intervals. The tablets should be swallowed whole with water.

4.3 Contraindications

Hypersensitivity to the active substances, to any other Sodium-Glucose-Co-Transporter-2 (SGLT2) inhibitor, to any other Dipeptidyl-Peptidase-4 (DPP-4) inhibitor, 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 DKA 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 SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Empaflo-L 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 DKA occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.

Renal impairment

In patients with an eGFR below 60 mL/min/1.73 m^2 or CrCl <60 mL/min, the daily dose of empagliflozin/linagliptin is limited to 10 mg/5 mg (see section 4.2). Empagliflozin/linagliptin is not recommended when eGFR is below 30 mL/min/1.73 m^2 or CrCl is below 30 mL/min. Empagliflozin/linagliptin 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/linagliptin 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.

Elevated hematocrits

Hematocrits 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 m2) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin.

Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic 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 (e.g. thiazide and loop diuretics, 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 Empaflo-L should be considered until the fluid loss is corrected.

Elderly

A higher risk of volume depletion adverse reactions were reported in patients aged 75 years and older, treated with empagliflozin, especially at 25 mg/day.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 is limited with Empaflo-L in patients > 75 years of age, and, no experience is available in patients aged 85 years and older. Initiation of therapy with Empaflo-L in this population is

not recommended.

Urinary tract infections
In Empaflo-L clinical trials, the incidence of urinary tract infections was overall similar between the patients treated with Empaflo-L and the patients treated with empagliflozin or linagliptin. The frequencies were comparable to the incidence of urinary tract infections in empagliflozin clinical trials.

In a pool of placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo and higher in patients treated with empagliflozin 10 mg. Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Pyelonephritis and urosepsis were not reported from the clinical trials in patients treated with Empaflo-L However, temporary interruption of Empaflo-L 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, Empaflo-L 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 trials 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 with empagliflozin in New York Heart Association (NYHA)

class I-II is limited, and there is no experience in clinical trials with empagliflozin in NYHA class III-IV. In the EMPA-REG OUTCOME trial, 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 trial population.

Urine laboratory assessments
Due to the mechanism of action of empagliflozin, patients taking Empaflo-L 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.

Acute pancreatitis
Use of dipeptidyl peptidase-4 (DPP-4) inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety trial (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis.

If pancreatitis is suspected, Empaflo-L should be discontinued; if acute pancreatitis is confirmed, Empaflo-L should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous pemphigoid
Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA trial, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Empaflo-L should be discontinued.

Use with medicinal products known to cause hypoglycaemia
Empagliflozin and linagliptin as single agents showed an incidence of hypoglycaemia comparable to placebo when used alone or in combination with other antidiabetics not known to cause hypoglycaemia (e.g. metformin, thiazolidinediones). When used in combination with antidiabetics known to cause hypoglycaemia (e.g.

sulphonylureas and/or insulin), the incidence of hypoglycaemia of both agents was increased.

There are no data about the hypoglycaemic risk of Empaflo-L when used with insulin and/or sulphonylurea. However, caution is advised when Empaflo-L is used in combination with antidiabetics. A dose reduction of the sulphonylurea or insulin may be considered.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed with Empaflo-L and other medicinal products; however, such studies have been conducted with the individual active substances. Based on results of pharmacokinetic studies, no dose adjustment of Empaflo-L is recommended when co-administered with commonly prescribed medicinal products, except those mentioned below.

Pharmacodynamic interactions

Insulin and sulphonylureas

Insulin and sulphonylureas may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or sulphonylureas may be required to reduce the risk of hypoglycaemia when used in combination with Empaflo-L. *Diuretics*

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

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

Empagliflozin is mainly excreted unchanged. A minor fraction is metabolised via uridine 5'- diphosphoglucuronosyltransferases (UGT); therefore, a clinically relevant effect of UGT inhibitors on empagliflozin is not expected (see section 5.2). The effect of UGT induction on empagliflozin (e.g. induction by rifampicin or phenytoin) has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy of empagliflozin. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Empaflo-L s appropriate.

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.
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. 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
Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.
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.

Effects of other medicinal products on linagliptin
Co-administration of rifampicin decreased linagliptin exposure by 40%, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-glycoprotein (P-gp) or cytochrome P450 (CYP) isozyme CYP3A4 inducer, particularly if these are administered long-term (see section 5.2). Co-administration with other potent inducers of P-gp and CYP3A4, such as carbamazepine, phenobarbital and phenytoin, has not been studied.
Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and Cmax of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4 to 5-fold after co-administration with ritonavir. Simulations of steady-state plasma concentrations of linagliptin with

and without ritonavir indicated that the increase in exposure will be not associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors.
Interaction studies conducted in healthy volunteers suggest that the pharmacokinetics of linagliptin were not influenced by co-administration with metformin and glibenclamide.

Effects of linagliptin on other medicinal products
Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency.
Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin, empagliflozin or oral contraceptives providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

4.6 Fertility, pregnancy, and lactation

Pregnancy
There are no data from the use of empagliflozin and linagliptin in pregnant women.
Animal studies have shown that empagliflozin and linagliptin cross the placenta during late gestation, but do not indicate direct or indirect harmful effects with respect to early embryonic development with either empagliflozin or linagliptin. Animal studies with empagliflozin have shown adverse effects on postnatal development As a precautionary measure it is preferable to avoid the use of Empaflo-L during pregnancy.

Breast-feeding
No data in humans are available on excretion of empagliflozin and linagliptin into milk. Available non-clinical data in animals have shown excretion of empagliflozin and linagliptin in milk. A risk to newborns or infants cannot be excluded. Empaflo-L should not be used during breast-feeding.

Fertility
No trials on the effect on human fertility have been conducted with Empaflo-L or with the individual active substances. Non-clinical studies

with empagliflozin and linagliptin as single agents do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines.

Empaflo-L 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 Empaflo-L is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin and analogues, sulphonylureas.

4.8 Undesirable effects

Urinary tract infection, Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, Nasopharyngitis, Hypoglycaemia,Thirst, Cough, Constipation, Pruritus, Rash, Increased urination, Amylase increased, Lipase increased.

Reporting of suspected adverse reactions:

Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms

In controlled clinical trials single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy volunteers 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 observedincrease in urine volume was not dose-dependent. There is no experience with doses above 800 mg in humans. During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were generally well tolerated. There is no experience with doses above 600 mg in humans.

Treatment

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required.

The removal of empagliflozin by haemodialysis has not been studied. Linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD19

Mechanism of action

Empaflo-L combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, DPP-4 inhibitor.

Empagliflozin

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of SGLT2. Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000 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 mellitus by reducing renal glucose re-absorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes mellitus 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 was 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 ofhypoglycaemia. 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 andosmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

Linagliptin

Linagliptin is an inhibitor of DPP-4 an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels.

Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000-fold selectivity versus DPP-8 or DPP-9 activity *in vitro*.

5.2 Pharmacokinetic properties

The rate and extent of absorption of empagliflozin and linagliptin in Empaflo-L are equivalent to the bioavailability of empagliflozin and linagliptin when administered as individual tablets. The

pharmacokinetics of empagliflozin and linagliptin as single agents have been extensively characterized in healthy subjects and patients with type 2 diabetes. Pharmacokinetics were generally similar in healthy subjects and in patients with type 2 diabetes.
Empaflo-L showed a similar food effect as the individual active substances. Empaflo-L can therefore be taken with or without food.

Empagliflozin

Absorption

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 area under the concentration-time curve (AUC) and C_{max} were 1,870 nmol.h and 259 nmol/L with empagliflozin 10 mg and 4,740 nmol.h 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.

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%.

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 suggest 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 empagliflozinwas 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 radioactivityexcreted in urine was unchanged parent drug.

Linagliptin

Absorption

After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

After once daily dosing of 5 mg linagliptin, steady-state plasma concentrations are reached by the third dose. Plasma AUC of linagliptin increased approximately 33% following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Due to the concentration dependent binding of linagliptin to DPP-4, the pharmacokinetics of linagliptin based on total exposure is not linear; indeed total plasma AUC of linagliptin increased in a less than dose-proportional manner while unbound AUC increases in a roughly dose- proportional manner.

The absolute bioavailability of linagliptin is approximately 30%. Co-administration of a high-fat meal with linagliptin prolonged the time

to reach C_{max} by 2 hours and lowered C_{max} by 15% but no influence on AUC_{0-72h} was observed. No clinically relevant effect of C_{max} and T_{max} changes is expected; therefore linagliptin may be administered with or without food.

The steady state plasma $AUC_{,ss}$ and $C_{max,ss}$ concentrations of linagliptin were 153 nmol*hr/L and 12.9 nmol/L for linagliptin 5 mg once daily for 7 days.

Distribution

As a result of tissue binding, the mean apparent volume of distribution at steady-state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1,110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75-89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 30-20% were unbound in plasma

Biotransformation

Following a [^{14}C] linagliptin oral 10 mg dose, approximately 5% of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13.3% of linagliptin at steady-state was detected which was found to be pharmacologically inactive and thus to not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Elimination

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours) that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the medicinal product. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours.

Following administration of an oral [^{14}C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal

clearance at steady-state was approximately 70 mL/min.

Renal impairment

Empagliflozin

In patients with mild, moderate or severe renal impairment (eGFR <30 to <90 mL/min/1.73 m^2) and patients with kidney failure or 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 .

Linagliptin

A multiple-dose, open-label trial was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal insufficiency compared to subjects with normal renal function. The trial included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with ESRD on haemodialysis. In addition patients with T2DM and severe renal impairment (<30 mL/min) were compared to T2DM patients with normal renal function.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7-fold was observed compared with control. Exposure in T2DM patients with severe RI was increased by about 1.4-fold compared to T2DM patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis (see section 4.2).

Hepatic impairment

Empagliflozin

In patients with mild, moderate and severe hepatic insufficiency (Child-Pugh classification), mean AUC and Cmax of empagliflozin increased (AUC by 23%, 47%, 75% and Cmax by 4%, 23%,48%) compared to subjects with normal hepatic function (see section 4.2).

Linagliptin

In non-diabetic patients with mild, moderate and severe hepatic insufficiency (according to the Child-Pugh classification), mean AUC and Cmax of linagliptin were similar to healthy subjects following administration of multiple 5 mg doses of linagliptin.

Body mass index

No dose adjustment is necessary for Glyxambi based on body mass index. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin or linagliptin based on population pharmacokinetic analysis.

Gender

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

Race

No clinically relevant difference in pharmacokinetics of empagliflozin and linagliptin were seen in population pharmacokinetic analysis and dedicated phase I trials.

Elderly

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin or linagliptin based on population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric patients

Empagliflozin

A paediatric Phase 1 trial examined the pharmacokinetics and

pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Linagliptin

A paediatric Phase 2 trial examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA1c (-0.63% vs -0.48%, n.s.). Due to the limited nature of the data set the results should be interpreted cautiously.

Drug interactions

No drug interaction trials have been performed with Glyxambi and other medicinal products; however, such trials have been conducted with the individual active substances.

In vitro assessment of empagliflozin

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.

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 Organic Anion Transporter 1 (OAT1) and Organic Cation Transporter 2 (OCT2). Empagliflozin is a substrate of P- glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions

with medicinal products 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 C_{max} of digoxin. These changes were not considered to be clinically meaningful.

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

In vitro assessment of linagliptin

Linagliptin was a substrate for OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2, suggesting a possible OATP8- mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and reabsorption of linagliptin *in vivo*. OATP2, OATP8, OCTN1, OCT1 and OATP2 activities were slightly to weakly inhibited by linagliptin

5.3 Preclinical safety data

General toxicity studies in rats up to 13 weeks were performed with the combination of empagliflozin and linagliptin.
Focal areas of hepatocellular necrosis were found in the combination groups at ≥15: 30 mg/kg linagliptin: empagliflozin (3.8 times the clinical exposure for linagliptin and 7.8 times the clinical exposure for empagliflozin) as well as in the group treated with empagliflozin alone but not in the control group. The clinical relevance of this finding remains uncertain.
At exposures sufficiently in excess of exposure in humans after therapeutic doses, the combination of empagliflozin and linagliptin was not teratogenic and did not show maternal toxicity. Adverse effects on renal development were not observed after administration of empagliflozin alone, linagliptin alone or after administration of the combined products.

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

Mannitol
Starch pregelatinized
Maize starch
Kollidon VA 64
Purified water
Kollidon CL
Purified talc
Magnesium stearate
Hypromellose 6 CPS
Purified talc
Titanium Dioxide
Polyethylene Glycol 6000
Red iron oxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage:

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-Alu blister pack of 3×10's in a printed unit box with literature included.

6.6 Special precautions for disposal and other handling:

Do not store above 30°C.Protect from direct sunlight. Keep all medicines out of reach of children Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Dawa Limited,
Plot No 7879/8, Baba Dogo Road –Ruaraka

P.O Box 16630-6200-Nairobi-Kenya.

Manufacturing site address:
Dawa Limited,
Plot No 7879/8, Baba Dogo Road –Ruaraka
P.O Box 16630-6200-Nairobi-Kenya.

Local Technical Representative:
Dawa Limited,
Plot No 7879/8, Baba Dogo Road –Ruaraka
P.O Box 16630-6200-Nairobi-Kenya.

8. Marketing authorization number
CTD10891

9. Date of first registration
16/02/2024

10. Date of revision of the text:
November 2024

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable