SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EMPAGOOD 25 L

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains :
Empagliflozin 25mg
linagliptin 5mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A Light Brick colored, round, biconcave, film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 Empalin do not provide adequate glycaemic control
- when already being treated with the free combination of empagliflozin and linagliptin

(See sections 4.2, 4.4, 4.5 and 5.1 for available data on combinations studied)

4.2 Posology and method of administration

Posology

The recommended starting dose is one film-coated tablet of EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg (10 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 EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg (25 mg empagliflozin plus 5 mg 3 linagliptin) once daily.
When EMPAGLIFLOZIN AND LINAGLIPTIN is used in combination with metformin, the metformin dose should be continued. When EMPAGLIFLOZIN AND LINAGLIPTIN 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 EMPAGLIFLOZIN AND LINAGLIPTIN 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 m2 (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]

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 linagliptin is 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.	

EMPAGLIFLOZIN AND LINAGLIPTIN 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 (see section 5.2). Therefore, EMPAGLIFLOZIN AND LINAGLIPTIN 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 patients 75 years and older

Paediatric population

Safety and efficacy of EMPAGLIFLOZIN AND LINAGLIPTIN in paediatric patients below 18 years of age have not been established. No data are available.

Method of administration

EMPAGLIFLOZIN AND LINAGLIPTIN 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.
The safety and efficacy of empagliflozin in patients with type 1 diabetes have not been established and empagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

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 (see section 4.8).
There are no data about the hypoglycaemic risk of Empalin when used with insulin and/or sulphonylurea. However, caution is advised when Empalin is used in combination with antidiabetics. A dose reduction of the sulphonylurea or insulin may be considered (see section 4.2 and 4.5).

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 study (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, Empalin should be discontinued; if acute pancreatitis is confirmed, Empalin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Monitoring of renal function

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function (see sections 4.2, 5.1 and 5.2). Therefore, assessment of renal function is recommended:
- prior to Empalin 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.

Use in patients with renal impairment

In patients with an eGFR below 60 mL/min/1.73 m^2 or CrCl <60 mL/min, avoidance, dose adjustment or discontinuation of Empalin may be necessary (for

details see section 4.2). Empalin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl is persistenly below 45 mL/min. In patients with end-stage renal disease or in patients on dialysis, Empalin should not be used, as empagliflozin is not expected to be effective in these patients (see section 5.2).

Use in patients at 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 (see section 5.1). Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy (e.g. thiazide and loop diuretics, see also section 4.5) 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 Empalin should be considered until the fluid loss is corrected.

Urinary tract infections

In Empalin clinical trials, the incidence of urinary tract infections was overall similar between the patients treated with Empalin and the patients treated with empagliflozin or linagliptin. The frequencies were comparable to the incidence of urinary tract infections in empagliflozin clinical trials (see section 4.8).
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 (see section 4.8). 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 Empalin. However, temporary interruption of Empalin 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, Empalin 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 ongoing 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.

Cardiac failure

Experience with empagliflozin in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. In the EMPAREG OUTCOME study, 10.1 % of the patients were reported with cardiac failure at baseline. The reduction of cardiovascular death in these patients was consistent with the overall study population.

Urine laboratory assessments

Due to the mechanism of action of empagliflozin, patients taking Empalin 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 1,5AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment (see section 4.8).

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 (see section 4.8). Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors). Therapeutic experience is limited with Empalin in patients > 75 years of age, and, no experience is available in patients aged 85 years and older. Initiation of therapy with Empalin in this population is not recommended (see section 4.2).

Bullous pemphigoid

Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on

treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Empalin should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed with Empalin 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 Empalin is recommended when coadministered 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 Empalin (see sections 4.2, 4.4 and 4.8).

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

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 Empalin is 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 C_{max} increased by 15 % and AUC increased by 59 % following co-administration. These changes were not considered to be clinically meaningful.
Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75 % increase in C_{max} and a 35 % increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.
Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by coadministration with metformin, glimepiride, pioglitazone,

sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Effects of empagliflozin on other medicinal products

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 Pglycoprotein (P-gp) or cytochrome P450 (CYP) isozyme CYP3A4 inducer, particularly if these are administed 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 C_{max} 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

The effects of Empalin on pregnancy, breast-feeding and fertility are not known. Effects related to the individual active substances are described below.

Pregnancy

There are no data from the use of empagliflozin and linagliptin in pregnant women.
Animal studies show 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 (see section 5.3). Animal studies with empagliflozin have shown adverse effects on postnatal development (see section 5.3). As a precautionary measure it is preferable to avoid the use of Empalin 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. Empalin should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted with Empalin 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reaction was urinary tract infection (7.5 % with Empalin 10 mg empagliflozin / 5 mg linagliptin and 8.5 % with Empalin 25 mg empagliflozin / 5 mg linagliptin) (see Description of selected adverse reactions). The most serious adverse reactions were ketoacidosis (< 0.1%), pancreatitis (0.2%), hypersensitivity (0.6%), and hypoglycaemia (2.4%) (see section 4.4).
Overall, the safety profile of Empalin was in line with the safety profiles of the individual active substances (empagliflozin and linagliptin). No additional adverse reactions were identified with Empalin.
The adverse reactions shown in the table below (see Table 1) are listed by system organ class and are based on the safety profiles of empagliflozin and linagliptin monotherapy. The information about adverse reactions not reported in Empalin clinical trials is based on the experience from empagliflozin and linagliptin.

Adverse reactions marked with an asterisk (*) are further discussed in section "Description of selected adverse reactions" below.

Tabulated list of adverse reactions

Frequency categories 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), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1 Adverse reactions

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Common Common Common Not known	Urinary tract infection[1,*] (including pyelonephritis and urosepsis)[4] Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections[1,*] Nasopharyngitis[2] Necrotising fasciitis of the perineum (Fournier´s gangrene)[#]
Immune system disorders	Uncommon Uncommon	Hypersensitivity[2] Angioedema[3,4], urticaria[3,4]
Metabolism and nutrition disorders	Common Common Rare	Hypoglycaemia (when used with sulphonylurea or insulin)* Thirst Diabetic ketoacidosis[4,#]
Respiratory, thoracic and mediastinal disorders	Common	Cough[2]
Gastrointestinal disorders	Uncommon Rare	Pancreatitis[2] Mouth ulceration[3]
Skin and subcutaneous tissue disorders	Common Common Not known	Pruritus[1] Rash3,4 Bullous pemphigoid[2,a]
Vascular disorders	Uncommon	Volume depletion[1,*]

Renal and urinary disorders	Common Uncommon	Increased urination[1,*] Dysuria[1]
Investigations	Common Common Uncommon Uncommon Uncommon	Amylase increased[2] Lipase increased[2] Haematocrit increased[1,5] Serum lipids increased[1,6] Blood creatinine increased/Glomerular filtration rate decreased[1,*]

[1] derived from empagliflozin experiences
[2] derived from linagliptin experiences
[3] derived from linagliptin postmarketing experience
[4] derived from empagliflozin postmarketing experience
[5] Mean changes from baseline in haematocrit were 3.3% and 4.2% for Empalin 10 mg/5 mg and 25 mg/5 mg, respectively, compared to 0.2% for placebo. In a clinical trial with empagliflozin, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.
[6] Mean percent increases from baseline for Empalin 10 mg/5 mg and 25 mg/5 mg versus placebo, respectively, were total cholesterol 3.2% and 4.6% versus 0.5%; HDL-cholesterol 8.5% and 6.2% versus 0.4%; LDL-cholesterol 5.8% and 11.0% versus 3.3%; triglycerides -0.5% and 3.3% versus 6.4 %.
[a] In the CARMELINA study (see section 5.1), bullous pemphigoid was reported in 0.2% patients treated with linagliptin and in no patients treated with placebo.
[#] see section 4.4
* see subsection below for additional information

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

Symptoms

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy 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 observed increase in urine volume was not dosedependent. 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

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

Empagliflozin

Empagliflozin is a reversible, highly potent (IC_{50} 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 of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment β (HOMA β) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by diuresis which may contribute to sustained and moderate reduction of blood pressure. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

Linagliptin

Linagliptin is an inhibitor of the enzyme 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

5.2 Pharmacokinetic properties

The rate and extent of absorption of empagliflozin and linagliptin in Empalin 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.
Empalin showed a similar food effect as the individual active substances. Empalin 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 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.

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 $AUC_{\tau,ss}$ 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 (see section 4.2).

Linagliptin

A multiple-dose, open-label study 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 study 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 C_{max} of empagliflozin increased (AUC by 23 %, 47 %, 75 % and C_{max} 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 C_{max} of linagliptin were similar to healthy subjects following administration of multiple 5 mg doses of linagliptin.

Body mass index

No dosage adjustment is necessary for Empalin 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 studies.

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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Microcrystalline Cellulose
Low Substituted HPMC-LH 11
Purified Water
Cross carmelose sodium
Colloidal Silicon dioxide
Magnesium Stearate
Ready Coat Red

Iso propyl Alcohol
Methylene Chloride

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage

Store below not exceeding 30°C. Keep medicine out of reach of children.

6.5 Nature and contents of container

Unit Carton containing 3 blisters strips of 10 tablets each with printed aluminum foil on one side and cold forming foil on other side.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

ZAIN PHARMA LIMITED
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road, Behind Nice And Lovely House,
P.O. Box: 100167-00101, Nairobi, Kenya
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8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/12/2025

10. DATE OF REVISION OF THE TEXT

06/12/2025