Summary of Product Characteristics
EMPAGOOD 25L
(FIXED DOSE COMBINATION OF EMPAGLIFLOZIN 25MG AND LINAGLIPTIN 5MG TABLETS)

1. Name of the medicinal product:

EMPAGOOD 25L (FIXED DOSE COMBINATION OF EMPAGLIFLOZIN 25MG AND LINAGLIPTIN 5MG TABLETS)

2. Qualitative and quantitative composition

Each film coated tablet contains 25 mg Empagliflozin 5 mg Linagliptin

Excipients of known effect:
Each tablet contains 70.0 mg of lactose monohydrate

3. Pharmaceutical Form:

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

4. Clinical particulars

4.1 Therapeutic indications

EMPAGLIFLOZIN AND LINAGLIPTIN, 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 EMPAGLIFLOZIN AND LINAGLIPTIN 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

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.

Summary of Product Characteristics
EMPAGOOD 25L
(FIXED DOSE COMBINATION OF EMPAGLIFLOZIN 25MG AND LINAGLIPTIN 5MG TABLETS)

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.

Method of administration
Oral

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.

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 5 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.

EMPAGLIFLOZIN AND LINAGLIPTIN should not be used in 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 m2 or CrCl<60mL/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 m2 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 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 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 (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 EMPAGLIFLOZIN AND LINAGLIPTIN 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 (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).

Urinary tract infections

In EMPAGLIFLOZIN AND LINAGLIPTIN clinical trials, the incidence of urinary tract infections was overall similar between the patients treated with EMPAGLIFLOZIN AND LINAGLIPTIN 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). Postmarketing 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 EMPAGLIFLOZIN AND LINAGLIPTIN. However, temporary interruption of EMPAGLIFLOZIN AND LINAGLIPTIN should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

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

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier´s gangrene is suspected, EMPAGLIFLOZIN AND LINAGLIPTIN 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.

Urine laboratory assessments

Due to the mechanism of action of empagliflozin, patients taking EMPAGLIFLOZIN AND LINAGLIPTIN 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, EMPAGLIFLOZIN AND LINAGLIPTIN should be discontinued; if acute pancreatitis is confirmed, EMPAGLIFLOZIN AND LINAGLIPTIN 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, EMPAGLIFLOZIN AND LINAGLIPTIN 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 (see section 4.8).
There are no data about the hypoglycaemic risk of EMPAGLIFLOZIN AND LINAGLIPTIN when used with insulin and/or sulphonylurea. However, caution is advised when EMPAGLIFLOZIN AND LINAGLIPTIN 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 EMPAGLIFLOZIN AND LINAGLIPTIN 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 EMPAGLIFLOZIN AND LINAGLIPTIN 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 EMPAGLIFLOZIN AND LINAGLIPTIN (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

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 EMPAGLIFLOZIN AND LINAGLIPTIN 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 (Cmax) and a 53% increase in 8 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 coadministration. 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 coadministration 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 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 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 (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 EMPAGLIFLOZIN AND LINAGLIPTIN 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. EMPAGLIFLOZIN AND LINAGLIPTIN should not be used during breast-feeding.

Fertility
No trials on the effect on human fertility have been conducted with EMPAGLIFLOZIN AND LINAGLIPTIN 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
EMPAGLIFLOZIN AND LINAGLIPTIN 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 AND LINAGLIPTIN 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 EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg empagliflozin/5 mg linagliptin and 8.5% with EMPAGLIFLOZIN AND LINAGLIPTIN 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 EMPAGLIFLOZIN AND LINAGLIPTIN was in line with the safety profiles of the individual active substances (empagliflozin and linagliptin). No additional adverse reactions were identified with EMPAGLIFLOZIN AND LINAGLIPTIN.

Tabulated list of adverse reactions

The adverse reactions shown in the table below (see Table 2) are listed by system organ class and are based on the safety profiles of empagliflozin and linagliptin monotherapy. 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 2 Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled trials and from post-marketing experience

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Urinary tract infection[1,*] (including pyelonephritis and urosepsis)[4]
	Common	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections[1,*]
	Common	Nasopharyngitis[2]
	Rare	Necrotising fasciitis of the perineum (Fournier´s gangrene)[a]
Immune system disorders	Uncommon	Hypersensitivity[2]
	Uncommon	Angioedema[3,4], urticaria[3,4]
Metabolism and nutrition disorders	Common	Hypoglycaemia (when used with sulphonylurea or insulin)[*]
	Common	Thirst
	Rare	Diabetic ketoacidosis[4,a]
Vascular disorders	Uncommon	Volume depletion[1,*,b]
Respiratory, thoracic and mediastinal disorders	Common	Cough[2]
Gastrointestinal disorders	Common	Constipation
	Uncommon	Pancreatitis[2]
	Rare	Mouth ulceration[3]
Skin and subcutaneous tissue disorders	Common	Pruritus[1]
	Common	Rash[3,4]
	Not known	Bullous pemphigoid[2,a]
Renal and urinary disorders	Common	Increased urination[1,*]
	Uncommon	Dysuria[1]
	Very rare	Tubulointerstitial nephritis[4]
Investigations	Common	Amylase increased[2]
	Common	Lipase increased[2]
	Uncommon	Haematocrit increased[1,5]
	Uncommon	Serum lipids increased[1,6]
	Uncommon	Blood creatinine increased/Glomerular filtration rate decreased[1,*]

Description of selected adverse reactions

Hypoglycaemia

In pooled clinical trials of EMPAGLIFLOZIN AND LINAGLIPTIN in patients with type 2 diabetes and inadequate glycaemic control on background metformin, the frequency of the reported hypoglycaemic events was 2.4%. The incidence of confirmed hypoglycaemic events was low (< 1.5%). There was no notable difference of the incidence in patients treated with different dose strengths of EMPAGLIFLOZIN AND LINAGLIPTIN compared to the treatment with empagliflozin or linagliptin.

One patient administered EMPAGLIFLOZIN AND LINAGLIPTIN experienced a confirmed (investigator-defined), major hypoglycaemic event (defined as an event requiring assistance) in the active- or placebo-controlled trials (overall frequency 0.1%).

Based on the experience with empagliflozin and linagliptin, an increase of the risk of hypoglycaemia is expected with the concomitant treatment of insulin and/or sulphonylurea (see section 4.4 and information below)

Hypoglycaemia with empagliflozin
The frequency of hypoglycaemia depended on the background therapy in the respective trials and was similar for empagliflozin and placebo as monotherapy, as add-on to metformin, and as add-on to pioglitazone +/- metformin. The frequency of patients with hypoglycaemia was increased in patients treated with empagliflozin compared to placebo when given as add-on to metformin plus sulphonylurea (empagliflozin 10 mg: 16.1%, empagliflozin 25 mg: 11.5%, placebo: 8.4%), add-on to basal insulin +/- metformin and +/-sulphonylurea (empagliflozin 10 mg: 19.5%, empagliflozin 25 mg: 28.4%, placebo: 20.6% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg and 25 mg: 36.1%, placebo 35.3% over the 78 week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 39.8%, empagliflozin 25 mg: 41.3%, placebo: 37.2% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 51.1%, empagliflozin 25 mg: 57.7%, placebo: 58% over the 52-week trial).

Major hypoglycaemia with empagliflozin (events requiring assistance) The frequency of patients with major hypoglycaemic events was low (< 1%) and similar for empagliflozin and placebo as monotherapy, as add-on to metformin +/- sulfonylurea, and as add-on to pioglitazone +/- metformin.

The frequency of patients with major hypoglycaemic events was increased in patients treated with empagliflozin compared to placebo when given as add-on to basal insulin +/- metformin and +/- sulphonylurea (empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo: 0% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo 0% over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 1.6%, empagliflozin 25 mg: 0.5%, placebo: 1.6% during initial 18 weeks treatment when insulin could not be adjusted and over the 52-week trial).

Hypoglycaemia with linagliptin
The most frequently reported adverse event in clinical trials with linagliptin was hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea (22.9% vs 14.8% in placebo).

Hypoglycaemias in the placebo-controlled trials (10.9%; N=471) were mild (80%; N=384), moderate (16.6%; N=78) or severe (1.9%; N=9) in intensity.

Urinary tract infection
In clinical trials with EMPAGLIFLOZIN AND LINAGLIPTIN, there was no notable difference of the frequency of urinary tract infections in patients treated with EMPAGLIFLOZIN AND LINAGLIPTIN (EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5

mg: 8.5%; EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg: 7.5%) compared to the patients treated with empagliflozin and linagliptin. The frequencies have been comparable to those reported from the empagliflozin clinical trials (see also section 4.4).

In empagliflozin trials, the overall frequency of urinary tract infection was similar in patients treated with empagliflozin 25 mg and placebo (7.0% and 7.2%), and higher in patients treated with empagliflozin 10 mg (8.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections was similar to placebo for mild, moderate and severe intensity reports. Urinary tract infection was reported more frequently in female patients treated with empagliflozin compared to placebo, but not in male patients.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection
In clinical trials with EMPAGLIFLOZIN AND LINAGLIPTIN, genital infections in patients treated with EMPAGLIFLOZIN AND LINAGLIPTIN (EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg: 3.0%; EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg: 2.5%) were reported more frequently than for linagliptin but less freqeuntly than for empagliflozin. Overall, the frequencies for EMPAGLIFLOZIN AND LINAGLIPTIN have been comparable to those reported from the empagliflozin clinical trials.

In empagliflozin trials, vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg (4.0%) and empagliflozin 25 mg (3.9%) compared to placebo (1.0%). These infections were reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe in intensity.

Increased urination
In clinical trials with EMPAGLIFLOZIN AND LINAGLIPTIN, increased urination in patients treated with EMPAGLIFLOZIN AND LINAGLIPTIN (EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg: 2.6%; EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg: 1.4%) was reported more frequently than for linagliptin and with similar frequency than for empagliflozin. Overall, the frequencies for EMPAGLIFLOZIN AND LINAGLIPTIN have been comparable to those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, increased urination (including the predefined terms pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin (empagliflozin 10 mg: 3.5%, empagliflozin 25 mg: 3.3%) compared to placebo (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin (< 1%).

Volume depletion
In clinical trials with EMPAGLIFLOZIN AND LINAGLIPTIN, there was no notable difference in the frequency of volume depletion in patients treated with EMPAGLIFLOZIN AND LINAGLIPTIN (EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg: 0.4%; EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg: 0.8%) compared to the patients treated with empagliflozin and linagliptin. The frequencies have been comparable to those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, the overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was similar in patients treated with empagliflozin (empagliflozin 10 mg: 0.6%, empagliflozin 25 mg: 0.4%) and placebo (0.3%). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2.3%) or empagliflozin 25 mg (4.3%) compared to placebo (2.1%)

Blood creatinine increased/Glomerular filtration rate decreased
In clinical trials with EMPAGLIFLOZIN AND LINAGLIPTIN, the frequency of patients with increased blood creatinine (EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg: 0.4%; EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg: 0%) and decreased glomerular filtration rate (EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg: 0.4%; EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg: 0.6%) has been comparable to those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, the overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%).

Elderly
In clinical trials, nineteen patients 75 years or older were treated with EMPAGLIFLOZIN AND LINAGLIPTIN. No patient was older than 85 years. The safety profile of EMPAGLIFLOZIN AND LINAGLIPTIN did not differ in the elderly. Based on empagliflozin experiences, elderly patients may be at increased risk of volume depletion

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to National Regulatory Agents.

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 observed increase 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

EMPAGLIFLOZIN AND LINAGLIPTIN 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 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 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 15 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.

Clinical efficacy and safety
A total of 2 173 patients with type 2 diabetes mellitus and inadequate glycaemic control were treated in clinical trials to evaluate the safety and efficacy of EMPAGLIFLOZIN AND LINAGLIPTIN; 1 005 patients were treated with EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg empagliflozin/5 mg linagliptin or 25 mg empagliflozin/5 mg linagliptin. In clinical trials, patients were treated for up to 24 or 52 weeks.

EMPAGLIFLOZIN AND LINAGLIPTIN added to metformin In a factorial design trial patients inadequately controlled on metformin were treated for 24-weeks with EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg, EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg, empagliflozin 10 mg, empagliflozin 25 mg or linagliptin 5 mg. The treatment with EMPAGLIFLOZIN AND LINAGLIPTIN resulted in statistically significant improvements in HbA1c (see Table 3) and fasting plasma glucose (FPG) compared to linagliptin 5 mg and also compared to empagliflozin 10 mg or 25 mg. EMPAGLIFLOZIN AND LINAGLIPTIN also provided statistically significant improvements in body weight compared to linagliptin 5 mg.

Table 3 Efficacy parameter

	EM+LN 25mg/5mg	EM+LN 10mg/5mg	Empa25	Empa 10	Lina 5
Primary endpoint: HbA_{1c} (%) – 24 weeks					
Number of patients analysed	**134**	**135**	**140**	**137**	**128**
Baseline mean (SE)	7.90 (0.07)	7.95 (0.07)	8.02 (0.07)	8.00 (0.08)	8.02 (0.08)
Change from baseline at week 24[1]: - adjusted mean[2] (SE)	-1.19 (0.06)	-1.08 (0.06)	-0.62 (0.06)	-0.66 (0.06)	-0.70 (0.06)
Comparison vs. empagliflozin[1]: - adjusted mean[2] (SE) - 95.0 % CI - p-value	vs. 25 mg -0.58 (0.09) -0.75, -0.41 <0.0001	vs. 10 mg -0.42 (0.09) -0.59, -0.25 <0.0001	--	--	--
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0 % CI - p-value	-0.50 (0.09) -0.67, -0.32 <0.0001	-0.39 (0.09) -0.56, -0.21 <0.0001	--	--	--

In a pre-specified subgroup of patients with baseline HbA1c greater or equal than 8.5%, the reduction from baseline in HbA1c at 24 weeks with EMPAGLIFLOZIN AND LINAGLIPTIN 25 mg/5 mg was -1.8% ($p< 0.0001$ versus linagliptin 5 mg, $p< 0.001$ versus empagliflozin 25 mg) and with EMPAGLIFLOZIN AND LINAGLIPTIN 10 mg/5 mg -1.6% ($p < 0.01$ versus linagliptin 5 mg, n.s. versus empagliflozin 10 mg).

Empagliflozin in patients inadequately controlled on metformin and linagliptin
In patients inadequately controlled on maximally tolerated doses of metformin, open label linagliptin 5 mg was added for 16 weeks. In patients inadequately controlled after this 16 week period, patients received double-blind treatment with either empagliglozin 10 mg, empagliflozin 25 mg or placebo for 24-weeks. After this double-blind period, treatment with both empagliflozin 10 mg and empagliflozin 25 mg provided statistically significant improvements in HbA1c, FPG and body weight compared to placebo; all patients continued treatment with metformin and linagliptin 5 mg during the trial. A statistically significant greater number of patients with a baseline HbA1c ≥7.0% treated with both doses of empagliflozin achieved a target HbA1c of <7% compared to placebo (see Table 4). After 24-weeks treatment with empagliflozin, both systolic and diastolic blood pressures were reduced, -2.6/-1.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 25 mg and -1.3/-0.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 10 mg.

After 24 weeks, rescue therapy was used in 4 (3.6%) patients treated with empagliflozin 25 mg and in 2 (1.8%) patients treated with empagliflozin 10 mg, compared to 13 (12.0%) patients treated with placebo (all patients on background metformin + linagliptin 5 mg)

Linagliptin 5 mg in patients inadequately controlled on metformin and empagliflozin 10 mg or empagliflozin 25 mg In patients inadequately controlled on maximally tolerated doses of

metformin, open label empagliflozin 10 mg or empagliflozin 25 mg was added for 16 weeks. In patients inadequately controlled after this 16 week period, patients received double-blind treatment with either linagliptin 5 mg or placebo for 24-weeks. After this double-blind period, treatment in both populations (metformin + empagliflozin 10 mg and metformin + empagliflozin 25 mg) linagliptin 5 mg provided statistically significant improvements in HbA1c compared to placebo; all patients continued treatment with metformin and empagliflozin during the trial. A statistically significant greater number of patients with a baseline HbA1c ≥7.0% and treated with linagliptin achieved a target HbA1c of >7% % and treated with linagliptin achieved a target HbA1c of <7% compared to placebo.

Cardiovascular safety
Empagliflozin cardiovascular outcome (EMPA-REG OUTCOME) trial The double-blind, placebo-controlled EMPA-REG OUTCOME trial compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with 18 type 2 diabetes and established cardiovascular disease. A total of 7 020 patients were treated (empagliflozin 10 mg: 2 345, empagliflozin 25 mg: 2 342, placebo: 2 333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA1c was 8.1%, and 71.5% were male. At baseline, 74% of patients were being treated with metformin, 48% with insulin, and 43% with a sulfonylurea. About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 m2 , 17.8% of 45-60 ml/min/1.73 m2 and 7.7% of 30-45 ml/min/1.73 m2 .

At week 12, an adjusted mean (SE) improvement in HbA1c when compared to baseline of 0.11% (0.02) in the placebo group, 0.65% (0.02) and 0.71% (0.02) in the empagliflozin 10 and 25 mg groups was observed. After the first 12 weeks glycaemic control was optimized independent of investigative treatment. Therefore the effect was attenuated at week 94, with an adjusted mean (SE) improvement in HbA1c of 0.08% (0.02) in the placebo group, 0.50% (0.02) and 0.55% (0.02) in the empagliflozin 10 and 25 mg groups

Empagliflozin was superior in preventing the primary combined endpoint of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg and confirmed by an improved overall survival (see Table 6). The effect of empagliflozin on the primary combined endpoint of CV death, non-fatal MI, or non-fatal stroke was largely independent of glycaemic control or renal function (eGFR) and generally consistent across eGFR categories down to an eGFR of 30 ml/min/1.73 m2 in the EMPA-REG OUTCOME study.

5.2 Pharmacokinetic properties
The rate and extent of absorption of empagliflozin and linagliptin in EMPAGLIFLOZIN AND LINAGLIPTIN 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. EMPAGLIFLOZIN AND LINAGLIPTIN showed a similar food effect as the individual active substances. EMPAGLIFLOZIN AND LINAGLIPTIN 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 tmax of 1.5 hours post dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma area under the concentration-time curve (AUC) and Cmax 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 Cmax 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 [14C]-empagliflozin solution to healthy 21 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 [14C]-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 Tmax) 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 Cmax by 2 hours and lowered Cmax by 15% but no influence on AUC0-72h was observed. No clinically relevant effect of Cmax and Tmax 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 [14C] 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 [14C] 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 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<80mL/min),Moderate(30 to<50mL/min),Severe (<30mL/min), as well as patients with ESRD on haemodialysis. In addition patients with T2DM and severe renal impairment (<30mL/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

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%) 23 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 ChildPugh 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 EMPAGLIFLOZIN AND LINAGLIPTIN 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
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.
In 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

In a 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 1 000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1 000 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 pre- and postnatal toxicity studies with empagliflozin in rats, reduced weight gain in 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 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.

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

In long-term toxicity studies in rodents and Cynomolgus monkeys, signs of toxicity were observed at exposures greater than 300-times the clinical dose of linagliptin.

Liver, kidneys and gastrointestinal tract are the principal target organs of toxicity in mice and rats. At exposures greater than 1 500-times the clinical exposure, adverse reactions on reproductive organs, thyroid and the lymphoid organs were seen in rats. Strong pseudo-allergic reactions were observed in dogs at medium doses, secondarily causing cardiovascular changes, which were considered dogspecific. Liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys at more than 450-times the clinical exposure. At more than 100-times clinical exposure, irritation of the stomach was the major finding in monkeys.

Oral 2-year carcinogenicity studies in rats and mice revealed no evidence of carcinogenicity in rats or male mice. A significantly higher incidence of malignant lymphomas only in female mice at the highest dose (>200-times human exposure) is not considered relevant for humans. Based on these studies there is no concern for carcinogenicity in humans.

Linagliptin had no adverse effects on fertility or early embryonic development at exposures greater 26 than 900-times the clinical exposure. Linagliptin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, linagliptin caused a slight retardation of skeletal ossification in the rat and increased embryofoetal loss in the rabbit.

In the pre- and postnatal toxicity study with linagliptin in rats, reduced weight gain in offspring was observed at maternal exposures approximately 1 500-times the maximal clinical exposure to linagliptin. No such effect was seen at systemic exposure 49-times the maximal clinical exposure to linagliptin

6. Pharmaceutical particulars
6.1 List of excipients

Sr. No	Name of Ingredients
1	Lactose Monohydrate
2	Microcrystalline Cellulose

3	Low Substituted Hydroxy propyl cellulose-LH 11
4	Purified Water
5	Cross carmellose sodium
6	Colloidal Silicon dioxide
7	Magnesium Stearate
8	Ready Coat Yellow
9	Iso propyl Alcohol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container
10 tablets are packed in ALU-ALU blister, such 3 blister are packed in one mono carton with insert

6.6 Special precautions for disposal and other handling
No special requirements

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER
Marketing Authorisation Holder:
ZAIN PHARMA LTD.
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

8. Marketing Authorization Number:
H2025/CTD11584/25330

9. Date of First <Registration> / Renewal of The <Registration>
Not Applicable

10. Date of Revision of the Text: Not Applicable