SUMMARY OF PRODUCT CHARACTERISTICS
EMPAGOOD 25L (Empagliflozin 25 mg and Linagliptin 5 mg Tablets)

1. NAME OF THE MEDICINAL PRODUCT

EMPAGOOD 25L (Fixed Dose Combination of Empagliflozin 25 mg and Linagliptin 5 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg empagliflozin and 5 mg linagliptin.

Excipients with known effect:

Each tablet contains 70.0 mg of lactose monohydrate. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light brick coloured, round, biconcave, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EMPAGOOD 25L 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 EMPAGOOD 25L 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 10 mg/linagliptin 5 mg 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 EMPAGOOD 25L (25 mg empagliflozin/5 mg linagliptin) once daily.

When used in combination with a sulphonylurea or insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.5).

Missed doses

If a dose is missed and it is 12 hours or more until the next dose, the missed dose should be taken as soon as remembered. If less than 12 hours remain until the next dose, the missed dose should be skipped. A double dose should not be taken to compensate.

Renal impairment

In patients with an eGFR below 60 ml/min/1.73 m² or CrCl <60 ml/min, the daily dose of empagliflozin/linagliptin is limited to 10 mg/5 mg. EMPAGOOD 25L (25 mg/5 mg) is not recommended when eGFR is below 60 ml/min/1.73 m². EMPAGOOD 25L should not be used in patients with ESRD or on dialysis. For cardiovascular risk reduction as add-on to standard of care in patients with eGFR <60 ml/min/1.73 m², a dose of 10 mg empagliflozin should be used.

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment. EMPAGOOD 25L is not recommended in patients with severe hepatic impairment due to limited therapeutic experience.

Elderly (≥65 years)

No dose adjustment based on age is required. Renal function and risk of volume depletion should be taken into account in patients 75 years and older.

Paediatric population

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

Method of administration

Oral. EMPAGOOD 25L can be taken with or without a meal at any time of day at regular intervals. Swallow tablets whole with water.

4.3 Contraindications

- Hypersensitivity to the active substances, to any other SGLT2 inhibitor or to any other DPP-4 inhibitor, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diabetic ketoacidosis (DKA)

Rare cases of DKA, including life-threatening and fatal cases, have been reported with SGLT2 inhibitors. The presentation may be atypical with only moderately elevated blood glucose levels (<14 mmol/L). 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. If DKA is suspected, discontinue EMPAGOOD 25L immediately. Treatment should be interrupted in patients hospitalised for major surgical procedures or acute serious medical illness. Do not use in type 1 diabetes.

Renal impairment and monitoring

EMPAGOOD 25L is not recommended when eGFR is below 30 ml/min/1.73 m². Assessment of renal function is recommended prior to initiation and at least yearly during treatment, as well as prior to initiation of any concomitant medicinal product with a potential negative impact on renal function.

Risk for volume depletion

Osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Exercise caution in patients with known cardiovascular disease, patients on antihypertensive therapy (e.g. thiazide and loop diuretics) with a history of hypotension, or patients aged 75 years and older. Temporary interruption of treatment should be considered until fluid loss is corrected.

Hepatic injury

Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship has not been established. Clinically monitor for signs of hepatic injury.

Urinary tract infections

Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported. Temporary interruption of EMPAGOOD 25L should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event requiring urgent surgical intervention and antibiotic treatment. If suspected, discontinue EMPAGOOD 25L and institute prompt treatment.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) was observed in long-term clinical trials with another SGLT2 inhibitor. The class effect is uncertain. Counsel patients on routine preventative foot-care.

Acute pancreatitis

DPP-4 inhibitor use has been associated with a risk of acute pancreatitis. In the CARMELINA trial, adjudicated acute pancreatitis was reported in 0.3% of linagliptin patients and 0.1% of placebo patients. If pancreatitis is suspected, discontinue EMPAGOOD 25L; if confirmed, do not restart. Exercise caution in patients with a history of pancreatitis.

Bullous pemphigoid

Bullous pemphigoid has been observed with linagliptin (0.2% in CARMELINA vs 0% with placebo). If suspected, discontinue EMPAGOOD 25L.

Hypoglycaemia with insulin or sulphonylurea

Empagliflozin and linagliptin as single agents showed an incidence of hypoglycaemia comparable to placebo when used alone or in combination with antidiabetics not known to cause hypoglycaemia. When used with sulphonylureas and/or insulin, a dose reduction of the sulphonylurea or insulin may be considered.

Lactose content

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Laboratory test interference

Patients taking EMPAGOOD 25L will test positive for glucose in their urine. Monitoring glycaemic control with the 1,5-AG assay is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Insulin and sulphonylureas:

May increase the risk of hypoglycaemia. A lower dose of insulin or sulphonylurea may be required.

Diuretics:

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

UGT inducers (rifampicin, phenytoin):

Co-treatment with known UGT inducers is not recommended due to a potential risk of decreased efficacy of empagliflozin. Monitor glycaemic control if co-administration is necessary.

Probenecid:

An inhibitor of UGT and OAT3; resulted in 26% increase in empagliflozin Cmax and 53% increase in AUC — not considered clinically meaningful.

Rifampicin (effect on linagliptin):

Co-administration decreased linagliptin exposure by 40%. The combination of a potent P-gp or CYP3A4 inducer with linagliptin may reduce linagliptin efficacy.

Lithium:

Empagliflozin may increase renal lithium excretion, decreasing blood lithium levels. Monitor serum lithium more frequently after empagliflozin initiation and dose changes.

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 on early embryonic development. Animal studies with empagliflozin have shown adverse effects on postnatal renal development. As a precautionary measure, EMPAGOOD 25L should be avoided during pregnancy.

Breast-feeding

Available non-clinical data show excretion of empagliflozin and linagliptin in the milk of lactating animals. A risk to newborns or infants cannot be excluded. EMPAGOOD 25L should not be used during breast-feeding.

Fertility

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

EMPAGOOD 25L 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 EMPAGOOD 25L is used in combination with 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 EMPAGOOD 10 mg/5 mg and 8.5% with EMPAGOOD 25L). The most serious adverse reactions were: ketoacidosis (<0.1%), pancreatitis (0.2%), hypersensitivity (0.6%) and hypoglycaemia (2.4%). The overall safety profile of the combination is consistent with the safety profiles of the individual active substances.

Selected adverse reactions

Hypoglycaemia: Confirmed hypoglycaemic events occurred with low incidence (<1.5%) overall. The risk increases significantly when combined with sulphonylureas or insulin (see section 4.4 for detailed frequency data by background therapy).

Urinary tract infections: Frequency was similar between EMPAGOOD 25L and empagliflozin monotherapy. Urinary tract infection was reported more frequently in female patients. Post-marketing complicated UTIs including pyelonephritis and urosepsis have been reported.

Genital infections: Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently with EMPAGOOD 25L than with linagliptin, and with similar frequency to empagliflozin. Generally mild to moderate in intensity.

Increased urination: Reported more frequently with EMPAGOOD 25L (25 mg/5 mg: 2.6%; 10 mg/5 mg: 1.4%) than with linagliptin and with similar frequency to empagliflozin.

Volume depletion: Frequency with EMPAGOOD 25L was comparable to empagliflozin. Risk increased in patients 75 years and older.

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 via the National Regulatory Authority.

4.9 Overdose

In controlled clinical trials, single doses up to 800 mg empagliflozin in healthy volunteers and multiple daily doses up to 100 mg empagliflozin in patients with type 2 diabetes did not show toxicity. Empagliflozin increased urine glucose excretion. Single doses up to 600 mg linagliptin in healthy subjects were generally well tolerated. In the event of overdose, employ usual supportive measures and remove unabsorbed material from the gastrointestinal tract. 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

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of SGLT2, which is responsible for the majority of renal glucose reabsorption from the glomerular filtrate. Empagliflozin is 5,000 times more selective for SGLT2 versus SGLT1. By inhibiting SGLT2, empagliflozin reduces renal glucose reabsorption, increasing urinary glucose excretion, and also reduces sodium reabsorption causing osmotic diuresis and reduction in intravascular volume. Empagliflozin improves glycaemic control independently of beta-cell function and the insulin pathway, contributing to a low intrinsic risk of hypoglycaemia. The EMPA-REG OUTCOME trial demonstrated that empagliflozin was superior to placebo in reducing the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in patients with type 2 diabetes and established cardiovascular disease.

Mechanism of action — Linagliptin

Linagliptin is an inhibitor of DPP-4, the enzyme involved in the inactivation of the incretin hormones GLP-1 and GIP. By inhibiting DPP-4, linagliptin increases active incretin levels, thereby increasing insulin biosynthesis and secretion from pancreatic beta cells, and reducing glucagon secretion from alpha cells, in a glucose-dependent manner. Linagliptin binds very effectively to DPP-4 in a reversible manner, with >10,000-fold selectivity versus DPP-8 and DPP-9.

Clinical efficacy and safety

In clinical trials involving 2,173 patients with type 2 diabetes mellitus inadequately controlled on metformin, EMPAGOOD 25L demonstrated statistically significant improvements in HbA1c, fasting plasma glucose and body weight compared to linagliptin 5 mg, and improvements in HbA1c and FPG compared to empagliflozin monotherapy. In patients with baseline HbA1c ≥8.5%, the reduction in HbA1c at 24 weeks with EMPAGOOD 25L was −1.8%.

5.2 Pharmacokinetic properties

The rate and extent of absorption of empagliflozin and linagliptin from EMPAGOOD 25L are equivalent to the bioavailability of the individual tablets. EMPAGOOD 25L can be taken with or without food.

Empagliflozin

Absorption: Rapidly absorbed; median Tmax 1.5 hours. AUC and Cmax increase dose-proportionally. Absolute bioavailability approximately 75%. Administration with a high-fat/high-calorie meal decreased Cmax by approximately 37% and AUC by approximately 16% — not considered clinically relevant.

Distribution: Volume of distribution approximately 73.8 litres. Plasma protein binding 86%.

Biotransformation: Three glucuronide conjugate metabolites as main metabolites (UGT2B7, UGT1A3, UGT1A8, UGT1A9); each <10% of total drug-related material.

Elimination: Apparent terminal half-life approximately 12.4 hours; approximately 54% excreted in urine and 41% in faeces.

Linagliptin

Absorption: Rapidly absorbed; median Tmax 1.5 hours. Absolute bioavailability approximately 30%. Food has no clinically relevant effect.

Distribution: Mean apparent volume of distribution at steady state approximately 1,110 litres. Plasma protein binding is concentration-dependent (99% at 1 nmol/L decreasing to 75–89% at ≥30 nmol/L due to saturation of binding to DPP-4).

Biotransformation: One main metabolite (13.3% relative exposure at steady state), pharmacologically inactive.

Elimination: Terminal half-life >100 hours (primarily related to tight, saturable DPP-4 binding, which does not contribute to accumulation). Effective half-life for accumulation approximately 12 hours. Approximately 85% excreted in faeces (80%) or urine (5%). Renal clearance at steady state approximately 70 ml/min.

Special populations

Renal impairment — Empagliflozin: AUC increased by approximately 18%, 20%, 66% and 48% in mild, moderate, severe impairment and ESRD, respectively. The glycaemic efficacy of empagliflozin is dependent on renal function. Linagliptin: Exposure comparable to healthy subjects in mild renal impairment; approximately 1.7-fold increase in moderate impairment. Not eliminated to a therapeutically significant degree by dialysis.

Hepatic impairment — Empagliflozin: AUC increased by approximately 23%, 47% and 75% in mild, moderate and severe hepatic impairment. Linagliptin: Mean AUC and Cmax were similar to healthy subjects across all degrees of hepatic impairment.

5.3 Preclinical safety data

General toxicity studies in rats up to 13 weeks with the combination found focal areas of hepatocellular necrosis at ≥15:30 mg/kg linagliptin:empagliflozin. The clinical relevance of this finding remains uncertain. At exposures sufficiently in excess of human therapeutic doses, the combination was not teratogenic and did not show maternal toxicity. No adverse effects on renal development were observed with either the combined or individual agents.

Empagliflozin was not carcinogenic in female rats at up to 700 mg/kg/day. Male mouse renal tumours at 1,000 mg/kg/day are considered not relevant to humans due to species-specific mechanism. Linagliptin did not show evidence of carcinogenicity in rats or male mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are present in the film-coated tablet:

No.	Ingredient
1	Lactose monohydrate (excipient with known effect)
2	Microcrystalline cellulose
3	Low-substituted hydroxypropylcellulose (LH-11)
4	Purified water
5	Croscarmellose sodium
6	Colloidal silicon dioxide
7	Magnesium stearate
8	Ready coat yellow (film coat)
9	Isopropyl 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. Keep out of the reach and sight of children.

6.5 Nature and contents of container

10 tablets packed in one ALU-ALU blister; 3 such blisters packed in one carton with package insert. Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. 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 AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)

H2025/CTD11584/25330

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

16.01.2025

10. DATE OF REVISION OF THE TEXT

16.01.2025