

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Generic Name: Empagliflozin & Linagliptin

Trade Name: Evaglip Tablet 10/5 mg

2. Qualitative and quantitative composition

Each tablet contains:

Empagliflozin10.00mg

Linagliptin 5.00mg

Excipient(s) with known effect:

Lactose monohydrate

For a full list of excipients see section 6.1.

3. Pharmaceutical form

Evaglip Tablet 10/5 mg is a yellow colored, round shaped, biconvex film coated tablet with both sides plain.

4. Clinical particulars

4.1 Therapeutic indications

As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate.

4.2 Posology and method of administration

The recommended dose of EVAGLIP® is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food. In patients tolerating EVAGLIP®, the dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.

4.3 Contraindications

EVAGLIP® is contraindicated in patients with a history of hypersensitivity reaction to linagliptin/empagliflozin, severe renal impairment, end-stage renal disease, or dialysis.

4.4 Special warnings and precautions for use

- Pancreatitis: There have been post marketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue EVAGLIP®.
- Hypotension: Before initiating EVAGLIP® assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.
- Impairment in Renal Function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR below 60 mL/min/1.73 m².
- Hypoglycemia: Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating EVAGLIP®.
- Genital Mycotic Infections: Monitor and treat as appropriate

- Urinary Tract Infections: Monitor and treat as appropriate.
- Hypersensitivity: In such cases, promptly discontinue EVAGLIP®, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.
- Increased LDL-C: Monitor and treat as appropriate.
- Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with EVAGLIP® or any other antidiabetic drug.

4.5 Interaction with other medicinal products and other forms of interaction

- Drug Interactions with Empagliflozin: Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia. Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
- Drug Interactions with Linagliptin: Suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

4.6 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. Discontinue EVAGLIP® for nursing mothers.

PEDIATRIC PATIENTS

Safety and effectiveness of EVAGLIP® in pediatric patients have not been established.

GERIATRIC PATIENTS

Higher incidence of adverse reactions related to volume depletion and reduced renal function

RENAL IMPAIRMENT

Higher incidence of adverse reactions related to reduced renal function.

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

Urinary tract infection, common cold symptoms, upper respiratory tract infections, genital yeast infection, increased

urination, joint pain, nausea, runny or stuffy nose, diarrhea etc can be seen infrequently.

4.9 Overdose

In the event of overdose, contact with physician as soon as possible.

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

Evaglip 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 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 > 10,000fold selectivity versus DPP-8 or DPP-9 activity in vitro.

5.2 Pharmacokinetic properties

The rate and extent of absorption of empagliflozin and linagliptin in Evaglip 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. Evaglip showed a similar food effect as the individual active substances. Evaglip 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 [¹⁴C]-empagliflozin solution to healthy 22 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 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%. Coadministration 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_{τ,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 (eGFR <30 to <90 mL/min/1.73 m²) and patients with kidney failure or end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure.

Linagliptin

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

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7-fold was observed compared with control. Exposure in T2DM patients with severe RI was increased by about 1.4fold 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.

Paediatric patients

Empagliflozin

A paediatric Phase 1 trial examined the pharmacokinetics and pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Linagliptin

A paediatric Phase 2 trial examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and

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

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 mineralization at approximately 4-times the clinical AUC exposure of empagliflozin

In a 2 years 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 embryo fetal 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 dose-specific. 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 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 embryofetal 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

L Microcrystalline Cellulose (Type 102)
Lactose Monohydrate (Spray Dried)
Crospovidone
Sodium Starch Glycolate (Type A)
Beta Cyclodextrin
Colloidal Anhydrous Silica
Magnesium Stearate
Instacoat Aqua-III Yellow A03R20115
Purified Water

6.2 Incompatibilities

None

6.3 Shelf-Life

2 years (24 months)

6.4 Special Precautions for storage

Store at temperature not exceeding 30°C in a dry place. Protect from light.

6.5 Nature and Content of container

10 Tablets are packaged in a Alu-Alu blister (Aluminium lid foil, 30 micron thickness and 3 layer Alu-PVC/OPA colorless film, 130 micron thickness), each inner carton contains 3 blisters, 3X10's.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder

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8. Marketing Authorization Number

H2025/CTD11065/24593

9. Date of first authorization/renewal of the authorization

8/10/2025

10. Date of revision of the text

8/10/2025