1.17 Summary of Product Characteristics (SPC)

1.17.1 Product information for Health Professionals (For All Products subject to Medical Prescription)

1. Name of the medicinal Product

XEMPALIN-10

2. Qualitative and quantitative composition

Each film coated tablet contains:

Empagliflozin	10 mg
Linagliptin	5 mg
Excipients	Q.S.
Color:	Green Lake Blend

3. Pharmaceutical form

Oral Tablet

4. Clinical particulars

4.1 Therapeutic indications

Empagliflozin and Linagliptin Tablets, fixed dose combination of empagliflozin and linagliptin, is inicated 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 Tablets 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 1 film-coated tablet of Empagliflozin 10 mg and Linagliptin 5 mg Tablets once daily.

In patients who tolerate this starting dose and require additional glycaemic control, the dose can be increased to 1 film-coated tablet of Empagliflozin 25 mg and Linagliptin 5 mg Tablets once daily.

When Empagliflozin and Linagliptin Tablets 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 Tablets should receive the same daily dose of empagliflozin and linagliptin in the fixed dose combination as in separate tablets. The metformin dose should be continued.

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. 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.

4.3 Contraindications

Hypersensitivity to the active substances, to any other Sodium-Glucose-Co-Transporter-2 (SGLT2) inhibitor, to any other Dipeptidyl-Peptidase-4 (DPP-4) inhibitor, or to any of the excipients which are used in manufacturing process.

4.4 Special warnings and precautions for use

Diabetic ketoacidosis (DKA)

Empagliflozin and Linagliptin Tablets should not be used for the treatment of diabetic ketoacidosis. Rare cases of DKA, including life-threatening cases, have been reported in clinical trials and post-marketing in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of empagliflozin.

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

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

Use with medicinal products known to cause hypoglycaemia

Empagliflozin and linagliptin as single agents showed an incidence of hypoglycaemia comparable to placebo when used alone or in combination with other antidiabetics not known to cause hypoglycaemia (e.g. metformin, thiazolidinediones). When used in combination with antidiabetics known to cause hypoglycaemia (e.g. sulphonylureas and/or insulin), the incidence of hypoglycaemia of both agents was increased.

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

Acute pancreatitis

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

of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis.

If pancreatitis is suspected, Empagliflozin and Linagliptin Tablets should be discontinued; if acute pancreatitis is confirmed, Empagliflozin and Linagliptin Tablets should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed with Empagliflozin and Linagliptin Tablets 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 Tablets 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 Tablets.

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. The effect of UGT induction on empagliflozin has not been studied. Co-administration with known inducers of UGT enzymes should be avoided because of a risk of decreased efficacy of empagliflozin.

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 area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin Cmax increased by 15 % and AUC increased by 59 % following co-administration. These changes were not considered to be clinically meaningful.

Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75 % increase in Cmax and a 35 % increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Effects of empagliflozin on other medicinal products

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. 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

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

Pregnancy: There are no data from the use of empagliflozin and linagliptin in pregnant women.

Animal studies show that empagliflozin and linagliptin cross the placenta during late gestation, but do not indicate direct or indirect harmful effects with respect to early embryonic development with either empagliflozin or linagliptin. Animal studies with empagliflozin have shown adverse effects on postnatal development. As a precautionary measure it is preferable to avoid the use of Empagliflozin and Linagliptin Tablets 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 Tablets should not be used during breast-feeding.

Fertility: No studies on the effect on human fertility have been conducted with Empagliflozin and Linagliptin Tablets 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 Tablets 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 Tablets is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin and analogues, sulphonylureas).

4.8 Undesirable effects

The common side effects are Urinary tract infection (including pyelonephritis and urosepsis) Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, Hypoglycaemia (when used with sulphonylurea or insulin), Pruritus, Rash, Bullous pemphigoid, Cough, Increased urination, Amylase increased, Lipase increased etc.

4.9 Overdose

Symptoms

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4 times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not 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.