SUMMARY PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Linempa-10/5 Tablets.

2. Qualitative and quantitative composition

Each film coated tablet contains: Empagliflozin 10.0mg and Linagliptin 5.0mg.

3. Pharmaceutical Form

Tablets.

Yellow, Arc Triangular, Biconvex, Bevel-edged, Film Coated Tablets, Plain on both sides.

4. Clinical Particulars

4.1 Therapeutic Indications

Linempa is a combination of Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor and Linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adult with type 2 diabetes mellitus and established cardiovascular disease.

Limitations of use:

- Not recommended in patients with type 1 diabetes mellitus, it may increase the risk of diabetic ketoacidosis in these patients.
- Has not been studied in patients with a history of pancreatitis.
- Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30mL/min/1.73m.

4.2 Posology and method of administration Method of administration: Oral.

Assess renal function before initiating and as clinically indicated.

The recommended dose of **LINEMPA** is 10mg Empagliflozin and 5mg Linagliptin once daily, taken in the morning, with or without food. Dose may be increased to 25mg Empagliflozin and 5mg Linagliptin once daily. When Linempa is used in combination with metformin, the metformin dose should be continued.

When **LINEMPA** is used in combination with sulphonylurea or with insulin, a lower dose of sulphonylurea or insulin may be considered to reduce the risk of Hypoglycaemia.

Patients switching from Empagliflozin (either 10mg or 25mg daily dose) and Linagliptin (5mg daily dose) to **LINEMPA** should receive the same daily dose of Empagliflozin and Linagliptin in the fixed dose combination as in separate tablets.

Missed dose

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 patients 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 Population

Patients with 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. Therefore, **LINEMPA** is not recommended for use in this population.

Renal impairment: Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of Empagliflozin. In patients with an estimated glomerular filtration rate (eGFR)≥60mL/min/1.73 m^2 or CrCI<60 mL/min, **LINEMPA** should not be initiated. In patients with eGFR <60 mL/min/1.73 m^2 or CrCI persistently below 45mL/min, treatment should be discontinued. In patients with end-stage renal disease or in patients on dialysis, **LINEMPA** should not be used as Empagliflozin is not expected to be effective in these patients.

Elderly: No dose adjustment based on age is required. However, renal function and risk of volume depletion should be taken into account in elderly patients. Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older.

Pediatrics: Safety and efficacy of **LINEMPA** in pediatric patients below 18 years of age have not been established. No data are available.

4.3 Contraindications

- Hypersensitivity to 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.
- Patients on dialysis.

4.4 Special warnings and precautions for use.

Pancreatitis: There have been reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue **LINEMPA.**

Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue **LINEMPA**, evaluate and treat promptly. Before initiating **LINEMPA**, consider risk factors for ketoacidosis. Patients on **LINEMPA** may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

Volume Depletion: Before initiating **LINEMPA**, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy.

Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia: Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating
LINEMPA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. **Genital Mycotic Infections:** Monitor and treat as appropriate.

Hypersensitivity Reactions: Serious hypersensitivity reactions (e. g. anaphylaxis, angioedema, and exfoliative skin conditions) have occurred with Empagliflozin and Linagliptin. If hypersensitivity reactions occur, discontinue **LINEMPA**, treat promptly, and monitor until signs and symptoms resolve.

Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitor. Consider as possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid: There have been reports of bullous pemphigoid requiring hospitalization. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue **LINEMPA.**

Heart failure: Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of **LINEMPA** in patients who have known risks factors for heart failure. Monitor for signs and symptoms.

4.5 Interaction with other medicinal products and other forms of interaction.

Drug Interactions

Empagliflozin may potentiate the diuretic effect of thiazide and loop diuretics when co-administered and may increase the risk of dehydration and hypotension. Before initiating **Empagliflozin,** assess volume status and renal function. In patients with volume depletion, correct this condition before initiating **Empagliflozin.** Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Insulin and Insulin secretagogues, such as sulphonylureas, case hypoglycaemia. A lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Empagliflozin in patients with type 2 diabetes mellitus.

Monitoring glycaemia control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control with 1,5AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Monitoring glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Linagliptin

Efficacy of Linagliptin may be reduced when administered in combination with a strong P-glycoprotein (P-gp) or CYP 3A4 inducer. Therefore, use of alternative treatments is strongly recommended when Linagliptin is to be administered with P-gp or CYP 3A4 inducer.

4.6 Pregnancy, Lactation and Fertility.

Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters.

Lactation: LINEMPA is not recommended when breastfeeding. Discontinue breastfeeding incases LINEMPA must be administered to nursing mothers.

Fertility: No studies on the effect on human fertility have been conducted for Empagliflozin and Linagliptin.

4.7 Effects on ability to drive and use machines

Empagliflozin and Linagliptin has a minor influence on the ability to drive and used 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.

- Pancreatitis
- Ketoacidosis
- Volume Depletion
- Urosepsis and Pyelonephritis
- Hypoglycemia with concomitant use with insulin and insulin Secretagogues
- Necrotizing Fascitis of the Perineum (Fournier's Gangrene).
- Genital Mycotic Infections
- Hypersensitivity Reactions • Severe and disabling arthralgia.
- Bolus Pemphigoid.
- Heart failure.

4.9 Overdose.

Following an overdosage with **LINEMPA,** supportive management is recommended. Removal of Empagliflozin by hemodialysis has not been studied, and removal of Linagliptin by hemodialysis or peritoneal dialysis is unlikely.

5. Pharmacological Properties.

5.1 Pharmacodynamic Properties.

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BD19.

Mechanism of action

LINEMPA® contains**:** Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and Linagliptin, a dipeptidyl peptidase-4(DPP-4) inhibitor.

Empagliflozin:

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2.By inhibiting SGLT2, Empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes 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 is continuous over the 24-hour dosing interval. Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78g/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.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. Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to,

increasing tubuloglomerular feedback and reducing intralocular pressure, lowering both pre-and afterload of the heart, and downregulating of sympathetic activity. Linagliptin:
Inhibits DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, Linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manne and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones 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.

Pharmacodynamics:

Empagliflozin:

Empagliflozin inhibits the sodium-glucose cotransporter 2(SGLT2) which is primarily located in the proximal tubule of the nephron. SGLT2 facilitates 90% of glucose resorption in the kidneys and so its inhibition allows for glucose to be excreted in the urine. This excretion allows for better glycemic control and potentially weight loss in patients with type 2 diabetes mellitus. The increase in urinary glucose excretion is associated with increased excretion urinary volume. The over excretion of glucose creates a sugar-rich urogenital infections-including urosepsis, pyelonephritis, mycotic infections, and even Fournier's gangrenein both male and female patients-monitor closely for signs and symptoms of developing infection.

Linagliptin:

Linagliptin binds to DPP-4 in a reversible manner and thus increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4 but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures.

5.2 Pharmacokinetic properties.

Administration of the fixed-dose combination with food results in no change in overall exposure of Empagliflozin or Linagliptin; however, the peak exposure is decreased 39% and 32% for Empagliflozin and Linagliptin, respectively. These changes are not likely to be clinically significant.

Absorption

Empagliflozin: Following oral administration of Empagliflozin, the peak plasma concentration is usually attained within 12/2 hours (T_{max}). Empagliflozin shows a steady state mean plasma AUC and C_{max} of 1870 nmol.h/l and 259 nmol with dose of 10mg and 4740 nmol.h/l with dose of 25 mg once daily. Systemic exposure of Empagliflozin increases in a dose-proportional manner. The single-dose and steady-state pharmacokinetic parameters of Empagliflozin are similar suggesting linear pharmacokinetics with respect to time. Administration with food does not significantly affect absorption thus Empagliz may be administered with or without food.

Linagliptin: The absolute bioavailability of Linagliptin is approximately 30%. Co-administration of a high-fat meal with linagliptin has no clinically relevant effect on the pharmacokinetics. Linagliptin may be administered with or without food.

Distribution

Empagliflozin: Empagliflozin is approximately 86.2% protein bound. Protein binding is not altered in patients with renal or hepatic impairment. The estimated apparent steady-state volume of distribution is 73.8L.

Linagliptin: As a result of tissue binding, the mean apparent volume of distribution at steady state following a single 5mg intravenous dose of Linagliptin to healthy subjects is approximately 1110 liters, indicating that Linagliptin extensively distributes to the tissues. Plasma protein binding of Linagliptin is concentration-dependent, decreasing from about 99% at 1nmol/L to 75-89% at ≥nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of Linagliptin.

Metabolism

Empagliflozin: Empagliflozin undergoes minimal metabolism. It is primarily metabolized via glucuronidation by 5'-diphosphoglucuronosyltransferases 2B&, 1A3, 1A8, and 1A (to yield three glucuronide metabolites: 2-O-, 3-O, and 6-O- glucuronide. No metabolite represents more than 10% of total drug-related material.

Linagliptin: An oral dose of Linagliptin is excreted primarily in the feces.90% of an oral is excreted unchanged in the urine and feces. The predominant metabolite in the plasma is CD1790 and the predominant metabolite recovered after excretion is M489 (1). Other metabolites are produced through oxidation, oxidative degradation, N-acetylation, glucuronidation, and cysteine adduct formation2. Other metabolites have been identified through mass spectrometry though no structures are determined. Metabolism of Linagliptin is medicated by cytochrome P450 3A4, aldo-keto reductases, and carbonyl reductases and carbonyl reductases.

Excretion

Empagliflozin: Empagliflozin and related metabolites are primarily eliminated via the urine (approximately 54%) and feces (approximately 41%). The apparent terminal elimination half-life of empagliflozin is estimated to be 12.4 hours and apparent oral clearance was 10.61/hour.

Linagliptin: About 84.7% of Linagliptin is eliminated in the feces and 5.4% is eliminated in the urine. The terminal half-life of Linagliptin is 155 hours. Renal clearance steady state is approximately 70mL/min.

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, nonadverse, 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 dog-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 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.

Mannitol, Starch 1500, White corn starch, Povidone K-30, Purified water, Crospovidone, Purified Talc, Magnesium Stearate, Hydroxypropyl Methylcellulose 5CPS, Titanium Dioxide, Polyethylene Glycol (PEG) 6000, Yellow Iron Oxide, Monopropylene Glycol, Isopropyl Alcohol & Methylene Dichloride.

6.2 Incompatibilities:

None known.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage: Store in a dry place below 30°C

Protect from light and moisture.

Keep all medicines out of reach of children.

6.5 Nature and contents of the container: Packed in blisters of 1x10's, 2x10's, 2x14's, 3x10's, 4x14's, 6x10's and 10x10's. Contained in a unit box along with literature insert.

6.6 Special precautions for disposal:

No special requirements

7. Registrant:

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8. Marketing Authorization Number
H2025/CTD11019/24077

9. Date of first marketing authorization /Renewal
20/01/2025

10. Date of revision of text
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