SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Empiget-LT Tablets 10mg + 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Empagliflozin……..…. 10mg
Linagliptin…….……. 5mg

3. PHARMACEUTICAL FORM

Mustard colored, oval shaped, biconvex film coated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Empiget-LT (Empagliflozin + Linagliptin) is indicated as an adjunct to diet and exercise in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycemic control when metformin and/or sulphonylurea (SU) and monotherapy of either of Empagliflozin and Linagliptin do not provide adequate glycemic control.
- when already being treated with the free combination of Empagliflozin and Linagliptin.

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

4.2 DOSAGE AND ADMINISTRATION

The recommended starting dose of Empiget-LT (Empagliflozin + Linagliptin) Tablets is 10mg Empagliflozin + 5mg Linagliptin once daily in the morning. It may be increased to 25mg Empagliflozin+ 5mg Linagliptin once daily for additional glycemic control. In patients already on Empagliflozin and Linagliptin, the dose of Empiget-LT (Empagliflozin + Linagliptin) Tablets should provide the dose of Empagliflozin and Linagliptin similar to the dose already been taken by the patient.
Prior to initiation of Empiget-LT (Empagliflozin + Linagliptin) Tablets:

- assess renal function as clinically indicated, and
- in patients with volume depletion, correcting this condition is recommended.

Method of administration
Empiget-LT (Empagliflozin + 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.

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.

Combination therapy
When 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 hypoglycemia
- with metformin, the metformin dose should be continued.

Special Population

Renal Impairment
Due to the mechanism of action, decreased renal function will result in reduced glycemic efficacy of Empagliflozin

- In patients with an estimated glomerular filtration rate (eGFR) ≥60mL/min/1.73m^2 or creatinine clearance (CrCl) ≥60mL/min, no dose adjustment is required.
- In patients with an eGFR <60mL/min/1.73m^2 or CrCl <60mL/min, Empiget-LT (Empagliflozin + Linagliptin) Tablets should not be initiated.
- In patients tolerating Empiget-LT (Empagliflozin + Linagliptin) Tablets whose eGFR falls persistently below 60mL/min/1.73m^2 or CrCl below 6 mL/min, the dose should be adjusted to or maintained at 10mg Empagliflozin plus 5mg Linagliptin once daily.
- When eGFR is persistently below 45mL/min/1.73m^2 or CrCl persistently below 45mL/min,
    - treatment should be discontinued.
- In patients with end-stage renal disease or in patients on dialysis, Empiget-LT (Empagliflozin + Linagliptin) Tablets should not be used as Empagliflozin is not expected to be effective in these patients.

Hepatic impairment
No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Elderly Patients
No dosage adjustment is recommended based on age. However, renal function and risk of volume depletion should be taken into account in elderly patients. Therapeutic experience in patients aged 75 years and older is limited. Initiation of therapy in this population is not recommended. Patients aged 75 years and older should be prescribed with caution.

4.3 Contraindications
The combination of Empagliflozin + Linagliptin is contraindicated in patients with 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 of the product.

4.4 Special warnings and special precautions for use

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

Use in patients at risk for volume depletion
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 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 hematocrit) and electrolytes is recommended for patients receiving Empagliflozin. Temporary interruption of treatment with Empagliflozin + Linagliptin Tablets should be considered until the fluid loss is corrected.

Cardiac Failure
Heart failure have been observed with other members of the DPP-4 inhibitor class. Consider the risks and benefits of Empagliflozin + Linagliptin Tablets prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Empagliflozin + Linagliptin Tablets.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

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

Urosepsis and Pyelonephritis
Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life threatening necrotizing infection requiring urgent surgical intervention, have been identified in post marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including Empagliflozin. Patients treated with Empagliflozin + Linagliptin Tablets presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Empagliflozin + Linagliptin Tablets closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections
Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections are more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Hypersensitivity Reactions
There have been reports of serious hypersensitivity reactions in patients treated with Empagliflozin and Linagliptin. If a hypersensitivity reaction occurs, discontinue Empagliflozin + Linagliptin Tablets treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin + Linagliptin Tablets is contraindicated in patients with a previous serious hypersensitivity reaction to Linagliptin or Empagliflozin. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Empagliflozin + Linagliptin Tablets.

Severe and Disabling Arthralgia
There have been post-marketing reports of severe and disabling arthralgia in patients taking DPP4 inhibitors. Patients experienced relief of symptoms upon discontinuation of the medication. Consider as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid
Post marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Empagliflozin + Linagliptin Tablets. If bullous pemphigoid is suspected, should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Surgery
Treatment with Empagliflozin + Linagliptin Tablets should be ceased prior to major surgery. Treatment with Empagliflozin + Linagliptin Tablets may be restarted once the patient's condition has stabilized and oral intake is normal.

Insulin or Insulin Secretagogues
Empagliflozin + Linagliptin combination with an insulin secretagogue (e.g., sulphonylurea) or insulin is associated with a higher rate of hypoglycemia. Coadministration of Empagliflozin + Linagliptin Tablets

with an insulin secretagogue (e.g., sulphonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia

Positive Urine Glucose Test
SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control

Elevated hematocrit
Hematocrit increase was observed with Empagliflozin treatment.

Interference with 1,5-anhydroglucitol (1,5-AG) assay
Monitoring glycemic control with 1,5-AG 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.

Effects on ability to drive and use machines
Empagliflozin + Linagliptin tablets has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when this product is used in combination with other antidiabetic medicinal products known to cause hypoglycemia (e.g. insulin and analogues, sulphonylureas).

4.5 DRUG INTERACTION

Diuretics
Coadministration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. Before initiating Empagliflozin + Linagliptin Tablets, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating therapy. Monitor for signs and symptoms of volume depletion and renal function after initiating therapy.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay
Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

Inducers of P-glycoprotein or CYP3A4 Enzymes
Rifampin decreased Linagliptin exposure, suggesting that the efficacy of Linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. 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

Pregnancy
There is a limited amount of data from the use of Empagliflozin and Linagliptin in pregnant women. It is recommended to avoid the use during pregnancy unless clearly needed.

Nursing Mothers
Because of the potential for serious adverse reactions in a breastfed infant, including the potential for Empagliflozin to affect postnatal renal development, advice patients that use of Empagliflozin + Linagliptin Tablets is not recommended while breastfeeding.

4.7 Undesirable effects

The safety profile of Empagliflozin + Linagliptin is in line with the safety profile of individual active substances. The most commonly reported adverse reactions during treatment with combination of Empagliflozin and Linagliptin are:

Common: Urinary tract infection (including pyelonephritis and urosepsis), vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, nasopharyngitis, hypoglycaemia (when used with sulphonylurea or insulin), thirst, cough, pruritus, rash, increased urination, amylase increased and lipase increased.

Uncommon: Hypersensitivity, angioedema, urticarial, pancreatitis, volume depletion, dysuria, hematocrit increased, serum lipids increased and blood creatinine increased/glomerular filtration rate decreased.

Not known: Necrotising fasciitis of the perineum (Fournier´s gangrene) and bullous pemphigoid.

Rare: Diabetic ketoacidosis and mouth ulceration.

4.8 Overdosage

In controlled clinical studies single doses of up to 800mg Empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100mg Empagliflozin (equivalent to 4 times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. During controlled clinical trials in healthy subjects, single doses of up to 600mg Linagliptin (equivalent to 120 times the recommended dose) were generally well tolerated.

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 hemodialysis has not been studied. Linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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.

Linagliptin

Linagliptin is an inhibitor of 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 manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. 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.

5.2 Pharmacokinetic properties

Absorption

Empagliflozin

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 10mg and 4,740 nmol.h and 687 nmol/L with Empagliflozin 25mg once daily. Systemic exposure of Empagliflozin increased in a dose proportional manner in the therapeutic dose range. Administration of Empagliflozin 25mg 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.

Linagliptin

After oral administration of a 5mg dose, Linagliptin was rapidly absorbed, with peak plasma concentrations (median t_{max}) occurring 1.5 hours post-dose. The absolute bioavailability of Linagliptin is approximately 30 %. Co-administration 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 AUC0-72h was observed.

Distribution

Empagliflozin

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-Empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Linagliptin

The mean apparent volume of distribution at steady state following a single intravenous dose of Linagliptin 5mg to healthy subjects is approximately 1110 L, 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% to 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% to 80% of Linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metabolism

Empagliflozin

No major metabolites of Empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. The primary route of metabolism of Empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Linagliptin

Following oral administration, the majority (about 90%) of Linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed Linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to Linagliptin.

Elimination

Empagliflozin

The apparent terminal elimination half-life of Empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady state, which was consistent with Empagliflozin half-life. Following administration of an oral [^{14}C]-Empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin

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 5mg Linagliptin, is approximately 12 hours. Following administration of an oral [^{14}C]-Linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Special Populations

Renal Impairment

Empagliflozin

In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, 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.

Linagliptin

Under steady-state conditions, Linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In patients with moderate renal impairment under steady-state conditions, mean exposure of Linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. Patients with type 2 diabetes and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%).

Hepatic Impairment

Empagliflozin

In patients with mild, moderate, and severe hepatic impairment according to the AUC of Empagliflozin increased by approximately 23%, 47%, and 75% and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin

In patients with mild hepatic impairment steady-state exposure ($AUC_{\tau,ss}$) of Linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUCss of Linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child- Pugh class C) had comparable exposure of Linagliptin in terms of AUC0-24 and approximately 23% lower C_{max} compared with healthy subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mannitol, Copovidone K-28, Pregelatinized Starch, Corn starch, Crospovidone, Magnesium Stearate, Opadry Yellow 03F520147, Purified Talc, Purified water.

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Do not store above 30°C
Protect from sunlight and moisture.

6.5 Nature and contents of container

Empiget-LT (Empagliflozin + Linagliptin) Tablets 10mg + 5mg are available in Alu-Alu blister packs of 3 x 10's (30's) tablets in a unit carton along with a package insert.

6.6 Instructions for use/handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. MARKETING AUTHORISATION HOLDER

Getz Pharma (Private) Limited
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8. PRODUCT REGISTRATION NUMBER

112552

9. DATE OF PRODUCT REGISTRATION ISSUED

30th April 2022