SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Empiget (Empagliflozin) Tablets 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Empagliflozin……. 25 mg

Each tablet contains Lactose monohydrate equivalent to 102.06 mg Lactose anhydrous

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

EMPIGET (Empagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus as:

Monotherapy
When diet and exercise alone do not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy
In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycemic control.

4.2 Posology and Method of Administration

Monotherapy and add-on combination
The recommended starting dose is 10 mg Empagliflozin once daily with or without food for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. In patients tolerating empagliflozin 10mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and need tighter glycemic control, the dose can be increased to 25mg once daily. The maximum daily dose is 25mg. When empagliflozin 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 hypoglycemia.

Special populations
Renal impairment
No dose adjustment is required for patients with an eGFR ≥60 ml/min/1.73 m^2 or CrCl ≥60 ml/min. Empagliflozin should not be initiated in patients with an eGFR <60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60ml/min/1.73 m^2 or CrCl below 60ml/min, the dose of empagliflozin should be adjusted to or maintained at 10mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45ml/min/1.73m^2 or CrCl persistently below 45ml/min. Empagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in these patients.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population.

Elderly

No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

Pediatric population

The safety and efficacy of empagliflozin in children and adolescents has not yet been established.

4.3 Contraindications

Empagliflozin is contraindicated in:

- Patients with known hypersensitivity to empagliflozin or to any excipient of the product.
- Severe renal impairment, end-stage renal disease, or dialysis.

4.4 Special warnings and special precautions for use

This tablets contain lactose. Patient with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product

- Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.

- Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment.

- Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulphonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.

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

- Empagliflozin increases the risk for urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Monitor and treat as appropriate. Discontinuation of empagliflozin may be considered in cases of recurrent urinary tract infections.

- Empagliflozin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (DKA). 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. In both cases, treatment with empagliflozin may be restarted once the patient's condition has stabilized.

- Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, 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 with a history of hypotension or patients aged 75 years and older.

- Empagliflozin 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 empagliflozin is used in combination with a sulphonylurea and/or insulin.

4.5 Interaction with other medicaments

- Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

- Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Empagliflozin.

- 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. Use alternative methods to monitor glycemic control.

- 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.

4.6 Pregnancy and Lactation

Pregnancy
There are no adequate and well-controlled studies of empagliflozin in pregnant women. Empagliflozin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known if empagliflozin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from empagliflozin, a decision should be made whether to discontinue nursing or to discontinue empagliflozin, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machine

Empagliflozin 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 is used in combination with a sulphonylurea and/or insulin.

4.8 Undesirable effects

Very Common
Hypoglycemia (when used with sulphonylurea or insulin).

Common
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection, pruritus (generalised) and increased urination.

Uncommon
Volume depletion, dysuria and blood creatinine increased / glomerular filtration rate decreased.

Rare
Diabetic ketoacidosis.

4.9 Overdosage

Symptoms
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. Empagliflozin increased urine glucose excretion leading to an increase in urine volume.

Treatment
In the event of an overdose with empagliflozin, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action
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.

5.2 Pharmacokinetic properties

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 AUC and C_{max} were 1870nmol.h and 259nmol/L with empagliflozin 10mg and 4740nmol.h and 687nmol/L with empagliflozin 25mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. 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.

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 [^{14}C]-empagliflozin solution, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Metabolism
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. The primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6L/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 [^{14}C]-empagliflozin solution, approximately 96% of the drug-related radioactivity was eliminated in feces (41%) or urine (54%). 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.

Special Population
Renal impairment
In patients with mild, moderate or severe renal impairment (eGFR <30 - <90 ml/min/1.73 m^2) and patients with kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively. 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.

Hepatic Impairment
In mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively.

Race
In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25 kg/m^2 compared to non-Asians with a body mass index of 25 kg/m^2.

Geriatric patients
Empagliflozin is expected to have diminished efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10mg, and empagliflozin 25mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Pharmatose DCL-11 (Anhydrous Lactose), Lactose Monohydrate, Avicel PH-102 (Microcrystalline Cellulose), Klucel EXF Pharm (Hydroxypropylcellulose), Croscarmellose Sodium, Aerosil 200 (Colloidal Anhydrous Silica), Magnesium Stearate, Pharmacoat 606 (Hypromellose 6CPS), P.E.G 6000 (Macrogols), Titanium dioxide, Ferric oxide Yellow, Purified Talc and 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 (Empagliflozin) Tablets 25 mg are available in Alu/PVC blister pack of 4 x 7's (28'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.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

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8. PRODUCT REGISTRATION NUMBER

TAN 22 HM 0040

9. DATE OF PRODUCT REGISTRATION ISSUED

10/01/2022

10. DATE OF REVISION OF THE TEXT