SUMMARY PRODUCT CHARACTERISTICS

1. Name of the medicinal product Empagliz-25.

2. Qualitative and quantitative composition

Each film coated tablet contains: Empagliflozin 25mg.

3. Pharmaceutical form

Tablets.

Pale Yellow, Oval, Biconvex Film Coated Tablets, Plain on both sides.

4. Clinical Particulars

4.1 Therapeutic Indications

Empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) Inhibitor Indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.
- To reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction. Limitations of use:
- **Empagliz®** is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- **Empagliz®** is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30mL/min/1.73m2.Empagliz is likely to be ineffective in this setting based upon its mechanism of action.

4.2 Posology and method of administration

Assess renal function before initiating Empagliz® and as clinically indicated. In patients with volume depletion, correct this condition before initiating treatment with Empagliz.

The recommended dose of Empagliz® is 10mg once daily in the morning, take with or without food. For additional glycemic control, the dose may be increased to 25mg in patients tolerating **Empagliz®**

4.3 Contraindications

Empagliz is contraindicated in patients with:

- History of serious hypersensitivity reaction to Empagliflozin
- Severe renal impairment (eGFR less than 30mL/min/1.73m2) in patients who are being treated for glycemic control without established cardiovascular disease or cardiovascular risk factors.
- Patients on dialysis.

4.4 Special warnings and precautions for use.

Warning and Precautions:

Volume depletion: *Before initiating* **Empagliz®,** assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.

Ketoacidosis in Patients with Diabetes Mellitus: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue **Empagliz®,** evaluate and treat promptly. Before initiating **Empagliz®,** consider

risk factors for ketoacidosis. Patients on Empagliz may require monitoring and temporary discontinuation of therapy in clinical situation known to predispose to ketoacidosis.
Urosepsis and Pyelonephritis: Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.
Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with **Empagliz®.**
Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life threatening cases have occurred in patients with diabetes, both female and males. Assess patients presenting with pain or tenderness, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.
Genital Mycotic Infections: Empagliz® may increase the risk of genital mycotic infections. Patients with a history of genital mycotic infections are more likely to develop genital mycotic infections. Monitor and treat if indicated. **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g. to reduce the risk of cardiovascular death plus hospitalization for heart angioedema) have occurred with **Empagliz®.**If hypersensitivity failure in adults with heart failure and reduced ejection fraction.(1) reactions occur, discontinue Empagliz, treat promptly, and monitor until signs and symptoms resolve. **Use in specific Populations**
Pregnancy: Advise females of potential risk to fetus especially during the second and third trimester.
Lactation: Empagliz® is not recommended in nursing mothers.
Pediatric Use: Safety and effectiveness of Empagliflozin in pediatric patients have not been established.
Geriatrics: Higher incidence of adverse reactions related to hypotension. No Empagliflozin dosage change is recommended based on age.
Renal Impairment: Higher incidence of adverse reactions related to hypotension and renal function. The impact of hemodialysis on Empagliflozin exposure is not known.
Hepatic Impairment: No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit risk for the use of Empagliflozin in patients with severe hepatic impairment should be individually assessed.

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

Drug Interactions

Empagliz® may potentiate the diuretic effect of thiazide and loop diuretics when co-administered and may increase the risk of dehydration and hypotension. Before initiating **Empagliz®,** assess volume status and renal function. In patients with volume depletion, correct this condition before initiating **Empagliz.** 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 as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor 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.

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4.6 Pregnancy and lactation.

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

Lactation: Empagliflozin is not recommended in nursing mothers.

Fertility: No studies on the effect on human fertility have been conducted for Empagliflozin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects.

Adverse Drug Reactions:

Volume Depletion

- Ketoacidosis in Patients with Diabetes Mellitus.
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant use with Insulin and Insulin Secretagogues.
- Necrotizing fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections, nasopharyngitis, and, and urinary tract infections especially in female.
- Hypersensitivity reactions.

4.9 Overdose.

Overdosage

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied

5. Pharmacological Properties.

5.1 Pharmacodynamic Properties.

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

A10BK03.

Mechanism of action

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of sodium-glucose cotransporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5000 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 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 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. In addition, urinary glucose excretion triggers calories 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 intraglomerular pressure, lowering both pre- and afterload of the heart, and downregulating of sympathetic activity.

Pharmacodynamic effects.

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 environment which increases the risk of urogenital infections-including urosepsis,pyelonephritis,mycotic infections and even Fournier's gangrene-in both male and female patients-monitor closely for signs and symptoms of developing infection.

5.2 Pharmacokinetic properties.

Absorption

Following oral administration of empagliflozin, the peak plasma concentration is usually attained within $1^{1}/_{2}$ hours(T_{max})Empagliflozin shows a steady state mean plasma AUC and Cmax of 1870 nmol.h/1 and 259nmol/1 with dose of 10mg and 4740 nmol.h/1 and 687nmol/1 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 pharmacokinetic with respect to time. Administration with food does not significantly affect absorption thus Empagliz may be administered with or without food.

Distribution

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.

Metabolism
Empagliflozin undergoes minimal metabolism. It is primarily metabolized via glucuronidation by 5'diphosphoglucuronosyltransferases 2B7, 1A3, 1A8 and 1A9 (to yield three glucuronide metabolites:2-O-,3-O-, and 6-Oglucuronide. No metabolite represents more than 10% of total-related material.
Excretion
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 clearenace was 10.61/hour.

5.3 Preclinical safety data
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 mineralization 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 associated with the 25 mg dose.

Empagliflozin is not genotoxic.
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 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1000 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 in rats, reduced weight gain of 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.

6. Pharmaceutical particulars.

1 List of excipients.

Microcrystalline Cellulose pH 101, Lactose Monohydrate, Croscarmellose sodium, Hydroxypropyl methylcellulose 5CPS, Colloidal silicon Dioxide, Magnesium Stearate, Titanium Dioxide, Purified Talc, Polyethylene Glycol 6000, iron Oxide Yellow, Isopropyl Alcohol 99% & Methylene Chloride.

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, 2x14's, 4x14's, 2x10's, 3x10's, 6x10's and 10x10's and contained in a unit box along with literature insert.

6.6 Special precautions for disposal:

Any unused product or waste material should be disposed off in accordance with local requirements.

6.7 Distribution Category: Prescription Only Medicine **(POM).**

7. Registrant:

Company name: LABORATORY & ALLIED LTD.

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8. Marketing Authorization Number
H2025/CTD11047/23314

9. Date of Market authorization or Renewal
20/01/2025

10. Date of revision of text
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