Summary of Product Characteristics

1. Name of the medicinal product

Dapagliz -10

2. Qualitative and quantitative composition

Each film-coated tablet contains Dapagliflozin Propanediol monohydrate equivalent to Dapagliflozin 10 mg.

Excipients with known effect
Each tablet contains Lactose monohydrate.
For the list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet (tablet).

Yellow, diamond-shaped biconvex film-coated tablets, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated in adults for:

Type 2 Diabetes Mellitus

- As an adjunct to diet and exercise to improve glycemic control.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors.

Heart Failure

- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV).

Limitations of use

- Dapagliflozin is not recommended for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

4.2 Dosage and administration

Type 2 Diabetes Mellitus

To improve glycemic control, the recommended starting dose of Dapagliflozin is 5 mg orally once daily, taken in the morning, with or without food. In patients tolerating Dapagliflozin 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.

To reduce the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus and established CVD or multiple CV risk factors, the recommended dose of Dapagliflozin is 10 mg orally once daily.

Heart Failure

The recommended dose of Dapagliflozin is 10 mg orally once daily.

4.3 Contraindications

Dapagliz is contraindicated in patients with:

- History of serious hypersensitivity reaction to Dapagliflozin.
- Severe renal impairment (eGFR less than 30 ml/min/1.73 m^2) in patients who are being treated for glycemic control without established cardiovascular disease or cardiovascular risk factors.
- Patients on dialysis.

4.4 Warnings and precautions

Volume depletion

Before initiating Dapagliz, 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 Dapagliz, evaluate and treat promptly. Before initiating Dapagliz, consider risk factors for ketoacidosis. Patients on Dapagliz may require monitoring and temporary discontinuation of therapy in clinical situations 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 Dapagliz.

Necrotizing fasciitis of the perineum (Fournier's gangrene)

Serious, life-threatening cases have occurred in patients with diabetes, 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

Dapagliz 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.

Use in specific populations

- Pregnancy: Advise females of potential risk to a fetus especially during the second and third trimesters.
- Lactation: Dapagliz is not recommended in nursing mothers.
- Pediatric use: Safety and effectiveness of Dapagliflozin in pediatric patients under 18 years of age have not been established.
- Geriatrics: Higher incidence of adverse reactions related to hypotension. No Dapagliflozin 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 Dapagliflozin 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 Dapagliflozin in patients with severe hepatic impairment should be individually assessed.

4.5 Drug interactions

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

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

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 Fertility, pregnancy and lactation

Pregnancy

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

Lactation

Dapagliz is not recommended in nursing mothers.

Fertility

The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

Geriatrics

Higher incidence of adverse reactions related to hypotension. No Dapagliflozin 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 Dapagliflozin 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 Dapagliflozin in patients with severe hepatic impairment should be individually assessed.

4.7 Effects on ability to drive and use machines

Dapagliz has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when Dapagliflozin is used in combination with sulphonylureas or insulin.

4.8 Adverse drug reactions

The following important adverse reactions are described below and elsewhere in the labeling:

- 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 urinary tract infections especially in female.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)
https://pv.pharmacyboardkenya.org

4.9 Overdose

Dapagliflozin has not shown any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of Dapagliflozin 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: A10BK01.

Mechanism of action

Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2. Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, Dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin 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, lowering both pre- and afterload of the heart and down regulation of sympathetic activity.

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose and/or low GFR, Dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtered glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action.

The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects

Dapagliflozin 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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of Dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in Dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of Dapagliflozin following the administration of a 10 mg dose is 78%. Administration of Dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and Dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment. The estimated apparent steady-state volume of distribution is 118 L.

Metabolism

The metabolism of Dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg

[14C]-Dapagliflozin dose and is the predominant drug-related component in human plasma.

Excretion

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for Dapagliflozin is approximately 12.9 hours following a single oral dose of Dapagliz 10 mg.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

6. Pharmaceutical particulars

6.1 List of excipients

- Microcrystalline cellulose pH 102
- Lactose monohydrate
- Silicon dioxide
- Magnesium stearate
- Pregelatinized starch
- Crospovidone
- Hydroxypropyl methylcellulose
- Talc purified
- Titanium dioxide
- PEG 6000
- Iron Oxide Yellow
- Isopropyl Alcohol
- Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Dapagliz Tablets are available in Alu-Alu blister packs of 1x7's, 1x10's, 1x14's, 2x10's, 2x14's, 3x10's, 4x14's, 6x10's, 8x14's or 10x10's and contained in a unit box along with literature insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder and manufacturing site addresses

Marketing authorisation holder

Company Name: Laboratory & Allied Ltd
Address: Plot No. 209/10349, Opposite Sameer Business Park, Next to Libra House, Mombasa Road, P.O. Box 42875 GPO 00100, Nairobi, Kenya
Telephone: +254 20 8040306
Telefax: +254 20 8040309
E-mail: info@laballied.com

Manufacturing site address

Company Name: LABORATORY & ALLIED LTD
Address: Plot No. 209/10349, Opposite Sameer Business Park, Next to Libra House, Mombasa Road, P.O. Box 42875 GPO 00100, Nairobi, Kenya
Telephone: +254 20 8040306
Telefax: +254 20 8040309
E-mail: info@laballied.com

8. Marketing Authorization Number

H2025/CTD11050/23067

9. Date of first authorization/renewal of the authorization

31/07/2023

10. Date of revision of the text

October 2022