Summary of Product Characteristics

1. Name of the medicinal product

DAPZIN 10 mg film-coated tablets.

2. Qualitative and quantitative composition

Each film-coated tablet contains Dapagliflozin 10 mg.

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

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Dapagliflozin is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic 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 glycaemic control.

4.2 Posology and method of administration

Posology

The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Special populations

Renal impairment: The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2). No dosage adjustment is indicated in patients with mild renal impairment.

Hepatic impairment: No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

Elderly (≥ 65 years): In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.

Paediatric population: The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Method of administration

Dapagliflozin can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Renal impairment

The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo. Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment. Dapagliflozin has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m^2) or end-stage renal disease (ESRD).

Monitoring of renal function is recommended as follows:

- Prior to initiation of dapagliflozin and at least yearly thereafter;
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter;
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2, dapagliflozin treatment should be discontinued.

Hepatic impairment

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances

Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose concentrations. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness such as gastrointestinal illness. Caution should be exercised in patients for whom a dapagliflozin-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 elderly patients.

For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status and electrolytes is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl).

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment with dapagliflozin 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 dapagliflozin may be restarted once the patient's condition has stabilised.

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve, patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced, and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients. 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.

The safety and efficacy of dapagliflozin in patients with type 1 diabetes have not been established and dapagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Urinary tract infections

Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo in a pooled analysis up to 24 weeks. Pyelonephritis was uncommon and occurred at a similar frequency to control. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis.

Elderly

Elderly patients are more likely to have impaired renal function and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function. The same recommendations for renal function apply to elderly patients as to all patients. Elderly patients may be at greater risk for volume depletion and are more likely to be treated with diuretics. Therapeutic experience in patients 75 years and older is limited; initiation of dapagliflozin therapy in this population is not recommended.

Cardiac failure

Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

Use in patients treated with pioglitazone

While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.

Elevated haematocrit

Haematocrit increase was observed with dapagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted.

Lower limb amputations

An increase in cases of lower limb amputation, primarily of the toe, has been observed in ongoing long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients, it is important to counsel patients on routine preventative foot care.

Urine laboratory assessments

Due to its mechanism of action, patients taking dapagliflozin will test positive for glucose in their urine.

Lactose

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogue: Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin.

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9). In vitro studies show dapagliflozin neither inhibited CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. Following co-administration with rifampicin, a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers is not expected.

Following co-administration of dapagliflozin with mefenamic acid, a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

In interaction studies conducted in healthy subjects, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin or warfarin, or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose

of dapagliflozin 20 mg and simvastatin resulted in a 19% increase in AUC of simvastatin and a 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Paediatric population: Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Lactation

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically mediated effects in nursing offspring. A risk to newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

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.

4.7 Effects on ability to drive and use machines

Dapagliflozin 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 a sulphonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile

In a pre-specified pooled analysis of 13 placebo-controlled studies, 2,360 subjects were treated with dapagliflozin 10 mg and 2,295 were treated with placebo. The most frequently reported adverse reaction was hypoglycaemia, which depended on the type of background therapy used in each study. The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add-on sulphonylurea and add-on insulin therapies. Combination therapies with sulphonylurea and add-on insulin had higher rates of hypoglycaemia.

Tabulated list of adverse reactions

The following adverse reactions have been identified in placebo-controlled clinical trials and post-marketing experience. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

System organ class	Very common	Common*	Uncommon**	Rare

Infections and infestations		Vulvovaginitis, balanitis and related genital infections*,b,c Urinary tract infection*,b,d	Fungal infection**	
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)b		Volume depletionb,e Thirst**	Diabetic ketoacidosisi
Nervous system disorders		Dizziness		
Gastrointestinal disorders			Constipation** Dry mouth**	
Skin and subcutaneous tissue disorders		Rashj		
Musculoskeletal and connective tissue disorders		Back pain*		
Renal and urinary disorders		Dysuria Polyuria*,f	Nocturia** Renal impairment**,b	
Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**	
Investigations		Haematocrit increasedg Creatinine renal clearance decreasedb Dyslipidaemiah	Blood creatinine increased**,b Blood urea increased** Weight decreased**	

a The table shows up to 24-week (short-term) data regardless of glycaemic rescue. b See corresponding subsection below for additional information. c Vulvovaginitis, balanitis and related genital infections includes vulvovaginal mycotic infection, vaginal infection, balanitis, genital fungal infection, vulvovaginal candidiasis and related terms. d Urinary tract infection includes urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis and related terms. e Volume depletion includes dehydration, hypovolaemia and hypotension. f Polyuria includes pollakiuria, polyuria and urine output increased. g Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus -0.33% for placebo. h Mean percentage changes from baseline for lipids were reported for total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. i See section 4.4. j Rash was identified through post-marketing surveillance.

* Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo. ** Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Hypoglycaemia: The frequency of hypoglycaemia depended on the type of background therapy used in each study. For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin, the frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo. Studies with

add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia.

Volume depletion: Reactions related to volume depletion, including dehydration, hypovolaemia or hypotension, were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively. Serious reactions occurred in < 0.2% of subjects and were balanced between dapagliflozin 10 mg and placebo.

Vulvovaginitis, balanitis and related genital infections: These infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, responded to standard treatment and rarely resulted in discontinuation from dapagliflozin treatment.

Urinary tract infections: Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo. Most infections were mild to moderate, responded to standard treatment and rarely resulted in discontinuation from dapagliflozin treatment.

Increased creatinine: Adverse reactions related to increased creatinine were grouped, including decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate. This grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

Parathyroid hormone (PTH): Small increases in serum PTH levels were observed, with larger increases in subjects with higher baseline PTH concentrations. Bone mineral density measurements in patients with normal or mildly impaired renal function did not indicate bone loss over a treatment period of two years.

Malignancies: During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin and placebo/comparator. No overall increased tumour risk associated with dapagliflozin was observed; however, numerical imbalances of breast, bladder and prostate tumours were to be further investigated in post-authorisation studies.

Special populations

Elderly (≥ 65 years): In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 7.7% of subjects treated with dapagliflozin and 3.8% of subjects treated with placebo. The majority of reactions were transient and reversible. Adverse reactions of volume depletion, most commonly reported as hypotension, were reported in 1.7% and 0.8% of dapagliflozin-treated and placebo-treated subjects, respectively.

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 did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time, with no reports of dehydration, hypotension or electrolyte imbalance and no clinically meaningful effect on QTc interval. In clinical studies where once-daily doses of up to 100 mg were administered for 2 weeks, rates of adverse events including dehydration or

hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters.

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: other antiepileptic's; ATC code: A10BK01.

Mechanism of action

Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. SGLT2 is selectively expressed in the kidney and is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption, leading to urinary glucose excretion. This glucose excretion 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. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia and acts independently of insulin secretion and insulin action. Urinary glucose excretion induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis. 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.

5.2 Pharmacokinetic properties

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin Cmax and AUC values following once-daily 10 mg doses were 158 ng/ml and 628 ng h/ml, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration with a high-fat meal decreased dapagliflozin Cmax by up to 50% and prolonged Tmax by approximately 1 hour but did not alter AUC; these changes are not considered clinically meaningful. Dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states such as renal or hepatic impairment. The mean steady-state volume of distribution of dapagliflozin was 118 litres.

Biotransformation

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. Formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver

and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Elimination

The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 ml/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

Linearity

Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg, and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, lactose anhydrous, crospovidone, polysorbate 80, colloidal silicon dioxide, magnesium stearate, talc, polyethylene glycol 6000 PF, and Opadry Yellow (polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, yellow iron oxide).

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Keep the medicine away from the reach of children.

6.5 Nature and contents of container

Packing: 10 tablets are packed in Alu/Alu blister.

7. Marketing authorisation holder

Micro Labs Limited
No. 27, Race Course Road
Bangalore-560010
India.

8. Marketing authorisation number(s)

H2022/CTD8597/16373

9. Date of first authorisation

21/08/2026

10. Date of revision of the text

March 2018