SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dapaflo-5mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Dapagliflozin propanediol monohydrate

Eq to Dapagliflozin .....5 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet. Yellow coloured, circular, film coated, biconvex tablets plain on both sides, Alu-Alu blister packed and in a unit box.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus

Indicated in adults for treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: as monotherapy when metformin is inappropriate due to intolerance, or in addition to other medicinal products for treatment of type 2 diabetes.

Type 1 diabetes mellitus

Indicated in adults for treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥27 kg/m2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

Heart failure

Indicated in adults for treatment of symptomatic chronic heart failure with reduced ejection fraction.

4.2 Posology and method of administration

Type 2 diabetes mellitus

Recommended dose is 10 mg once daily. When used with insulin or an insulin secretagogue, a lower dose may be considered to reduce hypoglycaemia risk.

Type 1 diabetes mellitus

Treatment initiated/supervised by specialists. Recommended dose is 5 mg once daily, only as adjunct to insulin. Before initiation, DKA risk factors should be assessed, ketone levels confirmed normal, and patients educated on ketone monitoring. A 20% reduction in first mealtime bolus insulin may be considered to avoid hypoglycaemia; no reduction in basal insulin recommended initially. Ketones should be monitored regularly, especially during initial 1-2 weeks, with recommended actions per elevated ketone levels (Table 1: Ketonaemia 0.6-1.5 mmol/L, Impending DKA >1.5-3.0 mmol/L, Probable DKA >3.0 mmol/L, each with corresponding actions including seeking medical advice and stopping Dapagliflozin).

Heart failure

Recommended dose is 10 mg once daily, in conjunction with other heart failure therapies (per the DAPA-HF study).

Special populations

Renal impairment (diabetes treatment): should not be initiated to improve glycaemic control at GFR <60 mL/min, discontinue at GFR persistently below 45 mL/min; no dose adjustment based on renal function otherwise. Renal impairment (heart failure treatment): no dose adjustment; limited experience at GFR <30 mL/min. Hepatic impairment: no adjustment for mild/moderate; starting dose 5 mg for severe impairment, may increase to 10 mg if tolerated. Type 1 diabetes: 10 mg not recommended for heart failure treatment in T1DM patients. Elderly (≥65): no dose adjustment based on age. Paediatric population: safety/efficacy in 0 to <18 years not established.

Method of administration

Taken orally once daily at any time, with or without food; tablets 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

For diabetes treatment: efficacy reduced in moderate renal impairment, likely absent in severe; should not be initiated below GFR 60 mL/min, discontinue below 45 mL/min persistently. Not studied in severe impairment (GFR<30) or ESRD. Monitoring recommended prior to initiation and at least yearly, and prior to concomitant medicines that may reduce renal function. For heart failure: limited experience at GFR<30 mL/min; consider additional glucose-lowering treatment if GFR falls persistently below 45 mL/min in patients with both conditions.

Hepatic impairment

Limited experience in patients with hepatic impairment; exposure increased in severe impairment.

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

Diuresis may lead to modest decrease in blood pressure, more pronounced with very high blood glucose. Caution in patients on anti-hypertensive therapy with history of hypotension, or elderly. Monitor volume status during intercurrent conditions leading to volume depletion; temporary interruption recommended.

Diabetic ketoacidosis

SGLT2 inhibitors should be used with caution in patients at higher risk of DKA (low beta-cell reserve, restricted food intake/severe dehydration, reduced/increased insulin requirements, alcohol abuse). Assess ketoacidosis risk factors in event of non-specific symptoms. Discontinue immediately if DKA suspected/diagnosed. Restarting after prior DKA not recommended unless clear precipitating factor resolved.

In type 2 diabetes, rare life-threatening/fatal DKA cases reported, sometimes with only moderately increased glucose (below 14 mmol/L). In type 1 diabetes, higher DKA rates observed versus placebo; Dapagliflozin 10 mg not recommended for heart failure treatment in T1DM. Extensive guidance provided for identifying higher-risk T1DM patients, ketone monitoring, and patient education (see section 4.2 Table 1).

Necrotising fasciitis of the perineum (Fournier's gangrene) / Urinary tract infections / Elderly / Cardiac failure / Lower limb amputations / Urine laboratory assessments / Lactose

Rare but serious Fournier's gangrene reported with SGLT2 inhibitors; discontinue and treat promptly if suspected. UTI risk increased; temporary interruption for pyelonephritis/urosepsis. Elderly (≥65) at greater risk of volume depletion/impaired renal function. Experience in NYHA class IV limited. Increase in lower limb amputation cases observed with SGLT2 inhibitors; counsel on foot care. Patients will test positive for urine glucose. Contains lactose - unsuitable for rare hereditary galactose intolerance/lactase deficiency/glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics: may add to diuretic effect, increasing dehydration/hypotension risk. Insulin/insulin secretagogues: risk of hypoglycaemia; dose reduction may be needed, especially in T1DM patients at risk of frequent/severe hypoglycaemia (done cautiously to avoid ketosis/DKA).

Pharmacokinetic interactions

Metabolised primarily via UGT1A9 glucuronide conjugation; does not inhibit or induce CYP450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4. Pharmacokinetics not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. Rifampicin decreased exposure by 22% (no dose adjustment needed; no clinically meaningful effect on glucose excretion). Mefenamic acid (UGT1A9 inhibitor) increased exposure by 55% (no dose adjustment needed). Dapagliflozin did not alter pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin, or warfarin; simvastatin/simvastatin acid AUC increased 19%/31% (not clinically relevant).

4.6 Fertility, pregnancy and lactation

Pregnancy

No data from use in pregnant women. Studies in rats show toxicity to developing kidney; use not recommended during second and third trimesters. Discontinue when pregnancy is detected.

Breast-feeding

Unknown if excreted in human milk; animal data show excretion and pharmacologically-mediated effects in nursing offspring. Should not be used while breast-feeding.

Fertility

Effect on human fertility not studied. No effects on fertility observed in male/female rats at any dose tested.

4.7 Effects on ability to drive and use machines

Dapagliflozin has no or negligible influence on ability to drive and use machines. Patients should be alerted to risk of hypoglycaemia when used with a sulphonylurea or insulin.

4.8 Undesirable effects

More than 15,000 patients with type 2 diabetes have been treated with Dapagliflozin in clinical studies; the most frequently reported adverse reactions across studies were genital infections. In two placebo-controlled studies in type 1 diabetes mellitus, the safety profile was similar to type 2 diabetes, but DKA was reported with common frequency. The DAPA-HF study (heart failure) safety profile was consistent with the known safety profile.

Common: Vulvovaginitis, balanitis and related genital infections; urinary tract infection; back pain; dysuria; polyuria; haematocrit increased; creatinine renal clearance decreased during initial treatment; dyslipidaemia; diabetic ketoacidosis (when used in type 1 diabetes mellitus). Very common: Hypoglycaemia (when used with SU or insulin). Uncommon: Fungal infection, volume depletion, thirst, constipation, dry mouth, nocturia, vulvovaginal/genital pruritus, blood creatinine increased during initial treatment, blood urea increased, weight decreased. Rare: Diabetic ketoacidosis (when used in type 2 diabetes mellitus). Very rare: Necrotising fasciitis of the perineum (Fournier's gangrene). Not known/post-marketing: Angioedema, rash.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested 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 toxicity in healthy subjects at single oral doses up to 500 mg (50x max recommended dose); detectable glucose in urine for a dose-related period with no reports of dehydration, hypotension or electrolyte imbalance, and no clinically meaningful effect on QTc. In studies of once-daily doses up to 100 mg (10x max dose) for 2 weeks, hypoglycaemia incidence was slightly higher than placebo but not dose-related, with no clinically meaningful changes in renal biomarkers. In event of overdose, initiate appropriate supportive treatment; removal 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 SGLT2 inhibitor, reducing glucose reabsorption in the proximal renal tubule with concomitant sodium reabsorption reduction, increasing sodium delivery to the distal tubule (believed to increase tubuloglomerular feedback and reduce intraglomerular pressure), leading to reduced volume overload, reduced blood pressure, and beneficial cardiac remodelling effects. Also increases haematocrit and reduces body weight; cardiac benefits are not solely dependent on glucose-lowering and are not limited to patients with diabetes (as shown in DAPA-HF).

Clinical efficacy - Type 2 diabetes mellitus

Fourteen double-blind studies with 7,056 subjects evaluated glycaemic efficacy/safety. Monotherapy and combination therapy (metformin, glimepiride, metformin+sulphonylurea, sitagliptin, insulin) resulted in statistically significant reductions in HbA1c, FPG, body weight and blood pressure versus placebo/comparators, sustained through extension studies up to 208 weeks. The DECLARE cardiovascular outcomes study (17,160 patients, median 4.2 years) showed non-inferiority for MACE and superiority for the composite of hospitalization for heart failure or cardiovascular death (driven by reduction in heart failure hospitalisation), plus reduction in nephropathy composite endpoint (HR 0.53).

Type 1 diabetes mellitus

Two 24-week placebo-controlled studies (1,646 patients) with a 28-week extension showed statistically significant HbA1c improvements with dapagliflozin 5 mg/10 mg versus placebo, without increased hypoglycaemia; reductions in blood glucose variability, insulin dose, and body weight were also demonstrated.

Heart failure

The DAPA-HF study (4,744 patients, median 18 months) in patients with NYHA class II-IV and LVEF ≤40% showed dapagliflozin was superior to placebo in preventing the composite of cardiovascular death, hospitalisation for heart failure, or urgent heart failure visit (HR 0.74), consistent in patients with and without diabetes; also improved patient-reported heart failure symptoms (KCCQ-TSS).

5.2 Pharmacokinetic properties

Rapidly and well absorbed; Cmax attained within ~2 hours in fasted state. Steady-state Cmax and AUCτ following 10 mg once daily were 158 ng/mL and 628 ng.h/mL, respectively; absolute oral bioavailability 78%. High-fat meal decreased Cmax by up to 50% and prolonged Tmax by ~1 hour, without altering AUC (not clinically meaningful); can be given with or without food.

Approximately 91% protein bound; mean steady-state Vd 118 L. Extensively metabolised via UGT1A9 to inactive dapagliflozin 3-O-glucuronide; CYP-mediated metabolism is a minor pathway. Terminal half-life 12.9 hours; primarily eliminated via urinary excretion (<2% unchanged); after a 50 mg [14C]-dose, 96% recovered (75% urine, 21% faeces).

Exposure increases proportionally over the dose range 0.1-500 mg, with no time-dependent pharmacokinetic changes upon repeated daily dosing for up to 24 weeks. Renal impairment increases systemic exposure by 32-87% across mild-severe impairment; impact of haemodialysis unknown. Hepatic impairment increases Cmax/AUC by up to 40%/67% in severe impairment (not clinically meaningful in mild/moderate).

5.3 Preclinical safety data

No special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and

fertility. No tumours induced in two-year carcinogenicity studies in mice or rats.

Reproductive and developmental toxicity

Direct/indirect exposure in weanling juvenile rats and during late pregnancy/lactation associated with increased incidence/severity of renal pelvic and tubular dilatations in progeny, which did not fully reverse within a 1-month recovery period in juvenile animals. Additional developmental toxicity (reduced pup body weights) observed only at doses ≥15 mg/kg/day. Neither maternal nor developmental toxicities observed in rabbits at any dose tested; in rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:

- Microcrystalline cellulose
- Lactose monohydrate
- Crospovidone
- Colloidal silica anhydrous
- Magnesium stearate

Film-coating:

- Tabcoat TC 580091 White
- Yellow iron oxide
- 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

Alu/Alu blister packs of 3 x 10's in unit box with literature insert.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Dawa Limited, Plot No 7879/8, Baba Dogo Road-Ruaraka, P.O Box 16630-6200-Nairobi-Kenya.

8. MARKETING AUTHORISATION NUMBER(S)

H2021/CTD8532/19123

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20-09-2021

10. DATE OF REVISION OF THE TEXT

August 2020.