Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DAPAGLIFLOZIN 5 mg GLENMARK (Film-coated tablet)

DAPAGLIFLOZIN 10 mg GLENMARK (Film-coated tablet)

DAPAGLIFLOZIN GLENMARK IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. DAPAGLIFLOZIN GLENMARK IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES AND NOT INDICATED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT TYPE 2 DIABETES.

There have been reports of metabolic acidosis, including ketoacidosis, which were serious, life-threatening or fatal in patients taking **DAPAGLIFLOZIN GLENMARK**.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 11 mmol/L. **DAPAGLIFLOZIN GLENMARK** should be discontinued and the patient should be promptly evaluated and managed accordingly.

Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with **DAPAGLIFLOZIN GLENMARK**.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. **DAPAGLIFLOZIN GLENMARK** is contraindicated in these patients.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DAPAGLIFLOZIN 5 mg GLENMARK: Each film-coated tablet contains 5 mg of dapagliflozin. Contains sugar: 28,025 mg of lactose anhydrous per film-coated tablet.

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DAPAGLIFLOZIN 10 mg GLENMARK: Each film-coated tablet contains 10 mg of dapagliflozin.

Contains sugar: 56,050 mg of lactose anhydrous per film-coated tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

DAPAGLIFLOZIN 5 mg GLENMARK: Yellow coloured, round, biconvex, film coated tablets with 'G' debossed on one side & '81' debossed on other side.

DAPAGLIFLOZIN 10 mg GLENMARK: Yellow coloured, modified capsule shaped, biconvex, film coated tablets with 'G' debossed on one side & '482' debossed on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Monotherapy:

As an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Add-on combination therapy:

In combination with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology:

Monotherapy and add-on combination therapy

The recommended dose is 10 mg **DAPAGLIFLOZIN GLENMARK** once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin, a

thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin.

When **DAPAGLIFLOZIN GLENMARK** is used in combination with insulin or an insulin secretagogue, such as a sulfonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Special populations:

Renal impairment:

No dosage adjustment for **DAPAGLIFLOZIN GLENMARK** is indicated for mild renal impairment. The efficacy of **DAPAGLIFLOZIN GLENMARK** is dependent on renal function. **DAPAGLIFLOZIN GLENMARK** should not be used in patients with moderate to severe renal impairment (defined as eGFR < 60 mL/min/1,73 m^2 by MDRD or CrCl < 60 mL/min by Cockcroft-Gault) (see *Sections 4.3*, *4.4* and *4.8*).

Monitoring of renal function is recommended as follows:

- Prior to initiation of **DAPAGLIFLOZIN GLENMARK** and at least annually thereafter.
- Prior to initiation of concomitant medicines 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 GLENMARK** treatment should be discontinued.

Hepatic impairment:

No dosage adjustment for **DAPAGLIFLOZIN GLENMARK** is necessary for patients with mild or moderate hepatic impairment. **DAPAGLIFLOZIN GLENMARK** is not recommended for patients with severe hepatic impairment as efficacy has not been established (see *Section 5.2*).

Patients at risk for volume depletion:

For patients at risk for volume depletion due to co-existing conditions or concomitant medicines,

such as loop diuretics, a 5 mg starting dose of **DAPAGLIFLOZIN GLENMARK** may be appropriate (see *Sections 4.4* and *4.8*).

Elderly:

No dosage adjustment for **DAPAGLIFLOZIN GLENMARK** is required based on age (see *Section 4.4*).

Paediatric population:

Safety and effectiveness of **DAPAGLIFLOZIN GLENMARK** in paediatric and adolescent patients have not been established.

Method of administration:

DAPAGLIFLOZIN GLENMARK is for oral use and can be taken without regard to meals. Do not crush, split, or chew the tablets.

4.3 Contraindications

- Hypersensitivity to dapagliflozin or to any of the excipients.
- Moderate and severe renal impairment with GFR < 60 mL/min, end stage renal failure or patients on dialysis.
- Diabetes Mellitus Type 1
- Pregnant women or women who are breast-feeding their infants (see *Section 4.6*).

4.4 Special warnings and precautions for use

General:

DAPAGLIFLOZIN GLENMARK may cause a decrease in systolic blood pressure and diastolic blood pressure. **DAPAGLIFLOZIN GLENMARK** should not be used for the treatment of diabetic ketoacidosis.

Metabolic acidosis including ketoacidosis:

There have been post-marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin, as contained in **DAPAGLIFLOZIN GLENMARK**. **DAPAGLIFLOZIN GLENMARK** is contraindicated for the treatment of patients with type 1 diabetes mellitus (see *Section 4.3*).

Patients treated with **DAPAGLIFLOZIN GLENMARK** who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 11 mmol/L (196 mg/dL). If ketoacidosis is suspected, **DAPAGLIFLOZIN GLENMARK** should be discontinued and the patient should be promptly evaluated.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders e.g. history of pancreatitis or pancreatic surgery. **DAPAGLIFLOZIN GLENMARK** is not indicated in these patients.

Acute kidney injury:

DAPAGLIFLOZIN GLENMARK causes intravascular volume contraction and can cause acute kidney injury.

Use in patients with renal impairment:

The efficacy of **DAPAGLIFLOZIN GLENMARK** is dependent on renal function. Therefore, renal function should be monitored prior to initiation of **DAPAGLIFLOZIN GLENMARK** and periodically thereafter (see *Section 4.2*). **DAPAGLIFLOZIN GLENMARK** is contraindicated in patients with moderate and severe renal impairment with GFR < 60 mL/min, end stage renal failure or on dialysis (see *Section 4.3*).

Use in patients at risk for volume depletion:

The diuretic effect of **DAPAGLIFLOZIN GLENMARK** is a potential concern for volume depleted patients. There is limited experience in clinical trials in patients at increased risk for volume

depletion.

For patients at risk for volume depletion due to co-existing conditions or concomitant medicines, such as loop diuretics, a 5 mg starting dose of **DAPAGLIFLOZIN GLENMARK** may be appropriate. **DAPAGLIFLOZIN GLENMARK** should be permanently discontinued in patients who develop volume depletion (see *Section 4.8*).

Urinary tract infections:

Urinary tract infections were more frequently reported for dapagliflozin, as contained in **DAPAGLIFLOZIN GLENMARK** compared to control in a placebo-pooled analysis up to 24 weeks. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of **DAPAGLIFLOZIN GLENMARK** should be considered when treating pyelonephritis or urosepsis (see *Section 4.8*). Treatment with **DAPAGLIFLOZIN GLENMARK** increases the risk for urinary tract infections. There have been post-marketing reports of serious urinary tract infections, including pyelonephritis, requiring hospitalisation in patients receiving **DAPAGLIFLOZIN GLENMARK** and other SGLT2 inhibitors. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Necrotising fasciitis of the perineum (Fournier's Gangrene):

Reports of necrotising fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotising infection required urgent surgical intervention, have been identified in post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin, as contained in **DAPAGLIFLOZIN GLENMARK**. Cases have been reported in both females and male. Serious outcomes have included hospitalisation, multiple surgeries and death.

Patients treated with **DAPAGLIFLOZIN GLENMARK** presenting with pain or tenderness, erythema or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotising fasciitis. Is suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue **DAPAGLIFLOZIN GLENMARK**, closely monitor blood glucose levels, and provide appropriate alternate therapy for glycaemic control.

Genital mycotic infections:

DAPAGLIFLOZIN GLENMARK increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections.

Use with medicines known to cause hypoglycaemia:

Insulin and insulin secretagogues, such as sulfonylureas, 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 GLENMARK** (see *Section 4.8*).

Paediatric use:

Safety and efficacy of **DAPAGLIFLOZIN GLENMARK** in paediatric patients have not been established.

Other populations:

In general, patients with severe renal impairment (eGFR < 30 mL/min/1,73 m^2) or End Stage Renal Disease or with recent (< 2 months) cardiovascular event or heart failure New York Heart Association class IV or who are breast-feeding or are pregnant, have been excluded from clinical studies.

Excipients:

DAPAGLIFLOZIN GLENMARK contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor. In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP1A2, 2C9, 2C19,

2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters.

The dependence of dapagliflozin elimination on dapagliflozin 3-O-glucuronide formation in humans also suggests the possibility of interactions mediated by UGT1A9. Ketoconazole is an *in vitro* inhibitor of dapagliflozin 3-O- glucuronide formation by UGT1A9 (IC50 = 32 µM).

*Effects of other medicines on **DAPAGLIFLOZIN GLENMARK**:*

In studies conducted in healthy subjects, the pharmacokinetics of dapagliflozin were not altered by metformin (a human OCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a human OAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an alpha-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). A 22 % decrease in dapagliflozin systemic exposure following co-administration with rifampicin was considered not to be large enough to warrant a dose adjustment.

*Effect of **DAPAGLIFLOZIN GLENMARK** on other medicines:*

In studies conducted in healthy subjects, dapagliflozin did not alter the pharmacokinetics of metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate, sitagliptin (a hOAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide, valsartan, simvastatin (a CYP3A4 substrate), digoxin (a P gp substrate) or warfarin (S warfarin, a CYP2C19 substrate, R warfarin or the anticoagulatory effects of warfarin as measured by the prothrombin time [International Normalised Ratio (INR)].

Other interactions:

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of

DAPAGLIFLOZIN GLENMARK have not been studied.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay:

Monitoring glycaemic control with 1,5-AG assay should not be used as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors, including **DAPAGLIFLOZIN GLENMARK**. Use alternate methods to monitor glycaemic control.

Positive Urine Glucose Test:

Monitoring glycaemic control with urine glucose tests is not recommended in patients taking SGLT2 Inhibitors, including **DAPAGLIFLOZIN GLENMARK**, as SGLT2 Inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycaemic control.

4.6 Fertility, pregnancy and lactation

Pregnancy:

DAPAGLIFLOZIN GLENMARK is contraindicated in pregnancy. Maternal exposure to **DAPAGLIFLOZIN GLENMARK** in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, **DAPAGLIFLOZIN GLENMARK** should be discontinued (see *Section 4.3*).

Breastfeeding

Mothers on **DAPAGLIFLOZIN GLENMARK** should not breast-feed their infants.

DAPAGLIFLOZIN GLENMARK must not be used by a nursing woman. Studies in rats have shown excretion of dapagliflozin in milk. Exposure to **DAPAGLIFLOZIN GLENMARK** must be avoided during the first 2 years of life (see *Section 4.3*).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients must bear in mind the possibility of hypoglycaemia and its effects on their motor skills.

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4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	Frequent*	Less frequent**
Infections and infestations	Vulvovaginitis, balanitis and related genital infections[b,c], urinary tract infection[b,e], including pyelonephritis, urosepsis, cystitis.	Vulvovaginal pruritus
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]	Volume depletion, dehydration, hypovolaemia, hypotension[b], thirst**
Gastrointestinal disorders		Constipation
Skin and subcutaneous tissue disorders	Rash	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Back pain	
Renal and urinary disorders	Glucosuria Dysuria, polyuria[d]	Nocturia
Investigations	Dyslipidaemia[f], haematocrit increased[g]	Blood creatinine increased; blood urea increased

[a]The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[b]See corresponding subsection below for additional information.

[c] Genital infection includes the preferred terms: Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess, balanoposthitis, genitourinary tract infection, penile abscess, posthitis.

[d] Polyuria includes the preferred terms: pollakiuria, polyuria, increased urine output, osmotic diuresis.

[f] Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 1,4 % versus -0,4 %; HDL cholesterol 5,5 % versus 3,8 %; LDL cholesterol 2,7 %

versus -1,9 %; triglycerides -5,4 % versus -0,7 %.

[g] Mean changes from baseline in haematocrit were 2,30 % for dapagliflozin 10 mg versus -0,33 % for placebo. Haematocrit values > 55 % were reported in 1,3 % of the subjects treated with dapagliflozin 10 mg versus 0,4 % of placebo subjects.

*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.

Additional adverse reactions in ≥ 5 % of patients treated with dapagliflozin 10 mg, ≥ 1 % more than patients in placebo/comparator, and reported in at least 3 more patients treated with dapagliflozin 10 mg and regardless of relationship to dapagliflozin reported by investigator, are described below by treatment regimen.

- Add-on to metformin studies: headache (5,3 % dapagliflozin 10 mg and 3,1 % placebo).
- Add-on to thiazolidinedione study: nasopharyngitis (7,9 % dapagliflozin 10 mg and 3,6 % placebo), diarrhoea (6,4 % dapagliflozin 10 mg and 4,3 % placebo).

In a study of patients with moderate renal impairment, a higher frequency of bone fractures was observed in groups treated with **DAPAGLIFLOZIN GLENMARK** dapagliflozin (8,2 %) compared with placebo (0 %) (see *Section 4.3*).

Description of selected adverse reactions

Volume depletion:

Events related to volume depletion (including reports of dehydration, hypovolaemia or hypotension) were reported in 0,7 %, 0,6 % and 0,4 % of patients who received dapagliflozin 10 mg, dapagliflozin 5 mg and placebo, respectively, in the short-term, placebo-pooled analysis. Serious events occurred in ≤ 0,2 % of patients in the 14 clinical studies and were balanced between dapagliflozin 10 mg, dapagliflozin 5 mg and comparator (see *Section 4.4*).

In the following subgroups, the proportion of patients with events related to volume depletion for dapagliflozin 10 mg, dapagliflozin 5 mg and placebo were: In patients who received loop diuretics: 2 patients (6,5 %), 0 patients, and 1 patient (1,8 %), respectively.

In patients ≥ 65 years of age: 2 patients (1,0 %), 1 patient (0,5 %) and 1 patient (0,4 %), respectively.

Genital infections:

Events of genital infections were reported in 4,8 % and 0,9 % of patients who received dapagliflozin 10 mg and placebo, respectively, in the short-term, placebo-pooled analysis. Infections were more frequently reported in females (6,9 % dapagliflozin 10 mg vs. 1,5% placebo) than in males (2,7 % dapagliflozin 10 mg vs. 0,3 % placebo).

Overall, treatment with dapagliflozin 5 mg was similar to dapagliflozin 10 mg treatment.

Urinary tract infections:

Events of urinary tract infections were reported in 4,3 % and 3,7 % of patients who received dapagliflozin 10 mg and placebo, respectively, in the short-term, placebo-pooled analysis. Infections were more frequently reported in females (7,7 % dapagliflozin 10 mg vs. 6.6 % placebo) than in males (0,8 % dapagliflozin 10 mg vs. 1 % placebo) (see *Section 4.4*).

Hypoglycaemia:

The frequency of hypoglycaemia depended on the type of background therapy used in each study. Studies with add-on sulfonylurea and add-on insulin therapies had higher rates of hypoglycaemia (see *Section 4.4*).

In an add-on to glimepiride study up to 24 weeks, episodes of hypoglycaemia were reported in 10 (6,6 %) patients in the dapagliflozin 10 mg plus glimepiride group and 3 (2,1 %) patients in the placebo plus glimepiride group.

In an add-on to insulin study up to 24 weeks, episodes of hypoglycaemia were reported in 79 (40,3 %) patients in the dapagliflozin 10 mg plus insulin group and in 67 (34 %) patients in placebo plus insulin group. Patients in this study could also be treated with a maximum of 2 oral anti-diabetes medications (OADs) including metformin.

Decrease on blood pressure:

In the pool of 13 placebo-controlled studies, a decrease in blood pressure was observed in patients treated with dapagliflozin 10 mg (mean seated systolic blood pressure change from baseline at Week 24 of -3,7 mmHg and mean seated diastolic blood pressure change of -1,8 mmHg for dapagliflozin 10 mg vs. -0,5 mmHg systolic and -0,5 mmHg diastolic blood pressure change for placebo group). Postural blood pressure measurement revealed orthostatic hypotension in 13,1 % of patients treated with dapagliflozin 10 mg vs. 11,3 % of patients treated with placebo over the 24-week treatment period. In addition, in 2 studies with patients with type 2 diabetes and hypertension, postural blood pressure measurement revealed orthostatic hypotension in 3,2 % of dapagliflozin 10 mg-treated patients versus 1,7 %of placebo-treated patients across the 2 studies over the 12-week treatment period.

Laboratory findings:

Haematocrit:

A moderate increase in haematocrit occurs and may be an indication of volume depletion.

Serum inorganic phosphorus:

Increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg treated patients compared with placebo (mean increases of 0,0549 mmol/L vs. 0,0097 mmol/L, respectively). Similar results were seen at Week 50. Higher proportions of patients with marketed laboratory abnormalities of hyperphosphatemia (≥ 1,81 mmol/L if age 17-65 or ≥ 1,65 mmol/L if ≥ age 66) were reported in dapagliflozin 10 mg group vs. placebo at Week 24 (1,7 % vs. 0,7 %, respectively) and during the short-term plus long-term phase (2,6 % vs. 1,5 %, respectively). The clinical relevance of these finding is unknown.

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Lipids:

Changes from baseline in mean lipid values were reported at Week 24 in dapagliflozin 10 mg treated patients compared with placebo. Mean percent change from baseline at week 24 for dapagliflozin 10 mg vs. placebo, respectively was as follows: total cholesterol 1,4 % vs. -0,4 %; HDL cholesterol 5,5 % vs. 3,8 %; LDL cholesterol 2,7% vs. -1,9 %; triglycerides -5,4 % vs. 0,7 %. Mean percent change from baseline at Week 50 for dapagliflozin 10 mg vs. placebo, respectively was as follows: total cholesterol 1,5 % vs. -0,7 %; HDL cholesterol 6,5 % vs. 2,5 %; LDL cholesterol 3,5 % vs. -0,7 %; triglycerides -3,9 % vs. 0,5 %. The ratio between LDL cholesterol and HDL cholesterol decreased for all treatment groups at Week 24.

Liver function tests:

In the placebo-pooled analysis, ALT > 3 x upper limit of normal (ULN) was reported in 0,8 % on dapagliflozin 10 mg and 1,1 % on placebo over 24 weeks. In the overall clinical programme, ALT or AST > 3 x ULN and bilirubin > 2 x ULN was reported in 5 patients (0,1 %) on dapagliflozin and 3 patients (0,2 %) on comparator. One patient receiving dapagliflozin experienced a liver adverse event with diagnosis of drug induced hepatitis and autoimmune hepatitis.

Post-marketing adverse events:

Spontaneous reports frequency unknown: Skin and subcutaneous tissue disorders – Rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, rash erythematous, ketoacidosis, acute kidney injury, necrotising fasciitis of the perineum (Fournier's Gangrene), genital mycotic infections, urosepsis and pyelonephritis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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4.9 Overdose

In overdose, adverse reactions may be elicited or exacerbated. Appropriate symptomatic and 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

A 21.2 Oral hypoglycaemics

Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (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. Despite the presence of hyperglycaemia in type 2 diabetes mellitus, reabsorption of filtered glucose continues. Dapagliflozin reduces 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 glomerular filtration rate (GFR). Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.
Urinary glucose excretion (glycosuria) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging. 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 3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

The urinary glucose excretion with dapagliflozin results in osmotic diuresis and increases in urinary volume. The increase in urinary volume may be associated with a transient increase in urinary sodium excretion that which may not be associated with changes in serum sodium concentrations.

Dapagliflozin may cause a decrease in systolic blood pressure and diastolic blood pressure.

Urinary uric acid excretion was also increased and accompanied by a reduction in serum uric acid concentration. At 24 weeks, changes in serum uric acid concentrations from baseline ranged from -0,0183 mmol/L to -0,0483 mmol/L.

5.2 Pharmacokinetic properties

Absorption

Dapagliflozin was absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %. Food had relatively modest effects on the pharmacokinetics of dapagliflozin healthy subjects. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50 % and prolonged T_{max} by approximately 1 hour but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution:

Dapagliflozin is approximately 91 % protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment).

Metabolism:

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Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12,9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61 % of a 50 mg [^{14}C]-dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42 % [based on $AUC_{(0-12h)}$] of total plasma radioactivity, similar to the 39 % contribution by parent compound. No other metabolite accounted for > 5 % of the total plasma radioactivity at any time point measured. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The 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:

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2 % as unchanged dapagliflozin. After administration of 50 mg [^{14}C]-dapagliflozin dose, 96 % was recovered, 75 % in urine and 21 % in faeces. In faeces, approximately 15 % of the dose was excreted as parent compound.

Renal impairment:

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin that were 32 %, 60 % and 87 % higher, respectively, than those of patients with type 2 diabetes mellitus and normal renal function. At dapagliflozin 20 mg once daily, higher systemic exposure to dapagliflozin patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The renal glucose clearance and 24-hour glucose excretion was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment.

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The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18, 11 g of glucose/ day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known. Dapagliflozin is contraindicated in patients whose GFR is less than 60 ml/min (see *Section 4.3*).

Hepatic impairment:

A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12 % and 36 % higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40 % and 67 % higher than matched healthy controls, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see *Section 4.4*).

Age:

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥ 18 to < 40 years [n=105] and elderly: ≥ 65 years [n=224]) was evaluated as covariate in a population pharmacokinetic model and compared to patients ≥ 40 to < 65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10,4 % lower than in the reference group [90 % CI: 125; 129 %]. These differences in systemic exposure were considered not to be clinically

meaningful.

Paediatric and adolescent:

Pharmacokinetics in the paediatric and adolescent population have not been studied.

Body weight:

In population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high body weight subjects (≥ 120 kg, n=91) were estimated to be 78,3 % [90 % CI: 78,2; 83,2 %] of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥ 120 kg) is recommended.

Subjects with low body weights (< 50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29 % higher than subjects with the reference group body weight. This difference is considered to be small and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (< 50 kg) is recommended.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Anhydrous lactose

Microcrystalline cellulose

Croscarmellose sodium

Sodium stearyl fumarate

Film-coating material:

Polyvinyl alcohol

Talc

Titanium dioxide

Glyceryl monocaprylocaprate

Sodium lauryl sulfate

Iron oxide yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

DAPAGLIFLOZIN 5 mg and **10 mg GLENMARK** are packed in Alu-Alu blister packs of cold forming base foil and peelable lidding foil (8 tablets per blister strip) in pack sizes of 16, 32, or 96.

The blisters are packed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Glenmark Pharmaceuticals South Africa (Pty) Ltd

34 Monte Carlo Crescent,

Block A, First floor,

Kyalami Park, Midrand,

1684

8. REGISTRATION NUMBER(S)

Dapagliflozin 5 mg Glenmark: 54/21.2/0562.560

Dapagliflozin 10 mg Glenmark: 54/21.2/0563.561

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10. DATE OF REVISION OF TEXT

11 June 2021