Professional Information for OLFID 5 and OLFID 10

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OLFID 5 mg film-coated tablets

OLFID 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OLFID 5: Each film-coated tablet contains 5 mg dapagliflozin.

OLFID 10: Each film-coated tablet contains 10 mg dapagliflozin.

Sugar free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

OLFID 5: Yellow coloured, round, biconvex, film-coated tablets debossed with "D1" on one side and "M" on other side.

OLFID 10: Yellow coloured, diamond, biconvex, film-coated tablets debossed with "D2" on one side and "M" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OLFID 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 dipeptidyl peptidase-4 (DPP-4) 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 OLFID once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin a thiazolidinedione, a sulfonylurea, a DPP-4 inhibitor, or insulin.

When OLFID 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

No dosage adjustment for OLFID is indicated for mild renal impairment. The efficacy of OLFID is dependent on renal function. OLFID 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 OLFID 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, OLFID treatment should be discontinued.

Hepatic impairment

No dosage adjustment for OLFID is necessary for patients with mild or moderate hepatic impairment. OLFID 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 medications, such as loop diuretics, a 5 mg starting dose of OLFID may be appropriate (see sections 4.4 and 4.8).

Elderly

No dosage adjustment for OLFID is required based on age (see section 4.4).

Paediatric and adolescent

Safety and effectiveness of OLFID in paediatric and adolescent patients have not been established.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to dapagliflozin or to any of the excipients (see section 6.1).
- 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 breastfeeding their infants (see section 4.6).

4.4 Special warnings and precautions for use

OLFID IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. OLFID 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 OLFID.

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. OLFID 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 OLFID.

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

Renal impairment

Treatment of diabetes mellitus

The glycaemic efficacy of OLFID is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment (see sections 4.2 and 5.2). In subjects with moderate renal impairment (GFR < 60 mL/min), a higher proportion of subjects treated with OLFID had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.

OLFID is contraindicated in patients with a GFR < 60 mL/min (see section 4.3). OLFID has not

been studied in severe renal impairment (GFR < 30 mL/min) or end-stage renal disease (ESRD) and is contraindicated in these patients.

Monitoring of renal function is recommended prior to initiation of OLFID and periodically thereafter (see section 4.2).

Hepatic impairment

There is limited experience in clinical studies in patients with hepatic impairment. OLFID exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).

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

OLFID may cause a decrease in systolic and diastolic blood pressure. Due to its mechanism of action, OLFID increases diuresis which may lead to the modest decrease in blood pressure. It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a OLFID-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with OLFID is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Diabetic ketoacidosis (DKA)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of DKA. Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 1 diabetes patients, type 2 diabetes patients with low C-

peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), 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. OLFID is contraindicated in patients with type 1 diabetes (see section 4.3).

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.
Before initiating OLFID, factors in the patient history that may predispose to ketoacidosis should be considered.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with OLFID may be restarted when the ketone values are normal, and the patient's condition has stabilised.

Type 2 diabetes mellitus

Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including OLFID. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).
In patients where DKA is suspected or diagnosed, OLFID treatment should be stopped immediately.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, OLFID should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of OLFID should be considered when treating pyelonephritis or urosepsis.

Treatment with OLFID 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 OLFID and other SGLT2 inhibitors. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Elderly (≥ 65 years)

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicines that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARBs). The same recommendations for renal function apply to elderly patients as to all patients (see sections 4.2,

4.4 and 5.2).

Cardiac failure

Experience with OLFID in NYHA class IV is limited.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Urine laboratory assessments

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Diuretics

OLFID may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Insulin and insulin secretagogues

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 OLFID in patients with type 2 diabetes mellitus (see section 4.2).

Pharmacokinetic interactions

The metabolism of OLFID is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, OLFID is not expected to alter the metabolic clearance of co-administered medicines that are metabolised by these enzymes.

Effect of other medicines on OLFID

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of OLFID are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.
Following co-administration of dapagliflozin with rifampicin (an inducer of various active transporters and medicine metabolising enzymes) 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 (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following co-administration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), 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 OLFID on other medicines

In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19 % increase in AUC of simvastatin and 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.

Other interactions

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of OLFID have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

OLFID is contraindicated in pregnancy (see section 4.3). There are no data from the use of OLFID 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.
When pregnancy is detected, treatment with OLFID should be discontinued.

Breastfeeding

Mothers on OLFID should not breastfeed their infants (see section 4.3). It is unknown whether OLFID and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk. OLFID should not be used while breastfeeding and exposure to OLFID should be avoided during the first 2 years of life (see section 4.2).

Fertility

The effect of OLFID 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

OLFID has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when OLFID is used in combination with a sulphonylurea or insulin. Taking OLFID can make patients feel dizzy. Patients taking OLFID should therefore be warned to be cautious when driving a vehicle or operating machinery.

4.8 Undesirable effects

Infections and infestations

Frequent: vulvovaginitis, balanitis and related genital infections[a], urinary tract infection[b], including pyelonephritis, cystitis

Less frequent: fungal infection, necrotising fasciitis of the perineum (Fournier's gangrene)

Immune system disorders

Less frequent: angioedema

Metabolism and nutrition disorders

Frequent: hypoglycaemia (when used with SU or insulin)

Less frequent: volume depletion[c], thirst, diabetic ketoacidosis, dehydration, hypovolaemia, hypotension

Nervous system disorders:

Frequent: dizziness

Gastrointestinal disorders:

Less frequent: constipation, dry mouth

Skin and subcutaneous tissue disorders:

Frequent: rash[e]

Less frequent: hyperhidrosis

Musculoskeletal and connective tissue disorders:

Frequent: back pain

Renal and urinary disorders:

Frequent: dysuria, polyuria[d], glycosuria

Less frequent: nocturia

Reproductive system and breast disorders:

Less frequent: vulvovaginal pruritis, genital pruritis

Investigations

Frequent: increased haematocrit, decreased creatinine renal clearance during initial treatment, dyslipidaemia

Less frequent: increased blood creatinine during initial treatment, increased blood urea, deceased weight.

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

[b] Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

[c] Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia,

hypotension.

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

[e] Adverse reaction was identified through post marketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of OLFID is important. It allows continued monitoring of the benefit/risk balance of OLFID. 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.

4.9 Overdose

Symptoms ***of overdose***

In overdose, side effects may be elicited or exacerbated (see section 4.8).

Treatment of overdose

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

Category and class: A 21.2 Oral hypoglycaemics

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

ATC code: A10BK01

Mechanism of action

Dapagliflozin is a highly potent (K_i: 0,55 nM), selective and reversible inhibitor of SGLT2.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling. Other effects include an increase in haematocrit and reduction in body weight. The cardiac benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF study. 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, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.
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

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in

subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3 – 7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -0,0483 mmol/L to -0,0183 mmol/L (-0,87 to -0,33 mg/dL).

5.2 Pharmacokinetic properties

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC_{τ} values following once daily 10 mg doses of dapagliflozin 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 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. Hence, OLFID can be administered with or without food.

Distribution

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

Biotransformation

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. 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. 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

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. 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 [^{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 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.

Special populations

Renal impairment

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32 %, 60 % and 87 % higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function.

The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. 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

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), 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. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40 % and 67 % higher than matched healthy controls, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see section 4.2).

Elderly (≥ 65 years)

There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Paediatric and adolescent population

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

Gender

The mean dapagliflozin AUC_{ss} in females was estimated to be about 22 % higher than in males.

Race

There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight

Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide (E551)

Crospovidone (E1202)

Magnesium stearate (E572)

Microcrystalline cellulose (E460(i))

Opadry Yellow (containing iron oxide yellow (E172), macrogol (E1521), talc (E553b), titanium dioxide (E171))

Polyvinyl alcohol (E1203)

Sodium lauryl sulfate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Blister strips: Keep in the outer carton until required for use.

HDPE containers: Keep in the original container until required for use.

6.5 Nature and contents of container

Aluminium/aluminium blister strips packed in an outer carton or white opaque HDPE containers containing 30 tablets, or HDPE containers containing 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBERS

OLFID 5: 56/21.2/0276

OLFID 10: 56/21.2/0277

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 September 2023

10. DATE OF REVISION OF THE TEXT