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## Professional Information for LIFLOZ 5 and LIFLOZ 10

### SCHEDULING STATUS

S4

#### 1. NAME OF THE MEDICINE

**LIFLOZ 5** mg film-coated tablets

**LIFLOZ 10** mg film-coated tablets

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

LIFLOZ 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.

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

LIFLOZ 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

LIFLOZ 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 LIFLOZ 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 LIFLOZ 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 LIFLOZ is indicated for mild renal impairment. The efficacy of LIFLOZ is dependent on renal function. LIFLOZ should not be used in patients with moderate to severe renal impairment (defined as eGFR < 60 mL/min/1,73 m<sup>2</sup> 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 LIFLOZ 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  $\text{CrCl} < 60 \text{ mL/min}$  or  $\text{eGFR} < 60 \text{ mL/min/1,73 m}^2$ , LIFLOZ treatment should be discontinued.

#### *Hepatic impairment*

No dosage adjustment for LIFLOZ is necessary for patients with mild or moderate hepatic impairment. LIFLOZ 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 LIFLOZ may be appropriate (see sections 4.4 and 4.8).

#### *Elderly*

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

#### *Paediatric and adolescent*

Safety and effectiveness of LIFLOZ 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  $\text{GFR} < 60 \text{ mL/min}$ , 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

**LIFLOZ IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. LIFLOZ 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 LIFLOZ.**

**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. LIFLOZ 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 LIFLOZ.**

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

#### ***Renal impairment***

##### *Treatment of diabetes mellitus*

The glycaemic efficacy of LIFLOZ 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 LIFLOZ had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.

LIFLOZ is contraindicated in patients with a GFR < 60 mL/min (see section 4.3). LIFLOZ 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 LIFLOZ and periodically thereafter (see section 4.2).

### ***Hepatic impairment***

There is limited experience in clinical studies in patients with hepatic impairment. LIFLOZ 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***

LIFLOZ may cause a decrease in systolic and diastolic blood pressure. Due to its mechanism of action, LIFLOZ 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 LIFLOZ-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 LIFLOZ 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. LIFLOZ 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 LIFLOZ, 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 LIFLOZ 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 LIFLOZ. 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, LIFLOZ 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, LIFLOZ 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 LIFLOZ should be considered when treating pyelonephritis or urosepsis.

Treatment with LIFLOZ 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 LIFLOZ 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 LIFLOZ 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 LIFLOZ will test positive for glucose in their urine.

## **4.5 Interaction with other medicines and other forms of interaction**

### ***Pharmacodynamic interactions***

#### ***Diuretics***

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

### ***Pharmacokinetic interactions***

The metabolism of LIFLOZ 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, LIFLOZ is not expected to alter the metabolic clearance of co-administered medicines that are metabolised by these enzymes.

### ***Effect of other medicines on LIFLOZ***

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of LIFLOZ 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 LIFLOZ 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 LIFLOZ have not been studied.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

LIFLOZ is contraindicated in pregnancy (see section 4.3). There are no data from the use of LIFLOZ 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 LIFLOZ should be discontinued.

### **Breastfeeding**

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

## **Fertility**

The effect of LIFLOZ 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**

LIFLOZ has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when LIFLOZ is used in combination with a sulphonylurea or insulin. Taking LIFLOZ can make patients feel dizzy. Patients taking LIFLOZ 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<sup>a</sup>, urinary tract infection<sup>b</sup>, 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<sup>c</sup>, 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<sup>e</sup>

*Less frequent:* hyperhidrosis

### **Musculoskeletal and connective tissue disorders:**

*Frequent:* back pain

### **Renal and urinary disorders:**

*Frequent:* dysuria, polyuria<sup>d</sup>, 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, decreased weight.

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

<sup>d</sup> Polyuria includes the preferred terms: pollakiuria, polyuria, increased urine output and osmotic diuresis.

<sup>e</sup> 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 LIFLOZ is important. It allows continued monitoring of the benefit/risk balance of LIFLOZ. 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  $AUC_T$  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, LIFLOZ 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 ( $\geq 65$ 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<sub>ss</sub> 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**

LIFLOZ 5: 56/21.2/0278.276

LIFLOZ 10: 56/21.2/0279.277

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26 September 2023

**10. DATE OF REVISION OF THE TEXT**