TABLE OF CONTENTS – CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION

SEPTEMBER 2024

S.D.

S.D.

CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION SEPTEMBER 2024

SCHEDULING STATUS: S4

[PRODUCT NAME] IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES [PRODUCT NAME] IS NOT INDICATED FOR WEIGHT CONTROL PROGRAMMES.

There have been reports of metabolic acidosis, including ketoacidosis, which were serious life-threatening or fatal, in patients taking [PRODUCT NAME].

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. [PRODUCT NAME] 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 or increased insulin requirements due to infections, illness, and surgery or alcohol abuse. Caution is advised in treating these patients with [PRODUCT NAME].

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

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

S.D.

1. NAME OF THE MEDICINE

[PRODUCT NAME] 5 mg (film-coated tablet)

[PRODUCT NAME] 10 mg (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[PRODUCT NAME] 5 mg: Each film-coated tablet contains 5 mg of dapagliflozin.

[PRODUCT NAME] 10 mg: Each film-coated tablet contains 10 mg of dapagliflozin.

Contains sugar– lactose monohydrate

[PRODUCT NAME] 5mg contains 25 mg lactose monohydrate per tablet.

[PRODUCT NAME] 10mg contains 50 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

[PRODUCT NAME] 5mg: Yellow coloured, round shaped, biconvex, film-coated tablet debossed with "F45" on one side and plain on the other side.

[PRODUCT NAME] 10 mg: Yellow coloured, diamond shaped, biconvex, film-coated tablet debossed with "F46" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Monotherapy:

S.D.

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 sulphonyl urea, a DPP4 inhibitor, or insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Heart failure

[PRODUCT NAME] is indicated in adults to reduce the risk of worsening heart failure or cardiovascular death, in patients with heart failure (NYHA class II-IV), and with a left ventricular ejection fraction (LVEF) ≤ 40 %.

Chronic kidney disease

[PRODUCT NAME] is indicated for the treatment of chronic kidney disease.

4.2 Posology and method of administration

Posology

Monotherapy and add-on combination therapy:

The recommended dose is 10 mg **[PRODUCT NAME]** once daily for monotherapy ad add-on combination therapy with other glucose-lowering medicines, including metformin, a thiazolidinedione, a sulphonyl urea, a DPP4 inhibitor, or insulin.

When **[PRODUCT NAME]** is used in combination with insulin or an insulin secretagogue, such as a sulphonyl urea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

S.D.

Heart failure

The recommended dose of **[PRODUCT NAME]** is 10 mg taken orally once daily at any time of the day regardless of meals. **[PRODUCT NAME]** can be used in conjunction with other heart failure therapies.

Chronic kidney disease

The recommended dose of **[PRODUCT NAME]** is 10 mg taken orally once daily at any time of the day regardless of meals. In the DAPA-CKD study, dapagliflozin was administered in conjunction with other chronic kidney disease related therapies (see section 5.1).

Special populations

Renal impairment

No dosage adjustment for **[PRODUCT NAME]** is indicated for mild renal impairment. The efficacy of **[PRODUCT NAME]** is dependent on renal function. **[PRODUCT NAME]** should not be used in patients with moderate to severe renal impairment (defined as eGFR, <45 ml/min/1, 73 m^2) (See sections 4.3, 4.4 and 4.8)

Monitoring of renal function is recommended as follows:

- Prior to initiation of **[PRODUCT NAME]** 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 eGRF<45 ml/ min/ 1,73 m^2, **[PRODUCT NAME]** treatment should be discontinued (see section 4.3).

Hepatic impairment

No dosage adjustment for **[PRODUCT NAME]** is necessary for patients with mild to moderate hepatic impairment. **[PRODUCT NAME]** is not recommended for patients with severe hepatic impairment as efficacy has not been established (see Section 5.2).

S.D.

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 **[PRODUCT NAME]** may be appropriate. (See sections 4.3 and 4.8)

Elderly:

No dosage adjustment for **[PRODUCT NAME]** is required based on age. (See section 4.3)

Paediatric and adolescent:

Safety and efficacy of **[PRODUCT NAME]** in pediatric and adolescent patients has not been established.

Method of administration

For oral use

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in 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 and breastfeeding women. (See section 4.6)
- Patients with history of pancreatitis or pancreatic surgery (see 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

General:

[PRODUCT NAME] may cause a decrease in systolic blood pressure and diastolic blood pressure.

[PRODUCT NAME] should not be used for the treatment of diabetic ketoacidosis.

S.D.

Metabolic acidosis including ketoacidosis in patients with diabetes mellitus

There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 2 diabetes mellitus taking **[PRODUCT NAME]. [PRODUCT NAME]** is contraindicated for the treatment of patients with Type 1 diabetes mellitus (see section 4.3).

Patients treated with **[PRODUCT NAME]** 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, **[PRODUCT NAME]** should be discontinued and the patient should be promptly evaluated.

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

Impairment of renal function/acute kidney injury

SGLT2 inhibitors such as [PRODUCT NAME] may cause a decrease in the glomerular filtration rate (GFR), with an increase in serum creatinine and serum urea. Acute kidney injury (AKI) has been reported with the use of SGLT2 inhibitors.

Based on their mode of action, SGLT2 inhibitors may cause glycosuria, osmotic diuresis, fluid and electrolyte loss with a risk of dehydration / hypovolaemia and hypotension, which may precipitate acute kidney injury. Renal function and hydration status should be assessed before treatment is initiated with SGLT2 inhibitor such as **[PRODUCT NAME]** and should be frequently monitored during treatment.

Other factors that may predispose patients to AKI during treatment with SGLT2 inhibitors include reduced oral intake of fluids, congestive heart failure, gastrointestinal fluid losses, excessive heat exposure, and concomitant use of medicines such as diuretics, NSAIDs, ACE inhibitors and ARBs. Discontinue treatment with SGLT2 inhibitors in patients with AKI and consider other appropriate

S.D.

treatment options for their diabetes mellitus.

SGLT2 inhibitors such as **[PRODUCT NAME]** are contraindicated in patients with moderate to severe renal impairment and in patients on dialysis (see section 4.3).

There is limited experience with **[PRODUCT NAME]** in patients with severe renal impairment (eGFR < 30 mL/min/1,73m^2) or end stage renal disease (ESRD).

Urinary tract and genital infections

SGLT2 inhibitors such as **[PRODUCT NAME]** have been associated with an increased risk of urinary tract infection and/or genital infection in both males and females caused by bacteria and/or fungi. Genital and fungal infections appear to be more common in females. Balanoposthitis in males may result in phimosis.

Treatment of diabetes mellitus

[PRODUCT NAME] is not recommended for use in the treatment of diabetes to improve glycaemic control when eGFR is below 45 mL/min/1,73m2 as the glycaemic efficacy of dapagliflozin is dependent on renal function. Renal function should be evaluated prior to initiation of **[PRODUCT NAME]** and periodically thereafter (see section 4.2).

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 **[PRODUCT NAME]** (see section 4.8).

Paediatric use

Safety and efficacy of **[PRODUCT NAME]** in paediatric patients has not been established.

Other populations:

Patients with severe renal impairment (eGFR < 30 mL/min/1,73 m^2) or End Stage Renal Disease or

S.D.

with recent (< 2 months) cardiovascular event or who are breastfeeding or are pregnant, have been included from clinical studies.

Hepatic impairment

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

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-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 dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

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 medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see sections 4.2, 4.4,

S.D.

4.8 and 5.1).

Cardiac failure

Experience with dapagliflozin 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 **[PRODUCT NAME]** will test positive for glucose in their urine.

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Diuretics

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (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 dapagliflozin in patients with type 2 diabetes mellitus (see sections 4.2 and

S.D.

4.8).

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase1A9 (UGT1A9).

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

Effect of other medicines on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin 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 drug-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 dapagliflozin 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 anti coagulatory 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%

S.D.

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 controlis advised.

4.6 Fertility, pregnancy and lactation

Pregnancy

[PRODUCT NAME] is contraindicated during pregnancy (see section 4.3)

Breastfeeding

[PRODUCT NAME] is contraindicated during lactation (see section 4.3).

Fertility

The effect of dapagliflozin on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

[PRODUCT NAME] has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin and possible dizziness.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions, during controlled clinical trials with dapagliflozin were genital infections.

Tabulated summary of adverse reactions

S.D.

System organ class

Frequent

Less frequent

Frequency unknown

Infections and infestations

Vulvovaginitis, balanitis and related genital infections.

Urinary tract infections including pyelonephritis, cystitis

Fungal infection

Necrotising fasciitis of the perineum (Fournier's gangrene)

Metabolism and nutrition disorders

Hypoglycaemia (when used with SU or insulin)

Volume depletion

Dehydration, hypovolaemia, hypotension,

Thirst

Diabetic ketoacidosis (when used in type 2 diabetes mellitus)

Nervous system disorders

Dizziness

Gastrointestinal disorders

Constipation, dry mouth

Skin and subcutaneous tissue disorders

Rash

Angioedema, hyperhidrosis

S.D.

Musculoskeletal and connective tissue disorders

Back pain

Renal and urinary disorders

Glucosuria

Dysuria,

Polyuria

Nocturia

Reproductive system and breast disorders

Vulvovaginal pruritis

Pruritis genital

Investigations

Haematocrit increased

Creatinine renal clearance decreased during initial treatment

Dyslipidaemia

Blood creatinine increased during initial treatment.

Blood urea increased

Weight decreased

a) 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, balanitiscandida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

b) Urinary tract infection includes the following preferred terms, listed in order of frequency reported:

S.D.

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, and hypotension.

d) Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

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

4.9 Overdose

In the event of an overdose, side effects 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

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 (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.

S.D.

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 tubule 0glomerular feedback and reduce intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and after load, 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 2diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin10 mg/day for up to 2 years.

S.D.

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 -48.3 to -18.3micromoles/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 1hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Hence, **[PRODUCT NAME]** 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 extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an

S.D.

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

Linearity:

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

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 of32%, 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.

S.D.

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.

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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Lactose monohydrate

S.D.

Crospovidone

Sodium lauryl sulphate

Methylene chloride

Colloidal silicon dioxide

Magnesium stearate

Insta moist shield Aqua II Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months for blister pack.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Tablets are packed in plain 25 micron aluminium foil and 25 micron OPA/ 45 micron aluminium foil/ 60 micron PVC on the other side. Pack sizes include 10's, 14's; 28's; 30's; 90's and 98's tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

S.D.

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

FARFLOZIN 5 mg: 56/21.2/0680

FARFLOZIN 10 mg: 56/21.2/0681

DAPIFLO 5 mg: 56/21.2/0682.680

DAPIFLO 10 mg: 56/21.2/0683.681

9. DATE OF FIRST AUTHORISATION

[PRODUCT NAME] 5 mg: 05 December 2023

[PRODUCT NAME] 10 mg: 05 December 2023

10. DATE OF REVISION OF THE TEXT

19 SEPTEMBER 2024

S.D.