SCHEDULING STATUS

S4

1. **NAME OF THE MEDICINE:**

   AVAXIGA 5 mg film coated tablet.

   AVAXIGA 10 mg film coated tablet.

AVAXIGA IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. AVAXIGA IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES.

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

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.

AVAXIGA 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 AVAXIGA.

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

AVAXIGA 5

Each film-coated tablet contains 5 mg Dapagliflozin.

Contains sugar: Lactose Anhydrous 25 mg.

AVAXIGA 10

Each film-coated tablet contains 10 mg Dapagliflozin.

Contains sugar: Lactose Anhydrous 50 mg.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM:

AVAXIGA 5

Yellow coloured biconvex, round shaped, film coated tablets with “120.” engraved on one side and plain on another side.

AVAXIGA 10

Yellow coloured biconvex, diamond shaped film coated tablets with “121.” engraved on one side and plain on another side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Type 2 diabetes mellitus

AVAXIGA is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- as monotherapy as an adjunct to diet and exercise to improve glycaemic control

- as add-on combination therapy, 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

Type 2 diabetes mellitus

Monotherapy and add-on combination therapy

The recommended dose is 10 mg **AVAXIGA** 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.

Use with medicines known to cause hypoglycaemia:

When **AVAXIGA** 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:

Treatment of diabetes mellitus

No dosage adjustment is required based on renal function.

As glycaemic efficacy is dependent on renal function (see sections 4.4 and 4.8), **AVAXIGA** is not recommended to improve glycaemic control in the treatment of diabetes in patients where eGFR is below 45 mL/min/1,73 m^2.

Monitoring of renal function is recommended as follows:

- Prior to initiation of **AVAXIGA** 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 eGFR < 45 mL/min/1, 73 m^2. **AVAXIGA** treatment should be discontinued (See sections 4.3).

Hepatic impairment:

No dosage adjustment for **AVAXIGA** is necessary for patients with mild or moderate hepatic impairment. **AVAXIGA** is not recommended for patients with severe hepatic impairment as

efficacy has not been established. (See section 5.2).

Elderly population:

No dosage adjustment for **AVAXIGA** is required based on age. (See section 4.4).

Paediatric population:

Safety and effectiveness of **AVAXIGA** in paediatric and adolescent patients have not been established. No data is available.

Method of Administration

For oral use.

4.3 Contraindications

- Hypersensitivity to dapagliflozin or to any of the excipients of **AVAXIGA**. (Listed in section 6.1)

- Moderate and severe renal impairment with GFR < 45 mL/min/1,73 m^2, end stage renal failure or patients on dialysis when used for type 2 diabetes mellitus indication.
- 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

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

AVAXIGA should not be used for the treatment of diabetic ketoacidosis.

Use with medicines known to cause hypoglycaemia

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 **AVAXIGA** (see section 4.8).

Renal impairment

There is limited experience with initiating treatment with dapagliflozin as in **AVAXIGA** in patients with eGFR < 25 mL/min/1,73 m^2.

Dapagliflozin as in **AVAXIGA** is not recommended for the treatment of type 2 diabetes mellitus to improve glycaemic control when eGFR is persistently below 45 mL/min/1,73 m2 as the glycaemic efficacy of dapagliflozin is dependent on

renal function (see section 4.2 Posology and method of administration).

However, treatment with **AVAXIGA** should be continued for the management of renal and cardiovascular comorbidities and additional glucose lowering treatment should be considered if further glycaemic control is needed.

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).

Diabetic ketoacidosis

Cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. 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).

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.

In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

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 dapagliflozin as in **AVAXIGA** may be restarted when the ketone values are normal, and the patient's condition has stabilised.

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

Patients who may be at higher risk of DKA include patients with a low beta cell function reserve (e.g. 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. SGLT2 inhibitors should be used with caution in these patients.

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.

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin should not be used for treatment of patients with type 1 diabetes.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Postmarketing 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 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, **AVAXIGA** 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 dapagliflozin as in **AVAXIGA** should be considered when treating pyelonephritis or urosepsis.

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 (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see sections 4.2, 4.4, 4.8 and 5.1).

Cardiac failure

Experience with dapagliflozin in NYHA class IV is limited.

Chronic kidney disease

There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria.

Dapagliflozin has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA-associated vasculitis), ongoing or recent requirements of

cytotoxic, immunosuppressive or other immunomodulating renal therapy, or in patients who received an organ transplant.

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 **AVAXIGA** will test positive for glucose in their urine.

AVAXIGA film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose - galactose malabsorption should not take **AVAXIGA**.

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 4.8).

Pharmacokinetic interactions

The metabolism of dapagliflozin 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, dapagliflozin is not expected to alter the metabolic clearance of coadministered 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 coadministration 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 coadministration 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 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.

Other interactions:

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy, and lactation

Pregnancy

AVAXIGA is contraindicated in pregnancy.

Maternal exposure to **AVAXIGA** in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

When pregnancy is detected, **AVAXIGA** should be discontinued (see section 4.3).

Breastfeeding

Mothers on **AVAXIGA** should not breast-feed their infants.

Alternatively, mothers breastfeeding their infants must not use **AVAXIGA**.

Studies in rats have shown excretion of **AVAXIGA** in milk. Exposure to **AVAXIGA** must be avoided during the first 2 years of life (see section 4.3).

Fertility

The effect of dapagliflozin 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 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.

4.8 Undesirable effects

Summary of the safety profile

Type 2 diabetes mellitus

In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In the dapagliflozin cardiovascular outcomes study in type 2 diabetes mellitus (DECLARE study, see section 5.1), 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Chronic kidney disease

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m^2. Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m^2.

The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. None were found to be dose related. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

Table 1. Adverse reactions in placebo-controlled clinical studies[a] and postmarketing experience

System organ class	Frequent	Less Frequent	Frequency Unknown
Infections and infestations	Vulvovaginitis, balanitis and related genital infections[*, b,c], Urinary tract infection[*, b,d] including pyelo-nephritis, cystitis.	Fungal infection**, Necrotising fasciitis of the perineum (Fournier's gangrene) [b,i]	
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]	Volume depletion[b,e], Thirst**, Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,i,k]	
Nervous system disorders	Dizziness		
Gastrointestinal disorders		Constipation**, Dry mouth**	

Skin and subcutaneous tissue disorders	Rash[j]	Angioedema, Hyperhidrosis	
Musculoskeletal and connective tissue disorders	Back pain*		
Renal and urinary disorders	Dysuria Polyuria*,[f] Glucosuria	Nocturia**	
Reproductive system and breast disorders		Vulvovaginal pruritus**, Pruritus genital**	
Investigations	Haematocrit increased [g], Creatinine renal clearance decreased during initial treatment [b], Dyslipidaemia [h]	Blood creatinine increased during initial treatment**,[b], Blood urea increased** Weight decreased**	

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

[b] See corresponding subsection below for additional information.

[c] 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.

[d] 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.

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

[f] Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

[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.

[h] Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides –2.7% versus -0.7%.

[I] See section 4.4.

[j] Adverse reaction was identified through postmarketing 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. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403),

the frequency of rash was similar for dapagliflozin (1.4 %) and all control (1.4%), respectively.

[k] Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

[*] 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.

Reporting side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of 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: hppts://www.sahpra.or.za/Publications/Index/8

4.9 Overdose

In 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 **AVAXIGA** by haemodialysis has not been studied.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Class of medicine: 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 reversible inhibitor of sodium glucose co-transporter 2 (SGLT2) that improves glycaemic control in patients with type 2 diabetes mellitus and provides cardiac benefits.

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. Secondary effects of SGLT2 inhibition with dapagliflozin also include a modest reduction in blood pressure, reduction in body weight, and an increase in haematocrit.

The cardiac benefits of dapagliflozin are not solely dependent on the blood glucose lowering effect. In addition to the osmotic diuretic and related hemodynarnic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis. adipokines and uric acid may be mechanisms underlying the cardio- renal beneficial effects of dapagliflozin.

The cardiac benefits of dapagliflozin are not solely dependent on the blood glucose lowering effect. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on

myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms underlying the cardio- renal beneficial effects of dapagliflozin.

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.

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 tDXA) and magnetic resonance imaging.

SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 3 000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects

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 mmo/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 in 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).

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. 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}CJ- 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.

Special populations

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 in 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 were lower in patients with moderate or severe renal impairment as compared to patients with normal

and mild renal impairment. 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 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 45 mL/min/1,73 m^2 (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 a 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: 87,9; 92,2 %] and 25 % higher in elderly patients compared to the reference group (90 % CI: 123;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 a 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

Acetone

Anhydrous Lactose

Colloidal Silicon Dioxide

Low Substituted Hydroxypropyl Cellulose

Magnesium Stearate

Microcrystalline Cellulose

Sepitrap

Opadry II Yellow

- Iron Oxide Yellow
- Macrogol
- Talc
- Titanium Dioxide

6.2 Incompatibilities

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

30's- 3x10 plain aluminum foil blisters, with an Alu-Alu film, in an outer mono carton with a package insert.

6.6 Special precautions for disposal and other handling

No special requirements. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. Holder of certificate of registration

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

AVAXIGA 5: A 57/21.2/0651

AVAXIGA 10: A 57/21.2/0652

9. Date of first authorization/Renewal of the authorization

02/07/2024

10. Date of revision of the text

01/10/2024