Professional Information for DAGLIF 5 and DAGLIF 10

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DAGLIF 5 mg film-coated tablets.

DAGLIF 10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DAGLIF 5: Each tablet contains 5 mg dapagliflozin.

DAGLIF 10: Each tablet contains 10 mg dapagliflozin.

Excipients with known effect:

Contains sugar.

DAGLIF 5: Each tablet contains 48,5 mg lactose anhydrous.

DAGLIF 10: Each tablet contains 97,0 mg lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

DAGLIF 5: White to off-white coloured, round shaped, film coated tablets, debossed with “1380” on one side and plain on the other side.

DAGLIF 10: White to off-white coloured, oval shaped film coated tablet, debossed with “1381” on one side and plain on the other side.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DAGLIF 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 sulphonylurea, 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 DAGLIF once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin, a thiazolidinedione, a sulphonylurea, a DPP^4 inhibitor, or insulin.

When DAGLIF 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 DAGLIF is indicated for mild renal impairment. The efficacy of DAGLIF is dependent on renal function. DAGLIF should not be used in patients with moderate to severe renal impairment (defined as eGFR < 60 mL/min/1,73 m^2 by MDRD or CrCl < 60 mL/min by Cockcroft-Gault) (see sections 4.3, 4.4 and 4.8).

Monitoring of renal function is recommended as follows:

- Prior to initiation of DAGLIF and at least annually, thereafter (see section 5.2).
- Prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 mL/min or eGFR < 60 mL/min/1,73 m^2, DAGLIF treatment should be discontinued.

Hepatic impairment

No dosage adjustment for DAGLIF is necessary for patients with mild or moderate hepatic impairment. DAGLIF 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 DAGLIF may be appropriate (see section 4.4).

Elderly

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

Paediatric and adolescent population

Safety and effectiveness of DAGLIF in paediatric and adolescent patients have not been

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established.

Method of administration

For oral adminstration.

4.3 Contraindications

- Hypersensitivity to dapagliflozin 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 women or women who are breastfeeding their infants (see section 4.6).

4.4 Special warnings and precautions for use

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

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting

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from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. DAGLIF is contraindicated in these patients.

Renal impairment

The glycaemic efficacy of DAGLIF 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 section 4.2). In subjects with moderate renal impairment (GFR < 60 mL/min), a higher proportion of subjects treated with DAGLIF had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.

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

Hepatic impairment

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

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

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Caution should be exercised in patients for whom a DAGLIF-induced drop in blood pressure could pose a risk, such as patients on antihypertensive therapy with a history of hypotension or elderly patients. A 5 mg starting dose of DAGLIF may be appropriate in these patients (see section 4.2).

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. DAGLIF should be permanently discontinued in patients who develop volume depletion (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. DAGLIF 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. If ketoacidosis is suspected, DAGLIF should be discontinued and the patient should be promptly evaluated.

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

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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 DAGLIF 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 SGLT inhibitors, including DAGLIF. 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, DAGLIF treatment should be stopped immediately.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended.

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 urogenital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, DAGLIF should be discontinued and prompt

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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 DAGLIF should be considered when treating pyelonephritis or urosepsis.

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

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 DAGLIF.

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 antihypertensive 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 and 5.2).

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Cardiac failure

There is no experience in clinical studies with dapagliflozin in New York Heart Association (NYHA) class IV.

Paediatric use

Safety and efficacy of DAGLIF in paediatric patients have not been established.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Urine laboratory assessments

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

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Diuretics

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

Pharmacokinetic interactions

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

Effect of other medicines on DAGLIF

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of DAGLIF 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 DAGLIF 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-glycoprotein substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by international normalised ration (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 DAGLIF have not been studied

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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Breastfeeding

Mothers on DAGLIF should not breastfeed their infants. It is unknown whether DAGLIF is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk.

DAGLIF should not be used while breastfeeding and exposure to DAGLIF should be avoided during the first 2 years of life (see section 4.2).

Fertility

The effect of DAGLIF 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

DAGLIF causes dizziness and may have an influence on the ability to drive and use machines. Patients should also be alerted to the risk of hypoglycaemia when DAGLIF is used in combination with a sulphonylurea or insulin. Patients should therefore be warned to be cautious when driving a vehicle or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

During clinical studies in type 2 diabetes, the most frequently reported adverse reactions were genital infections.

Tabulated list of adverse reactions

The following adverse reactions have been reported during clinical studies. None were found to be dose related.

System organ class	**Frequent**	**Less frequent**
Infections and infestations	Vulvovaginitis, balanitis and related genital infections, urinary tract infection.	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 disorders		Hyperhidrosis.
Musculoskeletal and connective tissue disorders	Back pain.	
Renal and urinary disorders	Glycosuria, dysuria, polyuria (including pollakiuria, polyuria, increased urine output, osmotic diuresis.	Nocturia.

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Reproductive system and breast disorders	Vulvovaginal pruritis, genital pruritis.	
Investigations	Haematocrit increased, creatinine renal clearance decreased during initial treatment, dyslipidaemia.	Blood creatinine increased during initial treatment, blood urea increased, weight decreased.

Additional adverse reactions were reported when DAGLIF 10 mg was included in the following treatment regimens:

- add-on to metformin studies: headache,
- add-on to thiazolidinedione study: nasopharyngitis, diarrhoea.

In patients with moderate renal impairment, a higher frequency of bone fractures may be observed when treated with DAGLIF (see section 4.3).

Post-marketing adverse events

Spontaneous reports

Skin and subcutaneous disorders:

Rash, generalised rash, pruritic rash, macular rash, maculopapular rash, pustular rash, vesicular rash, erythematous rash.

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

In clinical studies, the most vulvovaginitis, balanitis and related genital infections reported were mild to moderate, and subjects responded to an initial course of standard treatment and rarely

resulted in discontinuation from treatment. These infections are more frequent in females and subjects with a prior history are more likely to have a recurrent infection.

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

Urinary tract infections

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.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported post marketing in patients taking SGLT2 inhibitors, including DAGLIF (see section 4.4).

Laboratory findings

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DAGLIF is important. It allows continued monitoring of the benefit/risk balance of DAGLIF. Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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4.9 Overdose

Symptoms of overdose

In overdose, side effects may be elicited or exacerbated (see section 4.8). Studies indicate that DAGLIF did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose).

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: 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.
The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycaemia in type 2 diabetes, reabsorption of filtered glucose continues. 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

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kidney through this mechanism is dependent upon the blood glucose concentration and 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 beta-cell) has been observed in clinical studies with dapagliflozin.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 3 000 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.

The urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. The increase in urinary volume may be associated with a small and 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 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.

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. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. 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, DAGLIF 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

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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 is 12,9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. 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 compound.

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), 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 of 32 %, 60 % and 87 % higher, respectively, than those of patients 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 patients with type 2 diabetes mellitus and normal renal function or

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mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known. Dapagliflozin is contraindicated in patients whose GFR is less than 60 mL/min (see section 4.3).

Hepatic impairment

There are 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 (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12 % and 36 % higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40 % and 67 % higher than matched healthy controls, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see section 4.2).

Elderly (≥ 65 years)

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

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.

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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

Crospovidone (E1202)

Hypromellose (E464)

Lactose anhydrous

Microcrystalline cellulose (E460)

Opadry white (containing hypromellose(E464), macrogol (E1521), titanium dioxide (E171) and talc (E553b)

Poloxamer 407

Silicon dioxide (E551)

Sodium stearyl fumarate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original container until required for use.

6.5 Nature and contents of container

DAGLIF is packed in a white, round HDPE bottle with a white child resistant polypropylene closure and a 2 g desiccant bag.

Pack size: 30 tablets.

6.6 Special precautions for disposal

No special requirments.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

DAGLIF 5 : To be allocated by SAHPRA upon registration.

DAGLIF 10 : To be allocated by SAHPRA upon registration.

9. DATE OF FIRST AUTHORISATION

To be allocated by SAHPRA upon registration.

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10. DATE OF REVISION OF THE TEXT

Signed: _____