SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

REDIFARG 5

REDIFARG 10

Film-coated tablets

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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg Dapagliflozin.

Each film-coated tablet contains 10 mg Dapagliflozin.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Monotherapy

As an adjunct diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Add-on combination therapy

In combination with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 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 REDIFARG once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin.

When REDIFARG 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 REDIFARG is indicated for mild renal impairment. The efficacy of REDIFARG is dependent on renal function. REDIFARG should not be used in patients with moderate to severe renal impairment (defined as eGFR < 60 mL/min/1,73 m^2 by Modification of Diet in Renal disease (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 REDIFARG and at least annually, thereafter.
- Prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year.

If renal function falls below CrCl < 60 mL/min or eGFR < 60 mL/min/1,73 m^2, REDIFARG treatment should be discontinued.

Hepatic impairment

No dosage adjustment for REDIFARG is necessary for patients with mild or moderate hepatic impairment. REDIFARG is not recommended for patients with severe hepatic impairment as efficacy has not been established (See section 5.2).

Use in 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 REDIFARG may be appropriate (See sections 4.4 and 4.8).

Elderly (≥ 65 years) patients:

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

Paediatric and adolescent

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

Method of administration

REDIFARG can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of REDIFARG (see section 6.1).
- Moderate and severe renal impairment with GFR < 60 mL/min, end stage renal failure or patients on dialysis.
- Diabetes Mellitus Type 1.
- Pregnant women or women who are breast-feeding their infants (see section 4.6).
- Patients with history of pancreatitis or pancreatic surgery.

4.4 Special warnings and precautions for use

Renal impairment

There is limited experience with initiating treatment with REDIFARG in patients with eGFR < 25 mL/min/1.73m^2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m^2. Therefore, it is not recommended to initiate treatment with REDIFARG in patients with eGFR < 15 mL/min/1.73m^2 (see section 4.2).

The glucose lowering efficacy of REDIFARG is dependent on renal function, and is reduced in patients with eGFR < 45 mL/min/1.73m^2 and is likely absent in patients with severe renal impairment (see sections 4.2, 5.1 and 5.2).

In patients with moderate renal impairment (eGFR < 60 mL/min/1.73m^2), a higher proportion of patients

treated with REDIFARG had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.

Hepatic impairment

There is limited experience in 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, REDIFARG 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 (REDIFARG) 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 REDIFARG is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Diabetic ketoacidosis

Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of diabetic ketoacidosis (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.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual

fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

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

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

Type 2 diabetes mellitus

Cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including REDIFARG. 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, REDIFARG treatment should be stopped immediately. Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Type 1 diabetes mellitus

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. REDIFARG is contraindicated in treatment of patients with type 1 diabetes (see section 4.3).

Necrotising fasciitis of the perineum (Fournier's gangrene)

If patients 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, REDIFARG should be discontinued and prompt treatment should be instituted.

Urinary tract and genital infections

SGLT2 inhibitors such as REDIFARG 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.

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of REDIFARG should be considered when treating pyelonephritis or urosepsis. Discontinuation of dapagliflozin may be considered in cases of recurrent urinary tract infections, see section 4.8 Undesirable effects.

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 REDIFARG in NYHA (New York Heart Association) class IV is limited.

Chronic kidney disease

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

REDIFARG has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA (Antineutrophilic cytoplasmic antibody)-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, 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 assessment

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Diuretics

REDIFARG 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 sulphonylurea, 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 REDIFARG in patients with type 2 diabetes mellitus (see sections 4.2 and 4.8).

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily mediated by UGT1A9- dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O- glucuronide, is not an SGLT2 inhibitor.

In *in-vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Dapagliflozin is a weak substrate of the P- glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters.

The dependence of dapagliflozin elimination on dapagliflozin 3-O- glucuronide formation in humans also suggests the possibility of interactions mediated by UGT1A9. Ketoconazole is an *in vitro* inhibitor of dapagliflozin 3-O-glucuronide formation by UGT1A9 (IC50 = 32 µM).

Effect of other medicines on REDIFARG

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of REDIFARG were not altered by metformin (a human OCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a human OAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an alpha-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1, hOCT-2, hOAT-3, P-gp, CYP2C8, CYP2C9, CYP3A4, and other alpha-glucosidase inhibitor would not be expected.

A 22 % decrease in dapagliflozin systemic exposure following co-administration with rifampicin was considered not to be large enough to warrant a dose adjustment.

Coadministration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

Effect of REDIFARG on other medicines

In interaction studies conducted in healthy subjects, using mainly single dose design, dapagliflozin did not alter the pharmacokinetics of metformin (an hOCT 1 and hOCT 2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a hOAT 3 substrate and P- glycoprotein substrate), glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide, valsartan, simvastatin (a CYP3A4 substrate), digoxin (a P-gp substrate) or warfarin (S warfarin, a CYP2C19 substrate, R warfarin or the anticoagulatory effects of warfarin as measured by the prothrombin time [International Normalised Ratio (INR)]). Therefore, dapagliflozin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.

Co-administration of dapagliflozin and bumetanide did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio [INR]).

Interference with1,5-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 REDIFARG have not been studied.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

REDIFARG is contraindicated in pregnancy. Maternal exposure to dapagliflozin as in REDIFARG in rat studies is associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, REDIFARG should be discontinued (see section 4.3).

Breast-feeding

Mothers on REDIFARG should not breast-feed their infants.

Alternatively, mothers breastfeeding their infants must not use REDIFARG. Studies in rats have shown excretion of REDIFARG in milk. Exposure to REDIFARG 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 ability to drive and use machines

REDIFARG has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when REDIFARG is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: Frequent (very common and common), Less Frequent (uncommon, rare and vary rare), and Frequency not known (cannot be estimated from the available data).

Table 1: The following undesirable effects have been observed and reported during treatment with

Dapagliflozin

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Vulvovaginitis, balanitis and related genital infections, urinary tract infection, 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, 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	Hyperhidrosis	
Musculoskeletal and connective tissue disorders	Back pain		
Renal and urinary disorders	Glucosuria, Dysuria, Polyuria	Nocturia	
Reproductive system and breast disorders		Vulvovaginal pruritus, Pruritus genital	
Investigations	Haematocrit increased	Blood creatinine	

	Creatinine renal clearance decreased during initial treatment, Dyslipidaemia	increased during initial treatment, Blood urea increased, Weight decreased	

Additional adverse reactions in patients treated with REDIFARG are described below by treatment regimen:

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

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 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 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 REDIFARG by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.2 Oral hypoglycaemics

Pharmacotherapeutic group: Medicines used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK01

Pharmacodynamic properties

Dapagliflozin is a reversible inhibitor of sodium glucose co-transporter 2 (SGLT2). SGLT2 is selectively expressed in the kidney, and 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 mellitus, reabsorption of filtered glucose continues. 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 studies with dapagliflozin.

Urinary glucose excretion (glycosuria) 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 3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.
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 mmol/1 to -0,0483 mmol/1.

5.2 Pharmacokinetic properties

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC_T values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50 % and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state.

These changes are not considered to be clinically meaningful. Hence, REDIFARG 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 inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Elimination

The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary

excretion with less than 2 % as unchanged dapagliflozin. After administration of a 50 mg [^{14}C]-dapagliflozin dose, 96 % was recovered, 75% in urine and 21 % in faeces. In faeces, approximately 15 % of the dose was excreted as parent medicine.

Linearity

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

Special populations

Renal impairment

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32 %, 60 % and 87 % higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of haemodialysis on dapagliflozin exposure is not known.

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

Tablet core:

Colloidal silicon dioxide

Crospovidone (Polyplasdone XL)

Magnesium stearate

Microcrystalline cellulose (Avicel PH 102)

Sodium lauryl sulphate

Film-coat: (Opadry II yellow 85F42129)

Iron Oxide Yellow

Macrogol/PEG

Polyvinyl alcohol.

Talc

Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep containers well closed.

Keep blisters in carton until required for use.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

REDIFARG 5:

- HDPE container (60 cc) is packed with pre-printed carton along with instructions for use, containing 30 tablets.
- HDPE container (150 cc) is packed with pre-printed carton along with instructions for use, containing 500 tablets.
- Aluminium base Foil on one side and Aluminium lidding foil on another side in the form of a Alu-Alu blister pack and such 3 X 10 blisters are further packed in printed carton along with instructions for use, containing 30 tablets.

REDIFARG 10:

- HDPE container (60 cc) is packed with pre-printed carton along with instructions for use, containing 30 tablets.
- HDPE container (150 cc) is packed with pre-printed carton along with instructions for use, containing 500 tablets.
- Aluminium base Foil on one side and Aluminium lidding foil on another side in the form of a Alu-Alu blister pack and such 3 X 10 blisters are further packed in printed carton along with instructions for use, containing 30 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

South Africa.

8. REGISTRATION NUMBER(S)

REDIFARG 5: 56/21.2/0969

REDIFARG 10: 56/21.2/0970

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 September 2024

10. DATE OF REVISION OF TEXT