**Dr. Reddy's Laboratories (Pty) Ltd.**
**REDIFARG XR 5 mg/ 500 mg**
**REDIFARG XR 5 mg/ 1000 mg**
**REDIFARG XR 10 mg/ 500 mg**
**REDIFARG XR 10 mg/ 1000 mg**
**APPROVED PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

REDIFARG XR 5 mg/ 500 mg; Extended-release tablets

REDIFARG XR 5 mg/ 1000 mg; Extended-release tablets

REDIFARG XR 10 mg/ 500 mg; Extended-release tablets

REDIFARG XR 10 mg/ 1000 mg; Extended-release tablets

**REDIFARG XR IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. REDIFARG XR 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 component medicine of REDIFARG XR. 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. REDIFARG XR 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 XR.**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REDIFARG XR 5 mg/ 500 mg: Each extended-release tablet contains 5 mg dapagliflozin and 500 mg metformin hydrochloride.

Contains sugar: lactose monohydrate 108,950 mg.

REDIFARG XR 5 mg/ 1000 mg: Each extended-release tablet contains 5 mg dapagliflozin and 1000 mg metformin hydrochloride.

Contains sugar: lactose monohydrate 108,950 mg.

REDIFARG XR 10 mg/ 500 mg: Each extended-release tablet contains 10 mg dapagliflozin and 500 mg metformin hydrochloride.

Contains sugar: lactose monohydrate 103,950 mg.

REDIFARG XR 10 mg/ 1000 mg: Each extended-release tablet contains 10 mg dapagliflozin and 1000 mg metformin hydrochloride.

Contains sugar: lactose monohydrate 103,950 mg.

For the full list of excipients, (see section 6.1).

## 3. PHARMACEUTICAL FORM

Extended-Release Tablets.

REDIFARG XR 5 mg/ 500 mg: Light pink coloured, capsule shaped biconvex, film-coated tablets debossed with "MD6" on one side and plain on other side.

REDIFARG XR 5 mg/ 1000 mg: Light pink coloured, oval shaped, biconvex, film-coated tablets debossed with "MD5" on one side and plain on other side

REDIFARG XR 10 mg/ 500 mg: Brown coloured, capsule shaped, biconvex, film-coated tablets debossed with "MD7" on one side and plain on other side.

REDIFARG XR 10 mg/ 1000 mg: Brown coloured, oval shaped, biconvex, film-coated tablets debossed with "MD4" on one side and plain on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

REDIFARG XR is indicated in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate:

- for the treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise.

### 4.2 Posology and method of administration

**Posology**

The recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin

is 500 mg once daily, which can be titrated to 2000 mg once daily, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

In patients treated with metformin, the dose of REDIFARG XR should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose.

If no adequate strength of REDIFARG XR is available, individual mono-components should be used instead of the fixed dose combination.

It is recommended to not exceed a dose of dapagliflozin 10 mg daily (two tablets of 5 mg dapagliflozin/500 mg metformin or two tablets of 5 mg dapagliflozin/1000 mg metformin).

**Special populations**

***Patients with renal impairment***

Assess renal function prior to initiation of REDIFARG XR and periodically thereafter (see sections 4.4 and 5.2).

Renal impaired patients may have a higher incidence of adverse events.

**Table 1: Dosage in patients with renal impairment**

| **eGFR mL/min/ 1,73 $m^2$** | **Metformin XR** | **Dapagliflozin** |
|---|---|---|
| 60 - 89 | Maximum daily dose is 2000 mg. Dose reduction may be considered in relation to declining renal function. | Maximum total daily dose is 10 mg. |
| 45 - 59 | Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose. | Maximum total daily dose is 10 mg. |
| 30 - 44 | Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose. | Dapagliflozin is not recommended when eGFR is persistently below 45 L/min/1,73 $m^2$. |
| < 30 | Metformin is contraindicated | Dapagliflozin is contraindicated. |

***Mild renal impairment***

No dose adjustment of REDIFARG XR is required for patients with mild renal impairment (eGFR 60 - 89 mL/min/1,73 $m^2$ by Modified Diet in Renal Disease [MDRD] eGFR equation).

***Moderate renal impairment***

REDIFARG XR is not recommended for the treatment of diabetes in patients with eGFR persistently below 45 mL/min/1,73 $m^2$ (see section 4.4). No dose adjustment is required for patients with eGFR ≥ 45 mL/min/1,73 $m^2$).

***Severe renal impairment***

Due to the metformin component, REDIFARG XR is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1,73 $m^2$) (see section 4.3).

***Patients with hepatic impairment***

Since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin, REDIFARG XR should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment (see section 4.4).

***Elderly patients***

Because metformin is eliminated by the kidneys, and because elderly patients are more likely to have decreased renal function, REDIFARG XR should be used with caution as age increases. The renal function recommendations provided for all patients also apply to elderly patients (see section 4.4).

***Patients at risk for volume depletion***

For patients at risk for volume depletion due to co-existing conditions, a 5 mg starting dose of dapagliflozin may be appropriate (see sections 4.4 and 5.1).

**Paediatric population**

The safety and efficacy of REDIFARG XR in paediatric and adolescent patients have not been established. No data are available.

**Method of administration**

REDIFARG XR should be taken orally, once daily with the evening meal.

Patients should be informed that REDIFARG XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of REDIFARG XR will be eliminated in the faeces as a soft, hydrated mass that may resemble the original tablet.

**4.3 Contraindications**

REDIFARG XR is contraindicated in patients with:

- Patients with a history of any serious hypersensitivity reaction to dapagliflozin, metformin hydrochloride or to any of the excipients.
- Severe renal impairment [(metformin component)] (eGFR < 30 mL/min/1,73 $m^2$).
- Acute or chronic metabolic acidosis including diabetic ketoacidosis.
- 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**

**Lactic acidosis**

*Metformin hydrochloride*

Lactic acidosis is a very rare, but serious and potentially fatal in the absence of prompt treatment, metabolic complication that can occur due to metformin accumulation (metformin plasma levels generally > 5 mcg/L). Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, dehydration, any acute conditions associated with hypoxia or impacting renal function (see section 4.4).
Medicines that can acutely impair renal function, such as antihypertensives, diuretics and NSAIDs, should be initiated with caution in metformin-treated patients (see section 4.5). Patients and/or caregivers should be informed on the risk of lactic acidosis.

Lactic acidosis is characterized by symptoms such as acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with REDIFARG XR should be discontinued and the patient hospitalized

immediately.

**Use in patients with renal impairment**

REDIFARG XR is not recommended for the treatment of diabetes in patients with eGFR persistently below 45 mL/min/1,73 $m^2$ as the glycaemic efficacy of dapagliflozin is dependent on renal function (see section 4.2). The maximum dose of metformin in patients with an eGFR of 30 to less than 45 mL/min/1,73 $m^2$ is 1000 mg once daily.

Due to metformin, REDIFARG XR is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1,73 $m^2$) (see section 4.3).

Metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function (see section 4.4).

Assess renal function prior to initiation of REDIFARG XR and then periodically thereafter:

- at least annually
- at least two to four times a year in patients with renal function where eGFR levels are approaching 45 mL/min/1,73 $m^2$ and in elderly patients.

**Acute conditions associated with hypoxia or impacting renal function**

*Metformin hydrochloride*

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. Acute conditions such as dehydration, severe infections, and hypoperfusion, have potential to alter renal function. In these situations, metformin must be discontinued.

**Radiologic studies with intravascular iodinated contrast materials**

*Metformin hydrochloride*

Intravascular administration of iodinated contrast medicines in radiological studies can lead to an acute decrease in renal function and has been associated with lactic acidosis in patients receiving metformin. REDIFARG XR should temporarily be discontinued prior to, or at the time of the procedure and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be stable.

**Surgical procedures**

*Metformin hydrochloride*

Use of REDIFARG XR should be temporarily suspended before any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as stable.

The patient should receive regular monitoring of their blood glucose with the administration of soluble insulin perioperatively as indicated.

**Use in patients with hepatic impairment**

*Metformin hydrochloride*

Since impaired hepatic function has been associated with some cases of metformin-associated lactic acidosis, REDIFARG XR should be avoided in patients with clinical or laboratory evidence of hepatic disease.

**Excessive alcohol intake**

*Metformin hydrochloride*

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving REDIFARG XR.

**Ketoacidosis**

*Dapagliflozin*

There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors. REDIFARG XR is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with REDIFARG XR who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of REDIFARG XR should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction,

reduced caloric intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. REDIFARG XR should be used with caution in these patients.

**Change in clinical status of patients with previously controlled type 2 diabetes**

*Metformin hydrochloride*

A patient with type 2 diabetes previously well controlled on REDIFARG XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of lactic acidosis. Evaluation should include serum electrolytes, urine and serum ketones, blood glucose, blood pH, lactate, pyruvate, and metformin levels. If acidosis occurs, REDIFARG XR must be stopped immediately and other appropriate corrective measures initiated.

**Use in patients at risk for volume depletion**

*Dapagliflozin*

Due to its mechanism of action, dapagliflozin induces osmotic diuresis which may lead to the decrease in blood pressure observed in studies (see section 5.1). For patients at risk for volume depletion due to co-existing conditions, a starting dose of dapagliflozin 5 mg once daily may be appropriate as REDIFARG XR or individual components. Temporary interruption of REDIFARG XR should be considered for patients who develop volume depletion.

**Use with medications known to cause hypoglycaemia**

*Dapagliflozin*

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin (see section 5.1).

*Metformin*

Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering medicines (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking medicines.

**Necrotising fasciitis of the perineum (Fournier's gangrene)**

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, dapagliflozin and metformin HCl 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 treatment 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).

**Lower limb amputations**

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

**Lactose**

REDIFARG XR contains lactose. Patients with rare hereditary problems of galactose intolerance, e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take REDIFARG XR.

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

**Interaction with dapagliflozin and metformin**

Coadministration of multiple doses of dapagliflozin and metformin did not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects.

There have been no formal interaction studies for REDIFARG XR. The following statements reflect the information available on the individual active substances.

**Medicine interactions with dapagliflozin**

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 CYP1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicines that are metabolized by these enzymes, and medicines that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. 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. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

**Effect of other medicines on dapagliflozin**

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics properties of dapagliflozin were not altered by metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an α-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 α-glucosidase inhibitors would not be expected.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and medicine-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22 % decrease and a 51 % increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case.

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

**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, simvastatin, digoxin (a P-gp substrate), or warfarin (S-warfarin is a CYP2C substrate). 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.

Coadministration 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]).

**Interactions between metformin hydrochloride and other medicines**

*Cationic medicines*

Cationic medicines (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems.

Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine medicine-interaction studies, with a 60 % increase in peak metformin plasma and whole blood concentrations and a 40 % increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering medicine is recommended in patients who are taking cationic medications that are excreted via the proximal renal

tubular secretory system.

*Glyburide*

In a single-dose interaction study in type 2 diabetic patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and maximum concentration ($C_{max}$) were observed but were highly variable. The single dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

*Furosemide*

A single-dose, metformin-furosemide medicine-interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood $C_{max}$ by 22 % and blood AUC by 15 %, without any significant change in metformin renal clearance. When administered with metformin, the $C_{max}$ and AUC of furosemide were 31 % and 12 % smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32 %, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

*Nifedipine*

A single-dose, metformin-nifedipine medicine-interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin $C_{max}$ and AUC by 20 % and 9 %, respectively, and increased the amount excreted in the urine. $T_{max}$ and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

*Use with other medicines*

Certain medicines tend to produce hyperglycaemia and may lead to loss of glycaemic control. These medicines include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking medicines, and isoniazid. When such medicines are administered to a patient receiving metformin, the

patient should be closely observed for loss of blood glucose control. When such medicines are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycaemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen was not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and, therefore, is less likely to interact with highly protein-bound medicines such as salicylates, sulphonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

*Concomitant use not recommended*

*Iodinated contrast medicines*

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. REDIFARG XR must be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

*Combination requiring precautions for use*

Some medicines can adversely affect renal function which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

*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 metformin (see sections 4.2 and 4.8).

**Other interactions**

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

*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 alternative methods to monitor glycaemic control.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

REDIFARG XR is contraindicated in pregnancy. When pregnancy is detected REDIFARG XR should be discontinued.

In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

There are no adequate and well-controlled studies of REDIFARG XR in pregnant women.

**Breastfeeding**

REDIFARG XR must not be used by a nursing woman.

No studies in lactating animals have been conducted with the combined components of REDIFARG XR. In studies performed with the individual components, both dapagliflozin and metformin are excreted in the milk of lactating rats.

Direct and indirect exposure of dapagliflozin to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight gain associated with lactational exposure in weanling juvenile rats suggest that dapagliflozin must be avoided during the first 2 years of life.

**Fertility**

The effect of REDIFARG XR on human fertility has not been studied.

### 4.7 Effects on ability to drive and use machines

REDIFARG XR has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicine is used in combination with other glucose-lowering medicines known to cause hypoglycaemia.

### 4.8 Undesirable effects

**Tabulated summary of adverse reactions**

*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: within each frequency grouping, and listed in the table below.

| **Adverse reaction** | **Frequency of adverse reaction** |
|---|---|
| **Infections and infestations** | |
| Vulvovaginitis, balanitis *[b]<br>Genital infection[a,b]<br>Urinary tract infection*[a,c] | Frequent |
| Fungal infection**<br>Necrotising fasciitis of the perineum (Fournier's gangrene) | Less frequent |
| **Metabolism and nutrition disorders** | |
| Hypoglycaemia | Frequent |
| Volume depletion[i]<br>Thirst**<br>Lactic acidosis<br>Vitamin B12 deficiency[g] | Less frequent |
| **Nervous system disorders** | |
| Taste disturbance | Frequent |

| | |
|---|---|
| Dizziness | |
| **Gastrointestinal disorders** | |
| Gastro-intestinal symptoms[h] | Frequent |
| Constipation**<br>Dry mouth** | Less frequent |
| **Hepatobiliary disorders** | |
| Liver function disorders, hepatitis | Less frequent |
| **Skin and subcutaneous tissue disorders** | |
| Urticaria, erythema, pruritus | Less frequent |
| Rash (Rash, generalized rash, pruritic rash, macular rash, maculo-papular rash, pustular rash, vesicular rash, erythematous rash.) | Frequent |
| **Musculoskeletal and connective tissue disorders** | |
| Back pain[d] | Frequent |
| **Renal and urinary disorders** | |
| Pollakiuria[a], polyuria[a,e] and Dysuria | Frequent |
| Nocturia** | Less frequent |
| **Reproductive system and breast disorders** | |
| Vulvovaginal pruritus**<br>Pruritus genital** | Less frequent |
| **Investigations** | |
| Haematocrit increased<br>Creatinine renal clearance decreased during initial treatment<br>Dyslipidaemia | Frequent |
| Blood creatinine increased during initial treatment**<br>Blood urea increased**<br>Weight decreased** | Less frequent |

[a] Identified from 8 placebo-controlled studies, including 2 initial combination with metformin, 2 add-on to

metformin, 1 add-on to insulin, 1 add-on to sitagliptin, and 2 studies with combination add-on therapy.

[b] Multiple adverse events terms, including vulvovaginal infections and candidiasis, balanoposthitis, balanitis candida, penile abscess, penile infection, vulval abscess and vaginitis bacterial.

[c] Multiple adverse events terms, including genitourinary tract infection, cystitis, pyelonephritis, trigonitis, urethritis and prostatitis.

[d] Additional events identified from 13 placebo-controlled studies with dapagliflozin 10 mg in type 2 diabetes mellitus including 3 monotherapy, 1 initial combination with metformin, 2 add-on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone, 1 add-on to sitagliptin, 1 add-on to glimepiride, and 2 studies with combination add-on therapy.

[e] Represents multiple adverse events terms, including polyuria, urine output increased.

[g] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency. Consideration of such etiology is recommended if a patient presents with megaloblastic anaemia.

[h] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

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

*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.

**Description of selected adverse reactions**

*Genital Infections*

Events of genital infections were reported in 5,5 % and 0,6 % of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. The events of genital infections reported in patients treated with dapagliflozin 10 mg were all mild to moderate. Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0,2 % dapagliflozin 10 mg vs. 0 % in placebo). Infections were reported more frequently in

females (8,4 % dapagliflozin 10 mg vs. 1,2 % placebo) than in males (3,4 % dapagliflozin 10 mg vs. 0,2 % placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

*Urinary Tract Infections*

Events of urinary tract infections (UTI) were reported in 4,7 % and 3,5 % of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. Most events of urinary tract infections reported in patients treated with dapagliflozin 10 mg were mild to moderate. Most patients responded to an initial course of standard treatment, and urinary tract infections rarely caused discontinuation from the study (0,2 % dapagliflozin 10 mg vs. 0,1 % placebo). Infections were more frequently reported in females (8,5 % dapagliflozin 10 mg vs. 6,7 % placebo) than in males (1,8 % dapagliflozin 10 mg vs. 1,3 % placebo).

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 requested to report any suspected adverse drug reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration: Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100

**4.9 Overdose**

*Dapagliflozin*

Orally administered dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the MRHD).

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.

*Metformin hydrochloride*

High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is haemodialysis. Events of hypoglycaemia have been reported with overdoses of metformin.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacological classification: A.21.2 Oral Hypoglycaemics

Pharmacotherapeutic group: Medicines used in diabetes, Combinations of oral blood glucose lowering medicines, ATC code: A10BD15

*Mechanism of action*

REDIFARG XR combines two antihyperglycaemic medicines with complementary mechanisms of action to improve both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with type 2 diabetes mellitus: dapagliflozin, an SGLT2 inhibitor, and metformin hydrochloride, a biguanide.

*Dapagliflozin*

Dapagliflozin is a potent, selective, and reversible inhibitor of sodium glucose cotransporter 2 (SGLT2) that improves glycaemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).

SGLT2 is selectively expressed in the in the proximal renal tubules 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 mellitus, reabsorption of filtered glucose continues. Dapagliflozin reduces maximum tubular glucose transport by 55 % and reduces renal glucose reabsorption such that glucose appears in the urine at normal plasma glucose levels. Thus, dapagliflozin improves both fasting and postprandial plasma glucose levels. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in healthy subjects with

normal glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta-cell function (HOMA-2) has been observed in studies with dapagliflozin.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of weight reduction is 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 greater than 1 400 times more selective for SGLT2 *versus* SGLT1, the major transporter in the gut responsible for glucose absorption.

*Metformin hydrochloride*

Metformin is an antihyperglycaemic medicine which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances (see section 4.4) and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

**Pharmacodynamics**

*Dapagliflozin*

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients 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

patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day or up to 2 years.
This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a 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**

REDIFARG XR combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride XR administered together as individual tablets.
The administration of REDIFARG XR in healthy subjects after a standard meal compared to the fasted state results in the same extent of exposure for both dapagliflozin and metformin XR. Compared to the fasted state, the standard meal results in 35 % reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful.

**Absorption**

*Dapagliflozin*

Dapagliflozin is rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations ($C_{max}$) are usually attained within 2 hours after administration in the fasted state. The $C_{max}$ and AUC values increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %.

*Metformin hydrochloride*

Following a single oral dose of metformin extended-release, $C_{max}$ is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and $C_{max}$ are less than dose proportional for metformin extended-release within the range of 500 to 2 000 mg administered once daily. Peak plasma levels are approximately 0,6, 1,1, 1,4, and 1,8 µg/mL for 500, 1 000, 1 500, and 2 000 mg once-daily doses, respectively.

**Distribution**

*Dapagliflozin*

Dapagliflozin is approximately 91 % protein bound. Protein binding is not altered in various disease states (e.g., renal or hepatic impairment).

*Metformin hydrochloride*

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate release metformin 850 mg averages 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90 % protein bound. Metformin partitions into erythrocytes, most likely as a function of time.

**Biotransformation**

*Dapagliflozin*

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 is 12,9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounts for 61 % of a 50 mg [$^{14}$C]- dapagliflozin dose and is the predominant medicine-related component in human plasma, accounting for 42 % (based on AUC [0-12 h]) of total plasma radioactivity, similar to the 39 % contribution by parent compound.

Based on AUC, no other metabolite accounts for > 5 % of the total plasma radioactivity. 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 presents in the liver and kidney, and CYP mediated metabolism is a minor clearance pathway in humans.

*Metformin hydrochloride*

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

**Excretion**

*Dapagliflozin*

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2 % is unchanged dapagliflozin. After administration of 50 mg [$^{14}$C]-dapagliflozin dose, 96 % is recovered, 75 % in urine and 21 % in faeces. In faeces, approximately 15 % of the dose is excreted as parent compound.

*Metformin hydrochloride*

Renal clearance is approximately 3,5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90 % of the absorbed compound is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6,2 hours. In blood, the elimination half-life is approximately 17,6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

**Special populations**

***Renal Impairment***

*Dapagliflozin*

For dosing recommendations for patients with moderate to severe renal impairment (see section 4.2). 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 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 was 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.

*Metformin hydrochloride*

In patients with renal impairment, the plasma and blood half-life of metformin is prolonged in proportion to the decrease in renal function.

***Hepatic Impairment***

*Dapagliflozin*

For dosing recommendations for patients with moderate or severe hepatic impairment (see section 4.2). 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 patients with hepatic impairment 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. No dose adjustment is required for patients with severe hepatic impairment. However, the benefit risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

*Metformin hydrochloride*

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

***Age***

*Dapagliflozin*

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.

*Metformin hydrochloride*

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and $C_{max}$ is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

***Paediatric and adolescent***

*Dapagliflozin*

Pharmacokinetics in the paediatric and adolescent population have not been studied.

*Metformin hydrochloride*

After administration of a single oral metformin 500 mg tablet with food, geometric mean metformin $C_{max}$ and AUC differed less than 5 % between paediatric type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20 - 45 years of age), all with normal renal function.

***Gender***

*Dapagliflozin*

No dosage adjustment from the dose of 10 mg once daily is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUCs in females (n = 619) was estimated to be 22 % higher than in males (n = 634), (90 % CI:117,124).

*Metformin hydrochloride*

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender (males=19, females=16). Similarly, in controlled studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin was comparable in males and

females.

***Race***

*Dapagliflozin*

No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (White, Black, or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to Whites (n = 1147), Asian subjects (n = 47) had no difference in estimated mean dapagliflozin systemic exposures (90 % CI range 3,7 % lower, 1 % higher). Compared to Whites, Black subjects (n = 43) had 4,9 % lower estimated mean dapagliflozin systemic exposures (90 % CI range 7,7 % lower, 3,7 % lower).

*Metformin hydrochloride*

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n = 24).

***Body Weight***

No dose adjustments from the proposed dapagliflozin dose of 10 mg once daily is recommended on the basis of 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 patients with 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.

**5.3 Preclinical safety data**

No animal studies have been conducted with REDIFARG XR to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and metformin individually.

***Carcinogenesis, mutagenesis, impairment of fertility***

*Dapagliflozin*

There was no evidence of carcinogenicity with dapagliflozin in either mouse or rat carcinogenicity studies. Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

*Metformin hydrochloride*

There was no evidence of carcinogenicity with metformin in either mouse or rat carcinogenicity studies. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day, approximately 4 times the maximum recommended human daily dose of 2000 mg based on body-surface-area comparisons.

There was no evidence of a mutagenic potential of metformin.

***Teratogenicity and impairment of early development***

*Dapagliflozin*

In a study direct administration of dapagliflozin to weanling juvenile rats, and indirect exposure during late pregnancy and lactation (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation), are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15× the MRHD. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1- month recovery period.

In a separate study of pre-natal and postnatal development, maternal rats were dosed from gestation day (GD) 6 through PND 21 (also at 1, 15, or 75 mg/kg/day), and pups were indirectly exposed *in utero* and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups). Increased incidence or severity of renal pelvic dilatation was again observed in adult offspring of treated dams, although only at 75 mg/kg/day (associated maternal and pup dapagliflozin exposures were 1 415× and 137×, respectively, the human values at the MRHD). Additional developmental toxicity was limited to dose-related reductions in pup body weights and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29× the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity, 1 mg/kg/day, is associated with a maternal systemic exposure multiple that is approximately 19× the human value at the MRHD.

In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20, 60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 1191× the MRHD. In rats, dapagliflozin was neither embryo lethal nor teratogenic at doses up to 75 mg/kg/day (1441× the MRHD).

*Metformin hydrochloride*

In a study metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2 000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of foetal concentrations demonstrated a partial placental barrier to metformin.

***Animal toxicology***

A 3-month rat study was conducted with the combination of dapagliflozin and metformin. No toxicity was observed at AUC exposures 52 and 1,4 times the MRHD for dapagliflozin and metformin, respectively.

*Dapagliflozin*

Most of the effects observed in pivotal repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose and included decreases in body weights and/or body-weight gains, increased food consumption, and increases in urine volumes due to osmotic diuresis. In rats, the most noteworthy nonclinical toxicity finding of increased trabecular bone and tissue mineralization (associated with increased serum calcium), was only observed at high exposure multiples (≥ 2100x~ based on human exposures at the MRHD). There was no dose-limiting or target-organ toxicities identified in the 12-month dog study at exposure multiples of ≥ 3200x~ the human exposure at the MRHD.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Crospovidone XL (Polyplasdone XL)

Hypromellose (Metolose 90SH-100000 SR)

Iron Oxide Sicovit Red 30 E 172

Isopropyl alcohol

Lactose monohydrate (Supertab 30 GR)

Magnesium Stearate (Ligamed -MF-2-V)

Microcrystalline cellulose (Avicel PH102)

Opadry II purple 85F500030

Opadry II white 85F18422

Purified water

Silicon dioxide (Syloid 244 FP)

Sodium Carboxy methyl cellulose (CEKOL 2000 P)

Sodium Lauryl Sulfate (Kolliphor SLS Fine)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years.

Store at or below 25 ºC.

Keep the container tightly closed until required for use.

Keep the tablets in the blisters and the blisters in the outer carton until required for use.

Keep out of reach of children.

**6.4 Special precautions for storage**

This medicine does not require any special storage conditions.

**6.5 Nature and contents of container**

**HDPE Bottle 30's Pack**

REDIFARG XR 5/ 500 mg; 10/ 500 mg:

75 cc white opaque HDPE containers with 38 mm neck, closed with 38 mm CR with induction sealing ward with a 2 gm silica gel canister in the bottle.

REDIFARG XR 5/ 1000 mg; 10/ 1000 mg:

100 cc white opaque HDPE containers with 38 mm neck, closed with 38 mm CR with induction sealing ward with a 2 gm silica gel canister in the bottle.

**PVC/Aclar Alu Blister pack 10's / 30's / 60's**

REDIFARG XR 5/ 500 mg; 10/ 500 mg:

Aluminium base foil on one side and Aluminium lidding foil on another side in the form of a PVC/Aclar Alu blister pack.

REDIFARG XR 5/ 1000 mg; 10/ 1000 mg:

Aluminium base foil on one side and Aluminium lidding foil on another side in the form of a PVC/Aclar Alu blister pack.

Not all strengths and pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block C, Woodmead North Office Park,

54 Maxwell Drive,

Woodmead, Sandton, 2191,

Gauteng

## 8. REGISTRATION NUMBERS

REDIFARG XR 5/ 500 mg: 57/21.2/0885

REDIFARG XR 5/ 1000 mg: 57/21.2/0886

REDIFARG XR 10/ 500 mg: 57/21.2/0887

REDIFARG XR 10/ 1000 mg: 57/21.2/0888

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

27 January 2026

## 10. DATE OF REVISION OF TEXT