SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Glucarest XR, Extended Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Glucarest XR extended release tablet contains metformin hydrochloride 500 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-Release Tablets

White to off-white, round, biconvex tablet having BPL on one side and 023 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control. Glucarest XR can be given alone as initial therapy or can be administered in combination with other oral antidiabetic medicines or with insulin.

4.2 Posology and method of administration

Posology

Glucarest XR:

Adults

The usual starting dose is one tablet daily given with the evening meal. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dosage is 4 tablets daily. Dosage increases should be made in increments of 500 mg every 10 to 15 days, up to a maximum of 2 000 mg once daily with an evening meal. If glycaemic control is not achieved with Glucarest XR 4 tablets once daily, Glucarest XR 2 tablets twice daily

should be considered, with both doses given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3 000 mg daily.

Switching patients already treated with metformin tablets:

In patients already treated with metformin tablets, the starting dose of Glucarest XR extended release tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2 000 mg daily, switching to Glucarest XR extended release tablets is not recommended.

Switching patients from other oral antidiabetic medicines:

If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate Glucarest XR extended release tablets at the doses indicated above.

Combination therapy with insulin:

Glucarest XR extended release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is Glucarest XR once daily with the evening meal, while insulin dosage is adjusted on the basis according to blood glucose measurements. After titration, 1 000 mg of metformin extended release tablets can be considered.

Other combination therapy:

See section 4.4.

Elderly:

Due to the potential for decreased renal function. Regular assessment of renal function is necessary (see section 4.4).

Children:

In the absence of available data, Glucarest XR should not be used in children.

Method of administration

For oral administration with food.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 mL/min).
- Acute conditions with the potential to alter renal function such as:
- dehydration,
- severe infection,
- shock,
- intravascular administration of iodinated contrast media.
- Acute or chronic disease which may cause tissue hypoxia:
    - decompensated heart failure,
    - respiratory failure,
    - recent myocardial infarction,
    - shock,
    - pancreatitis.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (acute of chronic).
- Use in pregnancy is not advised.

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare, but serious, metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), Glucarest XR should be temporarily discontinued and contact with a healthcare professional is recommended.

Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicines that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Glucarest XR and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7,35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter – at least annually in patients with normal renal function and at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects. Decreased renal function in elderly subjects is frequent and asymptomatic. Glucarest XR is contraindicated in patients with creatinine clearance < 60 ml/min and should be temporarily discontinued in the presence of condition that alter renal function, see section 4.3.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency, see section 4.3.

Elderly

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, Glucarest XR initiation is not recommended in these patients.

Administration of iodinated contrast medicines

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Glucarest XR should 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 4.3 and 4.5.

Surgery

Glucarest XR must be discontinued 48 hours before surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Other precautions

All patients should continue their diet with a regular distribution of carbohydrate intake during the day.

Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Glucarest XR alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition, or hepatic impairment.

Avoid consumption of alcohol and alcohol-containing medicines.

Iodinated contrast medicines

Glucarest 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 4.3 and 4.4.

Combinations 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 medicines in combination with Glucarest XR, close monitoring of renal function is necessary.

Medicines with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the Glucarest XR dosage during therapy with the other medicine and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of Glucarest XR with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these medicines are co-administered with Glucarest XR, as metformin plasma concentration may increase. If needed, dose adjustment of Glucarest XR may be considered as OCT inhibitors/inducers may alter the efficacy of Glucarest XR.

Anticoagulants

Glucarest XR has been reported to diminish the activity of warfarin, and so dose adjustments and increased frequency of INR determinations should be considered.

Sulphonylurea

Concomitant therapy of Glucarest XR with sulphonylurea may cause hypoglycaemia.

Vitamins

Long-term treatment with Glucarest XR may cause vitamin B12 malabsorption in the gastrointestinal tract, thus a dose reduction of Glucarest XR should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3).

The use of Glucarest XR during pregnancy is not advised (see section 4.3). For diabetes it is recommended that insulin should be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus.

Breastfeeding

Glucarest XR is excreted into human breast milk. Limited data are available, and therefor breastfeeding is not recommended during Glucarest XR treatment.

Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machines

Glucarest XR monotherapy does not cause hypoglycaemia.

However, patients should be alerted to the risk of hypoglycaemia when Glucarest XR is used in combination with other antidiabetic medicines (e.g. sulphonylureas, insulin, or meglinitides).

4.8 Undesirable effects

a) Summary of the safety profile

During treatment initiation, the most frequent adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

b) Tabulated summary of adverse reactions

System Organ Class	Frequency	Description
Metabolism and nutrition disorders	*Less frequent*	Lactic acidosis (see section 4.4) decrease of vitamin B12 absorption with decrease of serum levels during long-term use of Glucarest XR. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.
Nervous system disorders	*Frequent*	Taste disturbance.
Gastrointestinal disorders	*Frequent*	Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepato-biliary disorders	*Less frequent*	Isolated reports of liver function tests abnormalities or hepatitis resolving upon discontinuation.
Skin and subcutaneous tissue disorders	*Less frequent*	Erythema, pruritus, urticaria

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. Healthcare 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

Hypoglycaemia can occur when Glucarest XR is given concomitantly with a sulphonylurea, insulin or alcohol. High overdose or concomitant risks of Glucarest XR may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. There is no specific antidote for overdose with Glucarest XR. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ORAL ANTI-DIABETICS

ATC code: A10BA02: Gastrointestinal tract and metabolism

Mechanism of action

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Pharmacodynamic effects

In clinical studies, the major non glycaemic effect of metformin is either weight stability or modest weight loss.

5.2 Pharmacokinetic properties

Absorption:

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2,5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2 000 mg of metformin prolonged release tablets is similar to that observed after administration of 1 000 mg of metformin immediate release tablets twice daily.

Intrasubject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30 % (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2 000 mg of metformin as prolonged release tablets. Although there is no information on the exposure after the 500 mg extended release tablets, it is presumed that similar increased exposure occurs with this formulation when given in the fed-state.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Biotransformation:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. There is no biliary excretion.

Elimination:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6,5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose

Magnesium Stearate

Microcrystalline Cellulose Type 101

Povidone K-30

Sodium Carboxymethyl Cellulose

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C in the original container.

Protect from light and moisture.

6.5 Nature and contents of container

60 Count: Packed in a white opaque 120 cc HDPE bottle with white opaque round, 38 mm polypropylene CR Closure with Translucent Inner Cap and heat seal liner.

100 Count: Packed in a white opaque 120 cc HDPE bottle with white opaque round, 38 mm polypropylene CR Closure with Translucent Inner Cap and heat seal liner.

500 Count: Packed in a white opaque 950 cc HDPE bottle with white opaque, round cylindrical high density polypropylene cap with heat seal liner.

1000 Count: Packed in a white opaque 1300 cc HDPE bottle with white opaque, round cylindrical high density polypropylene cap with heat seal liner.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd.

124 Elevation Avenue

Randjesfontein

Midrand

1683

South Africa

8. REGISTRATION NUMBER

52/21.2/0409

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2021

10. DATE OF REVISION OF THE TEXT

15 April 2021