Professional Information

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Glucophage XR 500 mg (prolonged release tablet)

Glucophage XR 1000 mg (prolonged release tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release **GLUCOPHAGE XR 500 mg** tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.

Each prolonged release **GLUCOPHAGE XR 1000 mg** tablet contains 1 000 mg metformin hydrochloride corresponding to 780 mg metformin base.

Sugar-free.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Glucophage XR 500 mg:	White to off-white, round, biconvex tablet of 12 mm diameter, debossed on one side with “500”.
Glucophage XR 1000 mg:	White to off-white, capsule-shaped, biconvex tablet of 22 mm length, debossed with “1000” on one face and “Merck” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Risk reduction or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with prediabetes (IGT* and/or IFG*, and/or increased HbA1c) and additional risk factors**, in whom lifestyle change has not resulted in adequate glycaemic control.

  Lifestyle modifications should be continued when metformin is initiated, unless the patient is unable to do so because of medical reasons.

  *IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose

  ** Identified risk factors include obesity, age, hypertension, cardiovascular disease, family history of diabetes, dyslipidaemia, gestational diabetes, and Polycystic ovary syndrome (PCOS).

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

4.2 Posology and method of administration

<u>Reduction in the risk or delay of the onset of type 2 diabetes:</u>

- Metformin should only be considered where intensive lifestyle modifications for 3 to 6 months have not resulted in adequate glycaemic control.
- The therapy should be initiated with Glucophage XR 500 mg once daily with the evening meal.
- After 10 to 15 days, dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1c values to be within the normal range). A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose is 2000 mg of Glucophage XR once daily with the evening meal.

- It is recommended to regularly monitor (every 3 – 6 months) the glycaemic status (OGTT and/or FPG and/or HbA1C value) as well as the risk factors to evaluate whether treatment needs to be adapted.

Monotherapy in Type 2 diabetes mellitus and combination with other oral antidiabetic agents:

Glucophage XR 500 mg:

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 2000 mg once daily with an evening meal. If glycaemic control is not achieved with Glucophage XR 500 mg 4 tablets once daily, Glucophage XR 500 mg 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 3000 mg daily.

Glucophage XR 1000 mg:

Glucophage XR 1000 mg should be taken once daily with the evening meal at a maximum recommended dose of 2 tablets daily.

Glucophage XR 1000 mg is intended as maintenance therapy for patients already treated with either 1000 mg (2 tablets of Glucophage XR 500) or 2000 mg (4 tablets of Glucophage XR 500) of sustained release metformin hydrochloride.

If glycaemic control is not achieved on once daily dosing of Glucophage XR at a maximum dose of 2000 mg a day, then a twice daily dosing schedule should be considered with both doses being given with food, at the time of the morning and evening meals.

If glycaemic control is still not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum daily dose of 3000 mg daily.

Switching patients already treated with metformin tablets

In patients already treated with metformin tablets, the starting dose of Glucophage XR prolonged release tablets should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Glucophage XR prolonged release tablets is not recommended.

Switching patients from other oral antidiabetic agents

If transfer from another oral antidiabetic agent is intended, discontinue the other agent and initiate Glucophage XR prolonged release tablets at the doses indicated above.

Combination therapy with insulin

Glucophage XR 500 and Glucophage XR 1000

Glucophage XR prolonged release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is Glucophage XR 500 mg once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, switch to Glucophage XR 1000 mg may be considered.

Other combination therapy

See Warnings and special precautions.

Elderly

Due to the potential for decreased renal function in elderly subjects, the dosage for the Glucophage XR range should be adjusted based on renal function. Regular assessment of renal function is necessary. (See section 6.)

Benefit in the treatment of prediabetic hyperglycaemia has not been established in patients 75 years and older and metformin initiation is therefore not recommended in these patients.

Children

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

Renal Impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR (mL/min)	Total maximum daily dose	Additional considerations
60-89	2000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

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.
- Disease (especially acute disease, or worsening of chronic disease) which may cause tissue hypoxia, such as unstable congestive heart failure, respiratory failure, recent myocardial infarction or shock
- Severe renal failure (CrCl below 30 mL/min or eGFR below 30 mL/min/1.73m^2).
- Acute conditions with the potential to alter renal function such as e.g. dehydration, severe infection or shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication.

Risk factors include poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, severe infection, hepatic insufficiency, and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction) or the concomitant use of medications which might cause lactic acidosis (such as NRTIs), (see also section 5).

Lactic acidosis can occur due to metformin accumulation.
Reported cases of lactic acidosis in patients on metformin have occurred primarily in - patients with acute worsening of renal function or cardiorespiratory illness or sepsis.

Special caution should therefore be paid to situations where renal function may become acutely impaired, for example in case of dehydration (severe or prolonged diarrhoea or vomiting) or when initiating medications which can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs).

In the acute conditions listed, Glucophage XR must be immediately and temporarily discontinued.

Patients and/or care-givers 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 metformin 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.

If metabolic acidosis is suspected, Glucophage should be discontinued, and the patient should be hospitalised **immediately.**

Medical practitioners must alert the patients on the risk and on the symptoms of lactic acidosis.
Patients should be instructed to immediately seek medical attention and to stop taking Glucophage XR.
Glucophage XR must be immediately discontinued, at least temporarily, until the situation is clarified. Reintroduction of Glucophage XR should then be discussed taking into account the benefit/risk ratio on an individual basis as well as renal function.

Renal function:

As Glucophage XR is excreted by kidney, it is recommended that CrCl (this can be estimated from creatinine levels by using Cockcroft-Gault formula) or eGFR should be determined before initiating treatment and regularly thereafter:

- At least annually in patients with normal renal function,
- At least every 3 to 6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m^2 and in elderly subjects.
- At least every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m^2.

In case CrCl is below 30 mL/min or eGFR is below 30 mL/min/1.73m^2 respectively, Glucophage is

contraindicated.

Decreased renal function in elderly subjects is frequent and asymptomatic.

Special caution should be exercised in situations where renal function may become acutely impaired, for example due to dehydration (severe or prolonged diarrhoea or vomiting), or when initiating medicines which can acutely impair renal function (such as antihypertensive therapy or diuretic therapy and when starting therapy with a NSAID).

In the acute conditions listed, Glucophage XR must be immediately and temporarily discontinued. In these cases, it is also recommended to check renal function before initiating treatment with Glucophage XR.

Cardiac function:

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Glucophage XR may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, Glucophage XR is contraindicated (see section 4.3).

Combination with iodinated contrast materials

Intravascular administration of iodinated contrast materials in radiodiagnostic examinations can lead to renal failure. This may induce metformin accumulation and an increased risk of lactic acidosis. Therefore, Glucophage XR must be discontinued 48 hours before the test in patients with CrCl below 45 mL/min or eGFR below 45 mL/min/1.73m^2 for intravenous administration and patients with CrCl below 60 mL/min or eGFR below 60 mL/min/1.73m^2 for intra-arterial administration. Glucophage XR may not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.

Surgery

Glucophage XR must be discontinued 48 hours prior to elective major surgical interventions and may not be reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further. The patient should receive soluble insulin perioperatively with monitoring of their blood glucose. (*Hyperglycaemia worsens with surgical stress and the diabetic patient cannot be left untreated).*

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.
- Glucophage XR alone does not cause hypoglycaemia, although caution is advised when it is used in combination with insulin, or other oral antidiabetics (e.g. sulfonylureas or meglitinides).
- The tablet shells may be present in the faeces. Patients should be advised that this is normal.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended:

Alcohol:

The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency.

It is recommended that consumption of alcohol and alcohol-containing medicines be avoided.

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in Glucophage accumulation and a risk of lactic acidosis.

Glucophage should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Contraindicated combinations

In patients with CrCL is below 45 mL/min or eGFR is below 45 mL/min/1.73m^2 for intravenous administration or in patients with CrCL is below 60 mL/min or eGFR below 60 mL/min/1.73m^2 for intra-arterial administration of iodinated contrast materials, Glucophage must be discontinued 48 hours before the test.

Combinations to be used with caution

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides, beta-2-agonists, danazol, and chlorpromazine at high dosages of 100 mg per day, diuretics): More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

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

Therefore, caution is advised when these drugs are co-administered with metformin and a dose adjustment may be considered, particularly in patients with renal impairment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased 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.

Safety in pregnancy and lactation has not been established in humans, however animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development (see section 5.3).

When the patient plans to become pregnant and during pregnancy, it is recommended that prediabetes and diabetes are not treated with metformin, but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Lactation:

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during metformin treatment.

Fertility:

Fertility of male and female rats were 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 machinery

Glucophage XR monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when Glucophage XR is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulins or meglitinides).

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to gradually increase the dose of Glucophage XR to the desired dosage.

Adverse reactions reported are listed below by system organ class and by frequency.
Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (< 1/10 000), very rare (< 1/10 000)

Metabolism and nutrition disorders:

Very rare:

- Decrease of vitamin B12 and folic acid absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.
- Lactic acidosis

Nervous system disorders:

Common:

- Taste disturbance.

Gastrointestinal disorders:

Very common:

- Gastrointestinal disorders such as 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 gradual increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

Very rare:

- Liver function tests abnormalities or hepatitis resolving on metformin discontinuation.

Skin and subcutaneous tissue disorder:

Very rare:

- Skin reactions such as erythema, pruritus, urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product 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

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. In excessive dosage, and particularly if there is a possibility of accumulation, lactic acidosis may develop. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacological classification: A 21.2 Oral hypoglycaemics.

Pharmacodynamic properties:

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:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3. 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 (GLUTs) known to date.

5.2 Pharmacokinetic Properties

***Absorption**:*

Following a single oral dose of Glucophage XR 500 mg, metformin absorption is significantly delayed compared to the immediate-release tablet (T_{max} at 2.5 hours) with a T_{max} at 7 hours.

Following a single oral dose of 1500 mg of Glucophage XR 750 mg, a mean plasma concentration of 1193 ng/ml is achieved after a median value of 5 hours (range of 4 to 12 hours).

Glucophage XR 750 mg was shown to be bioequivalent to Glucophage XR 500 mg, at a total daily dose of 1500 mg, with respect to C_{max} and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Glucophage XR 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved after a median time of 5 hours (range

of 4 to 10 hours). Glucophage XR 1000 mg was shown to be bioequivalent to Glucophage XR 500 mg, at a dose of 1000 mg, with respect to C_{max} and AUC in healthy fed and fasted subjects.

At steady-state, both C_{max} and AUC of metformin do not increase proportionally to the administered dose.

The AUC after a single oral administration of 2000 mg metformin prolonged-release is similar to that observed after administration of 1000 mg metformin immediate-release twice daily.

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

When 2 tablets of 500 mg metformin prolonged-release is administered in fed conditions the AUC is increased by approximately 70 % (both C_{max} and T_{max} are only slightly increased).

When the 1000 mg prolonged release tablet are administered in fed conditions the AUC is increased by 77 % (C_{max} is increased by 26 % and T_{max} is slightly prolonged by about 1 hour).

Metformin absorption from the prolonged-release formulation is not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg metformin prolonged-release.

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 Volume of Distribution ranged between 63 - 276 l.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

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.

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

The inactive ingredients are magnesium stearate, sodium carboxymethylcellulose; hydroxypropyl methylcellulose.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep out of reach of children.

Do not remove from carton until ready for use.

6.5 Nature and contents of container

30, 60, 90 or 120 tablets packed in transparent PVC or PVC/PVDC blisters with an aluminium backing.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE FOR REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein

1645

8. REGISTRATION NUMBERS

Glucophage XR 500 mg: A39/21.2/0027

Glucophage XR 1 000 mg: 45/21.2/0066

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 October 2007

10. DATE OF REVISION OF TEXT

12 April 2021