SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

METFORMIN 500 mg PHARMC, film-coated tablets

METFORMIN 850 mg PHARMC, film-coated tablets

METFORMIN 1000 mg PHARMC, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each METFORMIN 500 mg PHARMC tablet contains 500 mg metformin hydrochloride.

Each METFORMIN 850 mg PHARMC tablet contains 850 mg metformin hydrochloride.

Each METFORMIN 1000 mg PHARMC tablet contains 1000 mg metformin hydrochloride.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

METFORMIN 500 mg PHARMC White to off white, round biconvex film-coated tablets having “G” and “10” debossing on one side and plain on other side.

METFORMIN 850 mg PHARMC: White to off white, round biconvex film-coated tablets having “G” and “11” debossing on one side and plain on other side.

METFORMIN 1000 mg PHARMC: White to off white oval biconvex scored film-coated tablets debossed with "G" and "12" on either side of score line on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, METFORMIN PHARMC film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic medicines or with insulin.
- In children over 12 years of age and adolescents with type 2 diabetes, METFORMIN PHARMC film-coated tablets may be used as monotherapy or in combination with insulin.

4.2 Posology and method of administration

Posology

It is important that METFORMIN PHARMC tablets be taken in divided doses with meals.

Adults: Initially, one 500 mg tablet three times a day, or one 850 mg or 1000 mg tablet twice a day, with or after food. After 10 to 15 days the dose should be adjusted according to blood glucose measurements. A slow increase in dose may improve gastro-intestinal tolerability. Good diabetic control may be achieved within a few days, but it is not unusual for the full effect to be delayed for up to two weeks. If control is incomplete a cautious increase in dosage to a maximum of 2 550 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of METFORMIN PHARMC.

Children and adolescents: METFORMIN PHARMC can be used in children from 12 years of age and adolescents. The usual starting dose is 500 mg or 850 mg once daily, given during meals or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin is 2 000 mg daily, taken as 2 or 3 divided doses.

Elderly: METFORMIN PHARMC dose in the elderly should be adjusted based on renal function.

Combination therapy: see section 4.4.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients (see section 6.1).
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 µmol/L in males and > 110 µmol/L in females or creatinine clearance < 60 (ml/min).
- Acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock,
  - intravascular administration of iodinated contrast agents (see section 4.4).
- Acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock
  - pancreatitis.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to METFORMIN PHARMC accumulation. 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 assessing

also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis

Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (< 7,35), plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, METFORMIN PHARMC should be discontinued, and the patient should be hospitalised immediately.

Renal function

As METFORMIN PHARMC is excreted by kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function,
- 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. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a NSAID.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, METFORMIN PHARMC is contraindicated (see section 4.3).

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure, METFORMIN PHARMC should be discontinued prior to, or at the time of the test

and not reinstituted unit 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

METFORMIN PHARMC should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

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.
- METFORMIN PHARMC alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas.
- As Vitamin B12 deficiency and megaloblastic anaemia may develop with METFORMIN PHARMC use, Vitamin B12 levels should be assessed at least annually.

Paediatric population

The diagnosis of type 2 diabetes mellitus must be confirmed before treatment with METFORMIN PHARMC is initiated. No effect of METFORMIN PHARMC on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of METFORMIN PHARMC on these parameters in METFORMIN PHARMC treated children, especially pre-pubescent children, is recommended.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use not recommended

Alcohol

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

Avoid consumption of alcohol and alcohol-containing medicines.

Iodinated contrast agents

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

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 metformin, close monitoring of renal function is necessary. Reduced renal clearance of metformin has been reported during cimetidine therapy, so a dose reduction should be considered. An interaction between METFORMIN PHARMC and anticoagulants is a possibility and dosage of the latter may need adjustment.

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 metformin dosage during therapy with the respective medicine and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of METFORMIN PHARMC with:

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of METFORMIN PHARMC.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of METFORMIN PHARMC.

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

Safety in pregnancy has not been established in humans.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with METFORMIN PHARMC, 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.

Breastfeeding

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

Metformin 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 metformin is used in combination with other antidiabetic medicines (e.g., sulfonylureas, insulin or meglitinides).

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. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase the doses slowly.

b. Tabulated summary of adverse reactions

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as: frequent, less frequent and frequency unknown (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders:	Less frequent	Decrease of vitamin B12 and folic acid absorption with decrease of serum levels during long-term use of METFORMIN PHARMC. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia. Lactic acidosis.
Nervous system disorders	Frequent	Taste disturbance.
Gastrointestinal disorders	Frequent	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. To prevent them, it is recommended that METFORMIN PHARMC be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepato-biliary disorders	Frequency unknown	Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders	Less frequent	Skin reactions such as erythema, pruritus, urticaria.
	Frequency unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome).

Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10 – 16 years during 1-year, adverse event reporting was similar in nature and severity to that reported in adults.

Reporting of suspected adverse reactions

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

4.9 Overdose

Hypoglycaemia can occur when METFORMIN PHARMC is given concomitantly with a sulphonylurea, insulin or alcohol. 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 PHARMC is haemodialysis. Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and correcting blood glucose levels.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2 Oral Hypoglycaemic.

Pharmacotherapeutic Group: Blood glucose lowering drugs. Biguanides; ATC code: A10BA02

Metformin is a biguanide with antihyperglycaemic 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 utilization.

(3) Delay of intestinal glucose absorption.

5.2 Pharmacokinetic properties

Absorption:

After an oral dose of metformin, T_{max} is reached in 2,5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50 - 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20 - 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin.

Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC (area under the curve) and a 35-minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

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.

Biotransformation:

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.

Paediatrics:

Single dose study: After single doses of metformin 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Magnesium stearate

Povidone K 30

Povidone K 90

Pregelatinised starch

Film-coating

HPMC 2910/Hypromellose, Macrogol/PEG, Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in cool and dry place at or below 25 ºC.

Blisters: Do not remove the blisters from the outer carton until required for use.

HDPE bottles: Keep in the original container.

6.5 Nature and contents of container

500 mg & 850 mg:

Blister Pack

- 10 tablets in blister pack (PVC-aluminum) packed in an outer carton as 60, 90,120 tablets

  or

HDPE bottles

- 60 tablets in HDPE bottles (high-density polyethylene) with child resistant caps (polypropylene) and desiccant sachet activated carbon 1g, or
- 1000 tablets in HDPE bottles (high-density polyethylene) with continues thread caps (polypropylene) and desiccant sachet activated carbon 2 g.

1000 mg:

Blister pack

- 15 tablets in blister pack (PVC-aluminum) packed in an outer carton as 30, 60, 90,120 tablets or

HDPE bottles

- 60 tablets in HDPE bottles (high-density polyethylene) with child resistant caps (polypropylene) and desiccant sachet activated carbon 1g, or
  1000 tablets in HDPE bottles (high-density polyethylene) with continues thread caps (polypropylene) and desiccant sachet activated carbon 2 g.

Not all packs and pack sizes are marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACORP (PTY) LTD

29 Victoria Link, Route 21 Corporate Park

Irene, 0178, RSA

8 REGISTRATION NUMBERS

METFORMIN 500 mg PHARMC: 56/21.2/0102

METFORMIN 850 mg PHARMC: 56/21.2/0103

METFORMIN 1000 mg PHARMC: 56/21.2/0104

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 October 2023

10 DATE OF REVISION OF THE TEXT