SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

METFORMIN 500 BIOTECH, 500 mg, film-coated tablets

METFORMIN 850 BIOTECH, 850 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METFORMIN 500 BIOTECH: Each film-coated tablet contains 500 mg metformin hydrochloride.

METFORMIN 850 BIOTECH: Each film-coated tablet contains 850 mg metformin hydrochloride.

Contains sugar (lactose monohydrate).

METFORMIN 500 BIOTECH contains 10,8 mg lactose monohydrate per film-coated tablet.

METFORMIN 850 BIOTECH contains 14,4 mg lactose monohydrate per film-coated tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

METFORMIN 500 BIOTECH: White, biconvex oblong film-coated tablets, with a both sided score notch. One side engraved “M/500”. The surface is faultless. L: 17,0 to 17,4 mm, B: 7,0 to 7,4 mm, H: 5,6 to 6,4 mm.

METFORMIN 850 BIOTECH: White, oblong film-coated tablets. upside with “snap-tab” downside convex and engraved “M/850” and faultless surface. L: 19,0 to 19,4 mm, B: 8,0 to 8,4 mm.

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 BIOTECH 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 BIOTECH 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 BIOTECH tablets be taken in divided doses with meals.

Adults: Initially, one 850 mg tablet twice a day or one 500 mg tablet three times 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 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 BIOTECH.

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

Combination Therapy: See section 4.4.

Paediatric population

Children and adolescents:

METFORMIN BIOTECH 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.

METFORMIN BIOTECH is not recommended for use in children less than 12 years.

Method of administration

To be taken orally.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or any of the excipients of METFORMIN BIOTECH listed in section 6.1.
- Diabetic pre-coma and ketoacidosis.
- 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 medicines (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, a serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. METFORMIN BIOTECH accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In patients with a metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia) lactic acidosis should be suspected and METFORMIN BIOTECH therapy stopped. Lactic acidosis is a medical emergency which must be treated in hospital.

The use of METFORMIN BIOTECH is not advised in conditions which may cause dehydration (e.g., severe diarrhoea or vomiting, fever or reduced fluid intake) or in patients suffering from serious infections, trauma or on low calorie intake (see section 4.3).

Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in METFORMIN BIOTECH 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 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 BIOTECH 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

METFORMIN BIOTECH is excreted by the 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 (see section 4.3), for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a NSAID.

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. METFORMIN BIOTECH 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 section 4.5.

Surgery

METFORMIN BIOTECH therapy should be stopped at the time of 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.

Children and adolescents

The diagnosis of type 2 diabetes mellitus must be confirmed before treatment with METFORMIN BIOTECH is initiated.

No effect of METFORMIN BIOTECH 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 BIOTECH on these parameters in METFORMIN BIOTECH treated children, especially pre-pubescent children, is recommended.

METFORMIN BIOTECH can possibly cause ketoacidosis in children after exercise.

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.
- Patients receiving continuous METFORMIN BIOTECH therapy should have an annual estimation of Vitamin B12 levels because of reports of decreased Vitamin B12 absorption.
- METFORMIN BIOTECH 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).

Stabilisation of diabetic patients with METFORMIN BIOTECH and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the correct ratio of the two medicines has been obtained (see section 4.5).

METFORMIN BIOTECH contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take METFORMIN BIOTECH.

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 or malnutrition,
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medicines (see section 4.3).

Iodinated contrast medicines

METFORMIN BIOTECH 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 section 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 METFORMIN BIOTECH, 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 METFORMIN BIOTECH dosage during therapy with the respective medicine and upon its discontinuation.

Organic cation transporters (OCT)

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of METFORMIN BIOTECH.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of METFORMIN BIOTECH.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of METFORMIN BIOTECH 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 BIOTECH.
- An interaction between METFORMIN BIOTECH and anticoagulants is a possibility and dosage of the latter may need adjustment.

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

Other

Hypoglycaemia can occur when METFORMIN BIOTECH is given concomitantly with a sulphonylurea, or insulin (see section 4.4).

4.6 Fertility, pregnancy and lactation

The use of METFORMIN BIOTECH during pregnancy and lactation is contraindicated as safety has not been established (see section 4.3).

However, animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.

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

4.7 Effects on ability to drive and use machines

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

Patients should be alerted to the risk of hypoglycaemia when METFORMIN BIOTECH is used in combination with other antidiabetic medicines (e.g. sulfonylureas, insulin or meglitinides).

4.8 Undesirable effects

Tabulated summary of adverse reactions

Metabolism and nutrition disorders	
Frequent:	Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of METFORMIN BIOTECH (consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia).
Less frequent:	Lactic acidosis, sometimes fatal (see section 4.4).
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. To prevent them, it is recommended that METFORMIN BIOTECH 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	
Less frequent:	Liver function tests abnormalities or hepatitis resolving upon METFORMIN BIOTECH discontinuation.
Skin and subcutaneous tissue disorders	
Less frequent:	Skin reactions such as 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 METFORMIN BIOTECH 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 is haemodialysis.

Intense symptomatic and supportive therapy is recommended which should be particularly directed at correcting fluid loss and metabolic disturbance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.21.2 Oral hypoglycaemics

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

Metformin hydrochloride is a biguanide oral anti-hyperglycaemic agent. Its mode of action is thought to be multifactorial and includes delayed uptake of glucose from the gastrointestinal tract, increase peripheral glucose utilisation mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

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.

Paediatric population

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:

Colloidal silicone dioxide

Copolyvidone

Magnesium stearate

Microcrystalline cellulose.

Sodium starch glycolate

Tablet coating:

Opadry white OY- L-28900 consisting of:

Lactose monohydrate

Macrogol 4 000

Methylhydroxypropylcellulose

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C in a well-closed container.

Do not remove tablets from original packaging until required for use.

Protect from light and moisture.

6.5 Nature and contents of container

METFORMIN 500 BIOTECH:

Plain Pouch PRP (Patient Ready Pack): Plain laminated pouch made up of outer side metalised polyethylene terephthalate (PET) and inner side white opaque polyethylene (PE). Open from bottom side and zip lock with perforation on top side.

Pack size: 56's

White, opaque HDPE container with white, opaque screw type cap with induction sealing wad.

Pack size: 100's

METFORMIN 850 BIOTECH:

Plain Pouch PRP (Patient Ready Pack): Plain laminated pouch made up of outer side metalised polyethylene terephthalate (PET) and inner side white opaque polyethylene (PE). Open from bottom side and zip lock with perforation on top side.

Pack size: 28's

White, opaque HDPE container with white, opaque screw type cap with induction sealing wad.

Pack size: 60's, 84's

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand, 1685

South Africa

8. REGISTRATION NUMBER(S)

METFORMIN 500 BIOTECH: 35/21.2/0093

METFORMIN 850 BIOTECH: 35/21.2/0094

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 06 June 2003

10. DATE OF REVISION OF THE TEXT

09 January 2024