PROFESSIONAL INFORMATION FOR MACLOGLYMIN

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

MACLOGLYMIN 500 mg (Film-coated tablet)

MACLOGLYMIN 850 mg (Film-coated tablet)

MACLOGLYMIN 1000 mg (Film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MACLOGLYMIN 500 mg

Each film-coated tablet contains 500 mg metformin hydrochloride.

MACLOGLYMIN 850 mg

Each film-coated tablet contains 850 mg metformin hydrochloride.

MACLOGLYMIN 1000 mg

Each film-coated tablet contains 1 000 mg metformin hydrochloride.

Sugar free.

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

MACLOGLYMIN 500 mg

White to off white, circular, biconvex, film coated, bevelled edge, tablet debossed with “ C74” on one side and plain on other side.

MACLOGLYMIN 850 mg

White to off white, circular, biconvex, film coated, bevelled edge, tablets debossed with “C75” on one side and plain on other side.

MACLOGLYMIN 1000 mg

White to off white, oval shaped, biconvex, film coated tablet, debossed with “C” and “76” separated by breakline on one side and also breakline on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MACLOGLYMIN is indicated for the treatment of type II diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults **MACLOGLYMIN** 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 II diabetes, **MACLOGLYMIN** may be used as monotherapy or in combination with insulin.

4.2 Posology and method of administration

Posology:

It is important **MACLOGLYMIN** be taken in divided doses with meals.

Adults:

Initially, one 500 mg tablet three times a day, or one 850 mg or 1 000 mg tablet twice a day, with or after food. After 10 to 15 days the doses 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 usual 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 2550 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of **MACLOGLYMIN**.

Children and adolescents:

MACLOGLYMIN 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 2000 mg daily, taken as 2 or 3 divided doses.

Elderly:

MACLOGLYMIN dose in the elderly should be adjusted based on renal function.

Combination therapy and adolescents:

See section 4.4.

Method of administration:

Orally.

MACLOGLYMIN should be administered with or after food.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or any of the excipients of **MACLOGLYMIN** (see section 6.1).
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (e.g. serum creatine 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

Warnings

Lactic acidosis:

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to **MACLOGLYMIN** accumulation. Reported cases of lactic acidosis in patients on **MACLOGLYMIN** 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.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), **MACLOGLYMIN** 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 **MACLOGLYMIN**-treated patients.

Diagnosis:

Lactic acidosis is characterised 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.

Lactic acidosis has occurred to a greater extent in patients with contraindications to therapy. In patients with a metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia) lactic acidosis should be suspected and **MACLOGLYMIN** therapy stopped. Lactic acidosis is a medical emergency which must be treated in hospital.

Renal function:

As **MACLOGLYMIN** 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, 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. For patients with acute or chronic heart failure, **MACLOGLYMIN** is contraindicated (see section 4.3).

Administration of iodinated contrast agents:

As the intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure, **MACLOGLYMIN** 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.

Surgery:

MACLOGLYMIN should be discontinued 48 hours before elective surgery with general anaesthesia and clinical investigations such as intravenous urography and intravenous angiography and it should not be usually resumed earlier than 48 hours afterwards and only after control of renal function has been regained.

Children and adolescents:

The diagnosis of type II diabetes mellitus must be confirmed before treatment with **MACLOGLYMIN** is initiated.

No effect of **MACLOGLYMIN** 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 **MACLOGLYMIN** on these parameters in **MACLOGLYMIN** treated children, especially pre–pubescent children, is recommended.

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 test for diabetes monitoring should be performed regularly.
- Although **MACLOGLYMIN** alone never causes hypoglycaemia, caution is advised when it is used in combination with insulin or sulphonylureas.
- As Vitamin B_{12} deficiency and megaloblastic anaemia may develop with long-term **MACLOGLYMIN** use, Vitamin B_{12} levels should be assessed at least annually.
- **MACLOGLYMIN** is excreted by the kidney and regular monitoring of renal function is advised in all diabetics.
- The use of **MACLOGLYMIN** is not advised in conditions which may cause dehydration or in

patients suffering from serious infections, trauma or on low calorie intake.

- During concomitant therapy with a sulphonylurea, blood glucose should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with **MACLOGLYMIN** 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.
- Contraindications should be carefully observed.

4.5 Interaction with other medicines and other forms of interaction

Inadvisable combinations:

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.

Iodinated contrast agents:

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

MACLOGLYMIN 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 precaution for use:

Glucocorticoids (systemic and local routes), beta-2-agonists and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning treatment. If necessary, adjust the dosage of the antidiabetic medicine during therapy with the other medicine and upon its discontinuation.

ACE–inhibitors may decrease blood glucose levels. If necessary, adjust the dosage of the antidiabetic medicine during therapy with the ACE-inhibitor and upon its discontinuation.

Reduced renal clearance of **MACLOGLYMIN** has been reported during cimetidine therapy, so a dose reduction should be considered.

An interaction between **MACLOGLYMIN** and anticoagulants is a possibility and dosage of the latter may need adjustment.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin 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, trimethoprime, 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 drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established in humans (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 **MACLOGLYMIN** 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 in breastmilk. Limited data are available and therefore breastfeeding is not recommended during treatment with metformin (see Section 4.3)

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 use machines.

4.8 Undesirable effects

Table 1 side effects associated with MACLOGLYMIN therapy

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Less frequent	Megaloblastic anaemia, haemolysis
Immune system disorders	Less frequent	Hypersensitivity
Metabolism and nutrition disorders	Frequent	Decrease of vitamin B_{12} absorption with decrease of serum levels during long term use of **MACLOGLYMIN**.
	Less frequent	Decrease of folic acid absorption with decrease of serum levels during long term use of **MACLOGLYMIN**. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia. Lactic acidosis (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

System Organ Class	Frequency	Undesirable effects
		MACLOGLYMIN be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability
	Less frequent	Weight loss, pancreatitis
Hepatobiliary disorders	Less frequent	Liver function tests abnormalities or hepatitis resolving upon **MACLOGLYMIN** discontinuation.
Skin and subcutaneous tissue disorders	1.2 Less frequent	Skin reactions such as erythema, pruritus and 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. 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 can occur when **MACLOGLYMIN** 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 **MACLOGLYMIN** 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

Pharmaceutical groups: Oral Hypoglycaemics.

ATC code: A10BA02

A 21.2 Oral Hypoglycaemic

Metformin is a biguanide oral anti-hyperglycaemic medicine, 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.

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 % decreases in AUC (area under 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 liters.

Biotransformation: Metformin is excreted unchanged in 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.

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 and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

The tablets are coated with coating made up of hypromellose and polyethylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from the manufacturing date.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the HDPE container tightly closed.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

MACLOGLYMIN 500 mg:

HDPE Container Pack for 84's, 90's and 100's:

Tablets are packed in 100 ml white round heavy weight HDPE bottle with 38-400 mm screw neck finish closed with 38 mm closure with pulp and heat seal liner. Each HDPE bottle contains 1 absorbent cotton coil.

Pack size*: 84 tablets, 90 tablets and 100 tablets.

HDPE Container Pack for 112's:

Tablets are packed in 120 ml white round heavy weight HDPE bottle with 38-400 mm screw neck finish closed with 38 mm closure with pulp and heat seal liner. Each HDPE bottle contains 1 absorbent cotton coil.

Pack size: 112 tablets.

HDPE Container Pack for 500's:

Tablets are packed in 500 ml (for 500 tablets) white round heavy weight HDPE bottle with 53-400 mm screw neck finish closed with 53 mm closure with pulp and heat seal liner. Each HDPE bottle contains 3 absorbent cotton coils.

Pack size: 500 tablets.

MACLOGLYMIN 850 mg:

HDPE Container Pack for 60's:

Tablets are packed in 120 ml white round HDPE bottle with 38-400 mm screw neck finish closed with 38 mm closure with pulp and heat seal liner. Each HDPE bottle contains 1 absorbent cotton coil.

Pack size: 60 tablets.

HDPE Container Pack for 84's, 90's and 100's:

Tablets are packed in 150 ml white round heavy weight HDPE bottle with 38-400 mm screw neck finish closed with 38 mm closure with pulp and heat seal liner. Each HDPE bottle contains 1 absorbent cotton coil.

Pack size*: 84 tablets, 90 tablets and 100 tablets.

HDPE Container Pack for 500's:

Tablets are packed in 750 ml white round heavy weight HDPE bottle with 53-400 mm screw neck finish closed with 53 mm closure with pulp and heat seal liner. Each HDPE bottle contains 3 absorbent cotton coils.

Pack size: 500 tablets.

MACLOGLYMIN 1000 mg:

HDPE Container Pack for 60's:

Tablets are packed in 150 ml white round HDPE bottle with 38-400 mm screw neck finish closed with 38 mm closure with pulp and heat seal liner. Each HDPE bottle contains 1 absorbent cotton coil.

Pack size: 60 tablets.

HDPE Container Pack for 84's, 90's and 100's:

Tablets are packed in 200 ml white round heavy weight HDPE bottle with 38-400 mm screw neck finish closed with 38 mm closure with pulp and heat seal liner. Each HDPE bottle contains 1 absorbent cotton coil.

Pack size*: 84 tablets, 90 tablets and 100 tablets.

HDPE Container Pack for 500's:

Tablets are packed in 950 ml white round heavy weight HDPE bottle with 53-400 mm screw neck finish closed with 53 mm closure with pulp and heat seal liner. Each HDPE bottle contains 3 absorbent cotton coils.

Pack size: 500 tablets.

*Not all pack sizes will 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

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

MACLOGLYMIN 500 mg: 49/21.2/0088

MACLOGLYMIN 850 mg: 49/21.2/0089

MACLOGLYMIN 1000 mg: 49/21.2/0090

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 July 2021

10. DATE OF REVISION OF THE TEXT

11 September 2023

PM0015-03

Vanita Rajool

Digitally signed by Vanita Rajool
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