SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MENGEN 500 mg, film-coated tablet

MENGEN 850 mg, film-coated tablet

MENGEN 1 000 mg, film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MENGEN 500 mg: Each film-coated tablet contains 500 mg metformin hydrochloride equivalent to 390 mg metformin.

MENGEN 850 mg: Each film-coated tablet contains 850 mg metformin hydrochloride equivalent to 663 mg metformin.

MENGEN 1 000 mg: Each film-coated tablet contains 1000 mg metformin hydrochloride equivalent to 780 mg metformin.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

MENGEN 500 mg: White, biconvex, circular shaped film-coated tablets with ‘A’ debossed on one side and ‘60’ debossed on the other side.

MENGEN 850 mg: White, biconvex, circular shaped film-coated tablets with ‘A’ debossed on one side and ‘61’ debossed on the other side.

MENGEN 1 000 mg: White, biconvex, capsule shaped film coated tablets with break line on one side and 'A'

and '90' on other side separated by break line.

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, MENGEN 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, MENGEN 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 MENGEN tablets 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 dose should be adjusted according to blood glucose measurements. A slow increase in dose may improve gastrointestinal 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 2 250 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of MENGEN.

Elderly: MENGEN dose in the elderly should be adjusted based on renal function. See section 4.4

Combination therapy: See section 4.4

Paediatric population

Children and adolescents:

MENGEN 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.

Children: MENGEN is not recommended for use in type 1 diabetes mellitus.

Method of administration

To be taken orally.

Gastrointestinal disorders occur most frequently during initiation of therapy. To prevent them, it is recommended that MENGEN be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve the gastrointestinal tolerability.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients of MENGEN listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, 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 medicines (see section 4.4).

- Acute or chronic disease which may cause hypoxia such as:
  - cardiac failure and recent myocardial infarction;
  - pancreatitis;
  - respiratory failure;
  - shock.
- 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 metabolic complication which most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. MENGEN 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), MENGEN 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 MENGEN-treated patients.

Other risk factors for lactic acidosis are inadequately controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition 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 characterized by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking MENGEN and seek immediate medical attention. 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.

Renal function:

As MENGEN is excreted by the kidneys, 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.

Regular monitoring of renal function is advised in all diabetics.

Decreased renal function in elderly subjects is frequent and asymptomatic.

The administration of MENGEN may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

Cardiac function:

Patients with heart failure are more at risk of hypoxia and renal insufficiency.

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

Administration of iodinated contrast medicine:

Intravascular administration of iodinated contrast materials may lead to contrast induced nephropathy, resulting in MENGEN accumulation and an increased risk of lactic acidosis. MENGEN should be discontinued prior to, or at the time of the imaging procedure and not re-instituted until at least 48 hours afterwards, provided that renal function has been re-evaluated and found to be stable, see section 4.5.

Surgery:

MENGEN should be discontinued 48 hours before elective surgery with 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.

MENGEN therapy should be stopped 2 – 3 days before clinical investigations such as intravenous urography and intravenous angiography and reinstated only after control of renal function has been regained.

Children and adolescents:

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

No effect of MENGEN 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 MENGEN on these parameters in MENGEN 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 tests for diabetes monitoring should be performed regularly.

Although MENGEN alone never causes hypoglycaemia, caution is advised when it is used in combination with insulin or sulphonylureas.

During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with MENGEN and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained. Contraindications should be carefully observed.

The use of MENGEN is not advised in conditions which may cause dehydration, or in patients suffering from serious infections, trauma or on low calorie intake (see section 4.3).

Patients on long-term treatment with MENGEN should have an annual estimation of Vitamin B12 levels, since MENGEN may cause mal absorption of Vitamin B12, which may result in megaloblastic anaemia (see section 4.8).

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 medications.

Iodinated contrast medicine:

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

MENGEN 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 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 products in combination with metformin, 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 dosage of MENGEN 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 MENGEN 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 MENGEN, as metformin plasma concentration may increase. If needed, dose adjustment of MENGEN may be considered as OCT inhibitors/inducers may alter the efficacy of MENGEN.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

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

Pregnancy:

The use of MENGEN during pregnancy is contraindicated as safety has not been established (see section 4.3).

Breastfeeding:

The use of MENGEN during lactation is contraindicated as safety has not been established (see section 4.3).

Fertility:

No data is available

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of safety profile

During treatment initiation, the most frequent adverse reactions are nausea, vomiting, diarrhea, abdominal pa in and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take MENGEN in 2 or 3 daily doses and to increase the doses slowly.

b) 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 MENGEN (consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia).
Less frequent:	Lactic acidosis (see section 4.4).
Blood and the lymphatic system disorders:	
Less frequent:	Megaloblastic anaemia
Nervous system disorders:	
Frequent:	Taste disturbance
Renal and urinary disorders:	
Frequency unknown:	Ketoacidosis and ketonuria
Gastrointestinal disorders:	
Frequent:	Anorexia, nausea, vomiting, constipation, 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 MENGEN 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	Severe cholestatic hepatitis, liver test abnormalities or hepatitis resolving upon metformin discontinuation.
General disorders and administration site conditions:	
Frequency unknown	Hypersensitivity.
Skin and subcutaneous tissue disorders:	
Less frequent:	Skin reactions such as erythema, pruritus, urticaria.
Investigations:	
Less frequent:	Hypoglycaemia.

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 MENGEN 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 correcting blood glucose levels.

Treatment of Overdosage:

There is no specific antidote for overdose with MENGEN. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

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 oral anti-hyperglycaemic agent. Its mode of action is thought to be increased peripheral glucose utilization 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 concentrations were observed. The clinical relevance of these

decreases are 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

Magnesium stearate

Povidone

Opadry YS-1R-7006 consisting of:

- Hypromellose;
- macrogol 400;
- macrogol 6000.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blisters in the original carton until required for use.

6.5 Nature and contents of container

Blister Pack:

Tablets are packed in clear PVC (250 microns) coated with PVdC (60 gsm) as the forming material and aluminium foil (25 microns) as the lidding material OR clear PVC (250 microns) as the forming material and aluminium foil (25 microns) as the lidding material, in the following pack sizes:

MENGEN 500 mg: **500's** (50 x 10's), **100's** (10 x 10's), **84's** (6 x 14's - *Patient ready Packs*), **56's** (4 x 14's - *Patient ready Packs*)

MENGEN 850 mg**: 300's** (30 x 10's), **60's** (6 x 10's), **30's** (3 x 10's), **56's** (4 x 14's – *Patient ready packs*)

MENGEN 1 000 mg: **60's** (6 x 10's)

HDPE Container:

Tablets are packed in a HDPE container with a stock ribbed closure and induction sealing wad, in the following pack sizes:

MENGEN 500 mg: 56’s, 84’s, 100’s, 400’s, 500’s

MENGEN 850 mg: 56’s, 84’s, 100’s, 300’s, 400’s, 500’s

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd.

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene – Pretoria

South Africa

8 REGISTRATION NUMBER(S)

MENGEN 500 mg: A40/21.2/0638

MENGEN 850 mg: A40/21.2/0639

MENGEN 1 000 mg: A40/21.2/0640

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 13 April 2007

10 DATE OF REVISION OF THE TEXT

08 March 2023

FOR NAMIBIA ONLY:

Schedule: NS2

Registration Numbers:

Mengen 500 mg: 14/21.2/0647

Mengen 850 mg: 14/21.2/0648

Mengen 1000 mg: 14/21.2/0649