SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

DIAMIN-500 (film coated tablets)

DIAMIN-850 (film coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **DIAMIN-500** film coated tablet contains metformin hydrochloride 500 mg.

Contains sugar: each tablet contains 66,60 mg lactose monohydrate.

Each **DIAMIN-850** film coated tablet contains metformin hydrochloride 850 mg.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

DIAMIN-500 is a biconvex, white, film coated tablet with a slight distinctive odour.

DIAMIN-850 is a biconvex, white, film coated, round tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DIAMIN is indicated for Type II diabetes mellitus when diet has failed and especially if the patient is overweight.

DIAMIN can be given alone as initial therapy, or can be administered in combination with a sulphonylurea or insulin.

4.2 Posology and method of administration

Posology

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

Monotherapy or combination with other oral antidiabetic medicines

Adults:

Initially, one 500 mg tablet three times a day, with or after food. After 10 to 15 days, the dose should be adjusted, or increased to 850 mg or 1000 mg twice daily. A slow increase in dose may improve gastrointestinal tolerability. If control is incomplete, a cautious increase in dosage to a maximum of 3 g daily is justified. Once control has been obtained, it may be possible to reduce the dosage of DIAMIN.

If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate metformin at the dose indicated above.

Combination with insulin

DIAMIN and insulin may be used in combination therapy to achieve better blood glucose control. DIAMIN is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Paediatric patients

DIAMIN can be used in children from 12 years of age and adolescents as monotherapy or in combination with insulin.

• 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 DIAMIN is 2 000 mg daily, taken as 2 or 3 divided doses.

Patients with 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.

DIAMIN may be used in patients with moderate renal impairment stage 3 (creatinine clearance [CrCl] between 30 and 59 mL/min or estimated glomerular filtration rate [eGFR] between 30 – 59 ml/min/1.73m2) only in the absence of other conditions that may increase the risk of lactic acidosis (see section 4.4) and with the following dose adjustments:

The starting dose is 500 mg or 850 mg DIAMIN. The maximum daily dose is 1000 mg.

The renal function should be closely monitored:

• Every 3-6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m2.

• Every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m2.

If CrCl or eGFR fall below 30 mL/min or 30 mL/min/1.73m2 respectively, DIAMIN must be discontinued immediately.

GFR (mL/min)	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 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

Elderly:

Due to the potential for decreased renal function in elderly subjects, it is recommended that the DIAMIN dose be adjusted based on renal function. Regular assessment of renal function is necessary.

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older. Glucophage initiation is therefore not recommended in these patients (see section 4.4).

Method of administration

To be taken orally.

Gastrointestinal disorders occur most frequently during initiation of therapy. To prevent them, it is recommended that DIAMIN 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 DIAMIN listed in section 6.1.
- Any type of acute metabolic acidosis such as diabetic ketoacidosis.
- Diabetic pre-coma, or the history thereof.
- 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).
- Pancreatitis.
- Chronic liver disease.
- History of or states associated with lactic acidosis such as shock or pulmonary insufficiency.
- Cardiac failure and recent myocardial infarction.
- 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.
- Children as safety and efficacy has not been established.

4.4 Special warnings and precautions for use

Lactic acidosis

LACTIC ACIDOSIS ASSOCIATED WITH THE USE OF DIAMIN IN PATIENTS WITH A METABOLIC ACIDOSIS AND NOT HAVING EVIDENCE OF KETOACIDOSIS (KETONURIA AND KETONAEMIA), LACTIC ACIDOSIS SHOULD BE SUSPECTED AND DIAMIN THERAPY STOPPED. LACTIC ACIDOSIS IS A MEDICAL EMERGENCY, WHICH MUST BE TREATED IN HOSPITAL. DIAMIN IS EXCRETED BY THE KIDNEY AND REGULAR MONITORING OF RENAL FUNCTION IS ADVISED IN ALL DIABETICS.

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to DIAMIN accumulation. Reported cases of lactic acidosis in patients on DIAMIN 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, plasma lactate levels above 5 mmol/litre, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately.

Renal function

As DIAMIN 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 an NSAID (non-steroidal anti-inflammatory drug).

The administration of DIAMIN 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, DIAMIN is contraindicated (see section 4.3).

Administration of iodinated contrast agents

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

Surgery

DIAMIN 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.

DIAMIN 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.

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 on long-term treatment with DIAMIN should have an annual estimation of vitamin b_{12} levels, since DIAMIN may cause malabsorption of vitamin B_{12}, which may result in megaloblastic anaemia (see "Interactions").
- Although DIAMIN 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 DIAMIN and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two drugs has been obtained. Contra-indications should be carefully observed.
- The use of DIAMIN is not advised in conditions, which may cause dehydration, or in patients suffering from serious infections, trauma or on low calorie intake.

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 medications.

Iodinated contrast agents:

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

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

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics:

These drugs have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors:

These may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

Cimetidine:

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

Anticoagulants:

DIAMIN has been reported to diminish the activity of warfarin, and so dose adjustments of DIAMIN should be considered.

Sulphonylurea:

Concomitant therapy of DIAMIN with sulphonylurea may cause hypoglycaemia (see section 4.4).

Vitamins:

Long-term treatment with DIAMIN may cause vitamin B_{12} malabsorption in the gastrointestinal tract, thus a dose reduction of DIAMIN should be considered.

Organic Cation Transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of DIAMIN 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 DIAMIN, as metformin plasma concentration may increase. If needed, dose adjustment of DIAMIN may be considered as OCT inhibitors/inducers may alter the efficacy of DIAMIN.

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 DIAMIN, 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 DIAMIN during pregnancy is contraindicated as safety has not been established (see section 4.3).

Breastfeeding:

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

Fertility

Fertility of male and female rats was unaffected by Glucophage 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

DIAMIN 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 DIAMIN 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 pain 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.

Gastrointestinal disorders:	*Frequent:*	Anorexia, nausea, vomiting, constipation, diarrhoea, metallic taste.
Blood and lymphatic systemdisorders:	*Less frequent:*	Megaloblastic anaemia.
Endocrine disorders:	*Less frequent:*	Hypoglycaemia.
Nervous system disorders:	*Less frequent:*	Metallic taste.
Hepatobiliary disorders:	*Less frequent:*	Severe cholestatic hepatitis.
Skin and subcutaneous tissue disorders:	*Less frequent:*	Hypersensitivity reactions.
Renal and urinary disorders:	*Less frequent:*	Ketoacidosis and ketonuria.

b) Tabulated summary of adverse reactions

1	Blood and lymphatic system disorders	*Less frequent*	Megaloblastic anaemia
2	Endocrine disorders	*Less frequent*	Hypoglycaemia
3	Metabolism and nutrition disorders	*Frequent* *Less frequent*	Decrease of Vitamin B12 absorption with decrease of serum levels during long-term use of DIAMIN (consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia) Lactic acidosis (see section 4.4)
4	Nervous system disorders	*Less frequent*	Metallic taste (Taste disturbance)
5	Gastrointestinal disorders	*Frequent*	Anorexia, nausea, vomiting, constipation, diarrhoea, abdominal pain and loss of appetite
6	Hepato-biliary disorders	*Less frequent*	Severe cholestatic hepatitis, liver test abnormalities or hepatitis resolving upon metformin discontinuation
7	Skin and subcutaneous tissue disorders	*Less frequent*	Skin reactions such as erythema, pruritus, urticaria
8	Renal and urinary disorders	*Less frequent*	Ketoacidosis and ketonuria
9	General disorders and administration site conditions	*Frequency unknown*	Hypersensitivity
10	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 DIAMIN 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. 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 DIAMIN. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: 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 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 litres.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DIAMIN-500: Lactose monohydrate, Colloidal silicon dioxide, Gelatine, Sodium starch glycolate (type A), Magnesium stearate, Opadry 21S58835 white.

DIAMIN-850: Maize Starch, Colloidal silicon dioxide, Povidone K30, Sodium starch glycolate (type A), Magnesium stearate, Opadry 03G58836 white.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below at or below 25°C. Store in the original package to protect from light and moisture. Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

DIAMIN-500:

500 tablets are packed in white HDPE containers with white PP child resistant caps or screw-on caps.

10 tablets are packed in aluminium and clear PVC blister strips. Ten blister strips are packed in an outer carton.

Alternatively, 14 tablets are packed in aluminium and clear PVC blister strips. Two/four/six blister strips are packed in an outer carton or 28, 56 or 84 tablets are packed in Patient Ready Pack Pouches (for state tender purposes only).

DIAMIN-850:

300 tablets are packed in white HDPE containers with white PP child resistant caps or screw-on caps.

10 tablets are packed in aluminium and clear PVC blister strips. Six blister strips are packed in an outer carton.

Alternatively, 14 tablets are packed in aluminium and clear PVC blister strips. Two/four/six blister strips are packed in an outer carton or 28, 56 or 84 tablets are packed in Patient Ready Pack Pouches (for state tender purposes only).

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia, 1827

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8 REGISTRATION NUMBERS

DIAMIN-500: A40/21.2/0464

DIAMIN-850: A40/21.2/0465

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration:

DIAMIN-500: 8 February 2008

DIAMIN-850: 8 February 2008

10 DATE OF REVISION OF THE TEXT

3 March 2025