SCHEDULING STATUS: **S3**

PROPRIETARY NAME (and dosage form):

DIAMIN-500 (film coated tablets)

DIAMIN-850 (film coated tablets)

COMPOSITION:

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

List of excipients: colloidal silicon dioxide, gelatine, lactose monohydrate, magnesium stearate, sodium starch glycolate.

Film coating: Opadry 21S58835 white consisting of diethylphthalate, ethylcellulose, hypromellose and titanium dioxide.

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

List of excipients: colloidal silicon dioxide, magnesium stearate, maize starch, povidone K30, sodium starch glycolate.

Film coating: Opadry 03G58836 white consisting of hypromellose, macrogol, propylene glycol, purified talc and titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral Hypoglycaemic

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

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.

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.

CONTRA-INDICATIONS:

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma, or the history thereof.
- Impaired renal failure function.
- Pancreatitis.
- Chronic liver disease.
- History of or states associated with lactic acidosis such as shock or pulmonary insufficiency.
- Cardiac failure and recent myocardial infarction.
- Conditions associated with hypoxia.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Safety in pregnancy and lactation has not been established.
- Children as safety and efficacy has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

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.

Administration of iodinated contrast agents:

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

Surgery:

DIAMIN 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.
- 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.
- DIAMIN therapy should be stopped 2-3 days before surgery and before clinical investigations such as intravenous urography and intravenous angiography, and re-instated only after control of renal function has been regained. 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.

INTERACTIONS:

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 “Warnings and Special Precautions”).

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.

PREGNANCY AND LACTATION:

The use of DIAMIN during pregnancy is not advised. There is no information available concerning the safety of DIAMIN during lactation.

DOSAGE AND DIRECTIONS FOR USE:

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

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.

Children:

DIAMIN is not recommended for use in Type I diabetes mellitus.

Elderly:

- DIAMIN is indicated in the elderly, but not when renal function is impaired (see “Warnings and Special Precautions”).

Combination therapy:

See “Warning and Special Precautions”.

SIDE-EFFECTS

Gastrointestinal disorders:	Frequent:	Anorexia, nausea, vomiting, constipation, diarrhoea, metallic taste.
Blood and lymphatic system disorders:	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.
Gastrointestinal disorders:	Frequent:	Anorexia, nausea, vomiting, constipation, diarrhoea, metallic taste.
Renal and urinary disorders:	Less frequent:	Ketoacidosis and ketonuria.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

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

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

PRESENTATION:

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).

STORAGE INSTRUCTIONS:

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.

Keep out of reach of children.

REGISTRATION NUMBERS:

DIAMIN-500: A40/21.2/0464

DIAMIN-850: A40/21.2/0465

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia,

1827

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date of publication: 08 February 2008

Date of revision/update: 22 February 2021