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APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

REDORFIN 500 mg TABLETS (Tablet)

REDORFIN 850 mg TABLETS (Tablet)

REDORFIN 1000 mg TABLETS (Tablet)

COMPOSITION:

REDORFIN 500 TABLETS: Each film-coated tablet contains 500 mg metformin hydrochloride.

REDORFIN 850 mg TABLETS: Each film-coated tablet contains 850 mg metformin hydrochloride.

REDORFIN 1000 mg TABLETS: Each film-coated tablet contains 1 000 mg metformin hydrochloride.

Inactive excipients: magnesium stearate, Opadry YS-1R-7006 (comprised of Hypromellose 5cP, Macrogo 400 and Macrogol 6000) and povidone.

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral-Hypoglycaemic

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Metformin is a biguanide oral anti-hyperglycaemic agent. Its mode of action is thought to be due to increased peripheral glucose utilisation mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

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Pharmacokinetics:

Absorption:

After an oral dose of metformin, Tmax 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 is 20 - 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

Steady state plasma concentrations are reached within 24 to 48 hours.

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 is unknown.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak concentration is lower than the plasma peak concentration and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Volume of Distribution ranges between 63 - 276 l.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

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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:

REDORFIN is indicated for Type II diabetes mellitus when diet has failed and especially if the patient is overweight. **REDORFIN** can be given alone as initial therapy, or can be administered in combination with other oral antidiabetics, or insulin.

CONTRA-INDICATIONS:

• Hypersensitivity to metformin hydrochloride or to any of the excipients of **REDORFIN**.

• 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).

• Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents.

• Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock, and pancreatitis.

• Chronic liver disease.

• History of or states associated with lactic acidosis such as shock or pulmonary insufficiency.

• Hepatic insufficiency, acute alcohol intoxication, alcoholism.

• Pregnancy and lactation.

• Children: as safety and efficacy have not been established.

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 **REDORFIN** accumulation. The incidence of lactic acidosis may be reduced by assessing other associated risk factors such as poorly controlled diabetes mellitus type 2, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings include decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, **REDORFIN** should be discontinued and the patient should be hospitalised immediately.

Renal function

As **REDORFIN** 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.

Decreased renal function in elderly subjects is frequent and may be 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.

Administration of iodinated contrast agent

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

REDORFIN should be discontinued 48 hours before elective surgery with general anaesthesia and should not be resumed earlier than 48 hours afterwards.

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 **REDORFIN** accumulation and a risk of lactic acidosis.

REDORFIN 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.

Glucocorticoids (systemic and local routes), betà-2-agonists, and diuretics: have intrinsic hyperglycaemic activity. Medical practitioners should inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of **REDORFIN** during therapy with the other medicines and upon its discontinuation.

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

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

Anticoagulants: REDORFIN has been reported to diminish the activity of warfarin, and so dose adjustment of warfarin should be considered.

Sulphonylurea: Concomitant therapy of **REDORFIN** with sulphonylurea may cause hypoglycaemia.

Vitamins: Long-term treatment with **REDORFIN** may cause vitamin B12 mal-absorption in the gastrointestinal tract (see “Special Precautions”).

PREGNANCY AND LACTATION:

The use of **REDORFIN** during pregnancy and lactation is contraindicated as the safety has not been established. Metformin (contained in **REDORFIN**) crosses the placenta and is distributed into breast milk in small amounts. Patients using **REDORFIN** should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:

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

Adults: Initially, one 500 mg tablet three times a day, or one 850 mg or 1000 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 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 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 **REDORFIN.**

Children and adolescents: REDORFIN is not recommended for use in type 1 diabetes mellitus. **REDORFIN** 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 in dose may improve gastro-intestinal tolerability. The maximum recommended dose of **REDORFIN** is 2000 mg daily, taken as 2 or 3 divided doses.

Elderly: REDORFIN dose in the elderly should be adjusted based on renal function (See "Special Precautions").

Combination therapy: (See "Special Precautions").

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

Blood and the lymphatic system disorders

Less frequent: Megaloblastic anaemia.

Gastrointestinal disorders

Frequent: Anorexia, nausea, vomiting, constipation, diarrhoea, metallic taste.

Less frequent: Abdominal pain.

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Hepato-biliary disorders

The following side effects have been reported but the frequencies are unknown:

Severe cholestatic hepatitis, liver function abnormalities.

Immune system disorders

The following side effects have been reported but the frequencies are unknown:

Hypersensitivity

Investigations

Less frequent:

Hypoglycaemia

Metabolic and nutrition disorders

Less frequent: Hypoglycaemia and lactic acidosis (see "Special Precautions")

Unknown frequency: Decreased absorption of Vitamin B12 and folic acid (see "Special Precautions")

Special precautions:

Lactic acidosis associated with the use of **REDORFIN**. In patients presenting with metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and **REDORFIN** therapy stopped. Lactic acidosis is a medical emergency, which must be treated in hospital.

REDORFIN is excreted by the kidney and regular monitoring of renal function is advised in all diabetic patients with type 2 diabetes mellitus.

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

The use of **REDORFIN** is not advised in conditions which may cause dehydration, or in patients suffering from serious infections, trauma or on a low calorie intake. Patients on long-term treatment with **REDORFIN** should have an annual estimation of Vitamin B12 levels, since **REDORFIN** may cause mal-absorption of

Vitamin B12 and folic acid, which may result in megaloblastic anaemia. During concomitant treatment with sulphonylureas, blood glucose should be monitored because combined therapy may cause hypoglycaemia. Stabilisation of diabetic patients with **REDORFIN** and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained. Contra-indications should be carefully observed.

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.

Due to possible gastrointestinal intolerance it is recommended that treatment in the elderly be initiated with low doses, gradually adjusting based on renal clearance. Maximum doses should not be used.

Ability to Drive and Use Machines

There is no data to suggest that the ability to drive and operate heavy machinery may be impaired.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Hypoglycaemia can occur when **REDORFIN** is given concomitantly with other oral antidiabetics, insulin or alcohol. In excessive doses, 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. 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 **REDORFIN**. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances. Haemodialysis is the most effective way to remove lactate and metformin **(REDORFIN)**.

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IDENTIFICATION:

REDORFIN 500 mg TABLETS: White, biconvex, circular shaped film-coated tablets with 'A' debossed on one side and '60' debossed on the other side.

REDORFIN 850 mg TABLETS: White, biconvex, circular shaped film-coated tablets with 'A' debossed on one side and '61' debossed on the other side.

REDORFIN 1000 mg TABLETS: White, biconvex, oval shaped film-coated tablets with a scoreline in between '6' and '2' on one side and 'A' debossed on the other side.

PRESENTATION:

1. Blister Pack:

Tablets are packed in clear PVC/PVdC aluminium blister packs:

REDORFIN 500 mg TABLETS: 28's (2 x 14's), **56's** (4 x 14's), **84's** (6 x 14's).

REDORFIN 850 mg TABLETS: 28's (2 x 14's), **56's** (4 x 14's), **84's** (6 x 14's).

REDORFIN 1000 mg TABLETS: 28's (2 x 14's), **56's** (4 x 14's), **84's** (6 x 14's).

The blister pack is packed in a cardboard carton.

2. HDPE Container:

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

REDORFIN 500 mg TABLETS: 28's, 56's, 84's, 300's, 500's

REDORFIN 850 mg TABLETS: 28's, 56's, 84's, 300's, 500's

REDORFIN 1000 mg TABLETS: 28's, 56's, 84's, 300's, 500's

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No desiccant is included in the container.

The HDPE container is packed in a cardboard carton.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep container tightly closed. Keep blisters in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

REDORFIN 500 mg TABLETS (Tablet): 45/21.2/0204

REDORFIN 850 mg TABLETS (Tablet): 45/21.2/0205

REDORFIN 1000 mg TABLETS (Tablet): 45/21.2/0206

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

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1

53 Phillip Engelbrecht Avenue

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1448, Johannesburg

South Africa

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19 April 2013

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