DIABETMIN TABLET

eVIDIA01-0 (SIN)

DESCRIPTION

Diabetmin 500 mg Tablet: Round, white film-coated tablet, bevel-edged and shallow convex faces with deep score line on one side.
Diabetmin 850 mg Tablet: Round, white film-coated tablet with deep convex faces and 'hovid' embossed on one face.

COMPOSITION

Diabetmin 500 mg Tablet: Metformin Hydrochloride 500 mg per tablet.
Diabetmin 850 mg Tablet: Metformin Hydrochloride 850 mg per tablet.

ACTIONS AND PHARMACOLOGY

Metformin is a biguanide with antihyperglycaemic effects, 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) and delay of intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT). In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

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 was 20-30%. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are 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 (Cmax) 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 Vd ranged between 63-276 L.

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

Metformin is used in the treatment of non-insulin-dependent diabetes mellitus (type 2) in adults, not responding to exercise and dietary modification. Diabetmin may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

CONTRAINDICATIONS

This medication is contraindicated in patients with the following medical problems:

- Hypersensitivity to Metformin.
- Any condition needing close blood glucose control, such as: severe burns, dehydration, diabetic coma, diabetic ketoacidosis, hyperosmolar nonketotic coma, severe infection, major surgery, and severe trauma.
- Conditions associated with hypoxemia, such as: cardiorespiratory insufficiency, cardiovascular collapse, congestive heart failure, acute myocardial infarction.
- Severe, acute, or chronic hepatic disease.
- Active or history of lactic acidosis.
- Renal function impairment or renal disease.
- Diagnostic or medical examinations using intravascular iodinated contrast media such as: angiography, intravenous cholangiography, computed tomography (CT) scan, pyelography and urography.

PRECAUTIONS

Lactic Acidosis:

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin 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 acidosis dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyrute ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately.

Renal Function:

As metformin 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 2 to 4 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.

Administration of iodinated contrast agent:

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin 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:

Metformin should be discontinued 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.
- Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas.

USE IN PREGNANCY AND LACTATION

To date, no relevant epidemiological data are available. 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 metformin 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. Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

MAIN SIDE/ADVERSE EFFECTS

The following undesirable effects may occur under treatment with metformin.

Metabolism and nutrition disorders:

Very rare: Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloplastic anaemia.

Very rare: Lactic acidosis

Nervous system disorders:

Common: Taste disturbance

Gastrointestinal disorders:

Very common: Gastrointestinal disorders such as 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 metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

Very rare: Skin reactions such as erythema, pruritus, urticaria

DRUG INTERACTIONS

Concomitant use not recommended

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 metformin accumulation and a risk of lactic acidosis. Metformin 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 precautions 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 of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors 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.

OVERDOSE

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

DOSAGE AND ADMINISTRATION

Oral.

Monotherapy and combination with other oral antidiabetic agents:

Usual adult dose:

Diabetmin 500 mg Tablet: Initial dose of one tablet 2 to 3 times daily with or after meals.
Diabetmin 850 mg Tablet: Initial dose of one tablet 2 times daily with or after meals.

If necessary, medication can be increased gradually to a maximum of 3 g daily.
If transfer from another oral antidiabetic agent is intended; discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin:

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin is given at the usual starting dose of one tablet 2-3 times daily while insulin dosage is adjusted on the basis of blood glucose measurements.

Usual children dose: Metformin is not recommended for use in children.
Usual geriatric dose: Please refer to adult dose.
(Due to potential for decreased renal function, the dosage should be adjusted based on renal function and maximum doses are not advised for use in the elderly.)

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

Diabetmin 500 mg Tablet

Presentation/Packing: Blister pack of 10 x 10's, 100 x 10's and 5 x 20's. (Storage: Store below 30°C. Protect from light and moisture.)

Diabetmin 850 mg Tablet

Presentation/Packing: Blister pack of 10 x 10's, 100 x 10's and 5 x 20's. (Storage: Store below 30°C. Protect from light and moisture.)
Not all presentations may be available locally.

Manufactured / Batch Released by: HOVID Bhd., 121, Jalan Tunku Abdul Rahman, 30010 Ipoh, Malaysia.

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