DIABETMIN XR TABLET 500mg

eVIDIA02-0 (SIN)

DESCRIPTION

Oblong, white uncoated tablet with deep convex faces and 'HD' embossed on one face.

COMPOSITION

Metformin Hydrochloride 500mg per tablet (Extended-release)
Excipients: Hydroxypropyl Methylcellulose, Co Povidone, Carboxymethylcellulose Sodium, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water.

ACTIONS AND PHARMACOLOGY

Metformin is an oral biguanide antidiabetic agent. Its mode of action is thought to be multifactorial and includes delayed uptake of glucose from the gastro-intestinal tract; increased peripheral glucose utilization mediated by increased insulin sensitivity; and inhibition of increased hepatic and renal gluconeogenesis.

PHARMACOKINETICS

- **Absorption:** After an oral dose of the extended release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours. At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. When the extended release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected). Mean metformin absorption from the extended release formulation is almost not altered by meal composition.
- **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. Metformin should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. Special precaution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensives or diuretic therapy and when starting therapy with an NSAID.
- **Administration of iodinated contrast agent:** As the intravascular administration of iodinated contrast material in radiological studies can lead to renal failure, metformin should be discontinued 48 hours before the test when the renal function is known to be impaired, or at the time of the test when renal function is known to be normal and not reinstituted until 48 hours afterwards, and only after the renal function has been re-evaluated and found to be normal.
- **Surgery:** Metformin must be discontinued before elective surgery. Therapy may be started no earlier than 48 hours following surgery and only after renal function has been re-evaluated and found to be normal.
- **Hepatic function:** Because impaired hepatic function may significantly limit the ability to clear lactate and has been associated with some cases of lactic acidosis, Diabetmin XR is contraindicated in patients with clinical and laboratory evidence of hepatic disease.
- **Hypoxic states:** Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause perenal azotemia. When such events occur in patients on Diabetmin XR therapy, the drug should be promptly discontinued.
- **Hypoglycemia:** Hypoglycemia does not occur in patients receiving Diabetmin XR alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas, meglitinides and insulin) or ethanol.

  Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

- **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

- **Pregnancy:** Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

  A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. 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, it is recommended that 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.
- **Lactation:** Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account benefit of breast-feeding and the potential risk to adverse effect on the child.

MAIN SIDE/ADVERSE EFFECTS

The following adverse reactions may occur with metformin.

Frequencies are defined as follows: very common:>1/10; common ≥1/100, <1/10; uncommon ≥1/1000, <1/100; rare ≥ 1/10,000, <1/1000; very rare <1/10,000.

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. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and subcutaneous tissue disorders:

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

Metabolism and nutrition disorders:

Very rare:

- Lactic acidosis
- 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 megaloblastic anaemia.

Hepatobiliary disorders:

Very rare: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

DRUG INTERACTIONS

Concurrent use of this medication with the following may interact with metformin:

- Acute or chronic ingestion of alcohol.
- Cimetidine or other cationic medications excreted by renal tubular transport.
- Furosemide.
- Hyperglycemia-causing and hypoglycemia-causing medications.

OVERDOSE

- **Symptoms of overdose:** Hypoglycemia and lactic acidosis.
- **Treatment of overdose:**
  - For hypoglycemia: Treating with immediate ingestion of a source of glucose and counseling patient to obtain emergency medical assistance immediately.
  - For lactic acidosis: Hemodialysis with sodium bicarbonate.

DOSAGE AND ADMINISTRATION

Oral.

Monotherapy and combination with other oral antidiabetic agents:

Usual adult dose:

Initial dose of one tablet once daily with meals, maximum 4 tablets 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. Diabetmin XR Tablet 500 mg is given at the usual starting dose of one tablet 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.

Storage:

Store below 30°C. Protect from light and moisture.

Presentation/Packing:

Blister pack of 10 x 10's, 10 x 10 x 10's

Manufactured by: HOVID Bhd.
Lot 56442, 7 1/2 Miles, Jalan Ipoh/Chemor,
31200 Chemor, Perak, Malaysia.

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