Metformin STELLA 850 mg

COMPOSITION

One Metformin STELLA 850 mg film-coated tablet contains 850 mg metformin hydrochloride.

PHARMACODYNAMICS

Metformin hydrochloride is an anti-hyperglycemic agent which improves glucose tolerance in patients with type-2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and increases peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type-2 diabetes or normal subjects and does not cause hyper-insulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decreases.

PHARMACOKINETICS

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500 mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Once absorbed, protein binding in plasma is negligible; the drug is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours after oral doses. Metformin crosses the placenta and is distributed into breast milk in small amounts.

INDICATIONS

- Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. In type 1 diabetes, it may be given as an adjuvant to patients whose diabetic are poorly controlled.
- In adults, metformin film-coated tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, metformin film-coated tablets may be used as monotherapy or in combination with insulin.
- A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure.

DOSAGE AND ADMINISTRATION

Administration

Metformin STELLA 850 mg is administered orally with or after meals.

Dosage

Adults

- Monotherapy and combination with other oral anti-diabetic agents: The usual starting dose is one tablet 2 or 3 times daily. 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 metformin is 3 g daily, taken as 3 divided doses. If transfer from another oral anti-diabetic agent is intended: discontinue the other agent and initiate metformin hydrochloride at the dose indicated above.
- Combination with insulin: 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.

Children and adolescents

Metformin STELLA 850 mg film-coated tablet can be used in children from 10 years of age and adolescents.

Monotherapy and combination with insulin: The usual starting dose is one tablet of 500 mg or 850 mg once daily. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. The maximum recommended dose of metformin is 2 g daily, taken as 2 or 3 divided doses.

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.

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 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.

CONTRAINDICATIONS

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severely reduced kidney function (GFR < 30 mL/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Intra-vascular administration of iodinated contrast agents.
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.
- Lactation.

PRECAUTIONS

Lactic acidosis

- Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
- In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.
- Medicinal products that can acutely impair renal function (such as antihypertensive, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

– Patient and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Surgery

Metformin should be discontinued 48 hours before elective surgery with general anaesthesia.

Other precautions

All patients should continue their diet with 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 sulphonylureas.

Metformin may reduce vitamin B_{12} serum levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. In case of suspicion of vitamin B_{12} deficiency (such as anemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

ADVERSE EFFECTS

– Gastrointestinal adverse effects including anorexia, nausea, vomiting, and diarrhoea may occur with biguanides; patients may experience taste disturbance and there may be weight loss.
– Absorption of various substances, including vitamin B_{12} may be impaired.
– Metabolism and nutrition disorders: Common: Vitamin B_{12} decrease/deficiency.
– Skin reactions have been reported rarely.
– Hypoglycemia is rare with a biguanide given alone, although it may occur if other contributing factors or drugs are present.
– Lactic acidosis, sometimes fatal, has occurred with biguanides, primarily with phenformin. When it has occurred with metformin most cases have been reported in patients whose condition contraindicated the use of the drug, particularly those with renal impairment.

DRUG INTERACTIONS

– Anti-diabetic agents: Although hypoglycemia occurs infrequently in patients receiving metformin therapy alone, hypoglycemia may occur when the drug is used concomitantly with a sulfonylurea anti-diabetic agent (e.g., glyburide) and/or insulin.
– Diuretics: Thiazide diuretics can exacerbate diabetes mellitus, resulting in increased requirements of oral anti-diabetic agents, temporary loss of diabetic control, or secondary failure to the anti-diabetic agent.
– Nifedipine: Nifedipine increased the absorption; also the urinary excretion of metformin; half-life and time to peak plasma concentration of metformin remained unchanged. Metformin appears to have minimal effects on the pharmacokinetics of nifedipine.
– Cimetidine: Cimetidine may reduce the urinary excretion of metformin by competing for renal tubular organic cationic transport systems. Metformin has negligible effects on cimetidine pharmacokinetics, possibly because cimetidine has a higher affinity for renal tubular transport sites.
– Alcohol: Combined use of alcohol and metformin can increase the risk of hypoglycemia and lactic acidosis, since alcohol decreases lactate clearance and hepatic gluconeogenesis and may increase insulin secretion.

PREGNANCY AND LACTATION

Pregnancy

Determination of fetal concentrations of metformin HCl suggests that a partial placental barrier to the drug exists. Since abnormal maternal blood glucose concentrations during pregnancy may be associated with a higher incidence of congenital abnormalities, most experts recommend that insulin be used during pregnancy to maintain optimum control of blood glucose concentration.

Lactation

Since it is not known if metformin HCl is distributed into milk in humans, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman. If metformin HCl is discontinued in a nursing mother and dietary therapy is inadequate for glycemic control, insulin therapy should be considered.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other anti-diabetic agents (sulphonylureas, insulin, repaglinide).

OVERDOSAGE

Hypoglycemia has not been seen with ingestion of up to 85 grams of metformin hydrochloride, although lactic acidosis has occurred in such circumstance. Metformin is dialyzable with a clearance of up to 170ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal accumulated metformin from patients in whom metformin overdosage is suspected.

SHELF-LIFE AND STORAGE INSTRUCTIONS

The expiry date of this pack is printed on the box. Do not use this pack after this date.
Store in a well-closed container, in a dry place. Do not store above 30^0C.
Keep out of reach of children.

DOSAGE FORM AND PACKAGING AVAILABLE

Metformin STELLA 850 mg film-coated tablet appears as a white, oblong film-coated tablet with breaking notch on both sides. (Packs of 60 tablets).

USE ONLY AS DIRECTED BY YOUR PHYSICIANS

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