Informet®

Metformin Hydrochloride

500 mg, 850 mg, 500 mg LA and 750 mg LA Tablet

Description

Informet® is a preparation of metformin hydrochloride that belongs to a biguanide class of oral antidiabetic drugs. Metformin is used alone or with other medications, including insulin, to treat type 2 diabetes (condition in which the body does not use insulin normally and, therefore, cannot control the amount of sugar in the blood). It lowers both basal and postprandial plasma glucose. Unlike sulfonylureas, Metformin does not produce hypoglycemia. It is the drug of first choice in obese patients.

Mode of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin reduces hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, and stimulates intracellular glycogen synthesis by acting on glycogen synthase. In muscle, it increases insulin sensitivity, improving peripheral glucose uptake and utilization. Metformin also delays intestinal glucose absorption.
Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.
In humans, independently of its action on glycemia, metformin has favorable 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 triglycerides levels.
Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

Indications

Informet® (Metformin Hydrochloride), as monotherapy, is indicated as an adjunct to diet to lower blood glucose especially in overweight patients with non-insulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes mellitus whose hyperglycemia cannot be satisfactorily managed on diet alone. Informet® (Metformin Hydrochloride) may be used concomitantly with a sulfonylurea when diet and metformin hydrochloride or sulfonylureas alone do not result in adequate glycemic control.

Dosage and Administration

Informet® 500: Initial dosage is 500 mg tablet 2-3 times daily with or after meals, gradually increased if necessary to 2 to 3 g daily.

Informet® 850: Initial dosage is 850 mg tablet once or twice daily with or after meals, gradually increased if necessary to 2 to 3 g daily.

Informet® LA: The usual starting dose of Informet LA (Metformin Hydrochloride long acting) is 500 mg once daily with the evening meal.

Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved on Informet LA 2000 mg once daily, a trial of Informet LA 1000 mg twice daily should be considered.

The maximum recommended dose of metformin is 3 g daily.

Transfer from Other Antidiabetic Therapy: When transferring patients from standard oral hypoglycemic agents other than Chlorpropamide to Metformin HCl, no transition period generally is necessary. When transferring patients from

Chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of Chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Children and adolescents

Monotherapy and combination with insulin

- Metformin tablets can be used in children from 10 years of age and adolescents.
- The usual starting dose is one tablet of 500 mg or 850 mg once daily, given during meals or after meals.

After 10 to 15 days the 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 2 g daily, taken as 2 or 3 divided doses.

Elderly

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Renal Impairment

Metformin is contraindicated in patients with an eGFR < 30 mL/minute/1.73 m^2. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended. In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m^2.

Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients of the medication.
- Diabetic ketoacidosis, diabetic pre-coma
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min)
- 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
- Hepatic insufficiency, acute alcohol intoxication, alcoholism
- Lactation

Special Warnings and 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.

Lactic acidosis is characterized by acidotic 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/pyruvate 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 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.

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 hydrochloride should be discontinued 48 hours before elective surgery with general anesthesia and should not be usually resumed earlier than 48 hours afterwards.

Children and adolescents

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.

No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.

Children aged between 10 and 12 years:

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although metformin efficacy and safety in children below 12 did not differ from efficacy and safety in older children, particular caution is recommended when prescribing to children aged between 10 and 12 years.

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 hypoglycemia, although caution is advised when it is used in combination with insulin or sulphonylureas.

Drug Interactions

Concomitant use not recommended

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 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

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid,

sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Metformin HCl, the patient should be closely observed to maintain adequate glycemic control. 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.

Nifedipine

Nifedipine appears to enhance the absorption of Metformin. Metformin has minimal effects on nifedipine.

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.

Pregnancy and Lactation

Pregnancy

Pregnancy Category B.

Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development. There are no adequate and well-controlled studies in pregnant women.

Can be used in pregnancy for both preexisting and gestational diabetes. Women with gestational diabetes should discontinue treatment after giving birth.

Lactation

Metformin is excreted into milk in lactating rats. Similar data is 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 drug to the mother. May be used during breast-feeding in women with pre-existing diabetes.

Adverse Effects

Common or very common:

Abdominal pain, anorexia, diarrhea (usually transient), nausea, taste disturbance, vomiting.

Rare:

Decreased vitamin-B12 absorption, erythema, lactic acidosis (withdraw treatment), pruritus, urticarial.

Frequency not known:

Hepatitis.

Overdose

Hypoglycemia has not been seen with metformin doses up to 85g, 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 hemodialysis.

Pharmaceutical Precautions

Keep out of the reach of children. Do not store above 25°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

Commercial Pack

Informet® 500 Tab: Box containing 100 tablets in 10x10's blister strips. Each tablet contains Metformin Hydrochloride BP 500 mg.

Informet® 850 Tab: Box containing 60 tablets in 6x10's blister strips. Each tablet contains Metformin Hydrochloride BP 850 mg.

Informet® LA Tab: Box containing 100 tablets in 10x10's blister strips. Each long acting tablet contains Metformin Hydrochloride BP 500 mg.

Informet® LA 750 Tab: Box containing 60 tablets in 6x10's blister strips. Each long acting tablet contains Metformin Hydrochloride BP 750 mg.

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Manufactured by

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