



Glumet-forte

Metformin HCl 850mg

Tablet 850 mg

DESCRIPTION

White to off white, round, film-coated tablet with Pharmaniaga icon on one side and plain on the other.

COMPOSITION

Each tablet contains Metformin hydrochloride 850 mg.

PHARMACODYNAMICS

Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides

ATC code: A10BA02

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:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- 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 (GLUTs) known to date. The use of metformin is associated with either a stable body weight or modest body loss. Independently of its action on glycaemia, metformin has favourable effects on lipid metabolism in humans. At therapeutic doses, metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

PHARMACOKINETICS

Absorption:

After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of 500mg or 850mg metformin hydrochloride 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.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 hours and are generally less than 1 microgram/mL. Based on available data, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/mL, even at maximum doses. Food decreases the extent and slightly delays the absorption of metformin.

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 volume of distribution (V_d) 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.

Characteristics in specific groups of patients:

Renal impairment:

Dose adaptation should be made upon clinical efficacy/tolerability considerations.

Paediatrics population:

Paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

INDICATIONS

Treatment of type 2 diabetes mellitus, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Metformin 850 mg film-coated tablet 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 850 mg film-coated tablet 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.

CONTRAINDICATIONS

- Hypersensitivity to metformin 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 ($GFR < 30/min$). Acute conditions with the potential to alter renal function such as: dehydration, severe infarction, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

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 antidiabetic agents (sulfonylureas, insulin or meglitinides).

WARNINGS AND 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 diarrhoea 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 antihypertensives, 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.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised 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 after Metformin is contraindicated in patients with $GFR < 30$ mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Administration of iodinated contrast media

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

Hepatic Impairment

Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of metformin in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Deficiency

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Paediatric population

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 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 prepubescent children, is recommended.

Children aged between 10 and 12 years:

Although efficacy and safety of metformin in children aged between 10 and 12 years did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to these children.

Elderly

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Careful monitoring of renal function is required for this group of patients.

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 sulfonylureas.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin hydrochloride, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism.

DRUG INTERACTIONS

Concomitant use is not recommended

Alcohol:

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition, or hepatic impairment.

Iodinated contrast agents:

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Combinations requiring precautions for use

Medicinal products which increase the risk of lactic acidosis:

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Carbonic anhydrase inhibitors (e.g. topiramate, zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring of these patients may be considered.

Drugs affecting glycaemic control:

Thiazides and other diuretics, corticosteroids/ glucocorticoids (systemic and local routes), phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers and isoniazid tend to produce hyperglycaemia and may lead to loss of glycaemic control. More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation. When such drugs are withdrawn from a patient receiving metformin, observe the patient closely for hypoglycaemia.

Concurrent use of metformin and fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin) may result in changes in blood glucose and increased risk of hypoglycaemia or hyperglycaemia.

Concurrent use of metformin and beta-blockers (e.g. atenolol, bisoprolol, carvedilol) may result in hypoglycaemia, hyperglycaemia or hypertension.

Organic cation transporters (OCT):

Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If

needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Insulin secretagogues or insulin:

Coadministration of metformin with an insulin secretagogue (e.g. sulfonylurea) or insulin may increase the risk of hypoglycaemia. Thus, patients may require lower doses of the insulin secretagogue or insulin.

Cephalexin:

Concurrent use of metformin and cephalexin may result in an increase in metformin plasma levels and may increase risk of metformin side effects (nausea, vomiting, diarrhea, asthenia, headache).

Medicinal products which increase metformin plasma concentrations:

Concurrent use of amiloride, cimetidine, digoxin, glycopyrrolate, morphine, morphine sulfate liposome, quinidine, quinine, ranitidine, vancomycin or enalapril maleate with metformin may result in an increase in metformin plasma concentrations.

Medicinal products which results in excessive hypoglycaemia, CNS depression and seizures:

Concurrent use of metformin and linezolid or moclobemide or selegiline may result in excessive hypoglycemia, CNS depression and seizures.

PREGNANCY AND LACTATION

Pregnancy:

Uncontrolled diabetes during pregnancy (gestation 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, embryonic or foetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose level as close to normal as possible, to reduce the risk of malformations of the foetus.

Breast-feeding:

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborn or infants. However, as only limited data are available, breast feeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding and the potential risk to adverse effects on the child.

ADVERSE REACTIONS

Adverse reactions that are reported in to be greater in patients treated with metformin are diarrhoea, nausea/ vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache, abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnoea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation, cholestatic, hepatocellular, and mixed hepatocellular liver injury.

The following adverse reactions may occur under treatment with metformin:

Metabolism and nutrition disorders:

Very rare: Lactic acidosis

Common: Vitamin B₁₂ decrease/deficiency

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:

Very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

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

Paediatric population:

The adverse event reported in paediatric population was similar in nature and severity to that reported in adults.

DOSAGE AND ADMINISTRATION

Adults with normal renal function (GFR ≥ 90mL/min)

Monotherapy and combination with other oral antidiabetic agents

- The usual starting dose is 850 mg 2 or 3 times daily given during or after meals. 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 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 850 mg 2-3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly

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

Children and adolescents

Monotherapy and combination with insulin

- Metformin 850 mg film-coated tablet 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 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 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.

ROUTE OF ADMINISTRATION

Oral.

OVERDOSAGE

Hypoglycaemia has not been seen with metformin doses of 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 haemodialysis.

Symptomatic and supportive care is the mainstay of treatment in patients who present with mild to moderate biguanide toxicity. Activated charcoal can be considered after large ingestions.

STORAGE CONDITION

Store below 30°C.

Protect from light.

SHELF LIFE

Product should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION

Blister pack of 10's, 15's, 20's and 100's.

Date of revision: 1st July 2024

PRODUCT REGISTRATION HOLDER/MANUFACTURER:
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PRP 0495.4 010724