For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Glycomet-500/850/1000

Metformin Tablets BP 500/850/1000mg

DESCRIPTION:

Metformin Tablets BP 500 mg : White to off white, round, biconvex, film coated tablets plain on both sides.

Metformin Tablets BP 850 mg : White to off white capsule shaped, biconvex film coated tablets with scoreline on one side and plain on other side.

Metformin Tablets BP 1000 mg :White to off white oval shaped, biconvex, film coated tablets, deep breakline on one side and breakline on other side.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Metformin is a biguanide derivative of guanidine, used for treating type II diabetes mellitus. It has antihyperglycaemic effects, which lowers both basal and postprandial plasma glucose. It does not increase insulin secretion and hence, does not cause hypoglycaemia.

Metformin acts via 3 mechanisms:

(1) reduction in hepatic glucose production,

(2) reduction in intestinal glucose absorption, and

(3) increased insulin sensitivity (improved peripheral glucose uptake and utilization).

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism.

Unlike sulfonylureas and insulin, metformin does not cause weight gain.

Pharmacokinetics

Absorption:

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

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

Bioavailability for oral metformin is approximately 50-60% in healthy subjects.

Dose proportionality is lacking due to decreasing absorption with increasing doses.

Steady state plasma concentrations for metformin are reached within 24 to 48 hours and are generally less than 1 microgram/ml at recommended doses and dosing schedules.

Food decreases the extent and delays the time to achieve maximum absorption. The plasma peak concentration may be 40% lower with food administration.

Distribution:

Protein binding in plasma is negligible.

Metformin crosses the placenta and is distributed into breast milk in small amounts.

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 (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 450 to 540 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion.

The plasma elimination half-life is approximately 2 to 6 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.

Hemodialysis effectively removes metformin and corrects metabolic acidosis induced by metformin.

INDICATION

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

- In adults, metformin 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 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.

In Type I diabetes, metformin may be given as an adjuvant to patients whose diabetic are poorly controlled.

RECOMMENDED DOSE

Adults:

Monotherapy and combination with other oral antidiabetic agents:

- The usual starting dose is one tablet (500mg or 850mg) 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.
- In patients receiving a high meformin hydrochloride dose (2 to 3grams per day), it is possible to replace two Metformin 500mg tablets with one Metformin 1000mg tablet.
- The maximum recommended dose of metformin hydrochloride 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 hydrochloride is given at the usual starting dose of one tablet (500mg or 850mg) 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Children and adolescents:

Monotherapy and combination with insulin

- Metformin can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500 mg or 850 mg metformin hydrochloride once 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 hydrochloride 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.

MODE OF ADMINISTRATION

Oral

CONTRAINDICATION

- Hypersensitivity to metformin or to any of the excipients.
- 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.
- 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.
- Severely reduced kidney function (GFR <30 mL/min)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

WARNING & 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. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

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.

Administration of iodinated contrast agent:

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.

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 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 prepubescent children, is recommended.

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USV Private Limited	
Market/Country : Malaysia	**Co-ordinator Name :** Sachin
Software : Corel Draw	**Version :** 2023
SAP Code : 3018XXX	**Item type :** Packinsert **Date:** 26/04/2024
Artist Name : Gajanan	
Product Name : Glycomet 500/850/1000 mg Tablets	
Actual Size : 280 mm x 250 mm (L x H) Front & Back	**Reference SAP Code :** 3016376
Pharmacode : -------	**Layout No.** -----
CMYK/Pantone : Black	
Reason : Text change as per customer requirement	
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Prepared by RA-Artwork	Checked by RA-Artwork	Checked by CQA	Checked by Legal	Checked by Other Dept. (If required)	Approved by RA-Artwork

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 efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, 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 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 anemia 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.
Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

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 (e.g. sulfonylureas, insulin or meglitinides).

INTERACTION WITH OTHER MEDICAMENTS

Concurrent use of metformin and alcohol may result in an increased risk of lactic acidosis, particularly in case of: fasting or malnutrition, hepatic insufficiency.

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be temporarily stopped 48 hours before the examination, and withheld until normal renal function is confirmed.

Concomitant use of medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics with metformin may require more frequent blood glucose monitoring, especially at the beginning of treatment.

If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Concurrent use of metformin and diuretics, especially loop diuretics may result in an increased risk of lactic acidosis due to their potential to decrease renal function.

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

Concurrent use of metformin and acetazolamide may result in an additive risk of lactic acidosis.

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

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).

Concurrent use of metformin and danazol may result in an increased blood glucose levels.

Concurrent use of metformin and the following may result in an increase in metformin plasma concentrations:

- Amiloride
- Cimetidine
- Digoxin
- Glycopyrrolate
- Morphine
- Morphine Sulfate Liposome
- Quinidine
- Quinine
- Ranitidine
- Vancomycin
- Enalapril Maleate

Concurrent use of metformin and enalapril may result in hyperkalemic lactic acidosis.

Concurrent use of metformin and the following may result in reduced antidiabetic agent: effectiveness:

- Glucosamine
- Levothyroxine
- Thyroid

Concurrent use of metformin and the following may result in excessive hypoglycemia, CNS depression, and seizures:

- Linezolid
- Moclobemide
- Selegiline

Concurrent use of metformin and nifedipine may result in an increased absorption of metformin.

Concurrent use of metformin and topiramate may result in an additive risk of metabolic acidosis.

Concurrent use of metformin and trimethoprim may result in an increased metformin exposure.

PREGNANCY & LACTATION

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.There are limited data to suggest that metformin does not increase the risk of congenital abnormalities and does not adversely affect pregnancy outcome in diabetic women. Insulin is generally preferred for treatment of diabetes in women planning on becoming pregnant and during pregnancy to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Lactation

Metformin may be distributed into breast milk, and that the possible effects on the infant should be considered if women wish to breastfeed while receiving the drug.

Since only limited data are available, breast-feeding is not recommended during metformin treatment.A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breastfeeding and the potential risk to adverse effects on the child.

Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

SIDE EFFECTS

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.
The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common: ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:

Common:
Vitamin B12 decrease/deficiency.

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:

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
In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

SYMPTOMS & TREATMENT OF OVERDOSE

Symptoms

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

Treatment

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.

Hemodialysis is the most effective method in removing lactate and metformin.

PRESENTATION:

Glycomet-500
Metformin Tablets BP 500 mg

Each film coated tablet contains :
Metformin hydrochloride Ph. Eur. .... 500 mg
Colouring agent : Titanium Dioxide
Packing : A blister of 10 tablets,10 such blisters in a carton.

Glycomet-850
Metformin Tablets BP 850 mg

Each film coated tablet contains :
Metformin hydrochloride Ph. Eur. .... 850 mg
Colouring agent : Titanium Dioxide
Packing : A blister of 10 tablets,10 such blisters in a carton.

Glycomet-1000
Metformin Tablets BP 1000 mg

Each film coated tablet contains :
Metformin hydrochloride Ph. Eur. .... 1000 mg
Colouring agent : Titanium Dioxide
Packing : A blister of 10 tablets,10 such blisters in a carton.

Store below 30°C.

Keep all medicines out of reach of children.

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