daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

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.

Children: In the absence of available data, Metformin Sustained release tablets should not be used in children.

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	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.

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.

The following adverse reactions may occur with Glycomet - 500 SR.

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. 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

PRESENTATION:

Glycomet - 500 SR
(Metformin Hydrochloride Sustained Release Tablets 500 mg)
Each film coated sustained release tablet contains:
Metformin Hydrochloride Ph. Eur. .....500 mg)
Pack size available: 3 x 10's, 6 x 10's and 10 x 10's

Do not store above 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

Manufactured by :

USV Private Limited
H-13,16,16A,17,18,19,20,21,E-22, O.I.D.C.,
Mahatma Gandhi Udyog Nagar, Dabhel, Daman - 396210, India.
Date of Revision : April 2024

3018XXX

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

Glycomet-500 SR

Metformin Hydrochloride Sustained Release Tablets 500 mg

DESCRIPTION:

Glycomet - 500 SR - Off- white coloured, oval biconvex, film coated tablets plain on both sides.

CLINICAL PHARMACOLOGY:

Pharmacodynamic properties

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.

Metformin may act via 3 mechanisms:

(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis

(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation

(3) 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 (GLUT). In humans, independently of its action on glycemia, immediate release metformin has favourable effects on lipid metabolism.

Pharmacokinetic properties

Absorption

After an oral dose of the Sustained release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours).

When the Sustained release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected). Metformin absorption from the sustained release formulation is not altered by meal composition. No accumulation is observed after repeated administration of up to 2000 mg of metformin as sustained release tablets.

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 450 to 540 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 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 Sustained, leading to increased levels of metformin in plasma.

THERAPEUTIC INDICATIONS:

Treatment of type 2 diabetes mellitus in adults, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin extended release may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin. A reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure.

CONTRAINDICATIONS:

- Hypersensitivity to metformin hydrochloride 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, 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
- Severely reduced kidney function (GFR <30 mL/min)

210 mm

280 mm

USV Private Limited

Market/Country : Malaysia **Co-ordinator Name :** Sachin **Software :** Corel Draw
Version : 2023
SAP Code : 3018XXX **Item type :** Packinsert **Date:** 30/04/2024
Artist Name : Gajanan
Product Name : Glycomet - 500 SR
Actual Size : 280 mm x 210 mm (L x H) Front & Back **Reference SAP Code :** 3016377
Pharmacode : ------- **Layout No.** -----
CMYK/Pantone : Black
Reason : change in text
Path : M:\Govandi\Artwork\Venaa - Final Artworks in CDR\Current 08.2010\Formulation\Export\Malaysia

NOTE TO THE PRINTER:
Processor / Printer shall not make any correction / changes / deviation in the approved artwork.
If any discrepancy observed in the artwork, Printer / Processor shall return the artwork to USV.

Prepared by RA-Artwork	**Checked by RA-Artwork**	**Checked by CQA**	**Checked by Legal**	**Checked by Other Dept.** (If required)	**Approved by RA-Artwork**

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

WARNING AND PRECAUTION :

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.

Elderly:

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

Administration of iodinated contrast agents:

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.

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.

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 contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

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 other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

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 :

Study of specific drug interactions yielded following results:

Inadvisable combinations

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 reevaluated and found to be normal.

Combinations requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, have intrinsic hyperglycemic activity. 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.

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.

Pregnancy and 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 dose 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 effect 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.

SYMPTOMS AND TREATMENT OF OVERDOSE :

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

DOSAGE AND ROUTE OF ADMINISTRATION: Oral

Monotherapy and combination with other oral antidiabetic agents:

- The usual starting dose is one tablet once 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 gastro-intestinal tolerability. The maximum recommended dose is 4 tablets daily.
- Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal.
- In patients already treated with metformin tablets, the starting dose of Metformin Sustained release tablets should be equivalent to the daily dose of metformin immediate release tablets.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin sustained release tablets at the dose indicated above.

Combination with insulin: Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of metformin Sustained release tablets is one tablet once

210 mm

280 mm