GLYCOMINE (Tablets)

Metformin Hydrochloride

COMPOSITION: Each tablet contains:500mg Metformin Hydrochloride .

Excipients : Lactose,Starch,Magnesium stearate,Aerosil.

PHARMACODYNAMIC PROPERTIES:
Metformin is a biguanide with antihyperglycaemic effects. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.
Metformin may act via 3 mechanisms:
1-Reduction of hepatic glucose production by inhibiting gluconeogenisis and glycogenolysis.
2-In muscle by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
3-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.
In humans, independently of its action on glycaemia , metformin has favourable 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 triglyceride levels.

PHARMACOKINETIC PROPERITIES:
*Absorption: After an oral dose of metformin, maximum plasma concentration[Cmax]is reached in 2.5 hours [Tmax].Absolute bioavailability of a 500mg or 850mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose ,the non absorbed fraction recovered in feces was 20-30%.Food decreases the extent and slightly delays the absorption of metformin. The clinical relevance of these decreases is unknown.
*Distribution: Plasma protein binding is negligible.
*Metabolism: Metformin is excreted unchanged in the urine.
*Elimination: Renal clearance of metformin is >400ml/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.

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 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 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 hydrochloride or to any of the excipients.
Diabetic ketoacidosis ,diabetic pre- coma
*Moderate [stage3b] and severe renal failure or renal dysfunction [CrCl<45 ml/min or eGFR<45ml/min/1.73meter square].
*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:
respiratory failure, recent myocardial infraction, shock, decompensated heart failure.
*Hepatic insufficiency, acute alcohol intoxication, alcoholism.

SPECIAL WARNINGS AND PRECAUTIONS:
-Lactic acidosis: Lactic acidosis is a very rare ,but serious[high mortality rate 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 impaired renal failure or acute worsening of renal function .Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration[severe diarrhea or vomiting],or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug[NSAID].In the acute conditions listed, metformin should be temporarily discontinued.
Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake,hepatic insufficiency and any condition associated with hypoxia
Renal function:
As metformin is excreted by the kidney, creatinine clearance or eGFR should be determined before initiating treatment and regularly thereafter:
• At least annually in patients with normal renal function.
• At least two or four times a year in patients with creatinine clearance at the lower limit of normal and in elderly subjects.
-Cardiac function: 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.
-Surgery: Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.
-Pediatric population: The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.
Children aged between 10 and 12 years:
Although metformin efficacy and safety in these children did not differ from efficacy and safety in older children ,and adolscents, 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 does not cause hypoglycemia, although caution is advised when it is used in combination with insulin or other oral anti-diabetics.

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 medicines.
- Iodinated contrast media:
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.
*Combinations requiring precautions for use:
-Glucocorticoids [systemic and local routes],beta-2-agonists,and diuretics have intrinsic hyperglycaemic activity .Inform the patient and perform more frequent blood glucose monitoring ,especially at the beginning of treatment .If necessary adjust the dosage of the anti-diabetic drug during therapy with the other drug and upon its discontinuation.
-ACE-inhibitors: They may decrease the blood glucose levels. If necessary ,adjust the dosage of the anti-diabetic drug during therapy with the other drug and upon its discontinuation.
-Diuretics, especially loop diuretics: They may increase the risk of lactic acidosis due to their potential to decrease renal function.

PREGNANCY:
Uncontrolled diabetes during pregnancy[gestational or permanent]is associated with increased risk of congenital abnormalities and perinatal mortality.
When the patient plans to become pregnant and during pregnancy ,diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

BREAST-FEEDING:
Metformin is excreted into human breast milk. 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 breast-feeding and the potential risk of adverse effects on the child.

UNDESIRABLE EFFECTS:
During treatment initiation, the most adverse reactions are nausea, vomiting, diarrhea, 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 dose.
The following adverse reactions may occur under treatment with metformin:
*Metabolism and nutrition disorders: Very rare: Lactic acidosis ,Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. .
*Nervous system disorders: Common: Taste disturbance.
*Gastrointestinal disorders: Very common such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite.
*Hepatobiliary disorders: Very rare: Isolated reports liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
*Skin and subcutaneous tissue disorders: Very rare: Skin reactions such as erythema, pruritus, urticaria.

OVERDOSE:
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.

DOSAGE AND ADMINISTRATION:
-Adults:
*Monotherapy and combination with other oral anti-diabetic agents:
The usual starting dose is 500 or 850mg tab metfor min hydrochloride 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 3g daily, taken as 3 divided doses.
If transfer from another oral anti-diabetic agent is intended, discontinue the other agent and initiate metformin at the dose indicated above.
*Combination with insulin:
Metformin is given at the usual starting dose of 500or 850mg tab , 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 subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.
-Renal impairment:
Metformin may be used in patients with moderate renal impairment,stage3a[creatinine clearance(CrCl) 45-59ml/min or estimated glomerular filtration rate(eGFR) 45-59ml/min/1.73 meters square] only in the absence of other conditions that may increase the risk of lactic acidosis and with the following dose adjustments:
The starting dose is 500mg or 850mg metformin hydrochloride, once daily. The maximum dose is 1000mg daily, given as 2 divided doses. The renal function should be closely monitored[every 3-6 months].
If CrCl or eGFR fall<45ml/min or <45ml/min/1.73meters square, respectively, metformin must be discontinued immediately.
-Paediatric population:
*Monotherapy and combination with insulin: Metformin can be used in children from 10 years of age and adolescents. The usual starting dose is one tablet of 500mg 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 is 2g daily, taken as 2 or 3 divided doses.

STORAGE CONDITIONS: "Store at room temperature between (15-25 °C), away from moisture"

Packaging: Carton Box contains 20 tablet or 100 tablets as blisters,each one contains 10 tablets.

*** THIS IS A MEDICAMENT ***

- Keep out of reach of children.
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly doctor's prescriptions, the method of use and instructions of the pharmacist who sold the medicament.
- The doctor and pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

(Council of Arab Ministers) **(Union of Arab Pharmacists)**

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