xxxxxxxx-5343

METFORMIN Hydrochloride + GLIMEPIRIDE

AZULIX 1 MF
AZULIX 2 MF

500 mg / 1 mg Tablet
1 g / 2 mg Tablet
Oral Hypoglycemic

FORMULATION

Each tablet contains:	**500 mg / 1mg**	**1 g / 2mg**
Metformin Hydrochloride (In sustained Release Form)	500 mg	1 g
Glimepiride 1mg		2 mg

PHARMACODYNAMICS:
Glimepiride - the primary mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. **Metformin Hydrochloride** - an antihyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and post-prandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing the peripheral glucose uptake and utilization. Unlike sulfonyl ureas, Metformin does not cause hypoglycemia in either with patients with type 2 diabetes or normal individuals.
PHARMACOKINETICS:
Absorption:
Glimepiride - After oral administration, Glimeperide is completely (100%) absorbed from the GI tract. After oral administration of Glimepiride, maximum plasma concentration was observed after 1-8 hours. **Metformin** - The oral bioavailability of Metformin is about 50 to 60% and 30% of it is excreted via feces. Decrease in oral bioavailability could be due to first pass metabolism. Concomitant food intake may slightly impair the absorption. Following a single oral dose of metformin hydrochloride SR, Cmax is achieved with a median value of 6 hours and a range of 4 to 8 hours.
Distribution -
Glimepiride - The protein binding of glimepiride was greater than 99.5%. The volume of distribution was 113 mL/kg and clearance was 47.8 mL /min after an intra-venous dose of Glimepiride in normal subjects. **Metformin** - Binding of Metformin to plasma proteins is negligible. Distribution is rapid. Metformin accumulates in the kidneys, salivary glands and walls of esophagus, stomach and duodenum. Binding to blood cells increases progressively. It is excreted into breast milk in small quantities.
Metabolism :
Glimepiride - Is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl methyl derivative (M1) and carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of Glimepiride to M1 (active). M1 is further metabolized to M2 (inactive) by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3rd of the pharmacological activity as compared to its parent in an animal model. **Metformin** - Metformin is considered to be eliminated unchanged but some studies have indicated that some metabolic (about 20%) transformation may occur. No metabolites have been identified.
Excretion:
Glimepiride - After single oral dose of Glimepiride t1/2 was found to be 5.35 hours. No parent drug was recovered from urine to feces. **Metformin** - Metformin is excreted through the kidneys by active tubular secretion though the renal clearance of the drug can be correlated with creatinine clearance. Elimination half-life is 1.5 to 4.5 hours.
INDICATIONS
It is indicated in the treatment of patients with type 2 diabetes mellitus when diet, exercise and single agent do not result in adequate glycemic control.
CONTRAINDICATIONS
Glimepiride is contraindicated in patients with: known hypersensitivity to the drug, diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
Metformin is contraindicated in patients with: Renal disease or renal dysfunction (e.g. As suggested by serum creatinine levels 1.5 mg/dL [males], 1.4 mg/dL [females] or abnormal creatinine clearance), which may result also from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia, congestive heart failure requiring pharmacological treatment, known hypersensitivity to metformin hydrochloride, acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
WARNINGS AND PRECAUTIONS
Glimepiride - Risk of Cardiovascular Mortality - The administration of oral hypoglycemic has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. The warning is based on the study conducted by the University Group of Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in
patients with non-insulin-dependent diabetes. Results of study suggested that there is increased incidence of cardiovascular mortality in patients taking sulfonylurea class of drugs. Glimepiride unlike sulfonylureas is thought to have no effect on KATP channels in humans. **Hypoglycemia** - All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. **Loss of Control of Blood Glucose** - When patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with Glimepiride or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including Glimepiride, in lowering blood glucose to a desired level decreases in many patient over a period of time, which may be due to progression of severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with Glimepiride or metformin monotherapy combined therapy with Glimepiride and Metformin or Glimepiride and insulin may result in a response. Should secondary failure occur with combined Glimepiride/Metformin therapy, it may be necessary to initiate insulin therapy. **Use in Pregnancy and Lactation** - There are no adequate well-controlled studies in humans, but animal studies suggest that Glimepiride should not be used in pregnancy therapy. **Pediatric Use** - There are no adequate studies for safety and effectiveness of Glimepiride in pediatric population.
Metformin
Lactic Acidosis - Metformin is not generally recommended for patients with IDDM. But if this drug is planned to be given, it is always as an adjunct to insulin therapy in patients who are not at risk of ketoacidosis. Impaired renal function predisposes to lactic acidosis. A normal creatinine clearance is essential for treatment with Metformin. Serum creatinine should be monitored regularly during Metformin therapy. Lactic acidosis, which may be caused by Metformin, is of the Type B and is not associated with reduced tissue perfusion and hypoxia. Theoretically, diabetics may be predisposed to Type B lactic acidosis since insulin deficiency is associated with low levels of pyruvate dehydrogenase in the muscle, which may increase lactate production. Diabetics also tend to overproduce lactate during exercise. In spite of this predisposition Type B lactic acidosis is rare with Metformin until renal impairment is present. Even though Metformin is not associated with Type A lactic acidosis it should be given with caution to patients with risk factors for hypoxia such as sepsis, dehydration, congestive heart failure, seizures or alcoholism. Lactic acidosis patients with malignancy is thought to be due to a 'factor' produced by tumor, which inhibits phosphate dehydrogenase and increase lactate production. Caution is warranted if Metformin is used in such patients. Metformin should be withheld at least 2 days before IV urography or aortography where there is a risk for temporary renal insufficiency. Similarly, metformin should be stopped 2 days before major surgery. Insulin may be used until the patient is stable. Hepatic dysfunction has no significant effect on the clearance of Metformin but it predisposes to lactic acidosis. Since metformin therapy is associated with deficiency of vitamin B12 and folic acid, these two must be estimated periodically and supplements may be given. **Pediatric Use** - Safety and efficacy of sustained release formulation of Metformin in pediatric patients have not been established. **Use in Pregnancy and Lactation** - Sustained release formulations are not recommended for use in pregnancy.
ADVERSE REACTIONS:
Glimepiride - The adverse reactions encountered with Glimepiride are vomiting, gastrointestinal pain, diarrhea and allergic skin reactions. Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia and pancytopenia have been reported with sulfonyl ureas.
Metformin - The most severe side effect associated with Metformin is lactic acidosis. Enhanced glucose uptake and glycolytic flux predispose patients - in presence of high circulating levels of Metformin - to the development of lactic acidosis as occurs with Metformin overdose and/or renal insufficiency. The risk of lactic acidosis is markedly increased with any condition that reduces Metformin clearance (acute or chronic renal impairment) or compromises oxygen delivery and predisposes to tissue hypoxia (acute or chronic respiratory or cardiovascular insufficiency). Thus, in addition to renal dysfunction, the risk factors include congestive heart failure, trauma, severe dehydration, intravenous pyelography, arteriography, acute asthmatic attack, status epilepticus, rapid ascent to high attitude, and impending surgery (it should be discontinued 48 hrs prior to surgery). Therapy should be held following the use of a renal contrast substance until adequate renal function is ascertained. However, there is no need to discontinue Metformin therapy prior to such diagnostic procedures. Megaloblastic anemia has been reported in patients on Metformin.
Other reactions include GI symptoms. Diarrhea may be frequent. The GI symptoms may be due to accumulation of Metformin in the gastrointestinal mucosa. Sensitivity reactions such as rash, urticaria and pruritis may occur. Hypoglycemia does not occur with Metformin given alone. It may occur when a sulfonylurea is added or when alcohol is ingested.
DRUG INTERACTIONS:
Glimepiride - Drugs like NSAIDs, beta-adrenergic blocking agents, chloramphenicol, salicylates, probenecid, sulfonamides, miconazole, warfarin, and MAO inhibitors may potentiate the hypoglycemic action of Glimepiride. Patients must be observed closely for hypoglycemic events if these drugs have to be given to them and also while withdrawing the therapy for observing loss of glycemic control. Calcium channel blockers, estrogens, fibrates, HMG CoA reductase inhibitors, ACE inhibitors, Cimetidine, Ranitidine have no potential interactions with Glimepiride. **Metformin** - Low or absence of protein binding and lack of hepatic biotransformation make Metformin practically free from drug interactions. Alcohol, barbiturate, salicylate and phenothiazines may precipitate lactic acidosis. Alcohol may precipitate hypoglycemia as could sulfonylureas given in combination with Metformin. Furosemide - increased the Metformin plasma and blood Cmax 22% and blood AUC by 15%. Nifedipine - appears to enhance the absorption of Metformin.
DOSAGE AND ADMINISTRATION:
Should be given once daily with full meal preferably in the evening.
Therapy should be started with Metformin Hydrochloride + Glimepiride (Azulix 1 MF) one tablet daily, depending upon the glycemic control, dose may be titrated to 2 tablets once daily.
Alternatively, the therapy may be started with Metformin Hydrochloride + Glimepiride (Azulix 2 MF) one tablet daily, depending upon the glycemic control, dose may be titrated to 2 tablets once daily.
Maximum recommended dose is 2 tablets once daily.
Or as prescribe by the physician.
DIRECTION FOR USE:
"SWALLOW WHOLE TABLET, DO NOT CRUSH OR CHEW"
DIRECTION TO THE PATIENT:
Patients should be advised that they may pass empty matrix "ghosts" (tablets) in the stool, and that this is of no concern since the active medication has already been absorbed.
OVERDOSAGE:
Glimepiride - Sulfonylurea overdosage including Glimepiride can result in hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggrressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continous infusion of more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patient should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery. **Metformin** - Hypoglycemia has not been seen even with ingestion of up to 85 grams of metformin although lactic acidosis has occurred in such circumstances. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.
CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
STORAGE CONDITION:
Store at temperatures not exceeding 30^{O}C.Protect from light.
AVAILABILITY
Metformin Hydrochloride + Glimepiride (Azulix 1 MF) 500 mg / 1 mg Tablet - Alu-Alu Blister Pack x 10's - Box of 100's
Metformin Hydrochloride + Glimepiride (Azulix 2 MF) 1 g / 2 mg Tablet - Alu-Alu Blister Pack x 10's - Box of 100's

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