xxxxxxxx-5253

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

GLIMET 1 mg/500 mg SUSTAINED RELEASE TABLETS GLIMET 2 mg/1000 mg SUSTAINED RELEASE TABLETS

(Metformin Hydrochloride Sustained Release and Glimepiride Tablets)

BRAND OR PRODUCT NAME

GLIMET 1 mg/500 mg SUSTAINED RELEASE TABLETS
GLIMET 2 mg/1000 mg SUSTAINED RELEASE TABLETS

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

GLIMET 1 mg/500 mg SUSTAINED RELEASE TABLETS
Each uncoated tablet contains:

Metformin hydrochloride USP [In sustained release form]	500 mg
Glimepiride USP	1 mg

GLIMET 2 mg/1000 mg SUSTAINED RELEASE TABLETS
Each uncoated tablet contains:

Metformin hydrochloride USP [In sustained release form]	1000 mg
Glimepiride USP	2 mg

PRODUCT DESCRIPTION

GLIMET 1 mg/500 mg SUSTAINED RELEASE TABLETS:
White to off white flat oblong shaped uncoated tablet having one blue round inlay tablet near the center of one side.
GLIMET 2 mg/1000 mg SUSTAINED RELEASE TABLETS:
White to off white flat oblong shaped uncoated tablet having one pink round inlay tablet near the center of one side.

DOSAGE FORM

Uncoated Tablets

CLINICAL PHARMACOLOGY

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. In addition, extra pancreatic effects may also play a role in the activity of sulfonylurea such as Glimepiride.

Metformin

Metformin is an anti hyperglycemic 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 anti hyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing the peripheral glucose uptake and utilization. Unlike sulfonylurea, Metformin does not cause hypoglycemia in either with patients with type 2 diabetes or normal individuals.

Pharmacodynamics of Combination therapy:

Glimepiride is an oral glucose-lowering drug of the sulphonylureas class, which acts by increasing the release of insulin from the pancreatic beta cells. Metformin, a biguanides class, reduces the output of glucose from the liver and thus reduces the requirement of insulin at the level of liver. Thus, sulphonylureas and biguanides have additive action. Moreover, Metformin and Glimepiride are often co prescribed in clinical practice, and have proven to be efficacious in achieving the target glycemic control and also in preventing the multiple metabolic defects, which are often present in diabetic subjects.

PHARMACOKINETICS

Absorption

Glimepiride:

After oral administration, Glimepiride is completely (100%) absorbed from the GI tract. After oral administration of Glimepiride, maximum plasma concentration was observed after 2-3 hours.

Metformin:

The oral bioavailability of Metformin is about 50-60% 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 5 hours and a range of 4 to 6 hours.

Distribution

Glimepiride:

The protein binding of Glimepiride was greater than 99.5%. The Volume of distribution was 113ml/kg and clearance was 47.8ml/min after an intravenous dose of Glimepiride in normal subjects.

Metformin:

Binding of Metformin to plasma proteins is negligible. Distribution is rapid. Metformin accumulates in kidneys, salivary glands and walls of oesophagus, stomach and duodenum. Binding to blood cells increases progressively. It is excreted into breast milk in small quantities.

Metabolism

Glimepiride:

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the 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 5.35hours. No parent drug was recovered from urine or feces.

Metformin:

Metformin is excreted through the kidney 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.

INDICATION

GLIMET is indicated as an adjunct to diet and exercise in non-insulin dependent diabetes mellitus (NIDDM) (Type 2) patients who are unable to achieve sufficient glycaemic control with monotherapy of Metformin or Glimepiride alone or who are already treated with the combination of Metformin and Glimepiride as separate tablets.

DOSAGE AND ADMINISTRATION

The dosage of antidiabetic drugs should be individualized based on the patient's blood glucose levels. Generally, it should be recommended to initiate the lowest effective dose and increase the dose depending on the patient's blood glucose levels. Adequate monitoring of blood glucose levels should be performed.
GLIMET should be administered once per day during breakfast or the first main meal. The highest recommended dose per day should be 8mg of glimepiride and 2000mg of metformin.
When switching from combination therapy of Glimepiride plus Metformin as separate tablets, Glimet should be administered on the basis of dosage currently being taken.

CONTRAINDICATIONS

Glimepiride is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

Metformin is contraindicated in patients with:

1. 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 also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2. Congestive heart failure requiring pharmacological treatment.
3. Known hypersensitivity to Metformin hydrochloride.
4. 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 drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group 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 the study suggested that there is increased incidence of cardiovascular mortality in patients taking sulfonylurea class of drugs.
Glimepiride unlike other sulphonylureas 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 a 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 patients over a period of time, which may be due to progression of the 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

Risk Related to Diabetes: Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.
There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of glimepiride.
The excretion in human milk is unknown; however, Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, it is advised to discontinue breastfeeding during treatment with Glimet.

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 in patients with malignancy is thought to be due to a 'factor' produced by tumor, which inhibits phosphate dehydrogenase and increases 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 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.
Use in Pregnancy and Lactation
To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.
Consequently, Glimet should not be used during the whole pregnancy. In case of treatment by Glimet, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.
Sustained release formulations are not recommended for use in pregnancy.
The excretion in human milk is unknown; however, Metformin is excreted in rat milk.

Pediatric Use

Safety and efficacy of sustained release formulation of Metformin in pediatric patients have not been established.

INTERACTIONS WITH OTHER MEDICAMENTS

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, barbiturates, salicylate and phenothiazines may precipitate lactic acidosis. Alcohol may precipitate hypoglycemia, as could sulfonylureas given in combination with Metformin.
Glyburide:
In a single-dose interaction study in NIDDM subjects, co-administration of Metformin and Glyburide did not result in any changes in either Metformin Pharmacokinetics or Phamacodynamics.
Furosemide:
A single-dose, Metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the Metformin plasma and blood Cmax 22% and blood AUC by 15%.
Nifedipine:
A single-dose, Metformin-Nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of Nifedipine increased plasma Metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of Metformin.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

Glimepiride:

The adverse reactions encountered with Glimepiride are vomiting, gastrointestinal pain, diarrhea and allergic skin reactions. Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia and pancytopenia have been reported with sulfonylureas.

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 altitude, and impending surgery (it should be discontinued 48 prior to surgery) Therapy should be held following the use a renal contrast substance until adequate renal function is ascertained. However, there is no need to discontinue Metformin therapy prior to such diagnostic procedures.
In spite of the apprehensions about it the actual incidence of lactic acidosis due to Metformin is estimated to be 1:10,000 which is about 20 times less than with phenformin.
Retroanalysis of reported cases of Metformin - associated lactic acidosis has shown that almost all occurred when Metformin was given to patients with renal damage, which is a stated contraindication.
Early symptoms of lactic acidosis may be nonspecific consisting of nausea, vomiting, abdominal pain, and diarrhea. Evidence of nonketotic acidosis must be watched for and in suspicious cases blood lactate estimated.
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.

DIRECTION FOR USE

SWALLOW WHOLE TABLET, DO NOT CRUSH OR CHEW.

INFORMATION 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.

OVERDOSE AND TREATMENT

Glimepiride:

Sulfonylurea overdosage including Glimepiride can result in hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively 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 a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dl. Patients 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.

STORAGE CONDITIONS

Store below 30°C. Protect from light & moisture.

PACKAGING AVAILABLE

GLIMET 1 mg / 500 mg SUSTAINED RELEASE TABLETS and GLIMET 2 mg / 1000 mg SUSTAINED RELEASE TABLETS are available in Alu-Alu blister of 10 tablets. Such blisters containing 10 tablets are packed into a carton of 10's, 30's and 100's.Not all presentations may be available locally.

DATE OF REVISION OF PACKAGE INSERT

January 6, 2015

NAME AND ADDRESS OF MANUFACTURER

torrent PHARMA

Manufactured by:
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.