For the use of a Registered Medical Practitioner or a Hospital or a Laboratory xxxxxxxx-5253

METTA SR TABLETS 500 MG
METTA SR TABLETS 750 MG

Metformin Hydrochloride Extended Release Tablets 500 mg & 750mg

COMPOSITION
METTA SR TABLETS 750 MG
Each extended release tablet contains
Metformin Hydrochloride USP….750mg.
Colour: Red oxide of iron
METTA SR TABLETS 500 MG
Each extended release tablet contains
Metformin Hydrochloride USP….500mg.
PRODUCT DESCRIPTION:
METTA SR TABLETS 500 MG:
White to off-white coloured, capsule shaped, biconvex tablets with 'Torrent logo' debossed on one side and '500' on the other side.
METTA SR TABLETS 750 MG:
Pale red colored, capsule shaped, biconvex tablets with 'Torrent logo' debossed on one side and '750' on the other side.
CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with, type II diabetes, lowering both basal and postprandial 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 sulfonylureas, Metformin does not cause hypoglycemia in either with patients with type II diabetes or normal individuals.
PHARMACOKINETICS
Absorption
Metformin is absorbed incompletely after oral administration, about 30% of an oral dose recovered from the faeces. Oral bioavailability is about 50-60%. The drug may undergo some minor degree of first pass metabolism. It also gets concentrated in the walls of oesophagus, stomach and duodenum. Bioavailability is not improved when Metformin is given as an aqueous solution or rapidly dissolving tablets. Extended release formulations give lower bioavailability, as also do higher doses. Mean study state plasma levels of 505mcg/L were reached in 13 patients with doses of 1240 ± 560mg/day. Concominant food intake may slightly impair absorption.
Following a single oral dose of Metformin Hydrochloride Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours. Food did not have any significant effect on Cmax and Tmax of Metformin extended release formulation.
Distribution
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
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.
Elimination
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.
SPECIAL POPULATIONS
NIDDM subjects:
In presence of normal renal function there are no differences between single or multiple dose pharmacokinetics of Metformin between diabetics and non diabetics, nor is there any accumulation of Metformin in either group at usual clinical doses.
Renal insufficiency:
In subjects with decreased renal function [based on measured creatinine clearance], plasma and blood half life of Metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.
Hepatic insufficiency:
No pharmacokinetic studies have been conducted in subjects with hepatic insufficiency.
Geriatrics:
Limited date from the controlled studies of Metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half life is prolonged and C max is increased. This may be due to the change in renal function with ageing.
Gender:
Metformin parameters did not differ significantly in diabetic and non diabetic subjects when analyzed according to gender. Similarly in controlled clinical studies in patients with NIDDM, the antihyperglycemic effect was comparable in both males and females.
INDICATIONS
METFORMIN as monotherapy is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type II diabetes. METFORMIN may be used concomitantly with a sulfonylurea or insulin to improve glycaemic control.
CONTRAINDICATIONS
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
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
Pregnancy:-
Teratogenic Effects: Pregnancy Category B
Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Metformin Hydrochloride Tablets and Metformin Hydrochloride Extended Release Tablets should not be used during pregnancy unless clearly needed.
Lactation:-
Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
If Metformin Hydrochloride Tablets or Metformin Hydrochloride Extended Release Tablets is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.
ADVERSE REACTIONS
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.
DRUG INTERACTIONS
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 Pharmacodynamics.
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.
RECOMMENDED DOSAGE
Monotherapy and Combination with Other Oral Antidiabetic Agents: Usual Starting Dose: 1 tab once daily.
After 10 -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 doses for the 500mg and 750mg tabs are 4 and 2 tabs/day, respectively.
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 Metta SR 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 Metta SR at the dose indicated previously.
Combination with Insulin: Metformin and insulin may be used in combination therapy to achieve better blood glucose control.
Usual Starting Dose: 1 tab once 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, Metta SR should not be used in children.
MODE OF ADMINISTRATION
Should be taken with food (Take w/ evening meals. Swallow whole, do not chew/ crush).
DIRECTIONS FOR USE
THE TABLET SHOULD BE SWALLOWED WHOLE AND NOT TO BE CHEWED.
"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
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:
Store below 30^{o}C, Protect from light and moisture.
Keep out of reach of children.
PRESENTATION AND AVAILABILITY:
Metta SR tablets are packed in Alu-Alu blister of 10 tablets. Such blisters containing 10 tablets are packed into a carton of 10's, 30's , 60's and 100's.
Not all presentations may be available locally.
EXPIRY DATE:
Do not use later than the date of expiry.
DATE OF REVISION
28 August, 2014

torrent PHARMA

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