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

DIBETA SR

Metformin Hydrochloride Extended Release Tablets U.S.P. 500mg

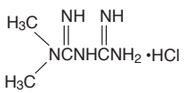
COMPOSITION

DIBETA SR

Each uncoated extended release tablet contains Metformin Hydrochloride U.S.P. …500 mg

PROPERTIES

Metformin Hydrochloride is an antihyperglycemic agent used in the management of type 2 diabetes. Chemically it is 1,1-dimethylbiguanide hydrochloride. It is white, crystalline powder, hygroscopic in nature, freely soluble in water, slightly soluble in ethanol (95%); practically insoluble in acetone, in chloroform, in dichloromethane and in ether. The empirical formula of Metformin Hydrochloride is $C_4H_{11}N_5$, HCl and molecular weight is 165.62. The structure of Metformin Hydrochloride is:



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with, type 2 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 2 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. Sustained 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 sustained 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.

INDICATIONS

DIBETA SR as monotherapy is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes. **DIBETA SR** may be used concomitantly with a sulfonylurea or insulin to improve glycaemic control.

CONTRAINDICATIONS

DIBETA SR 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.

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, 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 C_{max} 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 C_{max} 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.

DOSAGE AND METHOD OF ADMINISTRATION

Adults

There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with **DIBETA SR** or any other pharmacologic agent. Dosage of **DIBETA SR** should be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of **DIBETA SR** in adults is 2000 mg. **DIBETA SR** should generally be given once daily with the evening meal. **DIBETA SR** should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient. During treatment initiation and dose titration fasting plasma glucose should be used to determine the therapeutic response to **DIBETA SR** and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of **DIBETA SR** either when used as monotherapy or in combination with sulfonylurea, insulin sensitizers or insulin.

Transfer From Other Antidiabetic Therapy

When transferring patients from the standard oral hypoglycemic agents other than Chlorpropamide to **DIBETA SR**, no transition period generally is necessary. When transferring patients from Chlorpropamide therapy to **DIBETA SR** care should be taken as during first two weeks of therapy because of prolonged retention of Chlorpropamide in the body leading to overlapping drug effects and possible hypoglycemia.

Concomitant METFORMIN And Sulfonylurea Therapy

If patients have not responded to four weeks of the maximum dose of **DIBETA SR** or monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing **DIBETA SR** at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. With concomitant **DIBETA SR** and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.

Pediatric Use

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

Special Populations

Sustained release formulations are not recommended for use in pregnancy and in patients below the age of 10 years. The initial and maintenance dosing of sustained release formulation of Metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of sustained release formulations of Metformin Hydrochloride. Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly.

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.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 30°C, Protected from light & moisture.

KEEP MEDICATIONS OUT OF REACH OF CHILDREN

PRESENTATION AND AVAILABILITY

DIBETA SR

It is white to off white, capsule shaped uncoated tablet, available in blister strip of 10 tablets.

torrent PHARMA

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