Biocon

Metformin Hydrochloride Sustained Release Tablets IP 500 mg / 850 mg

METADOZE-IPR® 500 / METADOZE-IPR® 850 मेटाडोज़-आईपीआर 500/ मेटाडोज़-आईपीआर 850

COMPOSITION:
METADOZE-IPR®500
Each uncoated bilayered tablet contains:
Metformin Hydrochloride IP 500mg
(As sustained release form)
Excipients q.s.
Colour: Brilliant Blue FCF

METADOZE-IPR®850
Each uncoated bilayered tablet contains:
Metformin Hydrochloride IP 850mg
(As sustained release form)
Excipients q.s.
Colour: Brilliant Blue FCF

PHARMACEUTICAL FORM: Tablets
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic Group: Blood glucose lowering drugs, Excl. Insulins; Biguanides
ATC Code: A10BA02

Mechanism of action
Metformin hydrochloride is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both fasting and postprandial plasma glucose. Its pharmacologic mechanism of action is different from other classes of oral antihyperglycemic agents. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin hydrochloride does not produce hypoglycemia in patients with metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease type 2 diabetes or normal subjects and it does cause hyperinsulinemia. The importance of sustained release form (SR) is the absorption rate, timed as per the unique rate of release of the active ingredient to meet the therapeutic concentrations. It makes it possible to decrease the dosing frequency, decrease the cost of therapy and potentially improve the patient compliance.

Pharmacokinetic Properties Absorption
Metformin Hydrochloride has an incomplete absorption from small intestine; giving an oral bioavailability of about 50-60%.The bioavailability was not improved when metformin hydrochloride is given as an aqueous solution or rapidly dissolving tablets. About 30% is recovered from faeces. The drug does undergo some minor degree of first pass metabolism. There is lack of proportionality in the bioavailability of metformin hydrochloride with doses, which means a large dose of metformin hydrochloride may not be completely absorbed.

Concomitant food intake with conventional metformin hydrochloride tablets may decrease the rate of absorption and slightly prolong the time to achieve T_{max} and decrease the Cmax . In contrast, when the sustained release metformin hydrochloride formulations were administered with food, the bioavailability increased significantly without affecting the T_{max} and C_{max} and is achieved with a median value of 7 hours and a range of 4 to 8 hours.

Distribution
Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. Metformin hydrochloride accumulates in salivary glands, walls of esophagus, stomach and duodenum and also gets concentrated in kidneys.

Metabolism
Metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. But some studies indicate metabolic transformation to some extent (20%). No active metabolites have been identified.

Elimination
Metformin hydrochloride is excreted unchanged via kidneys by a combination of active tubular secretion and glomerular filtration. It has a plasma elimination half life of approximately 6.2 hours after oral administration of drug
.The renal clearance of drug can be correlated with creatinine clearance. When renal functions are impaired, renal clearance of drug is decreased in proportion to that of creatinine clearance, thus elimination half life is prolonged leading to accumulation of metformin hydrochloride in plasma.

CLINICAL PARTICULARS
Therapeutic Indications
METADOZE-IPR® 500 / METADOZE-IPR® 850 as monotherapy is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
METADOZE-IPR® 500 / METADOZE-IPR® 850 may be used concomitantly, in combination with a sulfonylurea or insulin or any other antidiabetic agent to improve glycemic control.

Posology and Method of Administration
There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with metformin hydrochloride sustained release tablet or any other pharmacologic agent. Dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily doses. The maximum recommended daily dose of metformin hydrochloride sustained release tablet in adults is 2000 mg.
Metformin hydrochloride sustained release tablet should generally be given once daily as preferred and tolerated. Metformin hydrochloride sustained release tablet 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 in the patient.
During treatment initiation and dose titration, fasting plasma glucose should be used to determine the therapeutic response of metformin hydrochloride sustained release tablet and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately 3 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 metformin hydrochloride sustained release tablet, either when used as monotherapy or in combination with sulfonylurea or insulin.

Transfer from Other Antidiabetic Therapy
When transferring patients from the standard oral hypoglycemic agents other than chlorpropamide to metformin hydrochloride sustained release tablet, no transition period generally is necessary. When patient on chlorpropamide is being shifted, careful monitoring should be done for first 2 weeks owing to prolonged retention period of chlorpropamide

Concomitant Metformin hydrochloride sustained release tablet and Sulfonylurea Therapy
If patients have not responded to metformin hydrochloride sustained release tablet monotherapy for about four weeks or so, of its maximum tolerable dose, consideration should be given to gradual addition of an oral sulfonylurea while continuing metformin hydrochloride sustained release tablet at an optimum titrated dose. With concomitant metformin hydrochloride sustained release tablet and sulfonyurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug.

Special Populations
Safety and efficacy of formulations of metformin hydrochloride in Pediatrics age group have not been established.

The initial and maintenance dosing of metformin hydrochloride 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 metformin hydrochloride. Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly.

Method of Administration
Metformin hydrochloride sustained release tablets must be swallowed whole, should not be crushed or chewed. Occasionally, the inactive ingredients of metformin hydrochloride sustained release tablet will be eliminated in the feces as a soft, hydrated mass.

Contraindications
Metformin hydrochloride sustained release tablets are 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 also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Known hypersensitivity to metformin hydrochloride.

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

Biocon

Metformin Hydrochloride Sustained Release Tablets IP 500 mg / 850 mg

METADOZE-IPR® 500 / METADOZE-IPR® 850 मेटाडोज़-आईपीआर 500/ मेटाडोज़-आईपीआर 850
Immediate and Patterned Release Technology

- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Special Warnings and Precautions for Use
Lactic Acidosis
Metformin hydrochloride is not recommended for patients with metabolic acidosis. But if the drug is indicated, it is always used 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 mandatory pre-requisite for treatment with metformin hydrochloride. Serum creatinine and creatinine clearance should be monitored, if renal dysfunction is suspected as a limitation during metformin hydrochloride therapy.
Lactic acidosis, which may be caused by metformin hydrochloride, is of the type B and is not associated with reduced tissue perfusion and hypoxia. Theoretically, diabetes patients 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. Diabetes patients also tend to overproduce lactate during exercise. Inspite of this predisposition, type B lactic acidosis is rare with metformin hydrochloride until renal functions are deranged. Metformin hydrochloride is not associated with type A lactic acidosis, but still should be given with caution to patients with risk factors for hypoxia such as sepsis, dehydration, congestive cardiac failure, alcoholism, or seizures. Lactic acidosis in patients with malignancy is thought to be due to a factor produced by a tumor, which inhibits pyruvate dehydrogenase and increases lactate production. Exercise caution with the use of metformin hydrochloride in such patients.
Metformin hydrochloride should be withheld at least 2-3 days before procedures like intravenous urography or aortography and should be compulsorily stopped 2 days before any major surgery as there may be risk of temporary "renal insufficiency". Insulin may be used instead until the patient is stable.
Hepatic dysfunction has no significant effect on the clearance of metformin hydrochloride but it predisposes to lactic acidosis. Since chronic metformin hydrochloride therapy is associated with deficiency of vitamin B12 and folic acid, these two must be estimated periodically and supplements may be given.

Drug Interactions
Low or absence of protein binding and lack of hepatic biotransformation make metformin hydrochloride practically free from drug interactions. Alcohol, barbiturates, salicylates and phenothiazines may precipitate lactic acidosis. Alcohol may precipitate hypoglycemia the same way as sulfonylureas when given in combination with metformin hydrochloride.

Glibenclamide
In a single-dose interaction study in type 2 diabetes patients, co administrationof metformin hydrochloride and glibenclamide did not result in any changes in either pharmacokinetics or pharmacodynamics of metformin hydrochloride.
Furosemide
A single-dose, metformin hydrochloride-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin hydrochloride plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin hydrochloride renal clearance.

Nifedipine
A single-dose, metformin hydrochloride-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin hydrochloride Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin hydrochloride. Metformin hydrochloride had minimal effects on nifedipine.

Pregnancy and Lactation
Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women, therefore metformin hydrochloride should not be used during pregnancy unless clearly needed. It is not known if metformin hydrochloride is excreted in milk. Because many drugs gets excreted in milk and the potential for hypoglycemia in nursing infants may exist with metformin hydrochloride, 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.

Effects on Ability to Drive and Use Machines
Metformin hydrochloride sustained release tablet monotherapy does not cause hypoglycemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycemia when metformin hydrochloride is used in combination with other antidiabetic agents.

Undesirable Effects
On starting metformin hydrochloride, approximately one-third of the patients are likely to have transient nausea, abdominal pain, anorexia and diarrhea, which can be attenuated by starting with low dose of sustained release therapy. Evidence of nonketotic acidosis must be watched for and in suspicious cases blood lactate should be estimated. Enhanced glucose uptake and glycolytic flux is observed in presence of high circulating levels of metformin hydrochloride. It predisposes patients to the development of lactic acidosis, in presence of renal insufficiency.

In addition to renal dysfunction, the risk factors include congestive heart failure, conditions leading to severe loss of blood or body fluids, intravenous pyelography, arteriography, acute asthmatic attack, status epilepticus, sudden ascent to high altitude.
However, there is no need to discontinue metformin hydrochloride therapy prior to diagnostic procedures if adequate renal function is ascertained.
Megaloblastic anemia has been reported in patients on metformin hydrochloride.
Hypoglycemia with metformin hydrochloride does not occur when given alone, but may occur when sulfonylurea is added or with consumption of alcohol.

Other Reactions
Asthenia, headache, abnormal stools, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

Overdose
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride 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 hydrochloride overdosage is suspected.

PHARMACEUTICAL PARTICULARS
Shelf Life: Refer carton/blister
Storage and Precautions
Storage: Store protected from light & moisture at a temperature not exceeding 30°C.

Keep out of reach of children.

Nature and Contents of Container
METADOZE-IPR® 500 / METADOZE-IPR® 850 are available in blister pack of 10 tablets.

Special Precautions for Disposal and Other Handling
Any unused product or waste material should be disposed off in accordance with local requirements.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park, Electronics City, Phase - II,
Bengaluru - 560 100, India.

® - Registered trademark

Leaflet revised on August 2019

BF/LL/3825/01

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e mail us at **drugsafety@biocon.com.**