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

Biocon

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Metformin Hydrochloride Prolonged-release and Glimepiride Tablets IP

BLISTO® - 1MF / 2MF ब्लिस्टो-१ एमएफ /२ एमएफ

COMPOSITION:
BLISTO®- 1MF
Each film coated tablet contains:

Metformin Hydrochloride IP (As prolonged release form)	500 mg
Glimepiride IP	1 mg
Excipients	q.s.

Colours: Ponceau 4R and Titanium Dioxide IP

BLISTO®- 2MF
Each film coated tablet contains:

Metformin Hydrochloride IP (As prolonged release form)	1000 mg
Glimepiride IP	2 mg
Excipients	q.s.

Colours: Iron Oxide Yellow and Titanium Dioxide IP

PHARMACEUTICAL FORM: film coated tablets

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group:
Blood glucose lowering drugs, Excl. Insulins; Combinations of oral blood glucose lowering drugs
ATC Code: A10BD02

Clinical Pharmacology :
This drug is combination of glimepiride, an oral hypoglycaemic drug and metformin, an antihyperglycaemic drug, giving a synergistic effect for the management of Type 2 diabetes mellitus.

Mechanism of Action :
Glimepiride is an Insulin secretagogue. The primary mechanism of action of glimepiride, a second generation sulphonylurea (sometimes referred as third generation) appears to be via stimulation of the release of Insulin by closing the ATP sensitive potassium channel in the pancreatic beta cell membrane. In addition, effects of glimepiride also may involve extra pancreatic processes.

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves Insulin sensitivity by increasing peripheral glucose uptake and utilization. It thus lowers both basal and postprandial plasma glucose without causing hypoglycemia.

Pharmacokinetics Properties :
After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Significant absorption occurs within 1 hour of administration and peak drug levels at 2 to 3 hours. Protein binding is reported to be greater than 99.5%. It is completely metabolised by oxidative biotransformation with 60% of the excretion via urine and the remaining via faeces.

Following a single oral dose of metformin hydrochloride sustained release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. Metformin has an absolute oral bioavailability of 50 to 60%. Higher oral doses are proportionately less bioavailable than lower doses (observed in doses of 0.5 to 1.5g). When given with food, AUC increased by 50% from the sustained release metformin tablet but there was no effect of food on C_{max} and T_{max} of metformin.

Following absorption, metformin is rapidly distributed and does not bind to plasma proteins. Metformin undergoes renal excretion and has plasma elimination half life of 6.2 hours after oral administration.

In patients with decreased renal function, the plasma and blood half life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance

Indications :
BLISTO®- 1 MF and BLISTO®- 2 MF are indicated in patients with type 2 diabetes mellitus when diet, exercise and single agent (Glimepiride / Metformin) therapy does not result in adequate glycaemic control.

Contraindications :
- Hypersensitivity to the active constituents or to any other ingredient of the formulation.
- Renal disease or renal dysfunction which may also result from conditions such as cardiovascular collapse, acute myocardial infarction and septicaemia.
- Congestive heart failure requiring pharmacological treatment.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with Insulin.

Dosage and Method of Administration :
Dosage of BLISTO®- 1MF and BLISTO®- 2MF should be individualized on the basis of both effectiveness and tolerance.

The highest recommended dose per day should be 6 mg of glimepiride and 2000 mg of metformin. Daily doses of glimepiride of more than 6 mg are more effective only in a minority of patients.
Starting dose for patients inadequately controlled on metformin monotherapy: Blisto 1MF or Blisto 2MF may be initiated once daily, and gradually titrated after assessing the therapeutic response.
Starting dose for patients who initially responded to glimepiride monotherapy and require additional glycemic control: Based on the initial starting dose of glimepiride (1 or 2 mg), Blisto 1 MF or Blisto 2MF may be initiated once daily, and gradually titrated after assessing the therapeutic response.
Starting dose for patients switching from combination therapy of glimepiride plus metformin as separate tablets: Blisto-1MF or Blisto-2MF may be initiated based on the dose of glimepiride and metformin already being taken.

Paediatrics : Safety and effectiveness of Glimepiride and Metformin Hydrochloride (Sustained Release) Tablets in paediatric patients have not been established.
Elderly: The initial and maintenance dose of Glimepiride and Metformin Hydrochloride (sustained Release) Tablets should be conservative in patients with advanced age. Dosage adjustment should be done carefully and titration to the maximum dose should generally be avoided.

Warning and Precautions :
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with this formulation. When it occurs, it is fatal in approximately 50% of cases.

The risk of lactic acidosis increases with the degree of renal insufficiency including both intrinsic renal disease and renal hypoperfusion.

Patients with CHF requiring pharmacological management, in particular those with unstable or acute CHF who are at risk of hypo-perfusion and hypoxemia, are at increased risk of lactic acidosis.

This drug should be discontinued in the presence of any condition associated with hypoxemia, dehydration or sepsis. Avoid use in patients with impaired hepatic function.

This drug should be temporarily discontinued prior to any intravasular radiocontrast study and for any surgical procedure.

Vitamin B_{12} levels should be routinely monitored in patients who are on metformin. Periodic monitoring of fasting blood glucose levels, glycosylated hemoglobin and haematologic parameters should be done.

This drug may cause hypoglycaemia especially in the elderly, debilitated or malnourished patients, in those with adrenal, pituitary or hepatic insufficiency, impaired renal function, deficient caloric intake, or after severe or prolonged exercise or ingestion of alcohol.

Alertness and reactions may be impaired due to hypoglycaemia, thus care should be taken while operating vehicle or machinery.

The administration of oral hypoglycaemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus Insulin. In isolated cases increase in liver enzymes values have been reported during treatment with sulphonylureas and also worsening of liver function with cholestasis, icterus and hepatitis.

When a patient stabilized on antidiabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control

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may occur. At such times it may be necessary to add Insulin temporarily. The effectiveness of any oral antidiabetic drug may decrease in patients over a period of time and is known as 'secondary failure', quite inherent in the group of sulphonylureas and may be corrected by adding Insulin.

BLISTO®- 1 MF and BLISTO®- 2 MF are not suitable for the Treatment of Type 1 diabetes mellitus.

There is no experience with the use of glimepiride in patients with severe impairment of liver function or dialysis patients. in such patients, change over to Insulin is indicated.

Pregnancy & Lactation :
Recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend the use of Insulin to maintain blood glucose levels during pregnancy.

There are no adequate and well controlled studies of this combination in pregnant women. It should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Metformin is excreted at low concentration in the milk of lactating rats. Although it is not known whether glimepiride is excreted in human milk or not other sulphonylureas are excreted in human milk. Because of the potential of hypoglycaemia in nursing infants, 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
Alertness and reaction time may be impaired due to hypo- or hyperglycaemia, especially when beginning or after altering treatment or when Amaryl is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.

Drug Interactions :
The hypoglycaemic action of sulphonylurea drugs may be potentiated by certain drugs that are highly protein bound, like nonsteroidal anti-inflammatory drugs. The others which can do the same are Insulin and other oral antidiabetics, ACE inhibitors, allopurinol, anabolic steroids and male sex hormones, chloramphenicol, coumarins, cyclophosphamide, disopyramide. fenfluramine, fibrates, fluoxetine, guanethidine, iphosphamide, beta blockers, MAO inhibitor, miconazole, para-amino salicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulphonamides, tetracyclines, tritoqualine, trofosfamide.

Weakening of the blood sugar lowering effect and, thus, raised blood sugar levels may occur when one of the following medicines are taken concomitantly, for example : acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, adrenaline and other sympathomimetic agents, glucagon, laxatives (after protracted use); nicotinic acid (in high doses), oestrogen and progestogen, phenothiazines, phenytoin, rifampicin, thyroid hormones.

H_2 receptor antagonists, clonidine and reserpine may lead to either potentiation or weakening of the blood sugar lowering affect.

Cationic drugs (e.g., Amiloride, Digoxin, Morphine, Procainamide, Quinidine, Quinine, Ranitidine, Triamterene, Trimethoprim and Vancomycin) which are eliminated by renal tubular secretion could have the potential for interaction with metformin by competing for common renal tubular transport systems. Concomitant use of cimetidine leads to 60% increase in peak metformin plasma and whole blood concentrations.

In a single dose study, metformin - furosemide increased the metformin plasma and blood C_{max} without altering metformin renal clearance. Nifedipine was reported to cause increase in plasma metformin C_{max} and AUC.

Side effects :
The most common adverse effect of glimepiride has been hypoglycaemia. Asthenia, dizziness, headache and nausea has also been reported, Occasionally, vomiting, gastrointestinal pain, diarrhoea, allergic reactions such as itching, urticaria or rashes may occur, Porphyria cutanea tarda, photosensitivity reactions, allergic vasculitis have also been reported with sulphonylureas. Moderate to severe thrombocytopenia. leucopaenia, erythrocytopaenia, agranulocytopaenia, agranulocytosis, hemolytic anemia and pancytopaenia. Hyponatraemia and changes in accommodation and / or blurred vision may occur with the use of glimepiride.
The most commonly occurring adverse reactions reported with sustained release metformin are diarrhoea, nausea and vomiting. Additional adverse effects reported were abdominal pain, constipation, abdomen distention, dyspepsia / heartburn, flatulence, dizziness, headache, upper respiratory tract infection taste disturbance and rarely lactic acidosis.

Overdosage :
Overdosage of glimepiride can induce hypoglycaemia. Mild hypoglycaemic symptoms with loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustment with drug dosage and / or meal patterns.

Severe hypoglycaemic reactions with coma, seizure or other neurological impairment occur infrequently but require immediate hospitalization. If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated glucose solution (50%), 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 100mg/dl. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycaemia may recur.

Lactic acidosis may occur with the overdose of metformin. Metformin is dialyzable with a clearance of up to 170 ml/min; haemodialysis may be useful for removal of accumulated drug from patients with lactic acidosis or in whom metformin overdosage is suspected.

PHARMACEUTICAL PARTICULARS
Incompatibilities
Not applicable

Storage: Store protected from moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

Shelf Life: Please refer carton/blister.

Special Precautions for disposal and other handling:
Any unused medicinal product should be disposed off in accordance with the local requirements.

Presentation :
BLISTO® -1MF / BLISTO® -2MF tablets are available in blister pack of 10 tablets.

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

BF/LL/3813/01

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Leaflet Revised on **August 2019**

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e mail us at **drugsafety@biocon.com**