Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

Biocon

℞

Metformin Hydrochloride Prolonged Release 500 mg, Glimepiride 1 mg and Voglibose 0.2 mg Tablets
Metformin Hydrochloride Prolonged Release 500 mg, Glimepiride 2 mg and Voglibose 0.2 mg Tablets

BLISTO® TRIO 1/BLISTO® TRIO 2 ब्लिस्टो ट्रायो १ / ब्लिस्टो ट्रायो २

COMPOSITION:
BLISTO® TRIO 1
Each uncoated bilayered tablet contains:

Metformin hydrochloride IP (In prolonged release form)	500 mg
Glimepiride IP	1 mg
Voglibose IP	0.2 mg
Excipients	q.s

Colour: Sunset yellow FCF

BLISTO® TRIO 2
Each uncoated bilayered tablet contains:

Metformin hydrochloride IP (In prolonged release form)	500 mg
Glimepiride IP	2 mg
Voglibose IP	0.2 mg
Excipients	q.s

Colours: Ferric Oxide USP-NF Yellow & Ferric Oxide USP-NF Red

Pharmaceutical form
Tablet

Pharmacotherapeutic group
Blood glucose lowering drugs, excl. insulins

ATC code: A10BA02, A10BB12, A10BF03

PHARMACOLOGICAL PROPERTIES
This is a combination of three oral antidiabetic drugs metformin, glimepiride and voglibose, giving a synergistic effect for the management of type 2 diabetes mellitus [Noninsulin dependent diabetes mellitus (NIDDM)].

PHARMACODYNAMICS:
Metformin
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 levels.

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

Voglibose
Voglibose is an **α**-glucosidase inhibitor which reduces intestinal absorption of starch, dextrin and disaccharides by inhibiting the action of the enzyme **α**-glucosidase in the intestinal brush border. Inhibition of this enzyme delays the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates; the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects. **α**-glucosidase inhibitors do not stimulate insulin release and therefore do not result in hypoglycaemia.

PHARMACOKINETICS
Metformin
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% . When given with food, AUC increased by 50% from the sustained release metformin tablet, but there was no effect of food on food on C_{max} and T_{max} of metformin. Following absorption, metformin is rapidly distributed and does not bind to plasma proteins. Metformin does not undergo hepatic metabolism. It undergoes renal excretion in an unchanged form and has plasma elimination half-life of 6.2 hours after oral administration.

Glimepiride
After oral administration, glimepiride is completely (100%) absorbed from the gastrointestinal 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, and 60% of the drug is excreted via urine and the remaining via faeces.

Voglibose
Voglibose is poorly absorbed after oral administration. Plasma concentration after oral dosing has been undetectable. After ingestion of voglibose, the majority of active unchanged drug remains in the lumen of the GI tract to exert its pharmacological activity. The drug is metabolised by the intestinal enzymes and by the microbial flora. Voglibose is mainly excreted in the faeces and negligible amount in the urine.

CLINICAL PARTICULARS
Therapeutic indications
BLISTO® TRIO is indicated as second-line or third-line therapy when diet, exercise, single agents or dual combination therapy fail to provide adequate glycaemic control in patients with type 2 diabetes.

Posology and method of administration
The dose of BLISTO® TRIO should be individualized on the basis of both effectiveness and tolerance.
The initial recommended dose is one tablet of BLISTO® TRIO 1, once daily with the meal, or as prescribed by the physician. If the effect is not sufficient, the dose may be increased to one tablet of BLISTO® TRIO 1 given two times daily given with the meals, or as prescribed by the physician. If better glycaemic control is needed, the initial dose can be one tablet of BLISTO® TRIO 2 given once a day with the meal, which can be increased up to one tablet given twice a day with the meals or as prescribed by the physician.
The tablet must be swallowed as a whole, should not to be crushed or chewed.

Dosage in renal failure
Metformin and glimepiride in BLISTO® TRIO are eliminated through the kidney, and the risk of complications like lactic acidosis is greater in patients with renal dysfunction. Therefore, this combination is contraindicated in the presence of renal failure. Regular assessment of renal function is necessary.

Paediatric use
Safety and efficacy of BLISTO® TRIO in paediatric patients has not been established.

Geriatric use
Since elderly patients generally have physiological hypofunction, it is desirable that such caution be taken as starting the administration at low dose. Metformin and glimepiride are known to be excreted by the kidneys and risk of adverse reactions such as hypoglycaemia and lactic acidosis are greater in patients with impaired renal function, such as elderly patients. Care should be taken in dose selection and regular renal function be monitored. Therapy with combination containing metformin should not be initiated in patients >80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Contraindications:
- Hypersensitivity to the drugs 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.
- Gastrointestinal obstruction or patients predisposed to it.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Lactic acidosis
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 approximately in 50% of cases. Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. The risk of acidosis increases with the degree of renal insufficiency including both intrinsic renal disease and renal hypoperfusion. This combination should be temporarily discontinued prior to any intravascular radiocontrast study and any surgical procedure, because such procedures may result in acute alteration of renal function.

Renal function
Before initiation of this combination therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and this combination discontinued if evidence of renal impairment is present.

OTHER PRECAUTIONS
- Patients with congestive heart failure (CHF) requiring pharmacological management, in particular those with unstable or acute CHF who are at risk of hypoperfusion and hypoxaemia, are at increased risk of lactic acidosis. This drug should be discontinued in the presence of any condition associated with hypoxaemia, dehydration or sepsis.
- In isolated cases increase in liver enzyme levels have been reported during treatment with sulphonylureas and also worsening of liver function with cholestasis, icterus and hepatitis. Avoid use in patients with impaired hepatic function.
- Impairment of vitamin B12 absorption has been reported in some patients. Therefore, serum vitamin B12 levels should be routinely monitored in patients who are on long-term treatment with metformin.
- This combination may cause hypoglycaemia, especially in 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 reflexes 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.
- Drug combinations containing voglibose should be administered with caution to the following patients: patients with history of laparotomy or ileus, patients with chronic intestinal disease accompanied by disturbance in digestion and absorption, patients with aggravating symptoms due to increased generation of intestinal gas (e.g., Roemheld syndrome, severe hernia, stenosis or ulcer of large intestine), and patients with serious hepatic disorders.
- Fasting and postprandial blood glucose should be monitored periodically to determine therapeutic response. Glycosylated haemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycaemic control. When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a loss of glycaemic control 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, known as 'secondary failure', is quite inherent in the group of sulphonylureas and may be corrected by adding insulin.
- BLISTO®TRIO is not suitable for treatment of type 1 diabetes mellitus.

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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 other which can do the same are: insulin and oral antidiabetic drugs, ACE inhibitors, allopurinol, anabolic steroids and male sex hormones, chloramphenicol, coumarins, cyclophosphamide, disopyramide, fenfluramine, fibrates, guanethidine, iphosphamide, beta blockers, monoamine oxidase (MAO) inhibitors, miconazole, para-amino salicylic acid, pentoxifylline (high dose, parenteral), phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulphonamides, tetracyclines, tritoqualine, trofosfamide.

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

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

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprime 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 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} and AUC.

PREGNANCY AND LACTATION:
There is no adequate and well controlled studies of this combination in pregnant women. Thus, this combination is not recommended for usage during pregnancy, unless the potential benefit justifies the potential risk to the foetus. Most experts recommend use of insulin to maintain blood glucose levels during pregnancy.

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. Animal studies have revealed a suppressive action of voglibose on body weight increase in newborns, presumably due to suppression of milk production in mother animals resulting from suppression of carbohydrate absorption. Because of potential of hypoglycaemia in nursing infants with this combination of drugs, 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 reactions may be impaired due to hypoglycaemia, especially when beginning or after altering treatment or when BLISTO® TRIO is not taken as per physician's advice. This may affect the ability to drive or to operate machinery.

UNDESIRABLE EFFECTS
Gastrointestinal disorders such as diarrhoea, loose stools, abdominal pain, constipation, anorexia, nausea, vomiting, diarrhoea, and abdominal pain may occur with this combination. Also abdominal distention, increased flatus, and intestinal obstruction-like symptoms due to an increase in intestinal gas, may occur with use of voglibose. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.
Skin and subcutaneous tissue disorders: very rarely skin reactions such as erythema, pruritis, urticaria have been seen.
Decrease of vitamin B_{12} absorption with decrease in serum levels may occur during long term use of metformin. Consideration of this etiology is recommended if a patient on metformin presents with megaloblastic anaemia.
There are isolated reports of liver function test abnormalities or hepatitis resolving upon metformin discontinuation. When voglibose is administered to patients with serious liver cirrhosis, hyperammonia may worsen with the development of constipation, followed by disturbance of consciousness. Elevation of SGOT (glutamate oxaloacetate), SGPT (glutamate pyruvate transaminase), LDH (lactate dehydrogenase), or alkaline phosphatase may infrequently occur.

Other rare adverse effects of voglibose include headache, anaemia, thrombocytopaenia, numbness, blurred vision, hot flushes, malaise, weakness, hyperkalaemia, and diaphoresis.

The most common adverse effect of glimepiride has been hypoglycaemia. Asthenia, dizziness, nausea, allergic reactions such as urticaria may also occur with glimepiride. Porphyria cutanea tarda, photosensitivity reactions, allergic vasculitis have also been reported with sulphonylureas. Changes in the blood picture may occur. Rarely (≥1/10,000 and <1/1000), thrombocytopaenia and, in isolated cases (<1/10,000), leucopaenia, haemolytic anaemia, erythrocytopaenia, granulocytopaenia, agranulocytosis or pancytopaenia may develop. In isolated cases, a decrease in serum sodium concentration may occur.

OVERDOSE
Overdosage of glimepiride, can produce hypoglycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated 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 hypoglycaemic reactions with coma, seizure, or other neurological impairment occur infrequently, but require immediate hospitalization. In case of overdosage, if hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous bolus of 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 level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycaemia may recur after apparent clinical recovery.
Lactic acidosis may occur with overdose of metformin. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.
Overdose of voglibose may cause abdominal discomfort and diarrhoea.

Incompatibilities
None reported.

Shelf life: Please refer carton/strip.

Storage and precautions
Keep out of reach of children
Storage: Store below 30° C. Protected from light and moisture.

The tablet should be swallowed as a whole and not be crushed or chewed.

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

Presentation: Available as blister pack of 10 tablets.

Pack Size: 10 x 10 Tablets

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

BF/LL/3719/01

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call the Toll Free Number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com**