Change
Innova Captab to Innova captab Ltd.

Product Name : Amaramet Tablets
Country : Philippines
Site : Innova Captab Ltd.
component : Carton
Dimension : 205x283 mm
Artwork Code : Required from Innova
Date : 01/04/2022

FRONT

GLIMEPIRIDE + METFORMIN HYDROCHLORIDE

AMARAMET

2 mg/500 mg Extended-Release Tablet
Oral Hypoglycemic

℞

Formulation:
Each uncoated-bilayered tablet contains:

Glimepiride B.P.	2 mg
Metformin Hydrochloride B.P. (As Extended-Release form)	500 mg
Excipients	q.s.

Pharmacological Properties:
ATC Classification A10BD02 - metformin and sulfonamides; Belongs to the class of combinations of oral blood glucose lowering drugs.

Pharmacology:
Glimepiride and Metformin hydrochloride contains two oral anti-hyperglycemic drugs used in the management of type-2 diabetes mellitus - Non-insulin dependent diabetes mellitus (NIDDM).

Glimepiride
Glimepiride reduces blood glucose levels by correcting both defective insulin secretion and peripheral insulin resistance. It interacts with specific receptors at the plasma membrane of the insulin releasing pancreatic b-cells where they inhibit ATP-sensitive K+ channels resulting in depolarization of the cell membrane, opening of voltage sensitive Ca+ channels, increase in intracellular calcium levels and subsequent insulin release.

Metformin
Metformin acts as an antihyperglycemic agent by improving hepatic and peripheral tissue sensitivity to insulin. It also appears to have beneficial effect on serum lipid levels and so on fibronolytic activity. Metformin therapy is not associated with increase in body weight. Metformin decrease glucose production, decreases levels and so on fibronolytic activity. Metformin therapy is not associated with increase in body weight. Metformin decreases glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Rationality for Combination of Glimepiride and Metformin:
Sulfonylureas and biguanides act complementary to each other. Both compounds have an additive antihyperglycemic effect without increasing the adverse effects of either pharmacological class.

Glimepiride acts via stimulating b-cells of pancreas to release insulin and also increases peripheral sensitivity of insulin. Metformin acts via enhanced peripheral glucose uptake and utilization. It also reduces hepatic glucose production, thereby metformin diminishes insulin resistance.
There are reports in which combination treatment of sulfonylureas with metformin has been reported to achieve satisfactory glycemic control for several years. The combination may therefore provide additional glycemic control (blood glucose lowering effect by 20%).

Glimepiride has less propensity to cause hypoglycaemia and increase in body weight as compared to other sulfonylureas. Since metformin is reported to have predominant peripheral mechanism of action, therefore it lacks the anabolic effects of sulfonylureas and does not cause weight gain.

Metformin is associated with a decrease in fasting and postprandial plasma insulin and triglyceride levels, increase in HDL-cholesterol, increase of tissue plasminogen activator, decrease in platelet aggregation.

Pharmacokinetically the two drugs appear to be compatible, as metformin is not plasma protein bound and does not get metabolized in liver. So interaction with glimepiride (having 99% plasma protein binding and metabolized via liver) does not appear to be possible. Hence, the combination of glimepiride and metformin would help in treatment of Non-Insulin Dependent Diabetes Mellitus (NIDDM).

Pharmacokinetic:
Absorption:
Glimepiride: After oral administration glimepiride is completely absorbed from the GI tract. Studies have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours. When glimepiride was given with meals, the mean Tmax (time to reach Cmax) was slightly increased (12%) and the mean Cmax and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

Metformin sustained-release: The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50-60%. Following a single oral dose of metformin sustained-release, Cmax is achieved within 4-8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin immediate release, however the extent of absorption (as measured by AUC) is similar to immediate release. Both high and low fat meals had the same effect on the pharmacokinetics of sustained-release.

Distribution:
Glimepiride: After intravenous dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg). Protein binding was greater than 99.5%. *Metformin sustained-release:* Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. Distribution studies with metformin sustained-release have not been conducted. At usual clinical doses and dosing schedules of immediate-release metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 µg/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism:
Glimepiride: Glimepiride is completely metabolized by oxidative biotransformation. The major metabolites are the cyclohexyl hydroxyl methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent; however, wether the glucose-lowering effect of M1 is clinically significant is not clear.

Metformin sustained-release: Metabolism studies with metformin sustained-release have not been conducted. However, intravenous single-dose studies in normal subjects demonstrate that metformin immediate release does not undergo hepatic metabolism or biliary excretion.

Excretion:
Glimepiride: When 14C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that of the recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces.

Metformin: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Renal clearance of metformin is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Indication:
Adjunct to diet and exercise in non-insulin dependent diabetes mellitus (type 2 diabetes) sufficiently controlled by sulfonylureas or metformin therapy alone or at maximum tolerated dose.

Dosage and Administration:
The dosage of antidiabetic drugs should be individualized based on the patient's blood glucose levels. Generally, it should be recommended to initiate the lowest effective dose and increase the dose depending on the patient's blood glucose levels. If sulfonylurea with long t1/2 has been used before taking Glimepiride + Metformin tablet, adequate monitoring of blood glucose levels should be performed for this.
Mistakes e.g., forgetting to take a dose, must never be corrected by subsequently taking a larger dose.
The highest recommended dose per day should be glimepiride 8 mg and metformin 2000 mg.
When switching from combination therapy of glimepiride plus metformin as separate tablets, Glimepiride + Metformin tablet should be administered on the basis of dosage currently being taken.

Administration: It should be administered once a day before or with breakfast or the 1st main meal.
Patients should be informed that Glimepiride + Metformin tablet must be swallowed whole and not crushed or chewed because this is a prolonged-release tablet.

Overdosage:
Overdose of glimepiride can result in hypoglycemia.
As soon as an overdose of glimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose.
Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium sulfate (laxative).

Contraindications:
Known hypersensitivity to any of the excipients of Glimepiride + Metformin tablet, sulfonylureas, sulfonamides or biguanide.
Insulin dependent (type 1) diabetes (e.g., diabetics with a history of ketonemia), diabetic ketonemia, diabetic coma or precoma.
Patients with severe hepatic dysfunction or hemodialysis. In case of severe hepatic or renal function disorders, a change over to insulin is required to achieve adequate control of blood glucose.

Warnings:
Lactic Acidosis: Lactic Acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with Glimepiride + Metformin tablet. Because impaired hepatic function may significantly limit the ability to clear lactate, Glimepiride + Metformin tablet should be generally avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Glimepiride + Metformin tablet, since alcohol potentiates the effects of metformin HCl on lactate metabolism.
Increased Risk of Cardiovascular Mortality: The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

Special Precautions:
General Precautions: Patients should be informed that Glimepiride + Metformin tablet must be swallowed whole and not crushed or chewed and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.
Diabetes-Like Symptoms: Glimepiride + Metformin tablet should be prescribed only for patients diagnosed with diabetes. They should be distinguished from diabetes-like symptoms (renal diabetes, geriatric glucose metabolism disorder, thyroid malfunction) including glucose intolerance, positive urine glucose. Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism.

Check List	Checked by Pkg.	Reviewed by RA	Approved by QA
Dimension		—	—
Colours		—	—
Composition			
Brand Name/Generic Name			
Other text matter as per RA Guideline	—		
Mfg. Lic./Code No.:			
Artwork Code			
Barcode/Space For 2D			
Sign/Date			
Name	Sunil Parab	Richa Bhandari	Anju Nair

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BACK

Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Glimepiride + Metformin tablet.

Use in children: Safety and effectiveness in pediatric patients have not been established.

Use in the elderly: Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Metformin is known to be substantially excreted by the kidney and the risk of serious adverse reactions to metformin is greater in patients with impaired renal function. It should only be used in patients with normal renal function.

Pregnancy and lactation:
Use in pregnancy: Glimepiride + Metformin must not be taken by pregnant or possibly pregnant women. In animal study, teratogenicity was reported and lactic acidosis is easy to occur. Pregnant patient or the patient planning a pregnancy must inform their physician about their diabetes and they should not be treated with metformin but insulin should be used to maintain blood glucose levels. Use in lactation: Studies in lactating rats show that metformin and glimepiride are excreted into milk. So, Glimepiride + Metformin must not be taken by breastfeeding women. If necessary, the patient must change over to insulin or must stop breastfeeding.

Effects on ability to drive and use machines:
Alertness and reactions may be impaired due to hypoglycemia or hyperglycemia, especially when beginning or after altering treatment or when Glimepiride + Metformin is not taken regularly.
This may affect the ability to drive or to operate machinery.
Patients should be advised to drive a car or operate machinery with caution.

Adverse Drug Reactions:
Digestive Tract: Gastrointestinal (GI) symptoms including nausea, vomiting, diarrhea, abdominal pain and anorexia. These symptoms are the most common in the initial stage of treatment and generally resolve spontaneously. Occasionally, temporary dose reduction may be useful. Because GI symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take Glimepiride + Metformin tablet with meals.
Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, Glimepiride + Metformin tablet should be temporarily discontinued. For patients who have been stabilized on Glimepiride + Metformin tablet, nonspecific GI symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis has been excluded.
Nervous System: About 3% of patients can feel taste disturbance or metallic taste during the initial stage of treatment with Glimepiride + Metformin tablet but they generally resolve spontaneously. Especially, transient vision disorder may occur due to change of blood glucose.
Dermatologic Reactions: Occasionally, allergic or pseudo-allergic reactions (e.g., itching, urticaria or rashes) may occur. These reactions are almost mild but may develop into serious reaction with dyspnea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria, a physician must therefore be notified immediately.
Blood: Changes in the blood picture may occur. Rarely, thrombopenia, in isolated cases, leukopenia or hemolytic anemia (e.g., erythrocytopenia, granulocytopenia, agranulocytosis) may develop. Because it is reported that aplastic anemia and pancytopenia may occur in sulfonylureas, careful monitoring should be performed. If these occur, the medication should be discontinued and adequate treatment taken.

Drug Interactions:
Glimepiride: When other drugs are concomitantly administered or withdrawn from a patient receiving glimepiride, both undesired increases and decreases in the hypoglycemic action of glimepiride can occur. Based on experience with glimepiride and with other sulfonylureas, the following interactions must be considered: Glimepiride is metabolized by cytochrome P-450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole).
Drugs Potentiating the Blood Glucose-Lowering Effect: Insulin and oral antidiabetic products, angiotensin-converting enzyme inhibitors, allopurinol, anabolic steroids, male sex hormones, chloramphenicol, coumarin anticoagulants, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, guanethidine, ifosfamide, MAOIs, miconazole, fluconazole, para-aminosalicyclic acid, pentoxifylline (high-dose parenteral), phenylbutazone, probenecid, quinolone antibiotics, salicylates, sulfinpyrazone, clarithromycin, sulfonamide, tetracyclines, tritoqualine, trofosfamide, sympathetic inhibitor.
Drugs Weakening the Blood Glucose-Lowering Effect: Acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, epinephrine (adrenaline) or sympathomimetics, glucagons, laxatives (long-term use), nicotinic acid (high dose), estrogens, progestogens, phenothiazines, phenytoin, rifampicin, thyroid hormones.
Drugs Potentiating or Weakening the Blood Glucose-Lowering Effect:
H2-antagonists, clonidine, reserpine.
Beta-blockers reduce glucose tolerance. Reduction of glucose tolerance may change metabolic control. Beta-blockers may increase the risk of hypoglycemia (due to failure of counter-regulation).
Drugs Reducing or Blocking the Signs of Adrenergic Counter-Regulation to Hypoglycemia: Sympatholytic drugs (e.g., β-blockers), clonidine, guanethidine, reserpine.
Both acute and chronic alcohol intake may potentiate or weaken the blood glucose-lowering action of glimepiride in an unpredictable fashion.
Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
Metformin HCl: Lactic acidosis may occur by concomitant administration of the following drugs. When these drugs are administered concomitantly, patients should be closely monitored: Iodinated contrast materials, antibiotic having strong nephrotoxicity (gentamicin).

The hypoglycemic action of co-administration with the following drugs may be potentiated or weakened. When these drugs are administered, the blood glucose level and patient should be observed closely.

Drugs Potentiating the Effect: Insulin, sulfonamides and sulfonylureas products, α-glucosidase inhibitor (alkalosis), anabolic steroids, guanethidine, salicylates (aspirin), β-blockers (propranolol), MAOIs, angiotensin-reversion enzyme inhibitor.

Drugs Weakening the Effect: Epinephrine, sympathomimetics, corticosteroids, thyroid hormones, estrogens, oral contraceptive, thiazide and other diuretics, pyrazinamide, isoniazid, nicotinic acid, phenothiazines, phenytoin, calcium channel blockers, β2-agonists e.g., salbutamol, formoterol.

Caution:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Storage Condition:
Store at temperatures not exceeding 30°C.
Protect from light. Keep out of reach of children.
Protect from humidity.

Availability:
Aluminum/PVC Clear blister pack x 10's (Box of 30's & 100's).

For suspected adverse drug reaction report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

DRP-6696
Date of leaflet revision: SEP 2017

Manufactured by:
Innova Captab Ltd.
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Corbridge Group Phils. Inc.
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Quezon City, Philippines

2021177

Check List	Checked by Pkg.	Reviewed by RA	Approved by QA
Dimension		—	—
Colours		—	—
Composition			
Brand Name/Generic Name			
Other text matter as per RA Guideline	—		
Mfg. Lic./Code No.:			
Artwork Code			
Barcode/Space For 2D			
Sign/Date			
Name	Sunil Parab	Richa Bhandari	Anju Nair