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Amaryl® M

Glimepiride BP
Metformin Hydrochloride BP

50085

Presentation:
Amaryl M 1mg : Each uncoated bilayer tablet contains Glimepiride BP 1.0 mg and Metforming Hydrochloride BP 500 mg (in sustained release).
Amaryl M 2mg : Each uncoated bilayer tablet contains Glimepiride BP 2.0 mg and Metforming Hydrochloride BP 500 mg (in sustained release).

Uses:
Amaryl M is indicated for the management of patients with type 2 diabetic mellitus when diet, exercise and single agent (glimepiride and Metformin alone) do not result adequate glycemic control.

Mode of action
Sulfonylureas and biguanides act complementary to each other. Both compounds have an additive antihyperglycaemic effect without increasing the adverse effects of either pharmacological class. Glimepiride acts via stimulating beta cells of pancreas to release insulin and also increases peripheral sensitivity of insulin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Dosage and Administration:
Dosage
In principle, the dosage of Amaryl M is governed by the desired blood glucose level. The dosage must be the lowest which is sufficient to achieve the desired metabolic control. During treatment with Amaryl M, glucose levels in blood and urine must be measured regularly. In addition it is recommended that regular determinations of the proportion of glycated hemoglobin be carried out. Mistakes e.g. forgetting to take a dose must never be corrected by subsequently taking a larger dose.

Initial dose:
One Amaryl M 1mg/one Amaryl M 2mg tablet should be administered as once daily with meals for those patients who are not already receiving glimepiride.

Maximum Dosing: For once daily administration maximum 2 tablets of Amaryl M can be given. For higher doses it may be necessary to divide the administration into 2 doses.
Upto 4 tablets of Amaryl M 1mg or 2mg can be given per day. Do not crush or chew the tablet. The whole tablet must be taken with water. As an improvement in control of diabetes is in itself, associated with higher insulin sensitivity, glimepiride requirements may fall as treatment proceeds. To avoid hypoglycernia timely dose reduction or cessation of Amaryl M therapy must there fore be considered. Correction of dosage must also be considered whenever,
- The patient's weight changes
- The patient's lifestyle changes
- Other factors arise which cause an increased susceptibility to hypoglycemia or hyperglycemia.

Pediatrics - Safety and effectiveness or Amaryl M in pediatric patients has not been established.

Specific Patient Populations
Amaryl M is not recommended for use in pregnancy. The initial and maintenance dosing of Amaryl M should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. There is limited information available on the use of Glimepiride in renal insufficiency. Patients with impaired renal function may be more sensitive to the glucose lowering effect of Amaryl M. 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 Amaryl M.

Contraindications:
Amaryl M must not be used:
- in patients with known hypersensitivity to metformin, glmepiride, other sulfonylureas or sulfonamides
- in patients with insulin-dependent (type 1) diabetes mellitus
- in acute or chronic acidosis, including diabetic ketoacidosis with or without coma
- in treatment of diabetic precoma or coma
- in patients with serious renal dysfunction. (as suggested by serum creatinine levels 1.4 mg/dL (females) or abnormal creatinine dearance),which may result from conditions such as cardiovascular collapse (shock),acute myocardial infarction and septicemia.
- in patients with serious hepatic dysfunction
- in pregnant women
- in breast feeding women
- in congestive heart failure requiring pharmacological treatment
- in paediatrics since the safety and effectiveness in paediatric patients have not been established Amaryl M should be temporarily discontinued in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Use in Pregnancy and Lactation:
Amaryl M must not be taken during pregnancy. The patient must change over to insulin during pregnancy. Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.
To prevent possible ingestion with breast milk, Amaryl M must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

Warnings:
- Periodic fasting blood glucose and glycosylated hemoglobin measurements must be performed to monitor therapeutic response to Amaryl M. Before initiation of Amaryl M, and at least annually thereafter, renal function should be also assessed and verified as normal. In those in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Amaryl M should be discontinued if evidence of renal impairment is present.

- In exceptional stress situations (e.g. trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

- Persons allergic to other sulfonamide derivatives may develop an allergic reaction to glimepiride as well.

- If any previously well-controlled patient develops laboratory abnormalities or clinical illness (especially vague and poorly defined) while on Amaryl M therapy, prompt evaluation for ketoacidosis or lactic acidosis must be carried out. If acidosis of either form occurs, Amaryl M must be immediately discontinued and appropriate corrective measures undertaken.

- Amaryl M must also be temporarily withdrawn when radiologic studies with contrast materials, or any surgical procedures are planned and done. Excessive alcohol intake, acute or chronic, is not recommended with Amaryl M. Those with inadequate vitamin B12 or calcium intake / absorption, may develop subclinical vitamin B12 levels whilst on metformin (in Amaryl M) therapy.

Precautions
Impaired hepatic function: Amaryl M must be preferably avoided in those with any evidence of hepatic disease.

Monitoring of renal function: Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Amaryl M. In patients with advanced age, Amaryl M should be carefully titrated to establish the minimum dose of adequate glycemic effect, because aging is associated with reduced renal function. Before initiation of Amaryl M therapy and every 6 months while on Amaryl M therapy, renal function should be assessed and verified as being within normal range. In patients in whom development of renal dysfunction is anticipated, renal function or result in significant hemodynamic change or may interfere with dispositions of Amaryl M such as cationic drugs that are eliminated by renal tubular secretion should be used with caution.

Hypoxic states: Cardiovascular collapse (shock) from whatever, cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such event occurs in patients on Amaryl M therapy, the drug should be promptly discontinued.

Surgical procedures: Amaryl M therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). Amaryl M should discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated asnormal.

Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Amaryl M.

Vitamin B12 levels: Impairment of Vitamin B12 and folic acid absorption has been reported in some patients. Therefore, measurements of serum Vitamin B12 and folic acid are advisable every one to two years in patients on long-term treatment with Amaryl M.

Hypoglycemia: In the initial weeks of treatment, the risk of hypoglycemia may be increased and necessitates careful monitoring. Hypoglycemia could also occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation or during concomitant use with other glucose lowering agents or ethanol. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar). It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycemia may recur. Patients must, therefore remain under dose observation. Severe hypoglycemia further requires immediate treatment and follow up by a physician and in some circumstances in-patient hospital care.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to with hold Amaryl M and temporarily administer insulin. Amaryl M may be reinstituted after the acute episode is resolved. The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy.

Laboratory tests: Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting blood glucose can be used to determine the therapeutic response. Therefore, both glucose and glyccosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control. Initial and periodic monitoring of hematologic parameters (e.g. hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis.

Lactic acidosis: It is a rare but serious metabolic complication that can occur due to metformin accumulation during treatment with Amaryl M. When it occurs, it is fatal in approximately 50% of cases. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Amaryl M treatment should not be initiated in patients 80 years of age, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as the patients are more susceptible to developing lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. In addition, Amaryl M should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Lactic acidosis is a medical emergency that must be treated in the hospital setting. In a patient with lactic acidosis who is taking Amaryl M, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin HCl is dialyzable (with clearance of up to 170mlL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. If acidosis of any kind develops, Amaryl M should be discontinued immediately.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS: Alertness and reactions may be impaired by hypo-or hyperglycemic episodes, especially when beginning or after altering treatment, or when Amaryl M is not taken regularly. This may, for example, affect the ability to drive or operate machinery.

Drug Interactions:
Glimepiride
Glimepiride is metabolized by cytochrome P4502C9 (cyP2C9). This should be taken into account when glimepiride is co-administered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP2C9. Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example; insulin and other, oral antidiabetics; ACE inhibitors; anabolic steroids and male sex hormones; chloramphenicol; coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine; fenyramidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; para-aminosali cylic acid; pentoxifyline (high dose parenteral); phenylbutazone; azapropazone; oxyphenbutazone; probenecid; quinolones; salicylates; sulfinpyrazone; sulfonamide antibiotics; tetracyclines; tritoqualine; trofosfamide. Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example: acetazolamide; barbiturates; corticosteroids; diazoxide; diuretics; calcium channel blocking drugs, epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (after protracted use); nicotinic acid (in high doses); oestrogens and progestogens; phenothiazines; phenytoin; ritampicin; thyroid hormones. H2 receptor antagonists, beta-blockers, donidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect. Under the influence of sympatholytic drugs such as beta-blockers, donidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood glucose-lowering action of glimepiride in an unpredictable fashion. The effect of coumarin derivatives may be potentiated or weakened.

Metformin
Furosemide: It is reported in a metformin-furosemide drug interaction study in healthy subjects that pharmacokinetic parameters of both compounds were affected by co-administration. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine
Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs
Cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Therefore, careful patient monitoring and dose adjustment of metformin or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion.

Other
Other drugs tend to produce hyperglycemia and may lead to a loss of blood sugar control. These include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to patients receiving metformin, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia. In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly proteinbound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to serum proteins.

Adverse Reactions:
Glimepiride
Hypoglycemia
As a result of the blood glucose lowering action of Amaryl M, hypoglycemia may occur. Possible symptoms of hypoglycemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, pareses, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness upto and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, again a pectoris and cardiac arrhythkmias. The clinical picture iof a severe hypoglycemic attack may resemble that of a stroke. The symptoms nearly always subside when hypoglycemia is corrected.

Eyes
Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the less, this being dependent ion blood glucose level.

Digestive tract
Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. In rare cases there may also be elevation of liver enzyme levels. Sulfonylureas, including glimepiride may also - in isolated instances - cause impairment of liver function (e.g. with cholestasis and jaundice) as well as and hepatitis which may also lead to liver failure.

Blood
Changes in the blood picture may occur: Rarely, thrombopenia and in isolated cases, leucopenia, hemolytic anemia, erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop.

Other adverse effects
Occasionally, allergic or pseudo allergic reactions may occur e.g. in the form of itching, urticaria or rashes. Such mild reactions may develop into serious reactions with dyspnoea and a fall in blood pressure, sometimes progressing to shock. In isolated cases, a decrease in serum sodium concentration and allergic vasculitis or hypersensitivity of the skin to light may occur.

Metformin
Amaryl M incorporates controlled release metformin and hence the incidence of gastrointestinal intolerance due to metformin is much less as compared to plain metformin. Most commonly reported adverse events include diarrhea, nausea and vomiting. Additionally the following adverse reactions have been more commonly reported in 1.0% - 5% of patients: Abdominal pain constipation, distension of abdomen, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbances.

Storage Condition: Store in a cool (not exceeding 25^0 C) and dry place, protected from light.

Pack Size: Amaryl M 1mg : 3 x 10's in Alu pvc blister.
Amaryl M 2mg : 3 x 10's in Alu pvc blister.

Manufactured by:
synovia
Synovia Pharma PLC., Station Road, Tongi, Gazipur.
Under License From **Sanofi, France.**

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Direction Slip artwork legend

Product Name	:	Amaryl M
Code number	:	542952
CCDS Version	:	00
Dimension	:	L 15.94 x W 5.15 inches
Min. size of text	:	8 pt
Used Colors	:	Black C ■ Pantone 186 C ■