Amaryl® M
Glimepiride + Metformin HCl 1/250 mg & 2/500 mg

Film Coated Tablets

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COMPOSITION

Each tablet Amaryl M 1/250 mg contains, as active ingredient, 1 mg glimepiride and 250 mg Metformin Hydrochloride

Each tablet Amaryl M 2/500 mg contains, as active ingredient, 2 mg glimepiride and 500 mg Metformin Hydrochloride

Excipients: lactose, sodium starch glycolate, povidone K30, microcrystalline cellulose, crospovidone, magnesium stearate, hydroxypropylmethylcellulose, macrogol 6000, titanium dioxide and carnauba wax.

PROPERTIES

PHARMACEUTICAL FORM

Amaryl M 1/250 mg tablets are white, oval, biconvex, film coated tablets, engraved with HD125" on one side

Amaryl M 2/500 mg tablets are white, oval, biconvex, film coated tablets, engraved with "HD25" on one side

Pharmacological Class

Glimepiride: Antidiabetic. Sulfonylurea.

Metformin: Antidiabetic. Biguanide.

ATC code: A10BD02

Mechanism of action: Glimepiride, the active ingredients of Amaryl M, is a blood-sugar-lowering agent belonging to the sulfonylurea group. The decrease in blood sugar is achieved principally by means of the stimulation of insulin release from pancreas ß-cells. This effect is predominantly based on improved responsiveness of these cells to the physiological glucose stimulus. Glimepiride augments the normal action of insulin on peripheral glucose uptake.

Moreover, it mimics such action as well as the glucose output of the liver. Good metabolic control over 24 hours can be achieved with a single dose of Amaryl.

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In patients with insufficient response to the maximum dose, combined use with an additional oral anti-diabetic containing metformin or with insulin improves metabolic control.

Metformin, the active ingredients of Amaryl M, is a blood-sugar-lowering agent belonging to the biguanid group. The decrease in blood sugar is achieved principally by not increasing insulin secretion. Moreover, metformin is not metabolized in liver, excretion through urine and feces.

INDICATIONS

As an adjunct to diet and exercise in NIDDM (type 2) patients
- In case that the monotherapy with glimepiride or metformin do not result in adequate glycemic control.
- Replacement of glimepiride and metformin combination therapy.

DOSAGE AND ADMINISTRATION

The dosage of anti-diabetic 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. Adequate monitoring of blood glucose levels should be performed for this.
It should be administered once or twice per day before or with the meals. When switching from combination therapy of glimepiride plus metformin as separate tablets, AMARYL®M should be administered on the basis of dosage currently being taken.

CONTRAINDICATIONS

For Glimepiride:

- Insulin-dependent (type I) diabetes (e.g., diabetics with a history of ketonemia), diabetic ketonemia, diabetic coma or precoma, acute or chronic metabolic acidosis.
- In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, or any of the excipients of Amaryl M.
- In pregnant women.
- Women of child-bearing potential.
- In breast-feeding women.
- Malnourished, starving, or debilitated patients, or patients with pituitary or adrenal insufficiency.

No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function and in dialysis patients. In patients with severe impairment of hepatic function, change-over to insulin is indicated, not least to achieve optimal metabolic control.

For Metformin:

- Insulin-dependent (type I) diabetes (e.g., diabetics with a history of ketonemia), diabetic ketonemia, diabetic coma or precoma, acute or chronic metabolic acidosis.
- Hypersensitivity to metformin or any of the excipients.
- 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.

- Acute conditions with the potential to alter renal function such as:
  - Dehydration
  - Severe infections, before and after surgery, serious trauma
  - Shock
  - Intravascular administration of iodinated contrast agents (see Section Warnings and Section Special Precaution)
- Acute or chronic disease which may cause tissue hypoxia such as:
  - Cardiac or respiratory failure
  - Recent myocardial infarction
  - Shock
  - Hepatic insufficiency.
  - Acute alcohol intoxication, alcoholism.
  - Lactation.
  - Malnourished, starving, or debilitated patients, or patients with pituitary or adrenal insufficiency.
  - Gastrointestinal disturbance including diarrhea and vomiting.

WARNINGS

For Glimepiride:

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.

For Metformin:

Lactic acidosis

Metformin accumulation occur at acute worsening of renal function and increase the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors associated to lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia as well as concomitant use of medicinal products that may cause lactic acidosis (see Section CONTRAINDICATIONS, and INTERACTIONS).

Patient and/or care-givers should be informed of the risk of lactic acidosis. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.

Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5mmol/L), and an increased anion gap, and increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patients-years, with approximately 0.015

fatal cases/1000 patients-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal multiple concomitant medical/surgical problems and multiple concomitant medications.

The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In addition, this drug should be withheld in the presence of any condition associated with hypoxemia or dehydration.

Because impaired hepatic function may significantly limit the ability to clear lactate, this drug should generally be 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 this drug, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, this drug should be temporarily discontinued prior to any intravascular radio-contrast study and for any surgical procedure. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur.
Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of this drug, gastrointestinal symptoms, which are common during initiation of therapy with metformin, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5mmol/L in patients taking this drug do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking this drug, 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 hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

Administration of iodinated contrast agent:
Intravascular administration of iodinated contrast agent may lead to contrast induces nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. This

drug should be discontinued at the time of or prior to the imaging procedure, and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see section CONTRAINDICATIONS and INDICATIONS.

Surgery:
This drug must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Increased risk of cardiovascular mortality
The administration of oral hypoglycemic drug has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP) to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes.
UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) or phenformin (100 mg/day) had a rate of cardiovascular mortality 2.5 times that of patients treated with diet alone and it resulted in discontinuation of the use of tolbutamide or phenformin. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of glimepiride and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) and one drug in the biguanide class (phenformin), it is prudent from a safety standpoint to consider that this warning may also apply to other hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

SPECIAL PRECAUTIONS
For Glimepiride
Careful monitoring should be required during the first treatment week because of increased risk of hypoglycemia. The patients or conditions at risk of hypoglycemia are as follows:
• Unwillingness or incapacity of the patient to cooperate (more commonly on older patients).
• Undernourishment, irregular mealtimes, skipped meals.
• Imbalance between physical exertion and carbohydrate intake.
• Alterations of diet.
• Consumption of alcohol, especially in combination with skipped meals.
• Impaired renal function.
• Severe impairment of liver function.
• Overdosage with glimepiride.
• Certain uncompensated disorders of the endocrine system (e.g., disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency): affecting carbohydrate metabolism or counter-regulation of hypoglycemia.
• Concurrent administration of certain other medicines (see under Section 7).

In these cases, close monitoring of blood glucose is necessary and patients should inform their doctors or pharmacists of these factors and if they had the symptoms of hypoglycemia. If such

risk factors of hypoglycemia are present, it may be necessary to adjust the dosage of this drug or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life style changes.
Those symptoms of hypoglycemia which reflect the body's adrenergic counter-regulation (see Adverse reactions) may be milder or absent where hypoglycemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine, or other sympatholytic drugs.

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

For Metformin
Regular monitoring of thyroid- stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see Section Adverse reaction). Long-term treatment with metformin has been associated with a decrease in vitamin B12 serum levels which may cause peripheral neuropathy. Monitoring of the vitamin B12 level is recommended (see Section Adverse Reaction).

General precautions
1) Adequate blood glucose levels should be maintained concomitantly by diet and exercise, if necessary by weight loss as well as by taking this drug regularly. Clinical signs is not adequately controlled blood glucose levels include oliguria, thirst, dipsia, dry skin, and etc.
2) Patients should be informed of the potential risks and advantage of this drug. They should also be informed about the importance of adherence to dietary instructions and of a regular exercise program. It should be emphasized that patient's positive cooperation is important
3) Hypoglycemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g., lump sugar, fruit juice including sugar, tea including sugar, and etc). Patients should carry approximately at least 20 g of sugar for this. Other's help may be necessary to avoid the complications. Artificial sweeteners have no effect.
4) If a patient receives a treatment from other physician or pharmacist (e.g., hospitalization, accident, needed to see a doctor a day off, and etc), he should inform him (or her) of his current diabetic situation and previous treatment
5) The dosage of this drug must be the lowest. Treatment with this drug requires regular monitoring of glucose levels in blood and urine. (In addition, determination of the proportion of glycosylated hemoglobin is recommended.) The effectiveness of therapy should be assessed and if not satisfactory, switch to another therapy should be promptly made.
6) Monitoring of renal function: This drug 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 this drug. In patients with advanced age, this drug should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and, generally, this drug should not be titrated to the maximum dose.

7) Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of this drug, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.
8) 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 events occur in patients on this drug therapy, the drug should be promptly discontinued.
9) Vitamin B12 levels: A decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, is observed in approximately 7% of patients receiving this drug in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of this drug or vitamin B12 supplementation. Measurement of hematological parameters on an annual basis is advised in patients on this drug and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at two-to three year intervals may be useful.

10) 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 glucose can be used to determine the therapeutic response. Therefore, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control. Periodic monitoring of hematological parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B12 deficiency should be excluded.

11) Change in clinical status of previously controlled diabetic: A diabetic patient previously well controlled on metformin hydrochloride tablets who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, this drug must be stopped immediately and other appropriate corrective measures initiated.
12) Information for patients: Patients should be informed of the potential risks and advantages of this drug and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematological parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the Warnings and General precautions sections should be explained to patients. Patients

should be advised to discontinue this drug immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of this drug, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related.

Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Metformin alone does not usually cause hypoglycemia, although it may occur when metformin is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

INTERACTIONS

Glimepiride

When other drugs are concomitantly administered to or withdrawn from a patient receiving this drug, both undesired increases and decreases in the hypoglycemic action of glimepiride can occur. Based on experience with glimepiride and other sulfonylureas, the following interactions must be considered:

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole).

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 anti-diabetics ; ACE inhibitors; allopurinol; anabolic steroids and male sex hormones; chloramphenicol; coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine; fenyramidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; para-aminosalicylic acid; pentoxifylline (high dose parenteral); phenylbutazone; azapropazone; oxyphenbutazone; probenecid,.; quinolones; salicylates; sulfinpyrazone; clarithromycin; 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; epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (long term use); nicotinic acid (in high doses); oestrogens and progestogens; phenothiazines; phenytoin; rifampicin; thyroid hormones.

H2 receptor antagonists, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

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).
Under the influence of sympatholytic drugs such as beta-blockers, clonidine, 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.

Bile acid sequestrant: Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore glimepiride should be administered at least 4 hours prior to colesevelam.

Metformin
Concomitant use not recommended:

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic insufficiency. Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents
Metformin must be discontinued at the time of or prior to the procedure, and withheld at least 48 hours subsequent to the procedure and restarted only after renal function has been re-evaluated and found to be stable. (see section CONTRAINDICATIONS and Section WARNINGS).

Combinations requiring precautions for use:

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglicaemicactivity (e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, and chlorpromazine at high dosages of 100 mg per day, diuretics): More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function (further to their intrinsic hyperglycaemic effect, see above).

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the anti-diabetic drug during therapy with the other drug and upon its discontinuation.

Others:
1) Lactic acidosis may occur by concomitant administration with antibiotics having strong nephrotoxicity (gentamicin, etc).
2) 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, Anabolic steroids, guanethidine, salicylates (aspirin, etc), beta-blockers(propranolol, etc), MAO inhibitors.
- Drugs weakening the effect. Epinephrine, corticosteroids, thyroid hormones, estrogens, diuretics, pyrazinamide, isoniazid, nicotinic acid, phenothiazines.
3) Glyburide: In a single-dose interaction study in type 2 diabetes subjects, co-administration of metformin and glyburide did not result on any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and Cmax were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamics effects, makes the clinical significance of this interaction uncertain.
4) Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.
5) Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Metformin had minimal effects on nifedipine.
6) Cationic drugs: Cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, 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. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple- dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.
7) Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid

products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed to maintain adequate glycemic control.
In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Metformin may decrease the anticoagulant effect of phenprocoumon. Therefore, a close monitoring of the INR is recommended.

Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated or stopped, and the dosage of metformin must be adjusted if necessary.

Organic caution transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration of metformin with
• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

PREGNANCY
For Glimepiride:
This drug must not be taken during pregnancy. Otherwise there is risk of harm to the child. Pregnant patient or the patient planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

For Metformin:
A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development.

However, when the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible.

LACTATION

For Glimepiride:

To prevent possible ingestion with the breast milk and possible harm to the child, glimepiride must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

For Metformin:

Metformin is excreted into milk in lactating rats. Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision should be made on whether to discontinue nursing or to discontinue metformin, taking into account the benefit and potential risk of adverse effect on the child and importance of the compound to the mother.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

For Glimepiride:

Alertness and reactions may be impaired due to hypo- or hyperglycaemia, especially when beginning or after altering treatment or when glimepiride is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.

For Metformin:

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other anti-diabetic agents (sulfonylureas, insulin, meglitinide).

ADVERSE REACTIONS

Glimepiride:

• Metabolism and nutrition disorders

Hypoglycemia: As a result of the blood-glucose-lowering action of this drug, hypoglycemia may occur, which-based on what is known of other sulfonylureas may also be prolonged. 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 up to 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, angina pectoris, and cardiac arrhythmias.

The clinical picture of a severe hypoglycemic attack may resemble that of a stroke. The symptoms nearly always subside when hypoglycemia is corrected.

• Eye disorders
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 lens, this being dependent on blood glucose level.

• Gastrointestinal disorders
Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur.
Hepatobiliary: In cases, elevation of liver enzymes levels and impairment of liver function (e.g., cholestasis and jaundice) may occur, as well as hepatitis which may progress to liver failure.

Dysgeusia (frequency not known)

• Blood and lymphatic system disorders
Changes in the blood picture may occur: Rarely, thrombocytopenia and, in isolated cases, leucopenia, haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia 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. Cases of severe thrombocytopenia with platelet count less than 10,000/µL and thrombocytopenic purpura have been reported in post-marketing experience (frequency not known).

• Skin and subcutaneous tissue disorders
Alopecia (frequency not known)

• General disorders
Occasionally, allergic or pseudoallergic 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 reactions with dyspnoea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must therefore be notified immediately.
In isolated cases, a decrease in serum sodium concentration and allergic vasculitis or hypersensitivity of the skin to light may occur.

• Investigations
Glimepiride, like all sulfonylureas, can cause weight gain (frequency not known)

Metformin:
o Hypoglycemia
o Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to this drug and are approximately 30% more frequent in patients on monotherapy than in placebo-treated patients, particularly during initiation of this

drug therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In clinical trials, this drug was discontinued due to GI reactions in approximately 4% of patients. Because GI symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take this drug with meals. Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, this drug should be temporarily discontinued. For patients who have been stabilized on this drug, nonspecific GI symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis has been excluded.

o Special senses: During initiation of this drug therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolve spontaneously.

o Skin reactions such as erythema, pruritus, urticarial are very rare.

o Rarely, anemia, leukocytopenia, or thrombocytopenia may occur. Approximately 9% of patients on this drug monotherapy and 6% of patients on this drug/sulfonylurea monotherapy developed asymptomatic subnormal serum vitamin B12 levels; serum folic acid levels did not decrease significantly. Only megaloblastic anemia have been reported with this drug administration.
Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation considered. However, cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in post-marketing experience (frequency not known) (see Section Special Precaution).

o Lactic acidosis is very rare

o Hemolytic anemia (frequency unknown)

o Reduction of thyrotropin level in patients with hypothyroidism (see Section Special Precaution) (frequency unknown)

o Hypomagnesemia in the context of diarrhea (frequency unknown)

o Encephalopathy (frequency unknown)

o Photosensitivity (frequency unknown)

o Hepatobiliary disorders: Reports of liver function tests abnormalities and hepatitis resolving upon metformin discontinuation

If the adverse reactions mentioned above, other undesirable reactions, or unexpected changes may occur, patients should promptly notify their health practitioner. Certain adverse reactions including severe hypoglycemia, special hematological change, severe allergic or pseudo-allergic reactions, and hepatic insufficiency may be life-threatening in certain conditions, and if these reactions occur, patients should promptly inform their physician and stop taking the drug until physician's instructions.
In local phase 1 and open phase 3 clinical trials, unexpected adverse reactions of this drug except for those of glimepiride and metformin already known have not been observed.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reaction via farmakovigilans@kalventis.com and Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan. Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pvcenter@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/

SPECIAL POPULATION

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Studies in maturity-onset diabetes of the young (MODY) have not been conducted.

Geriatric Use

Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function. Because aging is associated with reduced renal function, metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin.

OVERDOSAGE

SIGNS AND SYMPTOMS

For Glimepiride:

Acute overdosage as well as long-term treatment with too high a dose of glimepiride may lead to severe life-threatening hypoglycaemia.

MANAGEMENT

In case of overdosage with glimepiride, a doctor must be notified immediately. At the first signs of hypoglycaemia, the patient must immediately take sugar, preferably glucose, unless a doctor has already started care. Since hypoglycaemia and its clinical symptoms may recur after apparent clinical recovery (even after several days), close and continued medical supervision and possibly referral to a hospital are indicated. In particular, significant overdosage and severe reactions, e.g. with unconsciousness or other neurological dysfunctions, are emergency cases and require immediate care and hospitalization.

If hypoglycaemic coma is diagnosed or suspected, intravenous infusion of a 20 % glucose solution (adults: 40 to 100 ml) is indicated. Alternatively IV, SC, or IM administration of glucagons (adults: 0.5 to 1 mg) may be considered. In infants, glucose must be dosed very carefully and close monitoring of blood glucose is required to minimize the risk of potentially severe hyperglycaemia.

Patients who have ingested life-threatening amounts of glimepiride require detoxification (e.g. by gastric lavage and medicinal charcoal).

After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, hypoglycaemia, or the danger of slipping back into hypoglycaemia, may persist for several days.

For Metformin:
Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. Metformin is dialyzable with a clearance of up to 170mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Pancreatitis may occur in the context of a metformin overdose.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900mg/kg/day and 1500mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice.
Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day. No evidence of a mutagenic potential of metformin was found in the Ames test (S.typhimurium), gene mutation test (mouse lymphoma cells), chromosomal aberration test (human lymphocytes), or in vivo micronuclei formation test (mouse bone marrow). Fertility of male or female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis.

Drug abuse and dependence
Metformin hydrochloride product possesses no pharmacodynamics properties, either primary or secondary, which could be expected to result in abuse as a recreational drug or addiction.

Storing Amaryl M Tablet
Keep out of the reach and sight of children
Do not store above 30°C.
Do not use after expiry date printed on the blister and the carton.

PRESENTATION
Amaryl M Tablet 1/250 mg, white oval film coated tablet, Reg.No. DKL2221208617A1
Amaryl M Tablet 2/500 mg, white oval film coated tablet, Reg.No. DKL2221208617B1

Box 30 Tablets, 3 blisters @ 10 tablets

HARUS DENGAN RESEP DOKTER

Manufactured by:
Handok Inc, Chungcheongbuk-do - Korea.

DISETUJUI OLEH BPOM: 08/12/2025
ID: EREG100022VR12500347
EREG100022VR12500349

Registered by:
PT Kalventis Sinergi Farma, Jakarta, Indonesia.

Under license from:
Sanofi Winthrop Industrie, France.

Based on approval BPOM dated xxx - Standar Informasi Obat

LEAFLET KEMASAN: INFORMASI BAGI PENGGUNA

AMARYL M

1/250 dan 2/500 mg

Glimepiride / Metformin hydrochloride

Tablet salut selaput

sanofi

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai mengonsumsi obat ini, karena leaflet ini mengandung informasi yang penting untuk Anda.

• Simpan leaflet ini. Anda mungkin perlu membacanya lagi.

• Jika ada pertanyaan lebih lanjut, hubungi dokter tau apoteker atau perawat Anda.

• Obat ini telah diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal ini bisa membahayakan meskipun mereka memiliki tanda-tanda penyakit yang sama seperti Anda

• Jika Anda mengalami efek samping, diskusikan dengan dokter atau apoteker Anda. Ini termasuk setiap efek samping apapun yang mungkin tidak tercantum dalam leaflet ini. Lihat bagian 4.

Apa saja informasi yang terdapat dalam leaflet ini:

1. Apa itu AMARYL M dan apakah kegunaannya
2. Apa yang perlu diketahui sebelum menggunakan AMARYL M
3. Bagaimana menggunakan AMARYL M
4. Efek samping yang mungkin muncul
5. Bagaimana menyimpan AMARYL M
6. Isi kemasan dan informasi lainnya

1. Apa itu AMARYL M dan apakah kegunaannya

AMARYL M adalah obat yang diminum untuk membantu menurunkan kadar gula darah.

AMARYL M digunakan, dengan diet dan olahraga, untuk mengobati diabetes tipe 2 ketika:

• Penggunaan glimepiride atau metformin saja tidak dapat mengontrol gula darah Anda.

• Sebagai pengganti penggunaan kombinasi tablet glimepiride dan tablet metformin

2. Apa yang perlu diketahui sebelum menggunakan AMARYL M

Jangan gunakan AMARYL M

Untuk Glimepiride:

- Jika Anda menderita diabetes tipe 1
- Jika Anda menderita ketonemia diabetes
- Jika Anda dalam keadaan koma/pra-koma diabetes
- Jika Anda menderita asidosis metabolik akut atau kronis
- Jika Anda alergi terhadap glimepiride, bahan lain yang digunakan dalam obat ini, sulfonilurea, sulfonamide, atau biguanid
- Jika Anda kurang gizi, kelaparan, atau lemah, atau pasien insufisiensi kelenjar adrenal atau

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pituitari atau kekurangan cairan (termasuk diare dan muntah)

Untuk Metformin:
- Jika Anda menderita diabetes tipe 1
- Jika Anda menderita ketonemia diabetes
- Jika Anda dalam keadaan koma/pra-koma diabetes
- Jika Anda menderita asidosis metabolik akut atau kronis
- Jika Anda alergi terhadap metformin hidroklorida atau bahan lain yang digunakan dalam obat ini
- Jika Anda memiliki gangguan hati yang parah atau gangguan ginjal yang parah
- Jika Anda memiliki gangguan paru yang parah
- Jika Anda hamil, berencana hamil, atau menyusui
- Jika Anda mengalami atau pernah mengalami asidosis laktat (peningkatan jumlah asam laktat dalam tubuh)
- Jika Anda mengalami serangan jantung, atau menerima pengobatan untuk gagal jantung, atau memiliki masalah sirkulasi, atau kesulitan bernafas
- Jika Anda meminum banyak alkohol
- Jika Anda memiliki infeksi yang parah, sebelum atau setelah operasi, trauma serius
- Jika Anda kurang gizi, kelaparan, atau lemah, atau pasien insufisiensi kelenjar adrenal atau pituitari atau kekurangan cairan (termasuk diare dan muntah)
- Jika Anda akan melakukan pemeriksaan seperti X-ray atau pemeriksaan yang menggunakan injeksi obat-obatan kontras yang mengandung iodin. Anda harus menghentikan penggunaan AMARYL M saat itu juga dan beberapa hari setelah pemeriksaan tersebut
- Jika Anda memiliki gagal jantung kongestif

Peringatan dan tindakan pencegahan:
Ikutilah dengan seksama petunjuk untuk dosis, monitoring (tes darah dan urine), diet dan aktivitas fisik (kerja fisik dan olahraga) seperti yang diinstruksikan dokter Anda. Bicarakan dengan dokter atau Apoteker Anda sebelum menggunakan obat ini jika Anda dalam masa penyembuhan luka, operasi, infeksi disertai demam, atau bentuk stres lainnya, beritahu dokter Anda karena perubahan pengobatan mungkin diperlukan.

Informasi penting mengenai asidosis laktat:
Asidosis laktat meningkatkan jumlah asam laktat dalam darah. Hal ini merupakan efek samping metformin yang jarang terjadi, namun serius, yang memerlukan perawatan di rumah sakit, lebih sering terjadi pada pasien dengan penyakit ginjal yang parah. Anda harus berhati-hati terhadap konsumsi alkohol berlebih, akut maupun kronis saat menggunakan obat ini, karena alkohol meningkatkan efek metformin.
Jika Anda mengalami gejala antara lain: napas yang cepat, nyeri perut, mual, muntah, demam, dehidrasi (diare parah atau muntah atau asupan cairan berkurang), hentikan penggunaan Amaryl M dan segera hubungi dokter Anda.

Faktor beresiko lainnya antara lain penurunan fungsi hati, diabetes yang tidak terkontrol, ketosis, puasa dalam jangka waktu lama dan kondisi lainnya terkait kekurangan oksigen, termasuk penggunaan bersama obat-obatan lain yang dapat menyebabkan asidosis laktat.

Informasi penting mengenai hipoglikemia (kadar gula darah rendah)
Ketika Anda menggunakan AMARYL M, Anda dapat mengalami hipoglikemia. Lihat informasi berikut mengenai hipoglikemia, tanda-tanda, dan cara mengatasinya.
Faktor berikut dapat meningkatkan risiko terjadinya hipoglikemia:
• Kekurangan gizi, makan tidak teratur, lupa atau menunda waktu makan, puasa
• Jika Anda banyak olahraga dan Anda tidak makan yang cukup atau makan makanan dengan karbohidrat lebih rendah dari normal
• Mengubah diet Anda
• Minum alkohol (terutama ketika Anda lupa makan)
• Penurunan fungsi ginjal
• Gangguan hati yang parah
• Jika Anda menderita kelainan hormon seperti: gangguan kelenjar tiroid, kelenjar pituitari atau korteks adrenal
• Menggunakan obat tertentu lainnya (lihat informasi pada "Obat lain dan Amaryl M")
• Menggunakan Amaryl M lebih dari yang diperlukan

Jika Anda memiliki faktor risiko hipoglikemia tersebut, penyesuaian dosis AMARYL M mungkin diperlukan, bicarakanlah dengan dokter atau apoteker Anda. Hal ini juga berlaku jika Anda sakit selama pengobatan atau perubahan gaya hidup.
Gejala hipoglikemia:
Gejala hipoglikemia (lihat Bagian 4) mungkin lebih ringan atau tidak ada dalam situasi dimana hipoglikemia berkembang secara bertahap, pada orang tua, dan pada pasien dengan jenis penyakit saraf tertentu (neuropati otonom) atau mereka yang menerima pengobatan dengan obat lain yang disebut beta-blocker, klonidin, reserpin, guanethidine, atau simpatomimetik lainnya.

Mengobati hipoglikemia:
Dalam kebanyakan kasus, tanda-tanda menurunnya kadar gula darah akan hilang dengan sangat cepat saat Anda mengonsumsi beberapa bentuk gula, seperti gula batu, jus manis, atau the manis. Oleh karena itu Anda harus selalu membawa kira-kira minimal 20 g gula (misalnya gula batu). Ingat bahwa pemanis buatan tidak efektif.
Silakan menghubungi dokter Anda atau pergi ke rumah sakit jika mengonsumsi gula tidak membantu atau jika gejalanya kambuh kembali.

<u>Tes laboratorium</u>
Kadar gula dalam darah atau urine Anda harus diperiksa secara teratur. Dokter Anda mungkin melakukan tes darah untuk memantau kadar sel darah dan fungsi hati Anda.
Penurunan kadar hemoglobin dan penurunan sel darah merah (anemia hemolitik) dapat terjadi pada pasien yang tidak memiliki enzim glukosa-6-fosfat dehidrogenase.

Fungsi ginjal:

Fungsi ginjal Anda harus diperiksa sebelum memulai perawatan dan dipantau secara teratur.

Pembedahan atau injeksi obat kontras yang mengandung iodium untuk pemeriksaan

Jika Anda akan menjalani operasi atau jika Anda memerlukan injeksi obat kontras yang mengandung iodin dalam aliran darah Anda, misalnya untuk pemeriksaan sinar-X atau scan, Anda harus menghentikan penggunaan AMARYL M selama beberapa waktu sebelum dan setelah pemeriksaan atau operasi. Dokter Anda akan memutuskan apakah Anda memerlukan perawatan lain untuk saat ini. Penting bagi Anda untuk mengikuti instruksi dokter Anda dengan tepat.

Anak-anak dan remaja

AMARYL M belum pernah dilakukan penelitian pada anak-anak dan remaja yang berusia di bawah 18 tahun.

Obat-obatan lain dan AMARYL M

Beritahu dokter atau apoteker Anda jika Anda sedang mengonsumsi obat-obatan lain, telah mengonsumsinya, atau akan mengonsumsi obat-obatan lain. Dokter Anda akan mengubah dosis AMARYL M Anda jika Anda mengonsumsi obat lain yang dapat menurunkan atau meningkatkan efek AMARYL M pada kadar gula dalam darah Anda.

Obat-obatan berikut dapat meningkatkan efek penurunan gula darah AMARYL M. Hal ini dapat menyebabkan risiko hipoglikemia (gula darah rendah):

- Produk obat lain untuk pengobatan diabetes mellitus (seperti insulin atau antidiabetes lainnya)
- Produk obat untuk mengobati nyeri dan inflamasi atau peradangan (fenilbutazon, azopropazon, oxyphenbutazone)
- Produk obat untuk mengobati infeksi saluran kemih (seperti beberapa sulfonamida kerja panjang)
- Produk obat untuk mengobati infeksi bakteri dan jamur (tetrasiklin, flukonazol, mikonazol, kloramfenikol, kuinolon, klaritromisin)
- Produk obat untuk menghambat penggumpalan darah (derivat coumarin seperti warfarin)
- Produk obat untuk membantu pembentukan otot (anabolik steroid)
- Produk obat untuk terapi pengganti hormon seks pria
- Produk obat untuk mengobati depresi (fluoxetine, MAO-inhibitor)
- Produk obat untuk menurunkan kadar kolesterol tinggi (fibrat)
- Produk obat untuk menurunkan tekanan darah tinggi (ACE inhibitor)
- Produk obat berupa agen anti-aritmia yang digunakan untuk mengendalikan denyut jantung abnormal (disopyramide)
- Produk obat untuk mengobati asam urat (allopurinol, probenecid, sulfinpyrazone)
- Produk obat untuk mengobati kanker (siklofosfamid, ifosfamid, trofosfamid)
- Produk obat untuk menurunkan berat badan (fenfluramine)
- Produk obat untuk meningkatkan sirkulasi ketika pemberian infus intravena dosis tinggi (pentoxifylline)
- Produk obat untuk mengobati alergi rhinitis seperti hay fever (tritoqualine)
- Produk obat simpatolitik untuk mengobati tekanan darah tinggi, gagal jantung, atau gejala prostat.

• Obat yang menghambat OCT2 (seperti: simetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole

Obat-obatan berikut dapat menurunkan efek penurunan kadar gula darah AMARYL M. Hal ini dapat menyebabkan risiko hiperglikemia (kadar gula darah tinggi):
• Produk obat yang mengandung hormon seks wanita (estrogen, progestogen)
• Produk obat yang meningkatkan produksi urine (thiazide diuretic)
• Produk obat yang untuk merangsang kelenjar tiroid (levothyroxine)
• Produk obat untuk mengobati alergi dan inflamasi atau peradangan (glukokortikoid)
• Produk obat untuk mengobati gangguan jiwa parah (klorpromazin dan turunan fenotiazin lainnya)
• Produk obat untuk meningkatkan denyut jantung, untuk mengobati asma atau hidung tersumbat, batuk dan pilek, untuk menurunkan berat badan, atau digunakan dalam keadaan darurat yang mengancam jiwa (adrenalin dan simpatomimetik)
• Produk obat untuk mengobati kadar kolesterol tinggi (asam nikotinat)
• Produk obat untuk mengobati sembelit saat digunakan dalam jangka panjang (pencahar)
• Produk obat untuk mengobati kejang (fenitoin)
• Produk obat untuk mengatasi masalah kegugupan dan gangguan tidur (barbiturat)
• Produk obat untuk mengobati peningkatan tekanan pada mata (acetazolamide)
• Produk obat untuk mengobati tekanan darah tinggi atau menurunkan gula darah (diazoxide)
• Produk obat untuk mengobati infeksi, tuberkulosis (rifampisin)
• Produk obat untuk mengobati kadar gula darah rendah yang parah (glucagon)
• Produk obat untuk mengobati asma (agonis beta-2 seperti salbutamol)
• Obat yang menghambat OCT1 (verapamil)

Produk obat berikut ini dapat meningkatkan atau menurunkan efek penurunan kadar gula darah AMARYL M:
• Produk obat untuk mengobati tukak lambung (antagonis H2)
• Produk obat untuk mengobati tekanan darah tinggi atau gagal jantung seperti beta-blocker, clonidine, guanethidine dan reserpin. Obat ini juga bisa menyamarkan tanda-tanda hipoglikemia, sehingga perhatian khusus diperlukan saat meminum obat-obatan ini.
• Obat yang menghambat OCT1 dan OCT2 (crizotinib, olaparib)

Produk obat berikut ini dapat menyebabkan gangguan fungsi ginjal akut:
• Produk obat untuk mengobati tekanan darah tinggi
• Produk obat yang meningkatkan produksi urine
• Produk obat untuk mengobati inflamasi atau peradangan (NSAID)

AMARYL M dapat meningkatkan atau melemahkan efek dari obat-obatan berikut ini:
• Produk obat yang menghambat pembekuan darah (phencouromon, derivat coumarin seperti warfarin).

Kolesevelam, obat yang digunakan untuk mengurangi kolesterol, berpengaruh pada absorbs AMARYL M. Untuk menghindari efek ini, Anda harus mengonsumsi AMARYL M minimal 4 jam sebelum mengonsumsi kolesevelam.

Agen kontras Iodinasi
Penumpukan asam dalam darah (dikenal sebagai asidosis laktat) dapat terjadi jika Anda menggunakan bahan kontras Iodinasi untuk pemeriksaan khusus seperti sinar-X atau scan, Anda harus berhenti minum AMARYL M selama jangka waktu tertentu sebelum dan sesudah pemeriksaan (lihat bagian 2 "Peringatan dan tindakan pencegahan").

AMARYL M dengan alkohol
Anda harus menghindari minum alkohol dan penggunaan obat yang mengandung alkohol. Alkohol dapat meningkatkan atau menurunkan efek penurun gula darah AMARYL M dengan cara yang tidak terduga. Alkohol juga meningkatkan risiko asidosis laktat.

Kehamilan dan menyusui
Hindari penggunaan AMARYL M jika Anda hamil atau menyusui, memiliki potensi untuk hamil atau berencana untuk hamil, mintalah saran dari dokter atau apoteker Anda sebelum mengonsumsi obat ini.

Mengemudi dan menggunakan mesin
Kemampuan Anda untuk berkonsentrasi atau bereaksi dapat terganggu jika gula darah Anda menurun (hipoglikemia) atau meningkat (hiperglikemia) atau jika Anda mengalami masalah penglihatan akibat kondisi tersebut. Ingatlah bahwa Anda dapat membahayakan diri sendiri atau orang lain (misalnya saat mengemudi mobil atau menggunakan mesin). Tanyakan kepada dokter Anda apakah Anda bisa mengemudi mobil jika Anda:
• Sering mengalami hipoglikemia
• Memiliki beberapa atau tidak sama sekali gejala hipoglikemia.

AMARYL M mengandung laktosa.
Jika Dokter Anda mengatakan bahwa Anda tidak dapat menoleransi beberapa jenis gula tertentu, hubungi dokter Anda sebelum mengonsumsi obat ini.

3. BAGAIMANA MENGGUNAKAN AMARYL M
Anda harus mematuhi aturan pakai AMARYL M sesuai yang dikatakan Dokter atau Apoteker Anda. Anda harus menanyakan ke dokter atau apoteker jika Anda tidak yakin.
Dosis AMARYL M tergantung pada kebutuhan, kondisi dan hasil tes gula darah dan urine Anda yang ditentukan oleh dokter Anda. Jangan mengonsumsi tablet lebih dari yang diresepkan oleh dokter.

Dosis yang dianjurkan
Dosis awal yang dianjurkan adalah dosis efektif terendah, dan dokter dapat meningkatkan dosis tergantung kadar glukosa darah Anda.

Bila beralih dari terapi kombinasi glimepiride dan metformin sebagai tablet terpisah, AMARYL M harus diberikan berdasarkan dosis yang dikonsumsi saat ini.
• Jika berat badan Anda berubah atau jika Anda mengubah gaya hidup Anda, atau Anda dalam situasi stress, dapat menyebabkan perubahan dosis AMARYL M, segera beritahu dokter Anda.
• Jika Anda merasakan efek obat Anda terlalu lemah atau terlalu kuat jangan mengubah dosisnya sendiri, tapi tanyakan kepada dokter.

Cara minum AMARYL M
AMARYL M harus diminum langsung sebelum atau dengan makanan. Tablet harus diminum sekaligus dengan air secukupnya.

Jika Anda minum obat AMARYL M melebihi dosis yang seharusnya
Hipoglikemia: Jika Anda terlalu banyak minum AMARYL M atau dosis tambahan, dapat berisiko hipoglikemia (untuk tanda-tanda hipoglikemia, lihat bagian 4), oleh karena itu Anda harus segera mengonsumsi gula yang cukup (kira-kira minimal 20 g gula batu, jus manis, teh manis) dan segera hubungi dokter.

Pasien dalam keadaan tidak sadar tidak boleh diberi makanan atau minuman.
Keadaan hipoglikemia dapat berlangsung selama beberapa waktu, keadaaan pasien harus selalu dipantau sampai kondisi pasien membaik. Perawatan di rumah sakit mungkin diperlukan, juga sebagai tindakan pencegahan. Tunjukkan kepada dokter kemasan obat yang tersisa, agar dokter tahu apa yang telah dikonsumsi. Kasus hipoglikemia berat disertai dengan hilangnya kesadaran dan kegagalan neurologis yang parah adalah kasus-kasus darurat medis yang memerlukan perawatan medis segera dan perawatan rumah sakit. Harus dipastikan terdapat orang lain (yang mengetahui kondisi Anda) yang dapat segera menghubungi dokter jika ini terjadi pada Anda

Asidosis laktat: Obat ini mengandung metformin yang dapat menyebabkan asidosis laktat (lihat bagian 2 "Peringatan dan tindakan pencegahan"). Ini adalah keadaan darurat medis yang memerlukan perawatan di rumah sakit. Segera konsultasikan dengan dokter atau apoteker Anda.

Jika Anda lupa meminum obat AMARYL M:
Minum dosis selanjutnya sesuai jadwal biasa. Jangan minum 2 dosis sekaligus sebagai pengganti dosis yang terlupakan itu.

Jika Anda berhenti meminum obat AMARYL M
Jika Anda menghentikan perawatan, Anda harus menyadari bahwa efek penurunan gula darah tidak dapat tercapai atau keadaan penyakit dapat semakin memburuk.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini tanyakan kepada dokter atau apoteker atau perawat Anda.

4. EFEK SAMPING YANG MUNGKIN TIMBUL
Sebagaimana halnya dengan obat apapun lainnya, efek samping dapat terjadi setelah meminum obat ini, namun tidak semua orang mengalaminya.
Segera hubungi dokter jika Anda mengalami gejala berikut ini:

• Hipoglikemia (lihat juga bagian 2 "Peringatan dan tindakan pencegahan"):
Karena efek penurun gula darah AMARYL M, dapat menyebabkan hipoglikemia dan dapat berlangsung beberapa waktu.

Tanda-tanda hipoglikemia meliputi:
- Rasa lapar, sakit kepala, mual, muntah, lesu, mengantuk, gangguan tidur, gelisah, agresi, gangguan konsentrasi, berkurangnya kewaspadaan dan waktu reaksi, depresi, kebingungan, gangguan bicara dan visual, bicara kurang jelas, gemetar, kelumpuhan parsial, gangguan sensorik, pusing, tidak berdaya
- Tanda berikut dapat terjadi: berkeringat, kulit lembap, cemas, denyut jantung cepat, tekanan darah tinggi, palpitasi, rasa sangat nyeri tiba-tiba di bagian payudara yang mungkin menyebar ke daerah sekitarnya (angina pectoris dan aritmia jantung).
- Jika kadar gula darah terus menurun, Anda mungkin akan mengalami kebingungan (delirium), kejang, kehilangan kendali, napas pendek dan detak jantung melambat, Anda dapat kehilangan kesadaran. Gambaran klinis penurunan kadar gula darah berat dapat menyerupai stroke.

Mengobati hipoglikemia:
Dalam kebanyakan kasus, penurunan gula darah akan hilang dengan sangat cepat ketika Anda mengonsumsi beberapa bentuk gula, misal gula batu, jus manis, teh manis. Hubungi dokter Anda atau kunjungi rumah sakit jika mengonsumsi gula tidak membantu atau jika gejalanya kambuh lagi.

• Asidosis laktat (lihat bagian 2 "Peringatan dan tindakan pencegahan"):
Beberapa pasien telah mengalami kondisi yang disebut asidosis laktat (peningkatan asam laktat dalam darah), terutama mereka yang ginjalnya tidak berfungsi dengan baik. Gejalanya meliputi: menggigil atau tidak nyaman, mual atau muntah, sakit perut, atau bernafas cepat. **Jika Anda mengalami beberapa gejala ini, berhentilah minum AMARYL M dan segera berkonsultasi dengan dokter.**
• Reaksi alergi (termasuk inflamasi pada pembuluh darah, sering disertai ruam kulit) yang bisa berkembang menjadi reaksi serius dengan kesulitan bernapas, penurunan tekanan darah yang dapat berkembang menjadi syok. Jika gatal atau ruam terjadi, segera hubungi dokter.
• Alergi (hipersensitivitas) pada kulit seperti gatal, ruam, gatal-gatal dan peningkatan sensitivitas terhadap sinar matahari. Beberapa reaksi alergi ringan dapat berkembang menjadi reaksi serius
• Fungsi hati yang tidak normal termasuk menguningnya kulit dan mata (jaundice), gangguan aliran empedu (kolestasis), peningkatan enzim hati, radang hati (hepatitis) atau gagal hati.
• Gangguan pencernaan: merasa sakit, diare, merasa kenyang atau kembung, nyeri perut dan kehilangan nafsu makan.
• Gangguan rasa: Rasa seperti logam di mulut, disgeusia.
• Gangguan darah: Penurunan jumlah sel darah:
  - Trombosit (meningkatkan risiko pendarahan atau memar termasuk pendarahan berat yang tidak biasa atau memar di bawah kulit)
  - Sel darah putih (yang memungkinkan terjadinya infeksi)

- Sel darah merah (yang bisa membuat kulit pucat dan menyebabkan kelemahan atau sesak napas).

Masalah ini dapat menjadi lebih baik setelah Anda berhenti mengonsumsi AMARYL M.

• Penurunan kadar natrium dalam darah (ditunjukkan dengan tes darah).

• Penurunan kadar vitamin B12: Kadar vitamin B12 yang rendah dapat terlihat. Jika diperlukan, pantau kadar serum B12.

• Gangguan mata: gangguan penglihatan dapat terjadi ketika memulai pengobatan dengan AMARYL M. Hal ini disebabkan adanya perubahan kadar gula darah dan seharusnya segera membaik.

• Efek samping dengan frekuensi kejadian tidak diketahui: kebotakan, peningkatan berat badan, anemia hemolitik, penurunan kadar tirotrofin pada pasien hipotiroid, hipomagnesemia, ensefalopati, fotosensitivitas

Pelaporan efek samping

Jika Anda mengalami efek samping apapun, bicarakan dengan dokter atau apoteker. Efek samping ini termasuk efek samping apapun yang mungkin muncul yang tidak tercantum pada leaflet ini. Anda juga dapat melaporkan efek samping secara langsung ke Industri Farmasi dengan kontak berikut farmakovigilans@kalventis.com. Dengan melaporkan efek samping Anda dapat membantu memberikan informasi tentang keamanan obat ini.

5. CARA MENYIMPAN AMARYL M

Simpan pada suhu tidak lebih dari 30 ° C.

Jangan gunakan setelah tanggal kadaluwarsa yang tercantum pada blister dan karton. Tanggal kadaluwarsa mengacu pada hari terakhir bulan itu.

6. ISI KEMASAN DAN INFORMASI LAINNYA

Kandungan AMARYL M

AMARYL M 1/250 dan 2/ 500 mg, tablet salut selaput

- Bahan aktif glimepiride dan metformin hydrochloride.
- Tiap tablet AMARYL M 1/250 mengandung glimepiride 1 mg dan 250 mg metformin hydrochloride.
- Tiap tablet AMARYL M 2/500 mengandung glimepiride 2 mg dan 500 mg metformin hydrochloride.
- Bahan lainnya adalah: lactose, sodium starch glycolate, povidone K30, microcrystalline cellulose, crospovidone, magnesium stearate, hydroxypropylmethylcellulose, macrogol 6000, titanium dioxide dan carnauba wax.

Isi kemasan

Tiap tablet salut selaput Amaryl M 1/250 mg berwarna putih, berbentuk lonjong, cembung, berukir “HD125” pada satu sisi.

Tiap tablet salut selaput Amaryl M 2/500 mg berwarna putih, berbentuk lonjong, cembung, berukir “HD25” pada satu sisi.

Tiap kotak karton berisi 3 blister, masing-masing terdiri dari 10 tablet salut selaput dan leaflet.

Jauhkan obat dari jangkauan anak-anak.

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Persetujuan BPOM tanggal xxx – Standar Informasi Obat