Amaryl M Film-coated Tablet 1/250mg

[Composition]
1 tablet contains;
Glimepiride (KPC) ….. 1 mg
Metformin HCl (EP) ….250 mg

[Indications]
For the treatment of NIDDM (type 2) patients who are having inadequate glycemic control with metformin or sulfonylurea monotherapy.

[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.
The maximum daily dose for glimepiride is 8mg and metformin is 2gm (equivalent 8 tablets).
Metformin treatment should not start in patients older than 80 years old.
Metformin treatment should be cautious when use in elderly patients less than 80 years old.
To reduce the doses with a eGFR between 30-45ml/min/1.73m^2
It should be administered once or twice per day before or with the meals. The initial dose of Glimepiride/metformin 1/250mg is once per day.

[Precautions for use]
1. Warnings
1) Lactic acidosis

Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia.

Lactic acidosis is characterized by elevated blood lactate levels (>5mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl 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 hypoperfusion, often in the setting of 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 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.

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 HCl 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. Patients 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.

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 (ketouria 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 HCl is dialyzable (with a clearance of up to 170mL/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.

2) 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 (1.5g per day) or phenformin (100mg/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.

2. Contraindications
1) Insulin-dependent (type I) diabetes (e.g., diabetics with a history of ketonemia), any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma)
2) Known hypersensitivity to the active ingredient or any of the excipients of this drug, sulfonylureas, sulfonamides, or biguanide
3) There is no experience in 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.
4) Pregnant women, women of child-bearing potential, nursing mother.
5) Patients susceptiable to lactic acidosis, patients with a history of lactic acidosis, renal disease or severe renal failure (GFR < 30ml/min/1.73m^2), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
6) This drug should be temporarily discontinued in patients being administered iodinated contrast materials intravenously, because use of such products may result in acute alteration of renal function.
7) Severe infections, before and after surgery, serious trauma
8) Malnourished, starving, or debilitated patients, or patients with pituitary or adrenal insufficiency
9) Hepatic dysfunction, severe lung dysfunction, other condition likely to be with hypoxemia, excessive alcohol intake, dehydration, gastrointestinal disturbance including diarrhea and vomiting
10) Congestive heart failure requiring pharmacologic treatment

3. Special Precautions
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;
1) Unwillingness or incapacity of the patient to cooperate (more commonly on older patients)
2) Malnutrition, irregular mealtimes, skipped meals
3) Imbalance between physical exertion and carbohydrate intake
4) Alterations of diet
5) Consumption of alcohol, especially in combination with skipped meals
6) Impaired renal function
7) Severe impairment of liver function
8) Overdosage with this drug
9) 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
10) Concurrent administration of certain other medicines (see 6. Interactions)

Hypoglycemia: As a result of the blood-glucose-lowering action of this drug, hypoglycemia may occur, which 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.

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 4. adverse reactions) may be milder or absent where hypoglycemia develops gradually, in the elderly, and where there is autonaumic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine, or other sympatholytic drugs.

Glimepiride
Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulpfonylurea alternative should be considered.

Metformin
Metformin hydrochloride should be discontinued 48 hours before elective general anaesthesia and should not be usually resumed then 48 hours afterwards.

Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism.
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 lever is recommended (see Adverse Reactions).

4. Adverse Reactions

Glimepiride
Based on experience with this drug and on what is known of other sulfonylureas, the following adverse reactions have to be considered.

Blood and lymphatic system disorders
Changes in the blood picture may occur.
Rare: moderate to severe thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, erythrocytopenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication.
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).

Metabolism and nutrition disorders
Rare: hypoglycaemic reactions which mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycaemic therapies, on individual factors such as dietary habits and dosage (see further under "Special warnings and special precautions for use").

Eye disorders
Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Gastrointestinal disorders
Gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur.

In isolated cases, there may be hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice, which may progress to life-threatening liver failure.

Dysgeusia (frequency not known).

Skin and subcutaneous tissue disorders
Alopecia (frequency not known)

General disorders
Allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticarial or rashes. Mild reactions may develop into serious reactions with dyspnea and a fall in blood pressure, sometimes progressing to shock.

Cross-allergenicity with sulphonylureas, sulphonamides or related substances is possible.

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
1) Lactic acidosis: see 1.warnings and overdosage
2) Hypoglycemia
3) Gastrointestinal: GI symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorxia) 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.
4) Special senses: During initiation of this drug therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolve spontaneously.
5) Dermatologic reactions: The rash, etc may occur. In this case, this drug should be discontinued.
6) Hematologic: 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. However, cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in post-marketing experience (frequency not known) (see Special Cautions); serum folic acid levels did not decrease significantly. However, only megaloblastic anemia have been reported with this drug administration and no increased incidence of neuropathy has been observed. Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation considered.
7) Hepatic: Occasionally, impaired hepatic function may occur.
8) Hemolytic anemia (frequency unknown)
9) Reduction of thyrotropin level in patients with hypothyroidism (see Precautions)
10) Hypomagnesemia in the context of diarrhea (frequency unknown)
11) Encephalopathy (frequency unknown)
12) Photosensitivity (frequency unknown)

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 hematologic 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.

5. 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 20g of sugar for this. Other's help may be necessary to avoid the complications. Artificial sweeteners have no effect.
4) It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycemia may recur. Patients must, therefore, remain under close observation. Severe hypoglycemia further requires immediate treatment and follow-up by a physician, in some circumstances, in-patient hospital care.
5) 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.
6) 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.
7) 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.
8) Alertness and reactions may be impaired due to hypo- or hyperglycemia, especially when beginning or after altering treatment or when this drug is not taken regularly. This may affect the ability to drive or to operate machinery.
9) 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. GFR should be assessed

before treatment initiation and regularly thereafter. Metformin is contraindication in patients with GFR <30 ml/min/1.73m² and should be temporarily discontinued in the presence of conditions that alter renal function. 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. Special caution should be exercised in situations where renal function may become impaired.

10) 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.
11) Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with contrast materials): Intravascular administration of iodinated contrast agents may lead to contrast induces nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to, or at the time of 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.
12) 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.
13) Surgical procedures: Metformin 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.
14) 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 this drug.
15) Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, this drug should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
16) 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 hematologic 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.
17) Change in clinical status of previously controlled diabetic: A diabetic patient previously well controlled on metformin HCl 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.
18) 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 hematologic 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.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving this drug.

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.

6. 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 this drug and with other sulfonylureas, the following interactions must be considered:

1) This drug 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).
2) Drugs potentiating the blood-glucose-lowering effect
   Insulin and oral antidiabetic products, ACE inhibitors, allopurinol, anabolic steroids, male sex hormones, chloramphenicol, coumarin anticoagulants, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, guanethidine, ifosfamide, MAO inhibitors, miconazole, fluconazole, para-aminosalicylic acid, pentoxifylline(high dose parenteral), pheylbutazone, probenecid, quinolone antibiotics, salicylates, sulfinpyrazone, sulfonamide, tetracyclines, tritoqualine, trofosfamide
3) Drugs weakening the blood-glucose-lowering effect
   Acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, epinephrine (adrenaline) or sympathicomimetics, glucagons, laxatives (long term use), nicotinic acid(high dose), estrogens, progestogens, phenothizines, phenytoin, rifampicin, thyroid hormones
4) Drugs potentiating or weakening the blood-glucose-lowering effect
   H2 antagonists, clonidine, reserpine
5) 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).
6) Drugs reducing or blocking the signs of adrenergic counter-regulation to hypoglycemia: Sympatholytic drugs (e.g., beta-blockers), clonidine, guanethidine, reserpine
7) Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of this drug in an unpredictable fashion.
8) This drug may either potentiate or weaken the effects of coumarin derivatives.
9) 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

1) 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, antibiotics having strong nephrotoxicity (gentamicin, etc)
   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.
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, phenothizines
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 pharmacodynamic 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 paramethers 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 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 diurectics, 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.
8) Metfomin may decrease the anticoagulant effect of phenprocoumon. Therefore, a close monitoring of the INR is recommended.
9) 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 metformin must be adjusted if necessary.

Concomitant use not recommended:

10) Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic insufficiency.
11) Iodinated contrast agents: Metformin must be discontinued prior to, or at the time of 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.

7. Pregnancy and Lactation

1) 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.
2) To prevent possible ingestion with the breast milk and possible harm to the child, this drug must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

8. 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.

9. 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.

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
Factors that may increase the risk of lactic acidosis (see Warnings) should be reviewed before considering initiation of metformin in patients with GFR < 60mL/min/1.73m^2.
If no adequate strength of Amaryl M is available, individual monocomponents should be used instead of the fixed dose combination.

GFR ml/min/1.73m^2	Metformin	Glimepiride
60-89	Maximum daily dose is 3000mg Dose reduction may be considered in relation to declining renal function.	The highest recommended dose per day should be 8 mg of glimepiride
< 30	Metformin is contraindicated	

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 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. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B12 deficiency should be excluded.

11. Overdose

1) 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.

2) Management

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.
Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycaemia may recur after initial recovery.
Admission to hospital may sometimes be necessary even as a precautionary measure. In particular, significant overdose and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital.
If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.
If, for example, the patient is unconscious, an intravenous injection of concentrated glucose solution is indicated (for adults starting with 40ml of 20% solution, for example). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1mg i.v., s.c. or i.m., may be considered.
In particular when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be very carefully adjusted in view of the possibility of producing dangerous hypserglycameia, and must be controlled by close monitoring of blood glucose.
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. The most effective method to remove lactate and metformin is haemodialysis.

Pancreatitis may occur in the context of a metformin overdose.

12. 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 900mg/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 600mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis.

13. Drug abuse and dependence

Metformin HCl product possesses no pharmacodynamic properties, either primary or secondary, which could be expected to result in abuse as a recreational drug or addiction.

14. Precaution for application

Patients should be advised to drive a car or operate machinery with caution.

[Excipient]

Lactose monohydrate, sodium starch glycolate, povidone K-30, microcrystalline cellulose, crospovidone, magnesium stearate, hydroxypropylmethylcellulose 2910, polyethylene glycol 6000, titanium dioxide, carnauba wax

[Shelf life]

3 years.

[Storage condition]

Below 30℃, dry place with the original pack.

[Package]

2-1000 Tablets, Blister pack and Bottle pack.

[Manufacturing site]

Handok Pharmaceuticals Co., Ltd.
37, Daepung-ri, Daesomyeon, Eumseong-gun, Chungcheongbuk-do, Korea

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