[Indications]

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

[Dosage and administration]

The dosage of anti-diabetic drugs should be individualized based on the patient's blood glucose levels.

The starting dose of this drug should be recommended at the lowest effective dose referring to below.
1) Patient inadequately controlled with sulfonylurea or metformin monotherapy : the usual starting dose of this drug is 2mg/500mg administered once daily and it can be adjusted according to the concomitant drug or blood glucose level. The patient should be observed carefully for hypoglycemia when being transferred from long half-life sulfonylureas(e.g., chlorpropamide) due to potential overlapping of drug effect.
2) When switching from combination therapy of separate tablets : the usual starting dose is the dose of glimepiride and metformin already being taken.

If needed, the dose may be increased up to the highest recommended dose per day of 8mg of glimepiride and 2000mg of metformin, considering the current therapy, efficacy, or tolerance. An adequate monitoring of blood glucose levels should be performed for this.
Daily doses of glimepiride of more than 6 mg (or 8 mg) are more effective only in a minority of patients.

It should be administered once a day before or with breakfast or the first main meal.
Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose.

Patients should be informed that this drug must be swallowed whole and not crushed or chewed because this is prolonged-release tablet.

[Precautions for use]

1. Warnings

1) Serious lactic acidosis or hypoglycemia may occur. It has been reported of lactic acidosis related death.

Metformin accumulation occurs at acute worsening of renal function and increases 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. (refer to 2. Contraindication and 6. Interactions)

Diagnosis: 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. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5mmol/L), and an increased anion gap and lactate/pyruvate ratio.

Renal function: GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR<45mL/min/1.73m^2 and should be temporarily discontinued in the presence of conditions that alter renal function. Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when

initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

2) Increased Risk of Cardiovascular Mortality: The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP) which was designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) or diet plus a fixed dose of phenformin (100 mg/day), had a rate of cardiovascular mortality approximately 2.5 times that of patients treated with diet alone, resulting in discontinuation of both these treatments in the UGDP study. 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 this drug and alternative therapies. Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other related antidiabetic drugs, in view of the similarities in mode of action and chemical structure among the drugs in each category.

2. Contraindications

1) Insulin-dependent (type I) diabetes (e.g., diabetics with a history of ketonemia), Any type of acute metabolic acidosis (lactic acidosis, diabetic ketoacidosis, diabetic coma or precoma, acute or chronic metabolic acidosis)

2) Known hypersensitivity to any of the excipients of this drug, sulfonylureas, sulfonamides or biguanides

3) Patients with severe hepatic dysfunction or hemodialysis. In case of severe hepatic or renal function disorders, change over to insulin is required to achieve adequate control of blood glucose.

4) Moderate (stage3b) and severe renal failure (Creatinine clearance <45ml/min or GFR <45ml/min/1.73m2). Patients with renal disease or renal dysfunction (e.g., as suggested by

serum creatinine levels ≥1.5mg/dL[males], ≥1.4mg/dL[females], or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse(shock), acute myocardial infarction, and septicemia

5) Patients with congestive heart failure requiring pharmacological management, recent myocardial infarction, cardiovascular collapse, or respiratory disturbance

6) Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography(CT) scans with intravascular 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)

7) Severe infections, before and after surgery [This drug must be discontinued at the time of surgery under general, spinal or epidural anaesthesia (except minor operations with no limitation of food and solution intake). 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.], serious trauma

8) Malnourished, starving, or debilitated patients, or patients with pituitary or adrenal insufficiency

9) Hepatic dysfunction (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.), pulmonary infarction, severe lung dysfunction, other condition likely to be with tissue hypoxia (such as cardiac or respiratory failure, recent myocardial infarction, shock), alcoholic, dehydration, gastrointestinal disturbance including diarrhea and vomiting

10) Pregnant women, nursing mother

11) As this drug contains lactose, it should not be administered to a patient who has a genetic disease like galactose intolerance, Lapp lactose deficiency, or glucose-galactose malabsorption

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 in 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 (Patients with impaired renal function may be more sensitive to the glucose-lowering effect of this drug.)
7) Overdosage with this drug
8) Certain non-metabolic 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
9) Concurrent administration of certain other medicines (see 6. Interactions)

If such risk factors for hypoglycaemia 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 hypoglycaemia which reflect the body's adrenergic counterregulation may be milder or absent where hypoglycaemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with sympatholytic drugs.

4. Adverse Reactions

1) Lactic acidosis : refer to warning, general precautions
2) Hypoglycemia : refer to warning, general precautions
3) Digestive tract : GI symptoms (diarrhea, nausea, vomiting, abdominal fullness, flatulence and anorexia) are the most common adverse reactions and especially, in the initial stage of treatment, it occurs 30% more frequently in the metformin group compared with the placebo

group. These symptoms are generally temporary and resolve spontaneously. Occasionally, temporary dose reduction may be useful. Because GI symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take this drug with meals.

Because significant diarrhea and/ or vomiting may cause dehydration and extrarenal 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 the therapy unless intercurrent illness or lactic acidosis has been excluded.

4) Nervous system: about 3% of patients have taste disturbance or metallic taste during the initial stage of treatment with this drug but they generally resolve spontaneously. Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels.

In post-marketing experience, dysgeusia was occurred after administration of Glimepiride. (frequency not known)

5) Dermatologic reactions: Occasionally, allergic or pseudo-allergic reactions (e.g., itching, urticaria, or rashes) may occur. Most of these reactions are mild but may develop into serious reactions with dyspnea and a fall in blood pressure, sometimes progressing to shock. Therefore, in the event of urticaria, a physician must therefore be notified immediately.

6) Hematological abnormalities may occur. Rarely, thrombocytopenia, in isolated cases, leucopenia, or hemolytic anemia (e.g., erythrocytopenia, granulocytopenia, agranulocytosis) may develop. Because it is reported that aplastic anemia and pancytopenia may occur in other 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).

7) A decrease of plasma Vitamin B12 level was observed in patients who take metformin for a long time. Cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in post-marketing experience (frequency not known). Therefore, proper monitoring of plasma Vitamin B12 or periodic parenteral supplement of Vitamin B12 should be considered. Plasma folic acid level was not significantly decreased. But megaloblastic anemia was reported in connection with this drug.

8) Hepatobiliary: In cases, elevation of liver enzymes and impairment of liver function(e.g., cholestasis and jaundice) may occur, as well as hepatitis which may progress to liver failure.
9) Others: In isolated cases, allergic vasculitis, hypersensitivity of skin to light, or a decrease in serum sodium concentration may occur.
Additionally, below adverse events were occurred as unknown frequency.
- Reduction of thyrotropin level in patients with hypothyroidism
- Hypomagnesemia in the context of diarrhea
- Encephalopathy
- Alopecia, weight gain (after glimepiride administration)
10) In a 16-week controlled, double-blind, double-dummy, randomized, 2 arm parallel-group study for 207 Korean patients, to compare the efficacy and safety of Amaryl® -M(fixed dose combination product of glimepiride and metformin HCl IR) 1/250 mg b.i.d. vs. Amaryl® -Mex 2/500 mg o.d. in patients with Type 2 DM, a total of 106 patients received Amaryl® -M and 101 patients received Amaryl® -Mex.
The incidence of hypoglycemia is as below and statistical significant difference was not observed between two groups.

	Amaryl-Mex OD N=101		Amaryl M BID. N=106		p-value
	n(%)	event	n (%)	event	
Any hypoglycaemia†	43 (42.6%)	137	37 (34.9%)	100	0.2479
Symptomatic hypoglycaemia‡	39 (38.6%)	111	34 (32.1%)	82	0.3210
Nocturnal hypoglycemia	1 (1.0%)	1	5 (4.7%)	6	0.1083

†Hypoglycemia: symptomatic hypoglycemia. In case of the blood glucose measurement < 70 mg/dl without symptoms, it was also recorded as 'Hypoglycemia'.
‡Symptomatic hypoglycemia: The cases in which the subject experiences clinical symptoms due to hypoglycemia and it is rapidly reversible with oral administration of carbohydrate

Among 101 patients who administered this drug, the rate of overall adverse events was 34.7 % (60 events) and the most frequent AE was related with gastrointestinal tract (13.9%, 20 events) and respiratory system(11.9%, 14 events). The newly reported AE (more than 2%)

which was not reported in glimepiride, metformin HCl (including SR), Amaryl M treatment was cold (9 events).

AEs considered to be related with the investigational product were reported from 6 subjects (7 events) in Amaryl® -Mex OD group and from 7 subjects (8 events) in Amaryl® -M BID group. (Please refer to the below table.)

	Amaryl-Mex OD N=101	Amaryl M BID N=106
Number of patients with AEs possibly related to the drug	6 patients (5.9%)	7 patients (6.6%)
Number of events of AEs possibly related to the drug	7 cases	8 cases
Upper abdominal pain	2 patients (2.0%)	4 patients (3.8%)
Abdominal discomfort	1 patient (1.0%)	0
Abnormal bowel sounds	1 patient (1.0%)	0
Constipation	1 patient (1.0%)	0
Diarrhea	0	1 patient (0.9%)
Dyspepsia	0	1 patient (0.9%)
Nausea	0	1 patient (0.9%)
Thrombocytopenia	1 patient (1.0%)	0
Hyperkalaemia	0	1 patient (0.9%)

11) Post-marketing experiences in Korea

In a 4-year surveillance study in 643 patients for drug re-examination in Korea, the incidence of adverse events, regardless of causality, was reported to be 2.02%(13/643patients, 16 cases). The incidence of adverse drug reactions where causality to this drug could not be ruled out was reported to be 1.24%(8/643patients, 10 cases) including hypoglycemia in 0.62%(4/643 patients, 4cases), nausea in 0.47%(3/643 patients, 3cases), hypertension, diarrhea, flushing in 0.16% each(1/643 patients, 1case).

Unexpected adverse events where a causal relationship to this drug could not be ruled out were 0.31% (2/643 patients, 2 cases) including hypertension and flushing in 0.16% each(1/643 patients, 1case).

12) 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.

5. General precautions

1) Patients should be informed that this drug must be swallowed whole and not crushed or chewed, and that it is normal the film of the tablet may occasionally be eliminated in the feces.

2) Hypoglycemia : It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycemia may recur. Patients must, therefore, remain under close observation. Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, falling asleep, 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. Severe hypoglycemia further requires immediate treatment and follow-up by a physician, in some circumstances, in-patient hospital care. 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. The patients and his/her family should be educated about the dangerousness, symptoms, treatment and risk factors of hypoglycemia. Help may be necessary from other's to avoid complications. Artificial sweeteners have no effect in controlling of blood glucose.

3) Lactic acidosis : Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with this drug. When it occurs, it is fatal in approximately 50% of cases. Lactic acidosis frequently occurs in acute worsening of renal function, cardiopulmonary disease, septicemia. 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 plasma lactate levels(≥ 5mmol/L), decreased blood pH(<7.35), electrolyte disturbances with an increased anion gap, and increased lactate/ pyruvate ratio. When this drug is implicated as the cause of lactic acidosis, plasma levels >5μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving this drug is very low(approximately 0.03 cases/ 1000 patients a year, with approximately 0.015 fatal cases/ 1000 patients a year). 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 patients' age.

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 HCl on lactate metabolism.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, dyspnea, asthenia, pain, increasing somnolence, nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant brady-arrhythmias 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 (<7.35), lactate levels, and even 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 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.

4) 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 of not adequately controlled blood glucose levels include oligouria, thirst, polydipsia, and dry skin, etc.

5) 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.

6) 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. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control.

7) If a patient receives a treatment from other physician or pharmacist (e.g., due to hospitalization, accident, or going to the doctor on holiday), the patient should inform them of his current diabetic situation and previous treatment.

8) 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 a proper blood glucose control.

9) The treatment should be initiated using the lowest effective dose. Treatment with this drug requires regular monitoring of glucose levels in blood and urine. (In addition, determination of the proportion of glycosylated hemoglobin is also recommended.) The effectiveness of therapy should be assessed and if not satisfactory, switch to another therapy should be promptly made.

10) 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.

11) 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. Before initiation of this drug therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients with creatinine clearance under normal value and in the elderly, renal function should be assessed more frequently, e.g. 2~4 times a year. This drug should be discontinued in in patients with creatinine clearance <45ml/min (GFR <45ml/min/1.73m^2). In circumstances which causes acute damage on renal function, such as dehydration (severe or continuous vomiting or diarrhoea) or taking Mmdicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs), special caution is recommended. In this case, metformin should be immediately and temporarily discontinued.

12) Diabetes-like symptoms: This drug should be prescribed only for patients diagnosed with diabetes. They should be distinguished from diseases accompanying diabetes-like symptoms (renal diabetes, geriatric glucose metabolism disorder, thyroid malfunction, etc.) including glucose intolerance or positive urine glucose.

13) In some patients, oral antidiabetics may be not necessary any more or dose reduction may be required. The effectiveness of oral antidiabetic drugs decrease in many patients over a period of time due to such as progression of the underlying disease or complication of

infection. So, continuation, dose and concurrent drug should be decided based on food intake, weight change, blood glucose and infection, etc.

14) Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxia 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.

15) 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.

16) 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.

17) 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 2-3 year intervals may be useful.

18) 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.

19) Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, tremor, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold this drug and temporarily administer insulin. Metformin HCl may be reinstituted after the acute episode is resolved. Should secondary failure occur with metformin or sulfonylurea monotherapy, combined therapy with metformin and sulfonylurea may result in a response. Should secondary failure occur with combined metformin/ sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy. Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anesthesia and should not be usually resumed earlier than 48 hours afterwards.

20) Specific job workers: Patients who work in high altitude places or drive a car should be careful because severe lactic acidosis or serious delayed hypoglycemia may occur. In addition, patients and their family should be fully informed of the risk of lactic acidosis and hypoglycemia in order to draw their attention to the precautions to be taken.. Patients should be informed of the potential risks and benefits of metformin HCl and its 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.

21) Treatment of patients with G6PD-deficiency using sulfonylurea agents can lead to hemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be paid in patients with G6PD-deficiency and an alternative non-sulfonylurea should be considered.

22) Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism.

6. Interactions

<u>Glimepiride</u>

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). Therefore, it should be considered when CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole) are concomitant with this drug.

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, azapropazone, oxyphenbutazone, probenecid, quinolone antibiotics, salicylates, sulfinpyrazone, clarithromycin, sulfonamide, tetracyclines, tritoqualine, trofosfamide, sympathetic inhibitor

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, oral contraceptives, phenothizines, phenytoin, rifampicin, thyroid hormones, chlorpromazine, isoniazid

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 anticoagulants.

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 HCl

1) 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, alpha-glycosidase inhibitor (acarbose), anabolic steroids, guanethidine, salicylates (aspirin, etc), beta-blockers (propranolol, etc), MAO inhibitors, angiotensin reversion enzyme inhibitor

Drugs weakening the effect :

Epinephrine, sympathomimetics, corticosteroids, thyroid hormones, estrogens, oral contraceptive, thiazid and other diuretics, pyrazinamide, isoniazid, nicotinic acid, phenothizines, phenytoin, calcium channel blockers, beta-agonists (salbutamol, formoterol)

2) Glyburide: In a single-dose interaction study in type 2 diabetes subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases of 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.

3) 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.

4) 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. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

5) Drugs that can affect renal function, cause hemodynamic changes or cationic drugs, which are eliminated by renal tubular secretion: 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.

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.

6) 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.

7) 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.

8) Organic cation 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 coadministered 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.

9) Other: 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.

7. Pregnancy and Lactation

1) This drug must not be taken by pregnant women. In animal studies, teratogenecity was reported and lactic acidosis is easy to occur. Pregnant patient or the patient planning a pregnancy must inform their physician diabetes and they should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

2) Studies in lactating rats show that metformin and glimepiride are excreted into milk. So, 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.

9. Geriatric Use

The dosage of Metformin HCl should be at the lowest effective dose based on the patient's renal function as renal function is decreased in elderly and regular monitoring is recommended. Generally, highest dose is not recommended to elderly.

Metformin and glimepiride is known to be substantially excreted by the kidney and 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.

10. Laboratory test

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin HCl therapy, if this is suspected, vitamin B12 deficiency should be excluded.

11. Overdosage

As this drug contains glimepiride, overdosage of this drug can result in hypoglycemia. As soon as an overdose of glimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose.

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking soft drink or water containing activated charcoal (absorbent) and sodium-sulphate (laxative).

In particular, significant overdoses 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 glucose solution(e.g. a rapid intravenous injection of 50% concentrated glucose solution or 40 ml of 20% solution followed by a continuous infusion of a more diluted (10%) glucose solution at a rate that maintain the blood glucose at a level above 100 mg/dL). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1 mg i.v., s.c. or i.m., may be considered. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery. In particular when treating hypoglycaemia from accidental intake of glimepiride in infants and young children, the dose of glucose given should be very carefully adjusted and the blood glucose level should be closely monitored.

If large quantities have been ingested, gastric lavage is indicated first, and then followed by activated charcoal and sodium-sulphate.
Because metformin is contained in this drug, it may cause lactic acidosis. Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. 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.

12. Carcinogenesis, Mutagenesis, Impairment of Fertility

Glimepiride

1) Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

2) Glimepiride was non-mutagenic in in vitro and in vivo mutagenicity studies

3) There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Metformin HCl

1) 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.

2) 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).

3) 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. Precaution for Storage and Handling

1) It should be kept out of children's reach.

2) Change of container is not desirable because it may cause an accident and quality deterioration.