[Glimepiride/Metformin Hydrochloride Impact] Product Information

[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 glycaemic control;
- Replacement of combination therapy of glimepiride and metformin.

[Dosage and administration]

This drug should be administered once or twice per day immediately before or with the meals.

The dosage may be individualized based on the patient's current treatment regimen, efficacy and tolerability; adequate monitoring of blood glucose levels should be performed for this. Generally, it should be recommended to initiate the lowest effective dose and increase the dose depending on the patient's current medication and blood glucose levels. The initial daily dose of this drug in a clinical study was glimepiride / metformin hydrochloride 2 mg/500 mg which was gradually increased up to glimepiride / metformin hydrochloride 8 mg/2000 mg as per the blood glucose monitoring results. Although glimepiride monotherapy generally had little additional effects when dosed at 4 mg or more a day, some patients showed improved metabolic control when the dose was increased up to 6 mg (or 8 mg).

When switching from combination therapy, this drug should be administered based on the dosage and administration method of glimepiride and metformin hydrochloride that are being currently administered in combination.

Although the previous dose was omitted, do not overdose this drug for the next dose.

[Precautions for use]

1. **Warnings**

1) Serious lactic acidosis or hypoglycaemia may occur.

2) Increased risk of cardiovascular mortality

The administration of oral hypoglycaemic 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 mellitus.

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) are included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other hypoglycaemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

2. Contraindications

1) Patients with insulin-dependent (type I) diabetes mellitus (e.g., diabetic patients with a history of ketonemia), diabetic ketonemia, diabetic coma or pre-coma, acute or chronic metabolic acidosis.

2) Patients with a history of hypersensitivity to any of the excipients of this drug, or sulfonylureas, sulfonamides, or biguanides.

3) There is no experience in patients with severe hepatic dysfunction or haemodialysis. In case of severe hepatic or renal function disorders, a shift to insulin is required to achieve adequate control of blood glucose.

4) Women who are or are suspected of being pregnant, nursing mothers.

5) Patients susceptible to lactic acidosis, patients with a history of lactic acidosis, renal failure or renal dysfunction (e.g., as suggested by plasma 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 septicaemia.

6) Patients who receive radiologic tests involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials). Such tests can lead to acute renal dysfunction and have been associated with lactic acidosis in patients receiving this drug. Therefore, in patients for whom such test is planned, this drug should be temporarily discontinued 48 hours before the procedure, and reinstituted only after renal function has been re-evaluated and found to be normal. Besides, patients with acute symptoms with the potential to alter renal function (dehydration, severe infection, shock) should be contraindicated.

7) Severe infections, before and after surgery [this drug should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.], patients with 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 accompany hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock), excessive alcohol intake, dehydration, gastrointestinal disturbance including diarrhoea and vomiting.

10) Patient with congestive heart failure requiring pharmacologic management and recent myocardial infarction, severe cardiovascular collapse, or respiratory disturbance.

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. Administration with special precautions

Careful monitoring is required during the first week of treatment because of increased risk of hypoglycaemia. The patients or conditions at risk of hypoglycaemia are as follows:

1) Unwillingness or incapacity of the patient to cooperate (more common in older patients).

2) Malnutrition, irregular mealtimes, skipped meals.

3) Imbalance between physical exertion and carbohydrate intake, severe myokinesis.

4) Consumption of alcohol.

5) Renal insufficiency (may lead to a more sensitive reaction to the blood glucose lowering effect of glimepiride).

6) Severe hepatic insufficiency.

7) Overdosage with this drug.

8) Certain uncompensated disorders of the endocrine system (e.g., disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency): may affect carbohydrate metabolism or counter-regulation of hypoglycaemia.

9) Concurrent administration of certain other medicines (see section 6. Interactions).

If such risk factors of 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 lifestyle changes. Those symptoms of hypoglycaemia which reflect the body's adrenergic counter-regulation (see section 5. General precautions) 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 sections 1. Warnings and 5. General precautions.

2) Hypoglycaemia: refer to sections 1. Warnings and 5. General precautions.

3) Gastrointestinal system: GI symptoms (diarrhoea, nausea, vomiting, abdominal distention,

anorexia, dyspepsia, constipation, abdominal pain) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin 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, approximately 4% of patients discontinued metformin due to gastrointestinal reactions. 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 diarrhoea and/or vomiting may cause dehydration and prerenal azotaemia, 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 but may be related to concomitant illness or lactic acidosis.

Glimepiride therapy is occasionally associated with GI symptoms such as nausea, vomiting, epigastric bloating or tightness, abdominal pain, and diarrhoea.

4) Special senses: during initiation of metformin therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually 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 and hypersensitivity: occasionally, allergic or pseudo-allergic reactions (e.g., erythema, itching, urticaria, or rashes) may occur. Most of these reactions are 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. Crossover allergic reactions with sulfonylureas or sulfonamides and their derivatives may occur.

6) Following haematological abnormalities may occur rarely: thrombopenia, in isolated cases, leukopenia, or haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis, pancytopenia may develop. Because it is reported that aplastic anaemia may occur with 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 anaemia was reported in connection with this drug.

8) Hepatobiliary: in some 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 diarrhoea.
- Encephalopathy.
- Alopecia, weight gain (after glimepiride administration).

10) Adverse events in children: adverse events observed in a clinical trial of a small-size cohort comprised of children aged 10 to 16 treated with metformin for 1 year as well as adverse events published and reported from post-marketing experiences were similar as those reported in adults in terms of characteristics and severity.

11) In local phase 1 and open-label phase 3 clinical trials, unexpected adverse reactions of this drug except for those of glimepiride and metformin already known have not been observed.

12) Post-marketing experiences in Korea

In a 6-year post-marketing surveillance study in 1,235 patients with non-insulin dependent diabetes mellitus (type 2) for drug re-examination in Korea, the incidence of adverse events, regardless of causality, was reported to be 2.75% (34/1,235 patients, 35 cases).This included hypoglycaemia in 0.81% (10/1,235 patients, 10 cases), abdominal pain in 0.57% (7/1,235 patients, 7 cases), abdominal distention in 0.49% (6/1,235 patients, 6 cases), vomiting and dyspepsia, in 0.16% each (2/1,235 patients, 2 cases), prostatic hypertrophy, palpitation, dizziness, diarrhoea, nausea, leg oedema, cardiac arrest, and rectal cancer in 0.08% each (1/1,235 patients, 1 case). The incidence of adverse drug reactions where causality to this drug could not be ruled out was reported to be 2.02%

(25/1,235 patients, 26 cases) including hypoglycaemia in 0.81% (10/1,235 patients, 10 cases), abdominal distention and abdominal pain in 0.49% each (6/1,235 patients, 6 cases), palpitation, vomiting, dyspepsia, and dizziness in 0.08% each (1/1,235 patients, 1 case). Serious adverse events included cardiac arrest, and rectal cancer in 0.08% each (1/1,235 patients, 1 case), neither of which had a causal relationship to this drug. Unexpected adverse events were dyspepsia, in 0.16% (2/1,235 patients, 2 cases), prostatic hypertrophy, leg oedema and rectal cancer in 0.08% each (1/1,235 patients, 1 case). Of these, dyspepsia was an adverse drug reaction where a causal relationship to this drug could not be ruled out.

- Post-marketing experiences with glimepiride single agent therapy (oral) in Korea:

In a 6-year post-marketing surveillance study in 12,056 patients for drug re-examination in Korea, the incidence of adverse events, regardless of causality, was reported to be 1.2% (149/12,056 patients, 181 cases). Hypoglycaemia in 0.75% (90/12,056 patients, 102 cases) was the most frequently occurred adverse events, followed by vertigo (dizziness) in 0.08% (10/12,056 patients, 10 cases), hepatic dysfunction in 0.07% (8/12,056 patients, 8 cases), and abdominal pain in 0.06% (7/12,056 patients, 7 cases). Of these, newly reported adverse events that had not been identified in pre-marketing clinical trials were arthralgia, dyspepsia, facial oedema (2 cases each), impotence, alopecia, flushing, and gastritis (1 case each).

13) If the adverse reactions mentioned above, other undesirable reactions, or unexpected changes occur, patients should promptly notify their health practitioner. Certain adverse reactions including severe hypoglycaemia, special haematologic 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 getting the physician's instructions.

5. General precautions

1) Hypoglycaemia: it is known from other sulfonylureas that, despite of initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation by a physician or pharmacist. Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, fatigue, falling asleep, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression,

confusion, speech disorders, aphasia, visual disorders, tremor, paresis, sensory disturbances, dizziness, loss of self-control, delirium, cerebral convulsions, loss of consciousness, 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 hypoglycaemic attack may resemble that of a stroke. Severe hypoglycaemia further requires immediate treatment and follow-up by a physician, in some circumstances, in-patient hospital care. Hypoglycaemia can be almost 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. The patients and his/her family should be educated about the dangerousness, symptoms, treatment and risk factors of hypoglycaemia. Help may be necessary for others to avoid complications. Artificial sweeteners have no effect in controlling blood glucose.

2) Lactic acidosis: lactic acidosis is a 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 may also occur in association with several pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxia.

Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/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/year, with approximately 0.015 fatal cases/1000 patients/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 patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients on this drug and by using the minimum effective dose of this drug. In addition, this drug should be immediately withheld in the presence of any condition associated with hypoxemia, dehydration, or septicaemia.

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 test 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 bradyarrhythmia 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.

Plasma electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful to identify lactic acidosis. 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 HCl is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

3) 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 poorly controlled blood glucose levels include oliguria, thirst, polydipsia, dry skin etc.

4) At the initiation of administration, patients should be informed by their physician or pharmacist

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.

5) Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated haemoglobin 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 haemoglobin should be monitored. Measurements of glycosylated haemoglobin may be especially useful for evaluating long-term control.

6) If a patient receives a treatment from other physician or pharmacist (e.g., hospitalization, accident, in need of medical attention on holidays, etc.), the patient should inform them of one's current diabetic situation and previous medication.

7) 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.

8) The dosage of this drug must start from the lowest. Treatment with this drug requires regular monitoring of glucose levels in blood and urine. In addition, determination of the proportion of glycosylated haemoglobin is recommended. The effectiveness of therapy should be assessed and if not satisfactory, a switch to another therapy should be promptly made.

9) Alertness and reactions may be impaired due to hypoglycaemia or hyperglycaemia, 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.

10) Monitoring of renal function: metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with plasma 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 glycaemic 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. Before initiation of this drug therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be

assessed more frequently, and this drug discontinued if evidence of renal impairment is present.

11) 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. 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.

12) Diabetes-like symptoms: this drug should be prescribed only for patients diagnosed with type II diabetes mellitus. Also pay attention to diseases accompanying diabetes-like symptoms (renal diabetes, geriatric glucose metabolism disorder, thyroid malfunction, etc.) including glucose intolerance or positive urine glucose, other than diabetes.

13) Adjustment during treatment: 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 any 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 azotaemia. 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) Vitamin B12 levels: a decrease to subnormal levels of previously normal plasma vitamin B12 levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin 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 anaemia and appears to be rapidly reversible with discontinuation of this drug or vitamin B12 supplementation. Measurement of haematologic 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 tablets who develops laboratory abnormalities or clinical illness (especially fatigue, poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include plasma electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin HCl levels. If acidosis of either form occurs, metformin HCl treatment must be stopped immediately, and other appropriate corrective measures initiated.

18) 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 glycaemic control may occur. At such times, it may be necessary to withhold this drug and temporarily administer insulin. Should secondary failure occur with combined metformin HCl/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

19) Specific job workers: patients who work in high altitude places or drive a car should be careful because severe lactic acidosis or serious delayed hypoglycaemia may rarely occur. The risk of lactic acidosis and hypoglycaemia should be fully informed to patients and their family for special caution.

20) Information for patients: patients should be informed of safety, efficacy, and alternative modes of therapy of this drug. They should also be informed about the importance of regular meal and adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated haemoglobin, renal function, and haematologic parameters. And patient with obesity should keep low calorie diet. 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 metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. A physician should explain the patient and the family about the risk, symptoms, and occurrence condition of hypoglycaemia. Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving this drug.

21) Treatment of patients with 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.

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

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 hypoglycaemic 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). This fact should be considered in case of concomitant administration of CYP2C9 inducers (e.g., rifampicin) or inhibitors (e.g., fluconazole).

2) Drugs potentiating the blood-glucose-lowering effect: Insulin and oral anti diabetic products, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), 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 sympathomimetics, glucagon, laxatives (long term use), nicotinic acid (high dose), oestrogens, progestogens, oral contraceptives, phenothiazines, phenytoin, rifampicin, thyroid hormones, chlorpromazine, isoniazid.

4) Drugs potentiating or weakening the blood-glucose-lowering effectH2 antagonists, clonidine, reserpine.

5) Beta-blockers reduce glucose tolerance. Reduction of glucose tolerance may change metabolic

control in diabetic patients. Beta-blockers may increase the risk of hypoglycaemia (due to failure of counter-regulation).

6) Drugs reducing or blocking the signs of adrenergic counter-regulation to hypoglycaemia: 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 anticoagulant.

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.).

2) The hypoglycaemic 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 hypoglycaemic action: insulin, sulfonamides, and sulfonylureas products, meglitinides (repaglinide, etc.), alpha-glycosidase inhibitor (acarbose), anabolic steroids, guanethidine, salicylates (aspirin, etc.), beta-blockers (propranolol, etc.), MAO inhibitors, ACE (Angiotensin Converting Enzyme) inhibitors.

— Drugs weakening the hypoglycaemic action: epinephrine, sympathomimetics, corticosteroids, thyroid hormones, oestradiol, oestrogens, oral contraceptive, thiazide and other diuretics, pyrazinamide, isoniazid, nicotinic acid, phenothiazines, phenytoin, calcium channel blockers, beta-2-agonists (salbutamol, formoterol, etc.).

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

pharmacodynamics of metformin HCl. 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 metformin HCl blood levels and pharmacodynamic effects makes the clinical significance of this interaction uncertain.

4) Furosemide: a single-dose, metformin HCl-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin HCl plasma concentration and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin HCl renal clearance. When administered with metformin HCl, 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 HCl and furosemide when co-administered chronically.

5) Nifedipine: a single-dose, metformin HCl-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin HCl 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 HCl. Metformin HCl 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 HCl by competing for common renal tubular transport systems. Such interaction between metformin HCl and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin HCl-cimetidine drug interaction studies, with a 60% increase in peak metformin HCl plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin HCl AUC. There was no change in elimination half-life in the single-dose study. Metformin HCl had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin HCl and/or the interacting drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

7) Other: in healthy volunteers, the pharmacokinetics of metformin HCl and propranolol, and metformin HCl and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin HCl 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 plasma proteins.

7. Pregnancy and lactation

1) This drug must not be taken during pregnancy as teratogenicity was reported in animal studies and lactic acidosis is easy to occur to pregnant women. Pregnant patient or the patient planning a pregnancy must inform their physician in order to reduce the risk of foetal congenital anomaly caused by abnormal glycaemic levels. It is recommended that such patients change over to insulin to maintain the blood glucose level within a normal range if possible.

2) This drug must not be taken by breast-feeding women as glimepiride and metformin were reported to be excreted into milk in lactating rats. If necessary, the patient must change over to insulin, or must stop breast-feeding.

8. Paediatric use

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

<Metformin single agent>

Prior to metformin treatment, it should be confirmed whether the patient has a type 2 diabetes mellitus. Although a one-year controlled clinical trial confirmed that metformin did not affect growth and sexual maturation, no long-term study results are available for these specific points. Therefore, it is recommended that the impact of metformin on these parameters be carefully monitored when this drug is administered to children including those before puberty.

Children aged 10 to 12: only 15 children aged 10 to 12 participated in a controlled clinical trial in children and adolescents in the growth phase. Although the efficacy and safety of metformin in children aged 12 or below did not differ from those in children aged 12 or above, caution should be exercised when metformin is prescribed to children aged 10 to 12.

9. Geriatric use

With regard to decreased renal function of geriatric patients, the dosage of metformin HCl should be adjusted based on renal function of patients and regular monitoring of renal function is necessary. Metformin HCl and glimepiride are known to be mostly excreted by the kidney. 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.

10. Laboratory tests

Periodic monitoring of haematologic parameters (e.g., haemoglobin/haematocrit and red blood cell indices) and renal function (plasma creatinine) should be performed, at least on an annual basis. While megaloblastic anaemia has rarely been seen with metformin therapy, if this is suspected, possibility of vitamin B12 deficiency should be checked.

11. Overdosage

Because this drug includes glimepiride, overdosage of this drug can produce hypoglycaemia.

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.

Mild hypoglycaemia without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger.

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 case

quite a lot of amount is absorbed, gastric lavage should be conducted and the activated charcoal and sodium-sulphate should be used later.

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 hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated 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 hypoglycaemia 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.

Because this drug includes metformin, lactic acidosis may occur. Hypoglycaemia has not been seen with metformin HCl doses of up to 85 g. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis is most effective treatment 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 5,000 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 Observable Effect Level (NOEL) 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 2,500 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 4,000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Metformin

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 900 mg/kg/day and 1500 mg/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.

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* micro nuclei formation test (mouse bone marrow).

3) 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.

13. Additional information

1) Impact on body weight: compared to other commonly used glucose lowering medications (sulfonylureas, thiazolidines etc.), this drug presents more benefits as it does not lead to weight gain in patients with type 2 diabetes mellitus. Steady or reduced body weight resulting from the use of this drug limits other risk factors associated with weight gain. More stable glycaemic control and reduced risks of complications of diabetes can be obtained from a prolonged use of this drug. In a clinical trial in adults and children, this drug was shown to improve glycaemic control without weight gain or even with slight weight loss.

2) 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. Effects on ability to drive and use machines

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

15. Precautions for storage and handling

1) Keep out of reach of children.

2) Please note that keeping the drug in another container instead of its original container may cause an accident and is also undesirable for quality maintenance.

16. Manufacturer

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17. Date of revision of the text

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