MERICLE Tab.

(Glimepiride 2mg)

■ **COMPOSITION**

Each tablet contains Glimepiride 2mg

■ **INDICATIONS**

Non-insulin-dependent (type II) diabetes mellitus, whenever blood glucose levels cannot be controlled adequately by diet, physical exercise and weight reduction alone.

Mericle may also be used in combination with metformin (another oral antidiabetic) or insulin if your diabetes is not sufficiently controlled with Mericle alone.

■ **DOSAGE & ADMINISTRATION**

The dosage and administration should be adjusted for each patients. Normally a single daily dose of MERICLE is sufficient. MERICLE must be swallowed whole with sufficient amounts of water (approx. 1/2 glass of water). It is recommended that this dose be taken immediately before a substantial breakfast or immediately before the first main meal. It is very important not to skip meals after the tablets have been taken. Initial and maintenance Dose The usual initial dose is 1mg glimepiride once daily. If necessary, the daily dose can be raised at intervals of one to two weeks and in a stepwise manner by 1mg/day (according to the following dose steps : 1mg – 2mg – 3mg – 4mg glimepiride per day). If this program fails, the use of insulin or oral sulfonylurea should be considered.The maximum recommended dose is 6mg glimepiride per day.

Secondary dosage adjustment

As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glimepiride requirements may fall as treatment proceeds. To avoid hypoglycaemia timely dose reduction or cessation of MERICLE therapy must therefore be considered.

Correction of dosage must also be considered, whenever the patient's weight changes, the patient's life-style changes, other factors arise which cause an increased susceptibility to hypoglycaemia or hyperglycaemia (see under “Special Warnings and Precautions”).

Changeover from other oral antidiabetics to Mericle

There is no exact dosage relationship between glimepiride and other oral antidiabetics. When substituting MERICLE for other oral antidia betics, it is recommended that the procedure be the same as for initial dosage starting with daily doses of 1mg. Consideration must be given to the potency and duration of action of the previous antidiabetic agent.

Administration adjustment

During treatment with MERICLE glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determinations of the proportion of glycosylated haemoglobin be carried out.

Hypoglycaemia can almost always be promptly controlled by immediate intake of carbohydrates.

It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation.

Severe hypoglycaemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.

Combination therapy with Insulin

Combination therapy with MERICLE and insulin may also be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of >150 mg/dL in plasma or serum depending on the patient. The recommended MERICLE dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combinationtherapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA1c levels.

Combination therapy with Metformin

If patients do not respond adequately to the maximal dose of MERICLE monotherapy, addition of metformin may be considered.

Published clinical information exists for the use of other sulfonylureas including glyburide, glipizide, chlorpropamide, and tolbutamide in combination with metformin.

With concomitant MERICLE and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant MERICLE and metformin therapy, the risk of hypoglycemia associated with MERICLE therapy continues and may be increased. Appropriate precautions should be taken.

■ **PRECAUTIONS**

1. Contraindications : MERICLE must not be used in
   1) insulin dependent (type I) diabetes, diabetic coma, ketoacidosis
   2) patients hypersensitive to glimepiride, other suphonylureas, other sulfonamides, or any of the excipients (risk of hypersensitivity reactions).
   3) severe renal or hepatic function disorders. In this case a change over to insulin is indicated, not least to achieve optimal metabolic control.
   4) pregnant or breast-feeding women (see under “Pregnancy and lactation”).

2. Precaution

In the initial weeks of treatment, the risk of hypoglycaemia may be increased and necessitates especially careful monitoring.

Factors favouring hypoglycaemia include

1) unwillingness or (more commonly in older patients) incapacity of the patient to co-operate.
2) undernourishment, irregular mealtimes or 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 affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or corticoadrenal insufficiency).
10) concurrent administration of certain other medicines (see “Interactions”).

The patient must inform the physician about such factors and about hypoglycaemic episodes since they may indicate the need for particularly careful monitoring. If such risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of MERICLE 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 counter-regulation (see under “Adverse reactions”) 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 beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic drugs.

3. Adverse reactions

Based on clinical data of glimepiride and what is known of other sulfonylureas, following adverse reactions should be considered.

Hypoglycaemia

Hypoglycaemia (sometimes life-threatening) may occur as a result of the blood-glucose-lowering action of this drug Possible symptoms of hypoglycaemia 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 hypoglycaemic attack may resemble that of a stroke. The symptoms of hypoglycaemia nearly always subside when hypoglycaemia is corrected.

Eyes

Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels.

Digestive tract

Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur.

Liver

Rarely, elevation of liver enzymes may occur. In isolated cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

Blood

Potentially life-threatening changes in the blood picture may occur : rarely, thrombocytopenia and, in isolated cases, leucopenia may develop. Based on what is known of other sulfonylureas, drugs of this class may – in isolated instances – cause in addition to the above haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis and (e.g. due tomyelosuppression) pancytopenia.

Hypersensitivity

Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Based on what is known of other sulfonylureas, such mild reactions may develop into serious and even life-threatening 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.

Other adverse effects

In isolated cases, a decrease in serum sodium concentration and – based on what is known of other sulfonylureas – allergic vasculitis or hypersensitivity of the skin to light may occur.

In case above-mentioned adverse effects or other undesirable reactions, unpredicted changes occur, physician or pharmacist must be noticed. Because some adverse effects, including severe hypoglycaemia, specific changes in blood picture, severe allergic or pseudoallergic reactions, liver impairment, may be life threatening, in case sudden or severe reactions occur, notice the physicians and stop administration until there are instructions.

4. General precaution

1) To achieve the optimal control of blood glucose – adherence to correct diet, regular and sufficient physical exercise and, if necessary, reduction of body weight are just as necessary as regular ingestion of MERICLE. Clinical signs of a still insufficiently lowered blood glucose (hyperglycaemia) are, e.g., increased urinary frequency, intense thirst, dryness of the mouth, and dry skin.
2) The patients should be informed of the potential risks and advantages of glimepiride tablets, the effects of this drug when accompanied by diet, exercise and importance of patient's compliance.
3) Hypoglycaemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g., in the form of sugar lumps, sugar sweetened fruit juice or sugar sweetened tea). For this purpose patients must carry a minimum of 20 grams of glucose with them at all times. They may require the assistance of other persons to avoid complications. Artificial sweeteners are ineffective in controlling hypoglycaemia.
4) It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation.
Severe hypoglycaemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.
5) When undergoing treatment of other physician or pharmacist (e.g. in-patient hospital care, in case of accidents and on holidays) patients must notify them of the diabetic status and medication experiences.
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 treatment should be started from the low dose. During the treatment, glucose level in blood and urine must be measured(it is recommended that regular determination of proportion of glycosylated hemoglobin) to validate the effectiveness of glimepiride. If the efficacy is insufficient changeover to another therapy.
8) Alertness and reactions may be impaired due to hypo- or hyperglycaemia, especially when beginning or after altering treatment or when MERICLE is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.

5. Drug interaction

Patients who take or discontinue taking certain othermedicines while undergoing treatment with MERICLE may experience changes in blood glucose control. Based on experience with MERICLE and on what is known of other sulfonylureas, the following interactions must be considered.

1) Glimepiride is metabolized by Cytochrome P450 2C9(CYP2C9). Thus there is potential interaction of glimepiride with inhibitors(e.g. fluconazole) and inducers(e.g. rifampicin) of CYP2C9.
2) Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example : insulin and other oral antidiabetics, ACE inhibitors, anabolic steroids and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, guanethidine, ifosfamide, MAO inhibitors. Miconazole, para-aminosalicylic acid, pentoxifylline(high dose parenteral), phenylbutazone, azapropazone, oxyphenbutazon, probenecid, quinolones, salicylates, sulphinpyrazone, sulfonamide antibiotics, tetracyclines, tritoqualine, trofosfamide.
3) Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example : acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, epinephrine (adrenaline) and other sympathomimetic agents, glucagon, laxatives (after protracted use), nicotinic acid (in high doses), estrogens and progestogens, phenothiazines, phenytoin, rifampicin, thyroid hormones.
4) Drugs may lead to either potentiation or weakening of the blood-glucose-lowering effect H2 receptor antagonists, clonidine and reserpine
5) Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent.
6) Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of MERICLE in an unpredictable fashion.
7) The effect of coumarin derivatives may be potentiated or weakened.

6. Pregnancy and lactation

1) Mericle must not be taken during pregnancy. Otherwise there is risk of harm to the child. Patients 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, MERICLE must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

■ **STORAGE CONDITIONS**

Store at room temperature (1 - 30° C). Dispense in tight containers.

■ **USE TERM** : 3 Years

■ **PACKAGE** : 10Tabs/Blister, 3Blisters/Box

This drug is manufactured in accordance with Korea Good Manufacturing Practice (KGMP) as recommended by WHO.