

## AMIRAN

Tablets

### Composition

Each tablet contains Glimpiride 1, 2, 3 or 4 mg.

### Action

Glimpiride is a sulfonylurea anti-diabetic agent, which decreases blood glucose concentrations. The primary mechanism of action of glimepiride appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. Glimpiride acts in concert with glucose by improving the sensitivity of beta cells to physiological glucose stimulus, resulting in insulin secretion in the rhythm of meals. In addition, extrapancreatic effects (eg. reduction of basal hepatic glucose production and increased peripheral tissue sensitivity to insulin and glucose uptake) may also play a limited role in the activity of glimepiride.

In non-fasting diabetic patients, the hypoglycemic action of a single dose of glimepiride persists for 24 hours.

The efficacy of Glimpiride is not affected by age, gender, or weight. Amiran therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profile of patients. The physiological response to acute exercise (i.e. reduction of insulin secretion) is still present during glimepiride therapy.

### Pharmacokinetics

The pharmacokinetics of glimepiride are similar in males and females and in young and elderly (>65 years) patients. Intra-individual variability is low.

#### *Absorption*

Glimpiride is completely absorbed after oral administration. The peak serum concentration (C<sub>max</sub>) is reached in about 2.5 hours. There is a linear relationship between dose and both C<sub>max</sub> and AUC (area under the plasma concentration-time curve). Food does not significantly affect the rate or extent of absorption of glimepiride.

#### *Distribution*

The volume of distribution was 8.8 liters (113 ml/kg) and the total body clearance was 48 ml/min. Protein binding was greater than 99%.

Glimpiride is likely to be minimally removed by haemodialysis due to its high protein binding. There is no accumulation of drug in tissue depots.

#### *Metabolism and Excretion*

The elimination half-life of glimepiride at steady state is about 5 to 8 hours after oral administration. However, results of a pharmacokinetic study on NIDDM patients indicated that higher doses might be associated with a longer half-life.

Glimpiride is completely metabolized by oxidative biotransformation. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is the principal enzyme involved in the biotransformation of glimepiride to M1. M1 has been found to have about 40% of the pharmacological activity of glimepiride. It is eliminated via the urine and also by further metabolism to M2 via one or several cytosolic enzymes. M1 has a terminal elimination half-life of 3-6 hours after an oral dose. The formation of M1 is linear up to a dose of 16 mg glimepiride. The kinetics of M2 has not been fully elucidated due to low plasma levels. Its terminal elimination half-life after an oral dose is about 5-6 hours.

Following an oral dose of glimepiride, 35% of the dose is excreted in feces and 58% in urine.

#### *Renal insufficiency*

In patients with renal impairment, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination

because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall, there appears to be no increased risk of accumulation of glimepiride in these patients.

A multiple dose titration study in patients with mild to severe renal impairment showed that approximately 44% had adequate control of their glucose levels with a dosage regime of 1 mg once daily. The results from this study suggest that a starting dose of 1 mg Glimepiride may be given to a NIDDM patient with renal disease, and the dose may be titrated based on fasting blood glucose levels.

#### *Hepatic failure*

The effects of hepatic failure on the clearance of glimepiride have not been systematically examined.

### **Indications**

Amiran is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with non-insulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone. Amiran may be used concomitantly with Glucomet (metformin) when diet, exercise, and Amiran or Glucomet alone do not result in adequate glycemic control.

Amiran is not suitable for the treatment of insulin-dependent (type I) diabetes mellitus (e.g. for the treatment of diabetics with a history of ketoacidosis, of diabetic ketoacidosis, or of diabetic precoma or coma).

### **Contraindications**

- Hypersensitivity to glimepiride, other sulfonylureas, other sulfonamides, or any excipients.
- Severe impairment of renal function.
- Dialysis patients.
- Severe hepatic dysfunction.
- Pregnancy.
- Lactation.

Glimepiride is not suitable for the treatment of insulin-dependent (type I) diabetes mellitus (eg. for the treatment of patients with a history of ketoacidosis), nor for the treatment of diabetic ketoacidosis, nor for the treatment of diabetic precoma or coma.

### **Warnings**

#### **Special warning on increased risk of cardiovascular mortality**

The administration of oral hypoglycemic 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), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. UGDP reported that patients treated for 5 to 8 years with diet and a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 & 1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. 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 advantages of Glimepiride tablets and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class. In view of their close similarities in mode of action and chemical structure.

### **Adverse Reactions**

#### **Hypoglycemia**

Hypoglycemia (sometimes life threatening) may occur because of the blood-glucose-lowering action

of Glimepiride. This happens when there is an imbalance between Glimepiride dosage, carbohydrate intake (diet), physical exercise, and other factors influencing metabolism.

Possible symptoms of hypoglycemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, sleep disorders, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac arrhythmias.

The clinical picture of a severe hypoglycemic attack may resemble that of a stroke. The symptoms of hypoglycemia may persist if hypoglycemia is not corrected.

### **Dermatologic Reactions**

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of Glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued.

Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylurea's, including Glimepiride.

### **Eyes**

Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependent on blood glucose level.

### **Gastrointestinal Reactions**

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

In isolated cases, there may be elevation of liver enzyme levels, impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which may also lead to life-threatening liver failure.

### **Hematologic Reactions**

Potentially life-threatening changes in the blood picture may occur, such as thrombocytopenia and, in isolated cases, leucopenia. Glimepiride, in addition to the above, may cause hemolytic anemia or erythrocytopenia, granulocytopenia, agranulocytosis and (e.g. due to myelosuppression) pancytopenia.

Allergic or pseudo-allergic reactions may occur such as itching, urticaria, or rashes. These 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.

In isolated cases, a decrease in serum sodium concentration has been seen and allergic vasculitis or hypersensitivity of the skin to light may occur.

If any of these reactions occur, a doctor should be consulted.

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

### **Metabolic Reactions**

Hepatic Porphyria reactions and disulfiram-like reactions have been reported with sulfonylurea, including Glimepiride. Cases of hyponatremia have been reported with Glimepiride and all other

sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with sulfonylureas, including Glimepiride, and it has been suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

### **Precautions**

Treatment with Glimepiride must be initiated and monitored by a physician. The patient must take Glimepiride at the times and in the doses prescribed by the doctor, normally at the same time every day. To achieve the goal of treatment of Glimepiride - 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 Glimepiride.

Clinical signs of still insufficiently lowered blood glucose (hyperglycemia) are e.g. increased urinary frequency (Polyuria), intense thirst, dryness of the mouth and dry skin.

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

### **Pregnancy**

#### *Category C*

Glimepiride should not be used during pregnancy. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

### **Nursing Mothers**

Although it is not known whether Glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, Glimepiride should be discontinued in nursing mothers. If Glimepiride is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered.

### **Pediatric Use**

The profile of adverse reactions in pediatric patients treated with Glimepiride was similar to that observed in adults.

### **Geriatric Use**

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs.

In elderly, debilitated, or malnourished patients, or in patients with renal and hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents.

### **Drug Interactions**

Patients who take or discontinue taking certain other medicines while undergoing treatment with Glimepiride may experience changes in blood glucose control.

*The following interactions must be considered:*

Potentiating of the blood-glucose-lowering effect and, thus, in some instances hypoglycemia may occur when one of the following drugs is taken, for example:

Insulin and other oral Antidiabetic, MAO inhibitors, ACE inhibitors, miconazole, anabolic steroids and male sex hormones, para-aminosalicylic acid, chloramphenicol, pentoxifylline (high dose parenteral), coumarin derivatives, phenylbutazone, azapropazone, oxyphenbutazone, cyclophosphamide, probenecid, disopyramide, quinolones, fenfluramine, salicylates, fenylramidol, sulphinpyrazone, fibrates, sulfonamide antibiotics, fluoxetine, tetracycline, guanethidine, tritoqualine, ifosfamide, trofosfamide

Weakening of the blood-glucose-lowering effect and, thus raised glucose levels may occur when one of the following drugs is taken, for example:

Acetazolamide, laxatives (after protracted use), barbiturates, nicotinic acid (in high doses), corticosteroids, oestrogens and progestogens, diazoxide, phenothiazines, diuretics, phenytoin, epinephrine (adrenaline) and other sympathomimetic agents, Rifampicin, glucagon, thyroid hormones

H<sub>2</sub> receptor antagonists, beta-blockers, clonidine, and reserpine may lead to either potentiating or weakening of the blood-glucose-lowering effect. Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of Glimepiride in an unpredictable fashion.

The effect of coumarin derivatives may be potentiated or weakened.

### **Dosage and Administration**

There is no fixed dosage regimen for the management of diabetes mellitus with Amiran or any other hypoglycemic agent. The patient's fasting blood glucose and HbA<sub>1c</sub> must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

Short-term administration of Amiran may be sufficient during periods of transient loss of control in patients usually controlled well on diet and exercise.

#### **Usual Starting Dose**

The usual starting dose of Amiran as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be drugs that are more sensitive to hypoglycemic should be started at 1 mg once daily, and should be titrated carefully. No exact dosage relationship exists between Amiran and the other oral hypoglycemic agents.

The maximum starting dose of Amiran should be no more than 2 mg.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

#### **Usual Maintenance Dose**

The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA<sub>1c</sub> levels, for example, every 3 to 6 months.

#### **Amiran-Glucomet (metformin) Combination Therapy**

If patients do not respond adequately to the maximal dose of Amiran monotherapy, addition of Glucomet (metformin) may be considered. Published clinical information exists for the use of other

sulfonylurea's including glyburide, glipizide, chlorpropamide, and tolbutamide in combination with metformin.

With concomitant Amiran and Glucomet 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 Amiran and Glucomet therapy, the risk of hypoglycemia associated with Amiran therapy continues and may be increased. Appropriate precautions should be taken.

#### **Amiran-Insulin Combination Therapy**

Combination therapy with Amiran 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 Amiran 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, combination-therapy 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.

#### **Specific Patient Populations**

Glimepiride is not recommended for use in pregnancy or nursing mothers.

Data are insufficient to recommend pediatric use of Glimepiride. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

#### **Patients Receiving Other Oral Hypoglycemic Agents**

As with other sulfonylurea hypoglycemic agents, no transition period is necessary when transferring patients to Amiran. Patients should be observed carefully (1-2 weeks) for Hypoglycemia when being transferred from longer half-life sulfonylurea's (e.g., chlorpropamide) to Amiran due to potential overlapping of drug effect.

#### **Over Dosage**

Over Dosage of sulfonylureas, including Glimepiride can produce hypoglycemia. Mild Hypoglycemic symptoms 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.

Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dl. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

#### **Presentation**

##### **Amiran 1 mg**

Box of 30 tablets

##### **Amiran 2 mg**

Box of 30 tablets

##### **Amiran 3 mg**

Box of 30 tablets

##### **Amiran 4 mg**

Box of 30 tablets