SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

AMARYL 1 (tablets)

AMARYL 2 (tablets)

AMARYL 3 (tablets)

AMARYL 4 (tablets)

COMPOSITION:

Per tablet:

Glimepiride 1 mg

Glimepiride 2 mg

Glimepiride 3 mg

Glimepiride 4 mg

Excipients:

Each tablet also contains lactose, magnesium stearate, microcrystalline cellulose, polyvidone 25 000 and sodium starch glycolate. In addition the tablets contain colouring agents. The 1 mg tablets contain red ferric oxide; the 2 mg and 3 mg tablets contain yellow ferric oxide; and the 2 mg and 4 mg tablets contain indigo carmine aluminium lake.

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral hypoglycaemics

PHARMACOLOGICAL ACTION:

Glimepiride is a sulphonylurea. Glimepiride decreases blood glucose concentrations mainly by stimulating insulin release from pancreatic beta cells. This effect is based predominantly on an improved responsiveness of the pancreatic beta cells to the physiological glucose stimulus. Glimepiride also has extra pancreatic (insulin-sensitising and insulin-mimetic) effects.

The effect of glimepiride is dose-dependent over the dose range of 1 to 6 mg. The physiological response to acute physical exercise, i.e. reduction of insulin secretion, is still present with glimepiride.

There was no significant difference in effect regardless of whether glimepiride was given 30 minutes or immediately before a meal.

The absolute bioavailability of glimepiride is complete. Food intake has no relevant influence on absorption. Maximum serum concentrations are reached approximately 2,5 hours after oral intake and there is a linear relationship between dose and both maximum concentrations and area under the time/concentration curve.

Glimepiride has a high protein binding (> 99 %). Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After single-dose radiolabelled glimepiride, 58 % of the radioactivity was recovered in the urine, and 35 % in the faeces. No unchanged substance was detected in the urine. Pharmacokinetics were similar in males and females, as well as in young and elderly patients.

INDICATIONS:

AMARYL is indicated as an adjunct to diet and exercise to lower the blood glucose in patients

with non-insulin-dependent (Type 2) diabetes mellitus (NIDDM) whose hyperglycaemia cannot be controlled by diet and exercise alone.

Combination therapy with Metformin:

In patients not adequately controlled with the maximum daily dose of either glimepiride or metformin, combination therapy with both oral antidiabetic agents may be initiated.

CONTRAINDICATIONS:

AMARYL must not be used in patients hypersensitive to glimepiride, other sulphonylureas, sulfonamides, or any of the excipients (risk of hypersensitivity reactions), in pregnant or breastfeeding women as safety has not been shown, impaired liver function, and children. AMARYL is not suitable for the treatment of insulin-dependent (Type 1) diabetes mellitus.

WARNINGS:

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY. The administration of oral hypoglycaemic medicines 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 medicines in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes.

The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 supp. 2: 747-830, 1970). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1,5 grams per day) had a rate of cardiovascular

mortality approximately 2 to 2½ 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 AMARYL (glimepiride tablets) and of alternative modes of therapy.

Although only one medicine in the sulphonylurea 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 hypoglycaemic medicines in this class, in view of their close similarities in mode of action and chemical structure.

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.

INTERACTIONS:

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

Glimepiride is metabolised by cytochrome P450 2C9 (CYP2C9). This should be taken into account when AMARYL is co-administered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP 2C9.

The following interactions must be considered:

Potentiation of the blood-glucose-lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following medicines is taken, for example:

- insulin and other oral antidiabetics
- MAO-inhibitors
- ACE-inhibitors
- miconazole
- anabolic steroids and male sex hormones
- para-aminosalicyclic acid
- chloramphenicol
- pentoxifylline (high dose parenteral)
- coumarin derivatives
- phenylbutazone, azapropazone, oxyphenbutazone
- cyclophosphamide
- disopyramide
- quinolones
- salicylates
- sulphinpyrazone
- fibrates
- sulfonamide antibiotics
- fluoxetine
- tetracyclines
- guanethidine
- ifosfamide

- fluconazole
- clarithromycin

Weakening of the blood-glucose-lowering effect and, thus raised glucose levels may occur when one of the following medicines 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_2-receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect. Under the influence of sympatholytic medicines such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of AMARYL

in an unpredictable fashion.

The anticoagulant effect of coumarin derivatives may be potentiated or weakened.

PREGNANCY AND LACTATION:

AMARYL must not be used in pregnant or breastfeeding women, as safety has not been shown.

DOSAGE AND DIRECTIONS FOR USE:

The dosage of AMARYL is determined by the desired blood glucose level.

The dosage of glimepiride must be the lowest which is sufficient to achieve the desired metabolic control.

During treatment with AMARYL, glucose levels in blood and urine must be measured regularly.

In addition, it is recommended that regular determinations of the proportion of glycated haemoglobin be carried out.

If a patient forgets to take a dose, this must never be corrected by subsequently taking a larger dose. Measures for dealing with such situations (in particular forgetting a dose or skipping a meal) where a dose cannot be taken at the prescribed time must be discussed and agreed between physician and patient beforehand.

If it is discovered that too high a dose or an extra dose of AMARYL has been taken, a physician must be notified immediately.

Initial dose and dose titration:

The usual initial dose is 1 mg AMARYL once daily.

If necessary, the daily dose can be increased.

It is recommended that the increase be guided by regular blood glucose monitoring, and that the dose be increased gradually, i.e. at intervals of one to two weeks and according to the following dose steps: 1 mg - 2 mg - 3 mg - 4 mg - 6 mg.
Daily doses of more than 6 mg are more effective only in a minority of patients. A maximum of 8 mg per day may not be exceeded.

In patients not adequately controlled with the maximum daily dose of glimepiride, combination therapy with metformin may be initiated. The additional metformin treatment is started with a low dose, which is then titrated up depending on the desired level of metabolic control up to a maximum daily dose. The combination therapy should be initiated under close medical supervision.

Dose range in patients with well-controlled diabetes:

Usual daily dose is 1 to 4 mg AMARYL.

Distribution of doses:

Timing and distribution of doses are to be decided by the medical practitioner, taking into consideration the patient's current life-style.
Normally a single daily dose of AMARYL is sufficient to provide metabolic control over 24 hours.
It is recommended that this dose be taken immediately before a substantial breakfast or, if none is taken, immediately before the first main meal. It is very important not to skip meals after the tablet(s) have been taken.

Secondary dosage adjustment:

An improvement in the control of diabetes is associated with higher insulin sensitivity, therefore glimepiride requirements may fall as treatment proceeds.

To avoid hypoglycaemia, dose reduction or cessation of AMARYL therapy must therefore be considered, in time.

Correction of dosage must also be considered, whenever the patient's weight changes, the patient's lifestyle changes or other factors arise which cause an increased susceptibility to hypoglycaemia or hyperglycaemia (refer to SPECIAL PRECAUTIONS).

Duration of treatment:

Treatment with AMARYL is normally long-term therapy.

Change-over from other oral antidiabetics to AMARYL:

There is no exact dosage relationship between AMARYL and other oral antidiabetics.

When substituting AMARYL for other oral antidiabetics, it is recommended that the procedure be the same as for initial dosage, starting with daily doses of 1 mg. This applies even in cases where the patient is being switched from the maximum dose of another oral antidiabetic.

Administration:

AMARYL tablets must be swallowed whole with approximately half a glass of water.

Special Populations:

Renal Insufficiency: There is limited information available on the use of AMARYL in renal insufficiency. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of AMARYL.

Children: Data are insufficient to recommend paediatric use of AMARYL.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects

The following frequency rating has been used:

Very common: (≥ 1/10); Common: (≥ 1/100, < 1/10); Uncommon: (≥ 1/1000, < 1/100);

Rare: (≥ 1/10 000, < 1/1000); Very rare: (< 1/10 000), including isolated reports.

Metabolism disorders:

Very common: Hypoglycaemia (sometimes life-threatening) may occur as a result of the blood-glucose-lowering action of AMARYL. This happens when there is an imbalance between AMARYL dosage, carbohydrate intake (diet), physical exercise and other factors influencing metabolism.

Possible symptoms of hypoglycaemia 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 dysrhythmias.

The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke.

The symptoms of hypoglycaemia may persist if hypoglycaemia is corrected.

Eye disorders:

Common: 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 disorders:

Common: nausea or diarrhoea

Uncommon: vomiting, sensations of pressure or fullness in the epigastrium or abdominal pain

Hepato-biliary disorders:

Frequency unknown: hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice, which may progress to life-threatening liver failure

Blood and lymphatic system disorders:

Frequency unknown: potentially life-threatening changes in the blood picture may occur, such as thrombocytopenia and, in isolated cases, leucopenia, haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop

Local and systemic allergic reactions:

Common: rashes

Uncommon: itching or urticaria

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.

General disorders:

Frequency unknown: 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 hyperglycaemia, especially when beginning or after altering treatment, or when AMARYL is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.

Special precautions

Treatment with AMARYL must be initiated and monitored by a medical practitioner. The patient must take AMARYL at the times and in the doses prescribed by the medical practitioner, normally at the same time every day.

To achieve the goal of treatment of AMARYL; 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 AMARYL.

Clinical signs of still insufficiently lowered blood glucose (hyperglycaemia) 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 hypoglycaemia may be increased and necessitates especially careful monitoring.

Factors favouring hypoglycaemia include:

- Unwillingness or (more commonly in older patients) incapacity of the patient to co-operate.
- Combination therapy with other hypoglycaemic agents in patients 65 years or older.
- Undernourishment, irregular meal times, or skipped meals.

- Imbalance between physical exertion and carbohydrate intake.
- Alteration of diet.
- Consumption of alcohol, especially in combination with skipped meals.
- Impaired renal function.
- Severe impairment of liver function
- Overdosage with AMARYL.
- 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 cortico-adrenal insufficiency).
- Concurrent administration of certain other medicines (refer to INTERACTIONS).
- Treatment with AMARYL in the absence of any indication.

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 AMARYL 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 (refer to SIDE EFFECTS) 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 medicines.

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.

It is known from other sulphonylureas 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 medical practitioner and, in some circumstances, in-patient hospital care.

Insulin is the treatment of choice for non-insulin-dependent diabetes mellitus (NIDDM) with renal and hepatic dysfunction.

No experience has been gained concerning the use of AMARYL in patients with impairment of liver function. In patients with severe impairment of hepatic function, change-over to insulin is indicated, to achieve optimal metabolic control (refer to CONTRAINDICATIONS).

Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic anaemia. Since AMARYL belongs to the class of sulphonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

Important information about some of the excipients of AMARYL:

AMARYL contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Driving a vehicle or operating machinery:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Please refer to SPECIAL PRECAUTIONS and SIDE EFFECTS.

Treatment is symptomatic and supportive.

After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose/dextrose infusion in lower concentration so as to ensure that the hypoglycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, the danger of ongoing or recurring hypoglycaemia, may persist for several days.

IDENTIFICATION:

1 mg: Pink oblong tablets, biplanar with score-line on both sides

2 mg: Green oblong tablets, biplanar with score-line on both sides

3 mg: Pale yellow oblong tablets, biplanar with score-line on both sides

4 mg: Light blue oblong tablets, biplanar with score-line on both sides

PRESENTATION:

1 mg, 2 mg and 3 mg: 15 tablets in blister packs.

1 mg, 2 mg, 3 mg and 4 mg: 30 tablets in blister packs.

STORAGE INSTRUCTIONS:

Store below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

1 mg: 30/21.2/0060

2 mg: 30/21.2/0061

3 mg: 30/21.2/0062

4 mg: 30/21.2/0063

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd

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