PRODUCT INFORMATION

AMARYL

NAME OF THE MEDICINE

Amaryl

AUSTRALIAN APPROVED NAME

Glimepiride

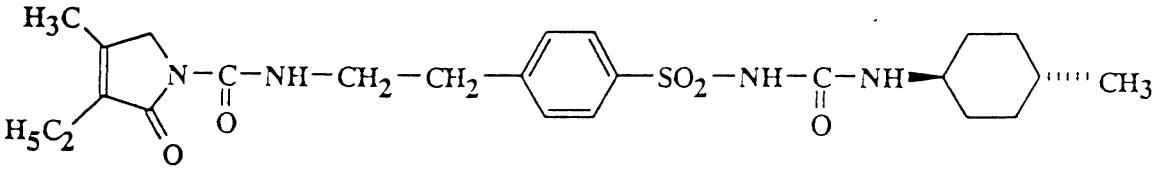
CHEMICAL STRUCTURE

Amaryl tablets contain glimepiride which is a member of the sulfonylurea group of oral antidiabetic agents.

Molecular Formula: $C_{24}H_{34}N_40_5S$

Molecular Weight: 491

Chemical Name: trans-1-{4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1 carboxamido) ethyl]-phenylsulfonyl}-3-(4-methylcyclohexyl) urea



CAS REGISTRY NUMBER

93479-97-1

DESCRIPTION

Glimepiride is a white odourless, crystalline powder, practically insoluble in methanol and water, slightly soluble in ethanol and sparingly soluble in methylene chloride.

Each Amaryl tablet contains glimepiride as active ingredient and the excipients: lactose monohydrate, sodium starch glycollate, povidone, microcrystalline cellulose and magnesium stearate. Additionally, each strength contains identifying pigment, viz: 1 mg tablet: iron oxide red; 2 mg tablet: iron oxide yellow and indigo carmine lake; 3 mg tablet: iron oxide yellow; 4 mg tablet: indigo carmine lake.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

Glimepiride 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. Glimepiride 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 (e.g. 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 hypoglycaemic action of a single dose of glimepiride persists for 24 hours.

Evidence from *in vitro* and animal studies suggests that there is lower glucagon secretion with glimepiride than glibenclamide and this may give rise to a prolonged reduction of blood glucose levels without increased plasma insulin levels. The clinical significance of these findings is yet to be clarified. A long-term, randomised, placebo-controlled clinical trial demonstrated that Amaryl therapy improves postprandial insulin/C-peptide responses and overall glycaemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels.

The efficacy of Amaryl is not affected by age, gender or weight. Amaryl 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 also in young and elderly (>65 years) patients. Intra-individual variability is low.

Absorption

Glimepiride is completely absorbed after oral administration. The peak serum concentration (C_{max}) is reached in about 2.5 hours. There is a linear relationship between dose and both C_{max} and

AUC (area under the plasma concentration-time curve). Food does not significantly affect the rate or extent of absorption of glimepiride.

Distribution

After intravenous dosing in normal subjects, the volume of distribution was 8.8 litres (113 mL/kg) and the total body clearance was 48 mL/min. Protein binding was greater than 99%.

Glimepiride is likely to be only minimally removed by haemodialysis due to its high protein binding.

Multiple-dose studies with glimepiride in diabetic patients demonstrated plasma concentration-time curves similar to single dose studies, indicating that there is no accumulation of drug in tissue depots.

Metabolism

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 patients with type 2 diabetes mellitus indicated that higher doses may be associated with a longer half-life.

Glimepiride is completely metabolised by oxidative biotransformation. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). *In vitro* studies indicate that 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 have not been fully elucidated due to low plasma levels. Its terminal elimination half life after an oral dose is about 5-6 hours.

Excretion

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

Renal Impairment

In a single-dose, open-label study conducted in 15 patients with renal impairment, glimepiride (3 mg) was administered to three groups of patients with different levels of mean creatinine clearance (CrCl); (Group I, CrCl = 77.7 mL/min, n=5), (Group II, CrCl = 27.4 mL/min, n=3), and (Group III, CrCl = 9.4 mL/min, n=7). Glimepiride was found to be well tolerated in all three groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{1/2}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Group I to III).

Results from a multiple-dose titration study conducted in 16 patients with renal impairment using doses ranging from 1-8 mg daily for 3 months were consistent with the results after a single dose. All patients with a CrCl < 22 mL/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggested that a starting dose of 1 mg Amaryl may be given to a patient with type 2 diabetes mellitus with renal disease, and the dose may be titrated based on fasting blood glucose levels (see **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION**).

It is not known if glimepiride is dialysable.

Hepatic Impairment

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

CLINICAL TRIALS

A placebo controlled study using fixed daily doses of 1 mg, 4 mg and 8 mg glimepiride found that all three doses were effective at reducing blood glucose levels. However, there was no significant difference in the reduction in fasting plasma glucose (FPG) between the 4 mg and 8 mg doses at any timepoint throughout the study.

In another placebo controlled dose-ranging study of glimepiride (1, 2, 3, 4, 6 and 8 mg/day), the majority of patients were controlled in the dose range of 1 to 4 mg daily. There was only a very small difference in the reduction in median FPG levels between the 4 mg and 8 mg doses (-3.08 mmol/L vs -3.16 mmol/L). The greatest change of -3.27 mmol/L was seen with the 2 mg dose. This supports the results of the aforementioned clinical study.

Two large multicentre studies involving approximately 1,900 patients were conducted to examine the dose-response effect of glimepiride on blood glucose and HbA_{1c} levels. In both these studies, a large proportion of patients achieved a FPG level below 8.32 mmol/L at the 1 mg/day dose, with a further 10% of patients achieving this level at the 2 mg/day dose. Some patients benefited by an increase in dose to 4 mg/day, but only a few patients - mainly those with very high baseline FPG levels - required higher doses. Based on the results of these studies, the WHO has set the defined daily dose (DDD) of glimepiride to be 2 mg.

An additional 161 patient, randomised, double blind crossover study, including four weeks active treatment each with 3 mg b.d. or 6 mg daily of glimepiride, indicated that some patients may have improved results when glimepiride is given twice daily. However, for the majority of patients, once daily dosing provided adequate control. It is important to note that the treatment period in this study was only 4 weeks and, as such, the long term safety benefit of twice daily dosing has not been established.

INDICATIONS

Amaryl is indicated as an adjunct to diet, exercise and weight loss, to lower the blood glucose in patients with non-insulin-dependent (type 2) diabetes mellitus.

CONTRAINDICATIONS

- Hypersensitivity to glimepiride, other sulfonylureas, other sulfonamides or any excipient.
- Severe impairment of renal function (CrCl <30 mL/min).
- Dialysis patients.
- Severe hepatic dysfunction.
- Pregnancy - see PRECAUTIONS, Use in Pregnancy.
- Lactation - see PRECAUTIONS, Use in Lactation.

Amaryl is not suitable for the treatment of insulin-dependent (type 1) diabetes mellitus (e.g. 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.

In patients with severe impairment of hepatic function, change-over to insulin is indicated to achieve optimal metabolic control.

PRECAUTIONS

Patients receiving glimepiride should be monitored with regular clinical and laboratory evaluations, including blood and urine glucose determinations, to determine the minimum effective dosage and to detect primary failure (inadequate lowering of blood glucose concentration at the maximum recommended dosage) or secondary failure (loss of control of blood glucose concentration following an initial period of effectiveness) to the drug. Glycosylated haemoglobin measurements may also be useful for monitoring the patient's response to glimepiride therapy.

Some improvement in glucose tolerance may take place after a few weeks of treatment with glimepiride. The clinical status should be checked within the first 4 to 8 weeks and at regular intervals thereafter to ascertain whether it is possible to reduce the dose.

The treatment of diabetes requires regular checks. 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.

In cases of unusual stress (e.g. trauma, emergency or elective surgery, febrile infection), blood glucose regulation may deteriorate and a temporary change to insulin may become necessary to maintain good metabolic control.

Amaryl tablets must not be used beyond the expiry date marked on the pack and must be stored out of the reach of children.

HYPOGLYCAEMIC REACTIONS

Hypoglycaemia is a potential risk from treatment with any sulfonylurea, particularly in the first month of treatment or when dosage is increased.

Debilitated patients, malnourished patients and patients with adrenal, pituitary, renal or hepatic insufficiency are particularly susceptible to the hypoglycaemic action of sulfonylureas and should therefore be carefully monitored. The dosage of glimepiride should be carefully adjusted in these patients.

Hepatic insufficiency may cause increased serum concentrations of glimepiride and may diminish gluconeogenic capacity, both of which increase the risk of severe hypoglycaemic reactions.

Alcohol ingestion, severe or prolonged exercise, deficient caloric intake or use of more than one antidiabetic agent may predispose patients to the development of hypoglycaemia.

If risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of glimepiride or the entire therapy. This also applies whenever illness occurs during therapy or the patient's lifestyle changes.

Hypoglycaemia may be difficult to recognise in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents.

Patients and responsible family members should be made aware of the signs and symptoms of hyperglycaemia (severe thirst, dry mouth, frequent micturition, dry skin) and hypoglycaemia (intense hunger, sweating, tremor, restlessness, irritability, depression, headache, disturbed sleep or transient neurological disorders) and the prompt action to be taken if either event should occur.

The potential for primary and secondary failure should also be explained.

Hypoglycaemia can almost always be promptly controlled by the intake of carbohydrates (glucose or sugar). It is known from other sulfonylureas that, despite initial successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation. Severe hypoglycaemia requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.

HAEMOLYTIC ANAEMIA

Treatment of patients with glucose-6-phosphate dehydrogenase (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.

USE IN PREGNANCY (CATEGORY C)

It is important to achieve strict normoglycaemia during pregnancy. Glimepiride must not be taken during pregnancy. Otherwise there is risk of harm to the child. The patient must change over to insulin during pregnancy. Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

The sulfonylureas may enter the foetal circulation and cause neonatal hypoglycaemia. In rats, dietary glimepiride at high doses (approx. 82 mg/kg) during gestation caused limb deformations. In rabbits, effects on pregnancy were characterised by increased incidences of abortions/total resorptions and malformations. Similar foetal wastage was not seen in rats although the finding of anophthalmia in a proportion of foetuses may be indicative of a treatment-related effect as eye malformations were found in the rabbit study. Adverse pregnancy outcomes in the rat and rabbit are probably due to the pharmacodynamic effects of glimepiride at excessive doses and are not substance-specific. Glimepiride had no recognisable effects on the rearing, physical development, functional and learning behaviour, memory or fertility of the progeny.

USE IN LACTATION

Studies in rats showed that glimepiride is excreted in milk. High doses caused hypoglycaemia in suckling young rats. Dietary administration of glimepiride (120-206 mg/kg) during lactation caused limb deformations in adolescent pups from day 4 of lactation onwards. To prevent possible ingestion of glimepiride with the breast milk and possible harm to the child, glimepiride must not be taken by breastfeeding women. Nursing mothers must either be changed over to insulin or cease breastfeeding.

PAEDIATRIC USE

The safety and efficacy of glimepiride in children have not been established. Glimepiride is not recommended for use in this age group.

CARCINOGENICITY / MUTAGENICITY

A standard battery of laboratory tests did not reveal any genotoxic or mutagenic potential for glimepiride. In a 2 year carcinogenicity study in mice receiving glimepiride in the diet up to 813 mg/kg/day, there was an increase in the incidence of pancreatic islet cell hyperplasia and islet cell adenomas; these are regarded to be the result of chronic stimulation of the pancreatic beta cells. In

a 30 month carcinogenicity study in rats receiving glimepiride in the diet up to 345 mg/kg/day, there was an increased incidence of pancreatic islet cell adenomas, however these were considered incidental as there was no dose relationship in either sex. There were no malignant tumours in rats or mice.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINERY

Alertness and reactions may be impaired due to hypo- or hyperglycaemia, 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.

INTERACTIONS WITH OTHER MEDICINES

Glimepiride is metabolised by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered with inducers, inhibitors or substrates of CYP2C9 (e.g. rifampicin, fluconazole, amiodarone, tolbutamide, diclofenac, ibuprofen, naproxen).

Based on experience with glimepiride and known interactions for other sulfonylureas, the following interactions must be considered.

In addition to insulin and other oral antidiabetic agents, drugs which may potentiate the hypoglycaemic action of glimepiride include:

ACE inhibitors, aminosalicylic acid, anabolic steroids and male sex hormones, azapropazone, chloramphenicol, clarithromycin, clofibrate, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluconazole, fluoxetine, guanethidine, ifosfamide, MAO-inhibitors, miconazole, oxpentifylline (high dose parenteral), oxyphenbutazone, para-aminosalicylic acid, phenylbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamide antibiotics, tetracyclines, tritoqualine, trofosfamide

Drugs which may attenuate the hypoglycaemic action of glimepiride include:

acetazolamide, barbiturates, calcium channel blockers, corticosteroids, diazoxide, diuretics, glucagon, isoniazid, laxatives (protracted use), nicotinic acid (high doses), oestrogens, phenothiazines, phenytoin, progestogens, rifampicin, adrenaline and other sympathomimetic agents, thyroid hormones

H_2 receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

Concomitant treatment with a beta-receptor blocker, clonidine, guanethidine or reserpine may mask the warning symptoms of a hypoglycaemic attack.

Acute and chronic alcohol intake may either potentiate or attenuate the activity of Amaryl in an unpredictable fashion.

The effect of coumarin derivatives may be potentiated or weakened.

ADVERSE EFFECTS

Amaryl is generally well tolerated. Clinical experience has shown that adverse reactions serious enough to compel discontinuation of therapy are uncommon, even during long-term treatment.

HYPOGLYCAEMIA

Hypoglycaemia is the greatest potential risk with all sulfonylureas. Based on what is known of other sulfonylureas, hypoglycaemia may be prolonged.

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, including 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 nearly always subside when hypoglycaemia is corrected.

VISUAL REACTIONS

Especially at the start of treatment, there may be temporary visual impairment (e.g. changes in accommodation and/or blurred vision) 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 (0.1 to 1% patients), gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur.

Dysgeusia, (taste disturbance or loss of taste) has been reported.

HAEMATOLOGIC REACTIONS

Changes in the blood picture may occur: thrombocytopaenia, leucopaenia, haemolytic anaemia, erythrocytopaenia, granulocytopaenia, agranulocytosis or pancytopaenia may develop. Cases of

severe thrombocytopaenia with platelet count less than 10,000/microlitre and thrombocytopaenic purpura have been reported in post-marketing experience (frequency not known). Anaemia, eosinophilia and aplastic anaemia have been reported with sulfonylureas.

DERMATOLOGIC REACTIONS

Allergic or pseudo-allergic skin reactions (e.g. itching, pruritus, erythema, urticaria, rashes, erythematous and maculo-papular and bullous skin eruptions or psoriasiform drug eruption) may occur in patients treated with sulfonylureas. If skin reactions persist, the drug should be discontinued. Mild reactions in the form of urticaria may develop into serious and even life-threatening reactions with dyspnoea and hypotension, sometimes progressing to shock. In the event of urticaria, a physician must be notified immediately. In isolated cases, a decrease in serum sodium concentration and allergic vasculitis or hypersensitivity of the skin to light may occur. Porphyria cutanea tarda and pellagra-like changes have been reported with sulfonylureas. It should be noted that cross reactivity exists between sulfonylureas and sulfonamides.

HEPATIC REACTIONS

In isolated cases, increased liver enzymes (AST, ALT), abnormal liver function, cholestasis, cholestatic hepatitis, granulomatous hepatitis, bilirubinaemia and liver failure have been reported with sulfonylureas. In isolated cases, there may be hepatitis, elevation of liver enzymes and/or cholestasis and jaundice which may progress to life-threatening liver failure but can regress after withdrawal of glimepiride.

ELECTROLYTE DISTURBANCE

In isolated cases, hyponatraemia has been reported in patients receiving glimepiride and other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatraemia or to increase release of antidiuretic hormone.

OTHER

Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Such mild reactions 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. Cases of alopecia and weight gain have also been reported.

DOSAGE AND ADMINISTRATION

In the management of type 2 diabetes mellitus, administration of an oral antidiabetic agent is not a substitute for appropriate dietary control.

In initiating treatment for type 2 diabetes mellitus, diet should be emphasised as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycaemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered. Use of Amaryl must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of Amaryl. During maintenance programs, Amaryl should be discontinued and insulin therapy initiated if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

The dosage of Amaryl must be the lowest which is sufficient to achieve the desired metabolic control. Dosage must be based on regular blood and urine glucose determinations, and must be carefully individualised to obtain optimum therapeutic effect. Periodic measurement of glycosylated haemoglobin is also recommended to monitor the patient's response to treatment. If appropriate glimepiride dosage regimens are not followed, hypoglycaemia may be precipitated.

Measures for dealing with errors in dosage such as forgetting to take a dose, skipping a meal or inability to take a dose at the prescribed time should be discussed with the patient at the time of initiating therapy. A missed dose must never be corrected by subsequently taking a larger dose.

Short term administration of Amaryl may be sufficient during periods of transient loss of metabolic control in patients usually well controlled on diet.

Food does not alter the bioavailability or other pharmacokinetic parameters of glimepiride.

INITIAL DOSE AND DOSE TITRATION

The initial dose of Amaryl is one 1 mg tablet once daily. The tablet should be swallowed whole without chewing with adequate liquid (e.g. half a glass of water) immediately before breakfast. Patients who eat only a light breakfast should defer the first dose of the day until the first main meal of the day (e.g. lunch). It is very important that meals are not skipped after the tablet has been taken.

If good metabolic control is achieved within the first week of treatment (as determined by blood and urine glucose), continue the daily dose of one 1 mg tablet as maintenance therapy.

If metabolic control is unsatisfactory after 1 - 2 weeks of treatment, increase the daily dose in increments of 1 mg at 1 to 2 week intervals, until satisfactory metabolic control is achieved. Most patients will achieve optimum control at doses of 1 mg to 4 mg once daily. Only in exceptional cases will doses of more than 4 mg glimepiride per day give better results. Normally, a single daily dose will maintain good blood glucose control for 24 hours.

SECONDARY DOSAGE ADJUSTMENT

Amaryl requirements may fall as treatment proceeds because an improvement in diabetes control results in greater insulin sensitivity. To avoid hypoglycaemia, timely dose reduction or cessation of therapy should be considered.

Correction of Amaryl dosage must also be considered whenever the patient's weight or life-style changes or other factors arise which affect glycaemic control.

Secondary failures should be treated by discontinuing Amaryl and starting insulin.

CHANGEOVER FROM OTHER ANTIDIABETIC AGENTS TO AMARYL

There is no exact dosage relationship between Amaryl and other oral antidiabetic agents. When transferring patients from another oral antidiabetic drug to Amaryl, it is recommended to begin with the usual starting dose of 1mg once daily. This recommendation applies even in cases where the patient is being switched from the maximum dose of another antidiabetic agent.

Depending on the pharmacokinetic and pharmacodynamic characteristics of the previous medication, a drug-free transition period may be necessary in order to avoid overlapping drug effects possibly resulting in hypoglycaemia.

RENAL IMPAIRMENT

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 (see **PHARMACOLOGY, Pharmacokinetics**, Renal insufficiency). In patients with mild (CrCl >50 mL/min) to moderate (CrCl 30-50 mL/min) renal impairment, a starting dose of 1 mg once daily must not be exceeded. The dose may then be carefully titrated upwards if necessary based on fasting blood glucose levels according to the protocol mentioned above (i.e. in increments of 1 mg at intervals of one to two weeks).

No experience has been gained in the use of Amaryl in dialysis patients. These patients should be changed over to insulin therapy to achieve optimum metabolic control.

HEPATIC IMPAIRMENT

No experience has been gained in the use of Amaryl in patients with severe hepatic impairment. These patients should be changed over to insulin therapy to achieve optimum metabolic control.

OVERDOSAGE

SIGNS AND SYMPTOMS

Accidental or intentional overdose may cause severe and prolonged hypoglycaemia which may be life-threatening.

MANAGEMENT

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

In case of overdosage with glimepiride, a doctor must be notified immediately. At the first signs of hypoglycaemia, the patient must immediately take sugar, preferably glucose, unless a doctor has already started care.

Since hypoglycaemia and its clinical symptoms may recur after apparent clinical recovery (even after several days), close and continued medical supervision and possibly referral to a hospital are indicated. In particular, significant overdosage and severe reactions, e.g. with unconsciousness or other neurological dysfunctions, are emergency cases and require immediate care and hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, intravenous infusion of a 20% glucose solution (adults: 40 to 100 mL) is indicated. Alternatively, IV, SC or IM administration of glucagon (adults: 0.5 to 1 mg) may be considered. In infants, glucose must be dosed very carefully and close monitoring of blood glucose is required to minimise the risk of potentially severe hyperglycaemia. Other symptomatic therapy (e.g. anticonvulsants) should be administered as necessary.

After acute glucose replacement has been completed, it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that 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, hypoglycaemia, or the danger of slipping back into hypoglycaemia, may persist for several days.

In cases of acute intake of large amounts of glimepiride, detoxification (e.g. by gastric lavage and administration of medicinal charcoal) is indicated.

PRESENTATION AND STORAGE CONDITIONS

Amaryl is available in blister packs of 10, 30◆, 50 and 100 tablets in the following strengths:

- 1.0mg: Pink, oblong, scored tablets debossed with “NMK” and the Hoechst logo on both sides.

- 2.0mg: Green, oblong, scored tablets debossed with “NMM” and the Hoechst logo on both sides.
- 3.0mg: Pale yellow, oblong, scored tablets debossed with “NMN” and the Hoechst logo on both sides.
- 4.0 mg: Light blue, oblong, scored tablets debossed with “NMO” and the Hoechst logo on both sides.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE ARTG

24 September 1996

DATE OF MOST RECENT AMENDMENT

25 August 2016

◆ Marketed pack