CPMP/343/96
EMEA/H/A/001/00/0/0

OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS PURSUANT TO ARTICLE 10 OF DIRECTIVE 75/319/EEC AS AMENDED

Medicinal product

Name:	AMARYL
International non-proprietary name:	Glimepiride
Strength:	1 mg
Pharmaceutical form:	Tablet
Route of administration:	Oral use
Package size:	30 or 120 tablets in blister packs of 10 tablets each

Basis for opinion

Hoechst Roussel B.V. submitted applications for Mutual Recognition of the marketing authorisation granted by The Netherlands for the above mentioned product in the framework of Article 9 of the Council Directive 75/319/EEC as amended.

The Reference Member State is The Netherlands.
Member States which have received and application for Mutual Recognition (concerned Member States) are: Austria, Greece, Italy, Portugal and Spain.

Member States, which have previously authorised the product under a national procedure, are Sweden and Denmark.

Member States having received an application under purely national procedure are Germany, Ireland, Belgium and France.

Finland issued a negative decision for granting a national marketing authorisation on 14 August 1995.

The concerned Members States have not been able to reach an agreement in respect of the mutual recognition of the marketing authorisation granted by the Reference Member State.

Detailed statements of the matters on which they have been unable to reach agreement and the reasons for their disagreement were submitted to the Agency on 21 December 1995 (letter from Austria), on 28 December 1995 (letter from Portugal) and are appended to this opinion.

The Netherlands, as Reference Member State, sent to all CPMP Members and the EMEA information on the Amaryl Mutual Recognition procedure on 28 December 1995, also appended to this opinion.

The matter was referred to the Committee on 18 January 1996.

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On the basis of the questions raised by Austria and Portugal, the points to be considered by the CPMP are:

1. Amaryl causes uterine adenocarcinomas in rats with an AUC which is less than 10-fold as compared to the AUCs in human therapeutic use. Until now, carcinogenicity has never been a problem in the long term clinical use of sulphonylurea derivatives, nor in the available toxicological studies. The relevance of this finding for man should be discussed in depth.

2. Glycemic control with Amaryl, as measured by HBA1c and fasting blood glucose levels, seems to be inferior as compared to glibenclamide (studies B19 and B21).

3. In view of the possible carcinogenic potential and the less effective glycemic control the benefit/risk ratio for Amaryl is considered to be negative.

Written explanation was provided by the company on 29 February 1996.

Opinion

The Committee, having considered the points of disagreement and the responses provided by the company as stated in the appended arbitration assessment report, is of the opinion that the objections raised by Austria and Portugal should not prevent the granting of a marketing authorisation and that the Summary of Product Characteristics of the Reference Member State should be amended as stated in Annex I. The amended Summary of Product Characteristics of the Reference Member State is included in Annex II.

The present opinion is forwarded to the Commission, to Member States and to the company together with the arbitration assessment report stating the reasons for its conclusions, its annexes and appendices.

London, 17 April 1996

Prof. J.-M. Alexandre
Chairman, on behalf of the Committee

ANNEX I

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Amendments to the Summary of Product Characteristics of the Reference Member State as agreed by the Committee.

The paragraph Posology and method of administration should include the following mention (in bold italic):

In some cases, *especially antidiabetics with a long half life (e.g. chlorpropamide*), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect.

The paragraph Preclinical safety data should be replaced as follow:

In subchronic and chronic toxicity studies in rats, mice and dogs, a decline in serum glucose as well as a degranulation of the beta cells of the pancreas were noted; these were shown to be, in principle, reversible and are regarded as signs of the pharmacodynamic effect.

In a chronic toxicity study in dogs, two of the animals receiving the highest dose (320 mg/kg body weight) developed cataract. In vitro studies in the bovine lens and investigations in rats demonstrated no cataractogenic or co-cataractogenic potential.

Glimepiride did not show any mutagenic or genotoxic effects.

Glimepiride caused a slight increased incidence of uterine adenocarcinomas in rats at a dose level of 345 mg/kg/day. The safety factors based on a comparison of systemic exposure (AUC values) of female rats and humans are high enough (about 20 times) to exclude a risk to patients at the proposed clinical doses.

In mice, there was an increased incidence if islet cell hyperplasia and of islet cell adenomas; these are regarded as resulting from the chronic stimulation of the beta cells.

Administration to rats revealed no effects of fertility, course of pregnancy or delivery. Malformation (e.g. eye malformations, fissures and bone anomalies) occurred in rats and rabbits, and – in rabbits only – the numbers of abortions and intrauterine deaths were increased.

ANNEX II

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS
(1mg Tablet as a relevant example)

1. NAME OF THE MEDICINAL PRODUCT

Amaryl

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amaryl contains as active ingredient the sulfonylurea glimepiride (INN). Tablets of 1 mg glimepiride are available.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amaryl is indicated for type II diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

4.2 Posology and method of administration

The basis for successful treatment of diabetes is a good diet, regular physical activity, as well as routine checks of blood and urine. Tablets or insulin can not compensate if the patient does not keep to the recommended diet.

Dosage is determined by the results of blood and urinary glucose determinations.

The starting dose is 1 mg glimepiride per day. If good control is achieved this dosage should be used for maintenance therapy.

If control is unsatisfactory the dosage should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1-2 weeks between each step, to 2, 3 or 4 mg glimepiride per day.
A dosage of more than 4 mg glimepiride per day gives better results only in exceptional cases.
The maximum recommended dose is 6 mg glimepiride per day.

Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or - if none is taken - shortly before or during the first main meal.
If a dose is forgotten, this should not be corrected by increasing the next dose.
Tablets should be swallowed whole with some liquid.

If a patient has a hypoglycaemic reaction on 1 mg glimepiride daily, this indicates that they can be controlled by diet alone.

In the course of treatment, as an improvement in control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycaemia timely dose reduction or cessation of therapy must therefore be considered. Change in dosage may also be necessary, if there are changes in weight or life style of the patient, or other factors that increase the risk of hypo-or hyperglycaemia.

Switch over from other oral hypoglyaemic agents to Amaryl:
A switch over from other oral hypoglycaemic agents to Amaryl can generally be done. For the switch over to Amaryl the strength and the half life of the previous medication has to be taken into account. In some cases, especially antidiabetics with a long half life (e.g. chlorpropamide), a wash out period of

a few days is advisable in order to minimize the risk of hypoglycaemic reactions due to the additive effect. The recommended starting dose is 1 mg glimepiride per day.
Based on the response the glimepiride dosage may be increased stepwise, as indicated earlier.

Switch over from Insulin to Amaryl:
In exceptional cases, where type II diabetic patients are regulated on insulin, a changeover to Amaryl may be indicated.
The changeover should generally be undertaken in a hospital.

4.3 Contra-indications

Amaryl should not be used in the following cases: insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders, hypersensitivity to glimepiride, other sulfonylureas or sulfonamides or excipients in the tablet.
In case of severe renal or hepatic function disorders, a change over to insulin is required.
Amaryl is contra-indicated in pregnancy and lactation.

4.4 Special warnings and special precautions for use

Amaryl must be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with Amaryl may lead to hypoglycemia. Possible symptoms of hypoglycemia include: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, 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 hypoglycaemic attack may resemble that of a stroke.
Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect.
It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur.
Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, require immediate medical treatment and occasionally hospitalization.

Factors favouring hypoglycaemia include:
- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate
- undernutrition, irregular mealtimes or missed meals or periods of fasting
- alterations in diet
- imbalance between physicial exertion and carbohydrate intake
- consumption of alcohol, especially in combination with skipped meals
- impaired renal function
- serious liver dysfunction
- overdosage with Amaryl
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counterregulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency)
- concurrent administration of certain other medicines (see Interactions)

Treatment with Amaryl requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of haemoglobin A1 and possibly of fructosamine is recommended.

Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with Amaryl.

In stress-situations (e.g. accidents, acute operations, infections with fever, etc.) a temporary switch to insulin may be indicated.

No experience has been gained concerning the use of Amaryl in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated.

4.5 Interaction with other medicinal products and other forms of interaction

If Amaryl is taken simultaneously with certain other medicines, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicines should only be taken with the knowledge (or at the prescription) of the doctor.
Based on the experience with Amaryl and with other sulphonylurea the following interactions have to be mentioned.

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:

phenylbutazone,azapropazon and oxyfenbutazone
insulin and oral antidiabetic products
metformin
salicylates and p-amino-salicylic acid
anabolic steroids and male sex hormones
chloramphenicol
coumarin anticoagulants
fenfluramine
fibrates
ACE inhibitors
fluoxetine
allopurinol
sympatholytics
cyclo-, tro-and iphosphamides
sulphinpyrazone
certain long acting sulphonamides
tetracyclines
MAO-inhibitors
quinolone antibiotics
probenecide
miconazol
pentoxyfylline (high dose parenteral)
tritoqualine

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:

oestrogens and progestagens,
saluretics, thiazide diuretics,
thyroid stimulating agents, glucocorticoids,
fenothiazine derivates, chlorpromazine,
adrenaline and sympathicomimetics,
nicotinic acid (high dosages) and nicotinic acid derivatives,
laxatives (long term use),
phenytoin, diazoxide,
glucagon, barbiturates and rifampicin.
acetozolamide

H2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.
Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion.

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.

4.6 Use during pregnancy and lactation

Amaryl is contra-indicated during pregnancy. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

In reproduction toxicity studies embryotoxicity, teratogenicity and development toxicity occurred. All reproduction toxicity effects are probably due to pharmacodynamic effects of extremely high doses and these are not substance-specific.

Because sulfonylurea-derivatives like glimepiride pass into the breast milk, Amaryl must not be taken by breast-feeding women.

4.7 Effects on ability to drive and use machines

Alertness and reaction time 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.

4.8 Undesirable effects

Based on experience with Amaryl and with other sulphonylureas the following side effects have to be mentioned.

Hypoglycaemia:
In rare cases hypoglycemic reactions have been observed after administration of Amaryl. These reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycaemic therapies, on individual factors such as dietary habits and the dosage (see further under "Special warnings and special precautions for use").

Eyes:
Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Gastro-intestinal:
Gastro-intestinal complaints like nausea, vomiting and diarrhoea, pressure or a feeling of fullness in the stomach and abdominal pain are very rare and seldom lead to discontinuation of therapy.
In isolated cases increase in liver enzyme values have been reported during treatment with sulphonylureas and also worsening of liver function with cholestasis, icterus and hepatitis. The symptoms generally disappear upon discontinuation of therapy, but severe hepatitis may progress to liver insufficiency.

Allergy:
Hypersensitivity reactions of the skin may occur as itching, rash and urticaria. In isolated cases mild reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. In isolated cases hypersensitivity to light may occur. Allergic vasculitis is possible in isolated cases.
Crossallergenicity with sulphonylureas, sulphonamides or related substances is possible.

Haematology:
Changes in haematology are rare during Amaryl treatment. Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, agranulocytopenia, agranulocytosis, haemolytic anemia and pancytopenia may occur.
These are in general reversible upon discontinuation of medication.

Various:
A decrease in the sodium serum concentrations may occur.

In placebo - controlled studies upper respiratory tract infections were more frequent with glimepiride (14.2%) than with placebo (7.8%). This was in no case considered treatment related by the investigator. Incidence of upper respiratory tract infections was similar between glimepiride (4.6%) and glibenclamide (4.2%).

4.9 Overdose

After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, coordination problems, sleepiness, coma and convulsions.

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbant) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In particular when treating hypoglycaemia due to accidental intake of Amaryl in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent diabetes mellitus.

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.
As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.

Insulin release:

Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results - by opening of calcium channels - in an increased influx of calcium into the cell.
This leads to insulin release through exocytosis.
Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulfonylurea binding site.

Extrapancreatic activity:

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.
The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.
Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.

Glimepiride inhibitis the glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which in its turn inhibits the gluconeogenesis.

General

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride.

There was no significant difference in effect regardless of whether the drug was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose.

Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total drug effect.

5.2 Pharmacokinetic properties

The absolute bioavailability of glimepiride is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C_{max}) are reached approx 2.5 hours after oral intake (mean 0,3 mg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve). Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (> 99%), and a low clearance (approx 48 ml/min). Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioacitivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites - most probably resulting from hepatic metabolism - were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmaco-kinetics, and the intraindividual variability was very low. There was no relevant cumulation.

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, 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 no additional risk of cumulation is to be assumed in such patients.
Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

In animals, glimepiride is excreted in milk.
Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

5.3 Preclinical safety data

In subchronic and chronic toxicity studies in rats, mice and dogs, a decline in serum glucose as well as a degranulation of the beta cells of the pancreas were noted; these were shown to be, in principle, reversible and are regarded as signs of the pharmacodynamic effect.

In a chronic toxicity study in dogs, two of the animals receiving the highest dose (320 mg/kg body weight) developed cataract. In vitro studies in the bovine lens and investigations in rats demonstrated no cataractogenic or co-cataractogenic potential.

Glimepiride did not show any mutagenic or genotoxic effects.

Glimepiride caused a slight increased incidence of uterine adenocarcinomas in rats at a dose level of 345 mg/kg/day. The safety factors based on a comparison of systemic exposure (AUC values) of female rats and humans are high enough (about 20 times) to exclude a risk to patients at the proposed clinical doses.

In mice, there was an increased incidence of islet cell hyperplasia and of islet cell adenomas; these are regarded as resulting from the chronic stimulation of the beta cells.

Administration to rats revealed no effects on fertility, course of pregnancy or delivery. Malformations (e.g. eye malformations, fissures and bone anomalies) occurred in rats and rabbits, and - in rabbits only - the numbers of abortions and intrauterine deaths were increased.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, sodium-starch-glycolate, magnesiun stearate, cellulose and polyvidon 25000.
Further as colouring agents in Amaryl 1 mg red iron oxyde (E172).

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

The stability date is indicated on the package with "Not to be used after ..." or "Exp...". The shelf life of Amaryl is 3 years.

6.4 Special precautions for storage

Store in a dry place at room temperature (15-25 °C) and keep out of reach of children.

6.5 Nature and contents of container

30 and 120 tablets Amaryl (in blister packs of 10 tablets each).

The tablets are oblong and scored on both sides. The Amaryl 1,0 tablets are 8x4 mm.
Amaryl 1 mg is pink.

6.6 Instructions for use, handling and disposal

No special information

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF TEXT

ANNEX III

OVERALL SCIENTIFIC SUMMARY

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF AMARYL

1. Safety issue in relation to uterine adenocarcinomas in rats

Glimepiride caused a slightly higher incidence (14%)of uterine adenocarcinomas in female rats at a level of 345 mg/kg/day than in those treated with lower doses (2-6%)
Glimepiride did not show any genotoxic effects *in vitro* assays or *in vivo* tests and did not cause increased incidence of uterine adenocarcinoma in the mouse carcinogenicity study. Mortality of animals, location of uterine tumours and histological characteristics were similar in treated group compared to control groups. All these facts provided strong evidence that the uterine tumours were not related to the treatment with glimepiride. In addition the safety margins based on a comparison of systemic exposure (AUC values) of female rats and humans were considered high enough (at least 20 times) to give an adequate assurance of the safety for glimepiride treatment in humans at the proposed clinical doses.

Moreover, since glimepiride did not increase serum oestradiol levels, the uterine tumour incidence after high dose of glimepiride appeared not due to a disturbance in oestrogen metabolism, an acceptede mechanism in the uterine tumour of humans.

All these data supported that glimepiride at doses up to 6 to 8 mg does not pose any safety problems for humans.

2. Efficacy issue s in relation to glycaemic control

Two large randomised double-blind studies were performed comparing glimepiride and glibenclamide. Efficacy was measured by HbA1c, blood glucose levels (fasting and post prandial), insulin and C-peptide levels. With respect to metabolic control, the therapeutic equivalence between both treatments was demonstrated.

Benefit/risk ratio

It was concluded that the carcinogenic potential of glimepiride found in female rats at high doses poses no safety concerns for humans and that therapeutic equivalence to glibenclamide exists.