IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0711/080/004
Case No: 2029953

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Glepid 4 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **12/03/2007** until **01/02/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glepid 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg glimepiride

For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
A light blue, flat, oblong, scored tablet encoded G breakline 4 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Glimepiride is indicated for type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

4.2 Posology and method of administration

For oral administration.

For the different dosage regimens appropriate strengths are available.

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 cannot 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 to 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.

In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, glimepiride therapy is started at a low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated. While maintaining the glimepiride dose, insulin therapy is started at low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

Methods of administration
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. Tablets should be swallowed whole with some liquid.

If a dose is forgotten, this should not be corrected by increasing the next dose.

If a patient has a hypoglycaemic reaction on 1 mg glimepiride daily, this indicates that the patient 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 hypoglycaemic agents to glimepiride
A switch over from other oral hypoglycaemic agents to glimepiride can generally be done. For the switch over to glimepiride the strength and the half-life of the previous medication has to be taken into account. In some cases, especially in anti-diabetics 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 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 glimepiride
In exceptional cases, where type 2 diabetic patients are regulated on insulin, a change-over to glimepiride may be indicated.

The change-over should be undertaken under close medical supervision.

Renal and hepatic insufficiency
See section 4.3.

Children
There is insufficient data of the efficacy and safety of glimepiride.

4.3 Contraindications

- Hypersensitivity to glimepiride, other sulphonylureas or sulphonamides or to any of the excipients
- Insulin dependent diabetes
- Diabetic coma
- Ketoacidosis
- Severe renal or hepatic function disorders

In case of severe renal or hepatic function disorders, a change over to insulin is required.

4.4 Special warnings and precautions for use

Glimepiride must be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with glimepiride may lead to hypoglycaemia. Possible symptoms of hypoglycaemia 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 sulphonylureas 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 hospitalisation.

Factors favouring hypoglycaemia include:
- Unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- Under-nutrition, irregular mealtimes or missed meals or periods of fasting
- Alterations in diet
- Imbalance between physical exertion and carbohydrate intake
- Consumption of alcohol, especially in combination with skipped meals
- Impaired renal function
- Serious liver dysfunction
- Overdose with glimepiride
- 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 adrenocortical insufficiency)
- Concurrent administration of certain other medicines (see section 4.5).

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. In elderly the first signs of low or high glucose levels in blood are not easily seen or do not occur at all. In addition determination of the proportion of glycosylated haemoglobin is recommended.

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

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 glimepiride 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g rifampicin) or inhibitors (e.g fluconazole).

Results from an in vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with glimepiride and with other sulphonylureas 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 medicinal products is taken, for example:

- Phenylbutazone, azapropazon and oxyfenbutazone
- Sulphinpyrazone
- Insulin and oral anti-diabetic products
- Certain long acting sulphonamides
- Metformin
- Tetracyclines
- Salicylates and p-amino-salicylic acid
- MAO-inhibitors
- Anabolic steroids and male sex hormones
- Quinolone antibiotics
- Chloramphenicol
- Probenecid
- Coumarin anticoagulants
- Miconazol
- Fenfluramine
- Pentoxifylline (high dose parenteral)
- Fibrates
- Tritoqualine
- Fluconazole
- ACE inhibitors
- Fluoxetine
- Allopurinol
- Sympatholytics
- Cyclo-, tro- and iphosphamides

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

- Oestrogens and progestagens
- Saluretics, thiazide diuretics
- Thyroid stimulating agents, glucocorticoids
- Phenothiazine derivatives, chlorpromazine
- Adrenaline and sympathicomimetics
- Nicotinic acid (high dosages) and nicotinic acid derivatives
- Laxatives (long term use)

- Phenytoin, diazoxide
- Glucagon, barbiturates and rifampicin
- Acetozolamide.

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

Under the influence of sympatholytic medicinal products such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation 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 Pregnancy and lactation

Pregnancy
Risk related to the diabetes
Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

Risk related to glimepiride
There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of glimepiride (see section 5.3).

Consequently, glimepiride should not be used during the whole pregnancy.

In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Lactation
The excretion in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

4.7 Effects on ability to drive and use machines

Glimepiride has minor or moderate influence on the ability to drive and use machines.

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

4.8 Undesirable effects

Based on experience with glimepiride and with other sulphonylureas the following undesirable effects have to be mentioned.

	UNCOMMON (>1/1,000, <1/100)	RARE (>1/10,000, <1/1,000)	VERY RARE (<1/10,000, including isolated reports)
Immune system disorders*			Mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Allergic vasculitis
Blood and lymphatic system disorders		Moderate to severe thrombocytopenia Leucopenia Erythrocytopenia Granulocytopenia Agranulocytosis Haemolytic anaemia Pancytopenia**	
Metabolism and nutrition disorders		Hypoglycaemia***	
Eye disorders	Transient visual disturbances****		
Gastrointestinal disorders			Gastrointestinal complaints such as nausea, vomiting, diarrhoea, pressure or a feeling of fullness in the stomach and abdominal pain*****
Hepato-biliary disorders			Impairment of the liver function such as cholestasis, jaundice and hepatitis.******
Skin and subcutaneous tissue disorders	Hypersensitivity reactions of the skin such as itching, rash and urticaria		Photosensitivity
Investigations			Decreased sodium serum concentrations Elevation of liver enzymes may also occur

*Cross allergy with other sulphonylureas, sulphonamides or related substances is possible.

**These reactions are in general reversible upon discontinuation of medication.

***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 section 4.4).

****These disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

*****The gastrointestinal complaints lead seldom to discontinuation of therapy.

******This may progress to liver failure.

4.9 Overdose

After ingestion of an overdose 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.

Symptoms
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 given activated charcoal (adsorbent) 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) overdose hospitalisation 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 glimepiride 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

Pharmacotherapeutic group: Oral blood glucose lowering medicinal products: Sulfonamides, urea derivatives.
ATC code: A10B B12

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 sulphonylureas 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 extra-pancreatic effects also postulated for other sulphonylureas.

Insulin release
Sulphonylureas 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 sulphonylurea-binding site.

Extra-pancreatic activity
The extra-pancreatic 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 that may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells.

Glimepiride inhibits 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 medicinal product 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 effect of the medicinal product.

Combination therapy with metformin
Improve metabolic control for concomitant glimepiride therapy compared to metformin alone in patients not adequately controlled with the maximum dosage of metformin has been shown in one study.

Combination therapy with insulin
Data for combination therapy with insulin are limited. In patients not adequately controlled with the maximum dosage of glimepiride, concomitant insulin therapy can be initiated. In two studies, the combination achieved the same improvement in metabolic control as insulin alone; however, a lower average dose of insulin was required in combination therapy.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of glimepiride after oral administration 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 µg/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).

Distribution
Glimepiride has a 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. Glimepiride is expected to cross the placenta. Passage of the blood brain barrier is low.

Biotransformation and elimination
After a single dose of radiolabelled glimepiride, 58% of the radioactivity 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 pharmacokinetics, and the intra-individual variability was low. There was no relevant accumulation of the medicinal product.

Characteristics in patients
Pharmacokinetics was 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 was similar to those in healthy persons.

5.3 Preclinical safety data

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), adverse effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Povidone K25
Magnesium stearate
Indigotine lake (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Blister Al/PVC: 36 months
HDPE tablet containers and closures: 30 months

6.4 Special precautions for storage

Blister Al/PVC:
Do not store above 30°C. Store in the original package.

HDPE tablet containers and closures:
Do not store above 25°C. Store in the original tablet container.
Keep the tablet container tightly closed.

6.5 Nature and contents of container

Clear or white blister Al/PVC 20, 28, 30, 60, 90, 100, 112 and 120 tablets

Polyethylene containers and closures (tamper evident)
20, 30, 90, 100 and 120 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Bantry
Co Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/80/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3rd February 2006

10 DATE OF REVISION OF THE TEXT

March 2007