Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Glimepiride 1mg tablets
Glimepiride 2mg tablets
Glimepiride 3mg tablets
Glimepiride 4mg tablets

(glimepiride)

UK/H/1001/01-04/DC
UK licence numbers: PL 20117/0032-0035

Morningside Healthcare Limited

LAY SUMMARY

On 10th February 2009, the MHRA granted Morningside Healthcare Limited Marketing Authorisations (licences) for the medicinal products Glimepiride 1mg, 2mg, 3mg, and 4mg tablets. These are prescription-only medicines (POM).

Glimepiride is used in the treatment of non-insulin dependent (Type II) diabetes mellitus. You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Type II diabetes can sometimes be controlled by good diet, physical exercise and weight reduction alone, but where this is not possible, Glimepiride is used in addition.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Glimepiride 1mg, 2mg, 3mg, and 4mg tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	Glimepiride 1mg tablets Glimepiride 2mg tablets Glimepiride 3mg tablets Glimepiride 4mg tablets
Type of Application	Generic, Article 10.1
Active Substance	Glimepiride
Form	tablets
Strength	1mg, 2mg, 3mg, and 4mg
MA Holder	Morningside Healthcare Ltd 115 Narborough Road, Leicester, LE3 0PA United Kingdom
Reference Member State (RMS)	UK
Concerned Member State / s (CMS)	BG, CZ, HU, LT, PL, RO, and SK
Procedure Number	UK/H/1001/01-04/DC
Timetable	Day 210 – 19th December 2008

Module 2

Summary of Product Characteristics

Glimepiride 1mg tablets

1 NAME OF THE MEDICINAL PRODUCT

Glimepiride 1 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glimepiride 1 mg tablets:

1 tablet contains Glimepiride 1 mg.

Excipient

Lactose Monohydrate

Each tablet of Glimepiride 1 mg contains 71.08 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Glimepiride 1mg is a Pink coloured capsule shaped tablet with embossing “GM” & “1” with score line on one side and score line on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glimepiride is indicated for the treatment of 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

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 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 glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment 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.

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 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 antidiabetic medicines 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 changeover to glimepiride may be indicated.

The changeover should be undertaken under close medical supervision.

•Use in renal or hepatic impairment

See section 4.3 Contraindications.

Children and adolescents:

There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy (see sections 5.1 and 5.2).The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended.

4.3 Contraindications

Glimepiride should not be used in the following cases: insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders, hypersensitivity to glimepiride, other sulphonylureas or sulphonamides or excipients in the tablet.

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 favoring 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,

- overdosage 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 Interactions).

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. 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.

Treatment of patients with 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.

This product contains lactose monohydrate. 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 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.

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

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

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

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, azapropazone and oxyfenbutazone, sulphinpyrazone, insulin and oral antidiabetic 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, miconazole, fenfluramine, pentoxifylline (high dose parenteral), fibrates, tritoqualine, ACE inhibitors, fluconazole. 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 drugs 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, , acetazolamide.

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 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

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia 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 side effects have to be mentioned.

•Immune system disorders

In very rare cases mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Allergic vasculitis is possible in very rare cases.

Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible.

•Blood and lymphatic system disorders

Changes in haematology are rare during glimepiride treatment. Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur.

These are in general reversible upon discontinuation of medication.

•Metabolism and nutrition disorders

In rare cases hypoglycaemic reactions have been observed after administration of glimepiride. 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").

•Eye disorders

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

•Gastrointestinal disorders

Gastrointestinal 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.

•Hepato-biliary disorders

Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

•Skin and subcutaneous tissue disorders

Hypersensitivity reactions of the skin may occur as itching, rash and urticaria.

In very rare cases hypersensitivity to light may occur.

•Investigations

In very rare cases, a decrease in the sodium serum concentrations may occur.

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, co-ordination problems, sleepiness, coma and convulsions.

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with 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) overdosage 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 drugs: 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 extrapancreatic 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.

•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 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 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.

•Combination therapy with metformin

Improved 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.

Children and adolescents

An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.Both glimepiride and metformin exhibited a significant decrease from baseline in HbA1c (glimepiride-0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of noninferiority to metformin in mean change from baseline of HbA1c. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin. Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

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 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).

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

•Biotransformation and elimination: 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 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 (major enzyme is CYP2C9)- 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 intraindividual variability was very low. There was no relevant accumulation.

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 accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Children and adolescents

A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last) , Cmax and t1/2 similar to that previously observed in adults.

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
Sodium lauryl sulphate
Povidone
Sodium starch glycolate
Magnesium Stearate
Microcrystalline cellulose
Red Iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25oC.

6.5 Nature and contents of container

Blister Pack of PVC-PVDC / Aluminium foil containing 15 tablets and each carton containing 2 blisters.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

115 Narborough Road, Leicester, LE3 0PA

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/02/2009

10 DATE OF REVISION OF THE TEXT

11/02/2009

Glimepiride 2mg tablets

1 NAME OF THE MEDICINAL PRODUCT

Glimepiride 2 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glimepiride 2 mg tablets:

1 tablet contains Glimepiride 2 mg.

Excipient

Lactose Monohydrate

Each tablet of Glimepiride 2 mg contains 141.90 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Glimepiride 2mg is a pale green coloured capsule shaped tablet with embossing “GM” & “2” with score line on one side and score line on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glimepiride is indicated for the treatment of 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

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 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 glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment 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.

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 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 antidiabetic medicines 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 changeover to glimepiride may be indicated.

The changeover should be undertaken under close medical supervision.

•Use in renal or hepatic impairment

See section 4.3 Contraindications.

Children and adolescents:

There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy (see sections 5.1 and 5.2).The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended.

4.3 Contraindications

Glimepiride should not be used in the following cases: insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders, hypersensitivity to glimepiride, other sulphonylureas or sulphonamides or excipients in the tablet.

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 favoring 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,

- overdosage 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 Interactions).

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. 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.

Treatment of patients with 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.

This product contains lactose monohydrate. 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 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.

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

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

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

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, azapropazone and oxyfenbutazone, sulphinpyrazone, insulin and oral antidiabetic 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, miconazole, fenfluramine, pentoxifylline (high

dose parenteral), fibrates, tritoqualine, ACE inhibitors, fluconazole. 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 drugs 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, , acetazolamide.

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 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

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia 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 side effects have to be mentioned.

•Immune system disorders

In very rare cases mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Allergic vasculitis is possible in very rare cases.

Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible.

•Blood and lymphatic system disorders

Changes in haematology are rare during glimepiride treatment. Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur.

These are in general reversible upon discontinuation of medication.

•Metabolism and nutrition disorders

In rare cases hypoglycaemic reactions have been observed after administration of glimepiride. 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").

•Eye disorders

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

•Gastrointestinal disorders

Gastrointestinal 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.

•Hepato-biliary disorders

Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

•Skin and subcutaneous tissue disorders

Hypersensitivity reactions of the skin may occur as itching, rash and urticaria.

In very rare cases hypersensitivity to light may occur.

•Investigations

In very rare cases, a decrease in the sodium serum concentrations may occur.

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, co-ordination problems, sleepiness, coma and convulsions.

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with 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) overdosage 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 drugs: 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 extrapancreatic 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.

•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 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 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.

•Combination therapy with metformin

Improved 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.

Children and adolescents

An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.Both glimepiride and metformin exhibited a significant decrease from baseline in HbA1c (glimepiride-0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of noninferiority to metformin in mean change from baseline of HbA1c. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin. Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

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 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).

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

•**Biotransformation and elimination:** 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 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 (major enzyme is CYP2C9)- 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 intraindividual variability was very low. There was no relevant accumulation.

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 accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Children and adolescents

A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last) , Cmax and t1/2 similar to that previously observed in adults.

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
Sodium lauryl sulphate
Povidone
Sodium starch glycolate
Magnesium Stearate
Microcrystalline cellulose
Yellow Iron oxide E172
Indigo carmine aluminum lake E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25oC.

6.5 Nature and contents of container

Blister Pack of PVC-PVDC / Aluminium foil containing 15 tablets and each carton containing 2 blisters.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

115 Narborough Road, Leicester, LE3 0PA

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/02/2009

10 DATE OF REVISION OF THE TEXT

11/02/2009

Glimepiride 3mg tablets

1 NAME OF THE MEDICINAL PRODUCT

Glimepiride 3 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glimepiride 3 mg tablets:

1 tablet contains Glimepiride 3 mg.

Excipient

Lactose Monohydrate

Each tablet of Glimepiride 3 mg contains 141.10 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Glimepiride 3mg is a pale yellow coloured capsule shaped tablet with embossing “GM” & “3” with score line on one side and score line on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glimepiride is indicated for the treatment of 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

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 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 glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment 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.

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 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 antidiabetic medicines 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 changeover to glimepiride may be indicated.

The changeover should be undertaken under close medical supervision.

•Use in renal or hepatic impairment

See section 4.3 Contraindications.

Children and adolescents:

There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy (see sections 5.1 and 5.2).The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended.

4.3 Contraindications

Glimepiride should not be used in the following cases: insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders, hypersensitivity to glimepiride, other sulphonylureas or sulphonamides or excipients in the tablet.

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 favoring 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,

- overdosage 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 Interactions).

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. 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.

Treatment of patients with 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.

This product contains lactose monohydrate. 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 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.

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

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

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

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, azapropazone and oxyfenbutazone, sulphinpyrazone, insulin and oral antidiabetic 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, miconazole, fenfluramine, pentoxifylline (high

dose parenteral), fibrates, tritoqualine, ACE inhibitors, fluconazole. 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 drugs 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, , acetazolamide.

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 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

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia 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 side effects have to be mentioned.

•Immune system disorders

In very rare cases mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Allergic vasculitis is possible in very rare cases.

Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible.

•Blood and lymphatic system disorders

Changes in haematology are rare during glimepiride treatment. Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur.

These are in general reversible upon discontinuation of medication.

•Metabolism and nutrition disorders

In rare cases hypoglycaemic reactions have been observed after administration of glimepiride. 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").

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

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Gastrointestinal 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.

•Hepato-biliary disorders

Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

•Skin and subcutaneous tissue disorders

Hypersensitivity reactions of the skin may occur as itching, rash and urticaria.

In very rare cases hypersensitivity to light may occur.

•Investigations

In very rare cases, a decrease in the sodium serum concentrations may occur.

4.9 Overdose

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Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with 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) overdosage 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

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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.

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

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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 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).

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

•**Biotransformation and elimination:** 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 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 (major enzyme is CYP2C9)- 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 intraindividual variability was very low. There was no relevant accumulation.

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 accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Children and adolescents

A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last) , Cmax and t1/2 similar to that previously observed in adults.

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
Sodium lauryl sulphate
Povidone
Sodium starch glycolate
Magnesium Stearate
Microcrystalline cellulose
Yellow Iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25oC.

6.5 Nature and contents of container

Blister Pack of PVC-PVDC / Aluminium foil containing 15 tablets and each carton containing 2 blisters.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

115 Narborough Road, Leicester, LE3 0PA

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/02/2009

10 DATE OF REVISION OF THE TEXT

11/02/2009

Glimepiride 4mg tablets

1 NAME OF THE MEDICINAL PRODUCT

Glimepiride 4 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glimepiride 4 mg tablets:

1 tablet contains Glimepiride 4 mg.

Excipient

Lactose Monohydrate

Each tablet of Glimepiride 4 mg contains 140.00 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Glimepiride 4mg is a light blue coloured capsule shaped tablet with embossing “GM” & “4” with score line on one side and score line on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glimepiride is indicated for the treatment of 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

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 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 glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment 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.

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 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 antidiabetic medicines 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 changeover to glimepiride may be indicated.

The changeover should be undertaken under close medical supervision.

•Use in renal or hepatic impairment

See section 4.3 Contraindications.

Children and adolescents:

There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy (see sections 5.1 and 5.2).The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended.

4.3 Contraindications

Glimepiride should not be used in the following cases: insulin dependent diabetes, diabetic coma, ketoacidosis, severe renal or hepatic function disorders, hypersensitivity to glimepiride, other sulphonylureas or sulphonamides or excipients in the tablet.

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 favoring 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,

- overdosage 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 Interactions).

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. 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.

Treatment of patients with 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.

This product contains lactose monohydrate. 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 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.

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

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

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

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, azapropazone and oxyfenbutazone, sulphinpyrazone, insulin and oral antidiabetic 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, miconazole, fenfluramine, pentoxifylline (high

dose parenteral), fibrates, tritoqualine, ACE inhibitors, fluconazole. 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 drugs 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, , acetazolamide.

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 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

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia 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 side effects have to be mentioned.

•Immune system disorders

In very rare cases mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock. Allergic vasculitis is possible in very rare cases.

Cross allergenicity with sulphonylureas, sulphonamides or related substances is possible.

•Blood and lymphatic system disorders

Changes in haematology are rare during glimepiride treatment. Moderate to severe thrombocytopenia, leucopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur.

These are in general reversible upon discontinuation of medication.

•Metabolism and nutrition disorders

In rare cases hypoglycaemic reactions have been observed after administration of glimepiride. 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").

•Eye disorders

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

•Gastrointestinal disorders

Gastrointestinal 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.

•Hepato-biliary disorders

Elevation of liver enzymes may occur. In very rare cases, impairment of liver function (e.g. with cholestasis and jaundice) may develop, as well as hepatitis which may progress to liver failure.

•Skin and subcutaneous tissue disorders

Hypersensitivity reactions of the skin may occur as itching, rash and urticaria.

In very rare cases hypersensitivity to light may occur.

•Investigations

In very rare cases, a decrease in the sodium serum concentrations may occur.

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, co-ordination problems, sleepiness, coma and convulsions.

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with 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) overdosage 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 drugs: 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 extrapancreatic 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.

•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 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 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.

•Combination therapy with metformin

Improved 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.

Children and adolescents

An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.Both glimepiride and metformin exhibited a significant decrease from baseline in HbA1c (glimepiride-0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of noninferiority to metformin in mean change from baseline of HbA1c. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin. Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.

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 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).

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

•**Biotransformation and elimination:** 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 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 (major enzyme is CYP2C9)- 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 intraindividual variability was very low. There was no relevant accumulation.

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 accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Children and adolescents

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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
Sodium lauryl sulphate
Povidone
Sodium starch glycolate
Magnesium Stearate
Microcrystalline cellulose
Indigo carmine aluminum lake E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25oC.

6.5 Nature and contents of container

Blister Pack of PVC-PVDC / Aluminium foil containing 15 tablets and each carton containing 2 blisters.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

115 Narborough Road, Leicester, LE3 0PA

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

11/02/2009

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Glimepiride 1 mg/2 mg/3 mg/4 mg Tablets

(Glimepiride)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT GLIMEPIRIDE IS AND WHAT IT IS USED FOR

Glimepiride is one of a group of medicines called oral hypoglycaemics, which are used for treatment of diabetes (a disease where the body does not produce enough insulin to control the level of blood sugar). Oral hypoglycaemics help control blood sugar level.

The active ingredient in your glimepiride tablets is Glimepiride.

Glimepiride is used in the treatment of non-insulin dependent (Type II) diabetes mellitus. You get diabetes if your pancreas does not make enough insulin to control the level of glucose in your blood. Type II diabetes can sometimes be controlled by good diet, physical exercise and weight reduction alone, but where this is not possible, Glimepiride is used in addition.

2. BEFORE YOU TAKE.

Do not take Glimepiride:

- If you are allergic (hypersensitive) to Glimepiride or any of the other ingredients of Glimepiride tablets.
- If you have insulin dependent (Type I) diabetes.
- If you have severe liver or kidney problems.
- If you had any problems with taking medicines in the past, especially medicines to treat high blood sugar content, sulphonamide antibiotics.
- If you have ketoacidosis (symptoms include slow, deep breath with a fruity odour, confusion, frequent urination, poor appetite).

Do not give this medicine to anyone in a diabetic coma.

Take special care with Glimepiride:

Treatment with glimepiride may lead to low blood sugar (hypoglycaemia).

Factors that increase the risk of low blood sugar:

- If you miss or delay meals or change your diet.
- If you do a different type of, more intense or longer physical exercise.
- If you are recovering from an injury.
- If you are planning an operation or dental surgery.
- If you are recovering from other illness.
- consumption of alcohol
- liver or kidney problems
- taking too much glimepiride
- certain thyroid problems and other hormonal problems

Signs of too little sugar in your blood (hypoglycaemia):

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, sweating, clammy skin, anxiety, tachycardia (fast heart beat), hypertension (raised blood pressure), palpitations strong (irregular heart beat), angina pectoris (chest pain) and cardiac arrhythmias.

While taking glimepiride, there is need for regular monitoring of blood sugar, and for liver and blood tests.

During some situations (operations, serious accidents, or severe infections), it may be necessary for your doctor to switch you to Insulin treatment instead of glimepiride.

Glimepiride Tablets contain lactose and patients with lactose intolerance, galactosaemia or the glucose-galactose malabsorption syndrome should not take this medicine.

If you are allergic to sulphonamides e.g. co-trimoxazole or sulfadiazine, you may be also be allergic to glimepiride.

If you have been told you have G6PD deficiency, check with your doctor before taking this medicine

The information available on the use of glimepiride in people under 18 years of age is limited. Therefore, its use in these patients is not recommended

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines obtained without a prescription since these medicines can affect the action of Glimepiride.

Increased blood sugar lowering effects:

- other anti-diabetic medicines or insulin
- azapropazone or phenylbutazone for treating arthritis or gout
- aspirin for pain, inflammation or blood thinning
- nandrolone for osteoporosis or testosterone
- sulfamethoxazole, chloramphenicol, quinolone antibiotics (e.g. ciprofloxacin) or tetracycline antibiotics (e.g. oxytetracycline) for treating infections
- warfarin for blood thinning (blood thinning may also be affected)
- fenfluramine for reducing appetite
- fibrates for lowering cholesterol (e.g. fenofibrate)
- ACE inhibitors for high blood pressure (e.g. captopril)
- monoamine oxidase inhibitors or MAOIs (e.g. phenelzine or moclobemide) or fluoxetine for depression
- selegiline for Parkinson's disease
- allopurinol or sulfinpyrazone for preventing gout
- cyclophosphamide for leukaemia or arthritis
- sulfasalazine for arthritis
- probenecid for preventing kidney damage during treatment of HIV infection
- miconazole for athlete's foot
- fluconazole for fungal infections
- pentoxifylline for poor circulation
- tritoqualine for allergy or pruritus

Reduced blood sugar lowering effects:

- oestrogen and progestogen hormones as contained in contraceptives or hormone replacement therapy (HRT)
- thiazide diuretics (e.g. bendroflumethiazide)
- levothyroxine for underactive thyroid
- dexamethasone or prednisolone for inflammation or allergic reactions
- chlorpromazine for mental illness
- prochlorperazine for feeling or being sick
- adrenaline for allergic reactions or operations
- the decongestant pseudoephedrine
- nicotinic acid for correcting blood fats
- use of laxatives over a prolonged period
- phenobarbital or phenytoin for epilepsy
- diazoxide for high blood pressure
- glucagon for correcting low blood sugar levels (hypoglycaemia)
- rifampicin for tuberculosis and other infections
- acetazolamide for glaucoma

Altered blood sugar effects (up or down):

- indigestion or anti-ulcer treatments (e.g. ranitidine)
- beta-blockers (e.g. atenolol) and reserpine for high blood pressure
- clonidine for flushing or migraine
- consumption of alcohol

Glimepiride may increase or decrease the effect of medicines to stop your blood clotting (e.g. warfarin).

Other medicines

- fluconazole for fungal infections such as thrush may alter blood levels of glimepiride

Taking Glimepiride with food and drink
The tablets should be swallowed whole with liquid before or with the first meal of the day.
It is important to take regular meals at regular times of the day whilst taking treatment with these tablets. Skipping or taking irregular meals whilst taking Glimepiride Tablets may lead to hypoglycaemia. You are advised not to drink alcohol with this medicine. Discuss this with your doctor if you have any questions.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine.

Tell your doctor if you are pregnant or planning a family. Your doctor will probably change your treatment.

You should not take this medicine, if you are pregnant or become pregnant.

Remind your doctor if you are pregnant and diabetic as your blood glucose levels must be closely monitored.

You should not breast-feed your baby whilst taking Glimepiride Tablets.

Speak to your doctor if you have any concerns.

Driving and using machines
Glimepiride tablets may rarely cause temporary problems with your vision. Hypoglycaemia can make you feel sleepy. Make sure you are not affected before you drive or operate machinery.
This medicine may cause side-effects that make it hard to concentrate or slow down your reactions. The reason may be too little or too much sugar in your blood. Other effects may include vision problems, dizziness, helplessness, loss of self-control and being in dream-like state.

If you have a reduced or absent awareness of warning symptoms of too little blood sugar, you should check with your doctor before driving or operating machinery.

Important information about some of the ingredients of Glimepiride
This medicine contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE GLIMEPIRIDE TABLETS.

Always take Glimepiride tablets exactly as your doctor has told you. You should check with your doctor if you are not sure. The usual starting dose is 1 mg Glimepiride daily which may be gradually increased by 1 mg every one or two weeks, by your doctor until the right dose for you is found. The maximum dose is 6 mg daily. If the highest dose does not control your blood sugar levels your doctor may start you on insulin.
The tablets should usually be taken with a glass of water shortly before or during a substantial breakfast or during the first main meal. Do not chew the tablets but swallow them whole with some liquid.

If you take more Glimepiride than you should
If you take more Glimepiride than you should, tell your doctor at once, or go to the nearest hospital casualty department immediately. If an overdose has been taken there may be signs of hypoglycaemia. These could include headache, severe hunger, feeling and being sick, weariness, sleepiness, restlessness, aggression, poor concentration, reduced alertness, slowed reactions, depression, confusion, problems with speech and vision, shakiness, paralysis, problems with touch and hearing, dizziness, helplessness, loss of self-control, strange behaviour, fits, tiredness, coma, shallow breathing and slow heartbeat.

If you forget to take Glimepiride
If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one.
Do not take a double dose to make up for a forgotten tablet. Take the remaining doses at the correct time.

If you stop taking Glimepiride
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Glimepiride can cause side effects, although not everybody gets them.

Rare (occur in between 1 in 1000 and 1 in 10000 people):
Hypoglycaemia, (see above "before you take for symptoms of low blood sugar. It is important to know what symptoms to expect when hypoglycaemia (low blood sugar) occurs. Ask your doctor or pharmacist for more information if you are not sure how to recognise this. Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect.
Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, requires immediate medical treatment and occasionally hospitalisation.
Temporary visual problems may occur with changes in blood sugar.

Allergic skin reaction such as itching, rash or itchy rash may occur rarely: tell your doctor.

Rarely, an elevation of the liver enzymes (detected in blood test) or an impairment of the liver functions may occur. Tell your doctor if you notice yellowing of the skin or eyes.

Tell your doctor if you get a lot of infections with sore throats or mouth ulcers, if you bruise more easily while you are taking this medicine, or if you look pale. These could be due to changes in blood counts (your doctor will test for these).

Very rare (occur in less than 1 in 10000 people):
Oversensitivity of the skin to sunburn, low blood sodium levels (detected in blood test) or with symptoms of confusion, irritability, and fits, a fall in blood pressure, breathlessness, or collapse due to an allergic reaction, or severe worsening of liver function. Seek urgent medical attention in these situations.
Feeling or being sick, diarrhoea, bloating, stomach ache: tell your doctor if these are problematic.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE GLIMEPIRIDE TABLETS

- Keep out of the reach and sight of children
- Do not take the tablets after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Do not store the tablets above 25°
- Keep in their original blister pack

6. FURTHER INFORMATION

What Glimepiride tablet contains
The active substance is Glimepiride.
The other ingredients are lactose, sodium starch glycolate, povidone, sodium lauryl sulphate, magnesium stearate, microcrystalline cellulose, red iron oxide E172 (1mg tablets), yellow iron oxide E172 (2mg and 3mg tablets) and indigo carmine aluminium lake E132 (2 mg and 4mg tablets).

What Glimepiride tablets looks like and contents of the pack
Glimepiride 1mg tablets are Pink coloured capsule shaped tablet with embossing "GM" & "1" with score line on one side and score line on the other side.
Glimepiride 2mg tablets are Pale green coloured capsule shaped tablet with embossing "GM" & "2" with score line on one side and score line on the other side.
Glimepiride 3mg tablets are Pale yellow coloured capsule shaped tablet with embossing "GM" & "3" with score line on one side and score line on the other side.
Glimepiride 4mg tablets are Light blue coloured capsule shaped tablet with embossing "GM" & "4" with score line on one side and score line on the other side.

Pack size: Cartons containing 30 tablets in two blisters, each of 15 tablets.

Marketing Authorisation Holder and Manufacturer
Morningside Healthcare Ltd
115 Narborough Road, Leicester, LE3 0PA
United Kingdom

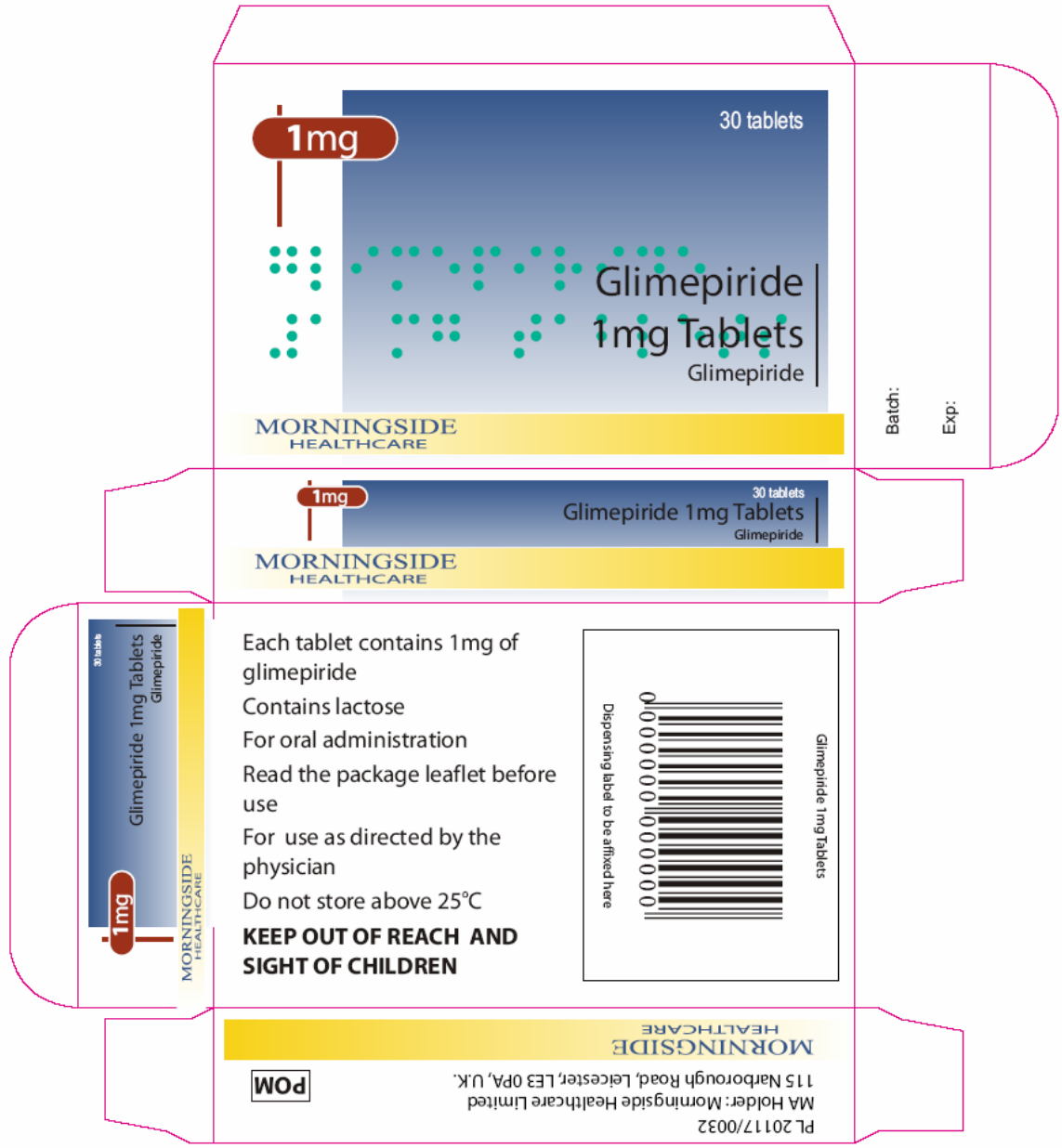
This leaflet was last updated in February 2009

Module 4

Labelling

Glimepiride 1mg tablets

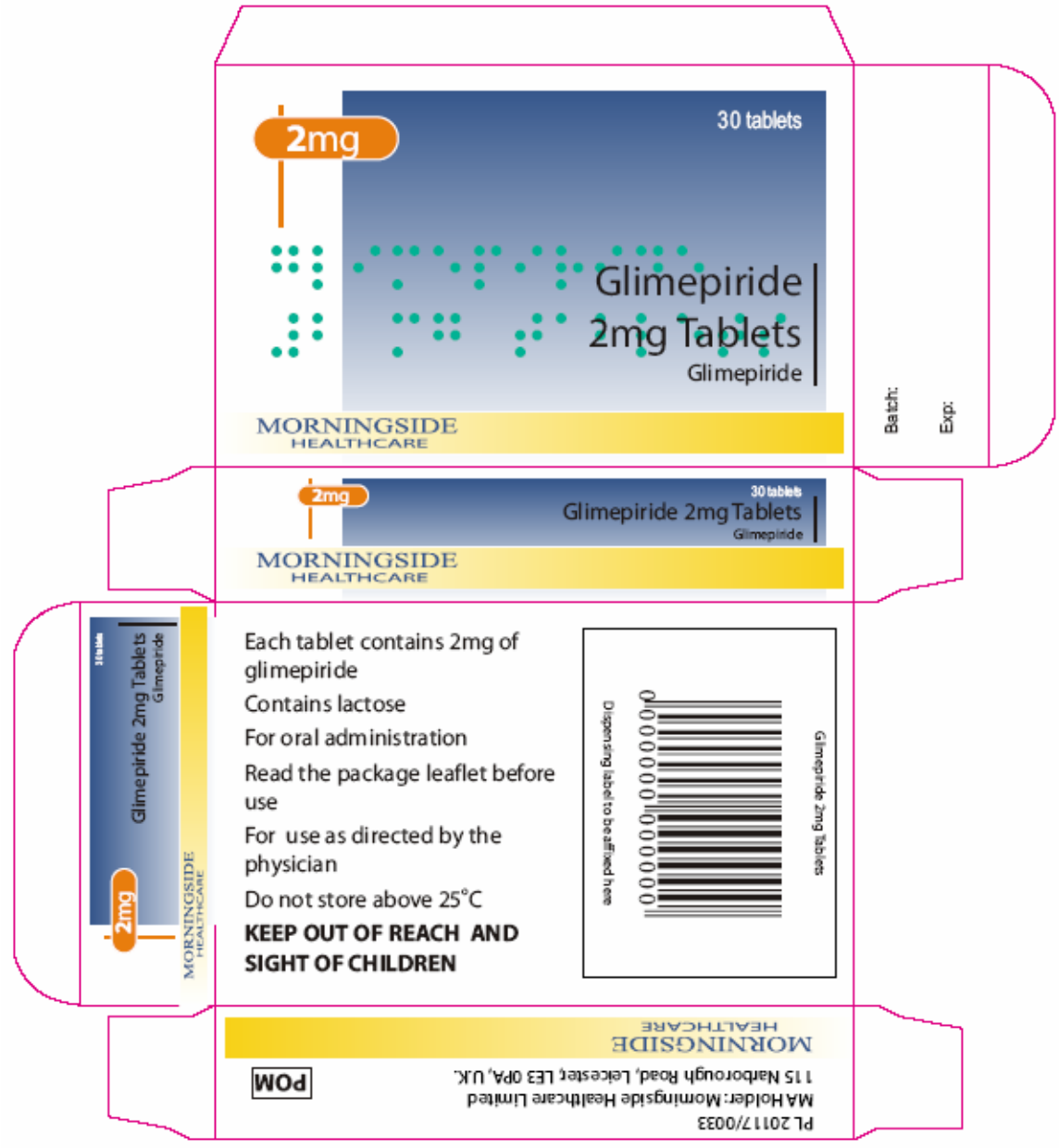
Blister carton - pack size 30 tablets



Braille translation

Glimepiride 2mg tablets

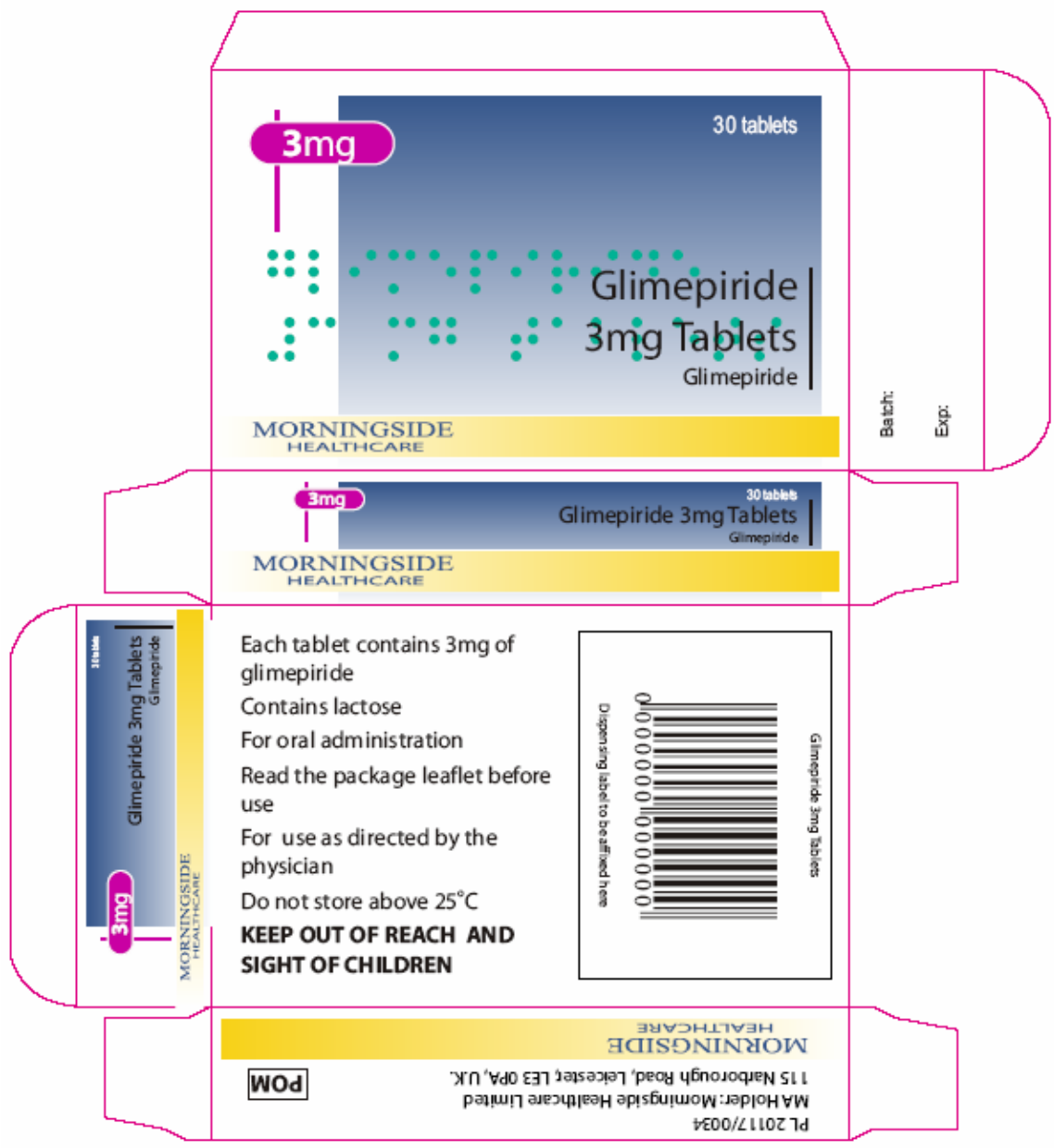
Blister carton - pack size 30 tablets



Braille translation

Glimepiride 3mg tablets

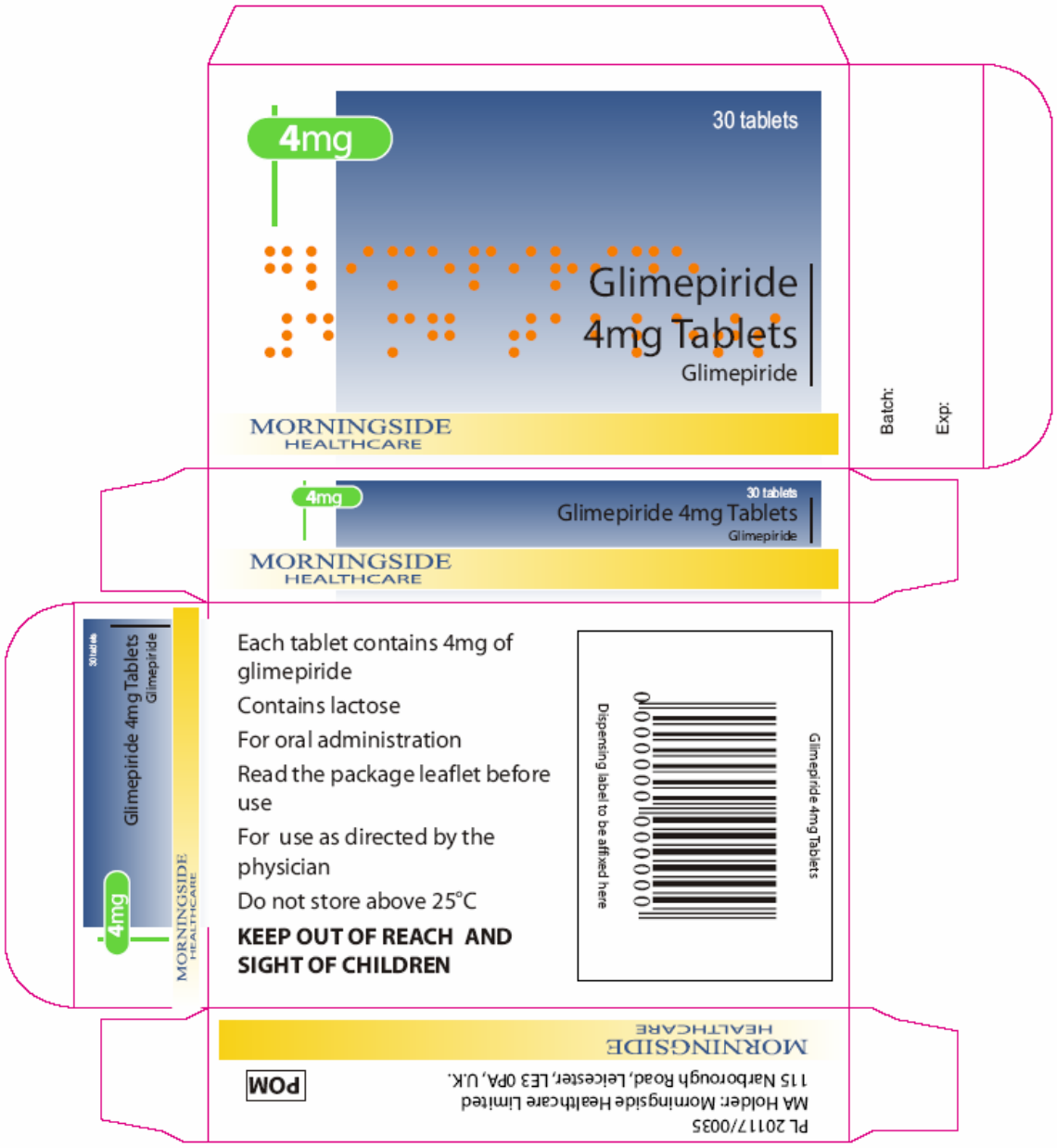
Blister carton - pack size 30 tablets



Braille translation

Glimepiride 4mg tablets

Blister carton - pack size 30 tablets



Braille translation

Blister foils

Glimepiride 1mg tablets

Glimepiride 2mg tablets

Glimepiride 3mg tablets

Glimepiride 4mg tablets

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Morningside Healthcare Limited Marketing Authorisations for the medicinal products Glimepiride 1mg, 2mg, 3mg, and 4mg tablets (PL 20117/0032-0035, UK/H/1001/01-04/DC) on 10th February 2009. The products are prescription-only medicines.

These are abridged applications for Glimepiride 1mg, 2mg, 3mg, and 4mg Tablets, four strengths of glimepiride, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the reference products, Amaryl 1mg, 2mg, 3mg, and 4mg Tablets (PL 13402/006-9 respectively), authorised to Hoechst Marion Roussel Limited on 8th November 1996. These are the innovator products. The innovator products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Glimepiride Tablets are indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate. Glimepiride is an orally active hypoglycaemic substance belonging to the sulfonylurea group. It acts mainly by stimulating insulin release from pancreatic beta cells.

Dosage is determined by the results of blood and urinary glucose determinations, and the starting dose is 1 mg glimepiride per day. The dosage can be increased to a maximum of 6mg glimepiride per day depending upon the response to treatment. In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated under close medical supervision.

No new preclinical or clinical efficacy studies were conducted, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Glimepiride 4mg Tablets, to that of the reference product, Amaryl 4 mg Tablets (PL 13402/009, Hoechst Marion Roussel Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Glimepiride 1mg tablets Glimepiride 2mg tablets Glimepiride 3mg tablets Glimepiride 4mg tablets
Name(s) of the active substance(s) (INN)	Glimepiride
Pharmacotherapeutic classification (ATC code)	Blood glucose lowering drugs: Sulfonamides, urea derivatives (A10B B12)
Pharmaceutical form and strength(s)	Tablets – 1mg, 2mg, 3mg, & 4mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1001/01-04/DC
Reference Member State	United Kingdom
Member States concerned	BG, CZ, HU, LT, PL, RO, and SK
Marketing Authorisation Number(s)	PL 20117/0032-0035
Name and address of the authorisation holder	Morningside Healthcare Ltd 115 Narborough Road, Leicester, LE3 0PA United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

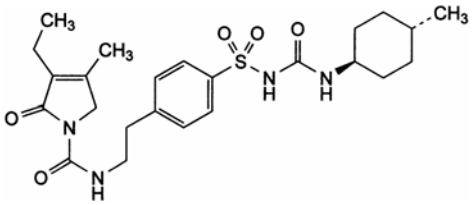
Glimepiride

Nomenclature:

INN: Glimepiride

Chemical name: 1-[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline- 1carboxamido) ethyl] benzenesulfonyl]-3 – (*trans*-4-methylcyclohexyl) urea

Structure:



Molecular formula: $C_{24}H_{34}N_4O_5S$

Molecular weight: 490.6

CAS No: 93479-97-1

Physical form: White or almost white crystalline powder

Solubility: Practically insoluble in water and in acid medium, slightly soluble in tetrahydrofuran and very slightly soluble in methanol and in 0.1 M sodium hydroxide

The active substance, glimepiride, is the subject of a European Pharmacopeia (EP) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in a double polyethylene bag which is placed into an opaque polyethylene drum. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bag in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in containers representative of the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 3 years.

DRUG PRODUCT

Description and Composition

The drug products are presented as capsule-shaped uncoated tablets, each containing 1mg, 2mg, 3mg, or 4mg of the active ingredient glimepiride. Full descriptions of the individual tablets may be found by referring to the SPCs / patient information leaflet.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, sodium lauryl sulphate, povidone, sodium starch glycolate, magnesium stearate, and microcrystalline cellulose. In addition, the 1mg tablets contain red iron oxide (E172); the 2mg tablets contain yellow iron oxide (E172) and indigo carmine aluminum lake (E132); the 3mg tablets contain yellow iron oxide (E172); and the 4mg tablets contain indigo carmine aluminum lake (E132). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of yellow and red iron oxide (E172), which comply with the US Pharmacopoeia, and indigo carmine aluminum lake (E132), which complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate and indigo carmine aluminum lake are of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. A TSE/BSE certificate was provided for lactose monohydrate.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution and impurity data were provided for each strength of the generic glimepiride tablets and their respective innovator products. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on three production scale batches for each of the strengths.

Finished product specification

The finished product specifications include tests and criteria to apply for both release and end of shelf life testing and are satisfactory; they provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in polyvinylchloride (PVC) - polyvinylidene chloride (PVDC) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in a pack size of 30 tablets (2 blister strips of 15 tablets).

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are 'Do not store above 25°C'.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Glimepiride 4mg Tablets, to the reference product, Amaryl 4 mg Tablets (PL 13402/009, Hoechst Marion Roussel Limited).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Glimepiride 4mg Tablets is a generic medicinal product of Amaryl 4 mg Tablets (Hoechst Marion Roussel Limited, UK; PL 13402/009) appears justified.

As the test products, Glimepiride 1mg, 2mg, 3mg, and 4mg Tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 1mg, 2mg, and 3mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of glimepiride, which is a widely used and well-known active substance.

III.3 CLINICAL ASPECTS

INDICATIONS

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

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

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. The dosage can be increased to a maximum of 6mg glimepiride per day depending upon the response to treatment.

In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated under close medical supervision. While maintaining the glimepiride dose, insulin treatment is started at low dose and titrated up depending on the desired level of metabolic control. Full details concerning the posology are provided in the SmPCs.

The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of glimepiride is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Glimepiride 4mg Tablets (test) and Amaryl 4 mg Tablets - PL 13402/009, Hoechst Marion Roussel Limited (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP).

This was a randomised, open-label, two-treatment, two-period, two sequence, single dose crossover bioavailability and bioequivalence study conducted in 34 (32 completed) healthy adult human male subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 5 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 48.0 hours after administration of test or reference product. The drug concentration levels in plasma were determined by a validated LCMS/MS method.

The primary pharmacokinetic parameters for this study were C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Results:

Two subjects were withdrawn - one tested positive for a prescribed substance and one was not present at the study. There were no deaths or serious adverse events. Adverse events were comparable between formulations.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for a randomised, two-treatment, two-period, single dose crossover study between the test and reference products. n=32 healthy subjects, dosed fasted; t=48 hours. Wash-out period: 5 days

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	2552.545 (1458.329)	2687.953 (1676.697)	367.703 (107.942)	3.3597 (1.67-5)	8.0206 (3.41-15.98)
Reference	2693.574 (1408.803)	2810.320 (1690.769)	407.907 (105.618)	3.3853(1.67-5)	8.0572 (3.36-19.99)
***Ratio (90% CI)**	94.14% (90.33-98.12)	93.64% (89.98-97.45)	89.19% (84.03-94.66)		
CV (%)	42.32	43.26	23.89		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

**ln-transformed values*

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test product and reference product are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Glimepiride 1mg, 2mg, 3mg, and 4mg Tablets. As Glimepiride 1mg, 2mg, 3mg, and 4mg Tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 1mg, 2mg, and 3mg strength products.

Clinical efficacy

No new data have been submitted and none are required. Efficacy is reviewed in the clinical overview. The efficacy of glimepiride is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. Safety is reviewed in the clinical overview. The safety profile of glimepiride is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Glimepiride 4mg Tablets, Morningside Healthcare Limited) and reference (Amaryl 4 mg Tablets; PL 13402/009, Hoechst Marion Roussel Limited) products within acceptance limits. The results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 1mg, 2mg, and 3mg strength products.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Glimepiride 1mg, 2mg, 3mg, and 4mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Glimepiride 4mg Tablets, and the reference product, Amaryl 4 mg Tablets (PL 13402/009, Hoechst Marion Roussel Limited, UK).

As Glimepiride 1mg, 2mg, 3mg, and 4mg Tablets were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 1mg, 2mg, and 3mg strength products, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with glimepiride is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome