UKPAR Glimepiride 1mg, 2mg, 3mg and 4mg Tablets

GLIMEPIRIDE 1MG TABLETS
   PL 17907/0106
GLIMEPIRIDE 2MG TABLETS
   PL 17907/0107
GLIMEPIRIDE 3MG TABLETS
   PL 17907/0108
GLIMEPIRIDE 4MG TABLETS
   PL 17907/0109

UKPAR

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PL 17907/0108
GLIMEPIRIDE 4MG TABLETS
PL 17907/0109

LAY SUMMARY

On 22nd November 2007, the MHRA granted Bristol Laboratories Limited (licences) for the medicinal products Glimepiride 1mg, 2mg, 3mg and 4mg Tablets (PL 17907/0106-9). These are prescription only medicines (POM) for the treatment of type 2 diabetes (also known as maturity-onset diabetes or non-insulin dependent diabetes, where the body does not produce enough insulin to control blood sugar levels). Type II diabetes can sometimes be controlled by a good diet, physical exercise and weight reduction alone, but where this is not possible, glimepiride is used in addition.

Glimepiride 1mg, 2mg, 3mg and 4mg Tablets contain the active ingredient glimepiride, which belongs to a group of medicines called sulphonylureas. These are a type of oral hypoglycaemic drug that are used to increase the secretion of insulin and thereby reduce the levels of sugar (glucose) in the blood.

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.
GLIMEPIRIDE 1MG TABLETS  
PL 17907/0106

GLIMEPIRIDE 2MG TABLETS  
PL 17907/0107

GLIMEPIRIDE 3MG TABLETS  
PL 17907/0108

GLIMEPIRIDE 4MG TABLETS  
PL 17907/0109

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Glimepiride 1mg, 2mg, 3mg and 4mg Tablets to Bristol Laboratories Limited (PL 17907/0106-9) on 22nd November 2007. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to the original products Amaryl Tablets (Hoechst Marion Roussell Limited) which have been authorised in the EU for more than 10 years.

The products contain the active ingredient glimepiride and are indicated for the treatment of a 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 sulphonylurea group.

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

Glimepiride acts at ATP-sensitive potassium channels (K_{ATP}) on pancreatic β-cells to promote insulin release. It binds to 65 kD protein on β-cells, which appears to be a part of the same sulphonylurea receptor that bind glibenclamide. Glimepiride after oral administration lowers blood glucose 3.5 times more potently than glibenclamide.

It may be used in non-insulin dependent diabetes mellitus.
PHARMACEUTICAL ASSESSMENT

Active substance
INN: Glimepiride

Chemical Name: 1) \( H\)-pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[trans-4-methylcyclohexyl] amino] carbonyl] amino] sulfonyl] phenyl] ethyl]-2-oxo-trans-.  
2) 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl] phenyl]sulphonyl]-3-(trans-4-methylcyclohexyl) urea.

Molecular Formula: \( \text{C}_{24}\text{H}_{34}\text{N}_{4}\text{O}_{5}\text{S} \)

Structure:

\[
\text{Structure Image}
\]

Molecular Weight: 490.62

Glimepiride is a white or almost white powder with a melting point of 205.0 to 208.0°C. It is practically insoluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride and very slightly soluble in methanol.

Glimepiride exhibits polymorphism. Glimepiride is a trans-isomer.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance glimepiride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Appropriate proof of structure has been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Acceptable certificates of analysis have been provided for all reference standards used.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated to support the proposed retest period.

Other ingredients
Other ingredients consist of lactose monohydrate, sodium starch glycollate, indigo carmine lake (4mg and 2mg strengths only), yellow iron oxide (2mg and 3mg strengths only), red iron oxide (1mg strength only), povidone, purified water,
microcrystalline cellulose, magnesium stearate and colloidal anhydrous silica. With the exception of indigocarmine lake, yellow iron oxide and red iron oxide, all excipients comply with their respective European Pharmacopoeia monographs. Yellow iron oxide and red iron oxide comply with US National Formulary specifications. Indigo carmine lake is controlled to a suitable in-house specification that complies with Commission Directive 95/45 /EC (with regard to specific purity criteria for colours in foodstuffs).

Lactose monohydrate is the only ingredients that come from an animal source. The lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption, using calf rennet.

**Product development**
The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for Glimepiride 1, 2, 3 and 4mg Tablets versus equivalent strengths of Amaryl Tablets.

**Manufacture**
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results at pilot-scale. Additionally, a commitment has been provided that the first three consecutive commercial production batches will be validated.

**Finished product specification**
The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specifications. The applicant has confirmed that all impurities are identical to those in the drug substance. Acceptable certificates of analysis have been provided for all reference standards used.

**Container closure system**
The commercial packaging consists of aluminium/polyvinylchloride blisters packed into cardboard boxes in pack sizes of 10, 20, 30 and 60 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging has been shown to comply with current regulations concerning contact with foodstuff.
Stability of the product
Stability data in compliance with ICH guideline for tablets produced by the finished product manufacturer in the packaging proposed for marketing have been provided. These data support a shelf-life of 2 years, with storage conditions ‘Store in original package’ and ‘Do not store above 25°C’ for all strengths and all finished packaging types.

The applicant has committed to placing the first three commercial-scale batches on stability studies.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable. The marketing authorisation holder has provided a commitment to update the marketing authorisation no later than 1st July 2008 with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups.

CONCLUSION
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products and bioequivalence demonstrated to an appropriate reference product.
PRECLINICAL ASSESSMENT

These applications for generic products claim essential similarity to Amaryl 1mg, 2mg, 3mg and 4mg Tablets (Hoechst Marion Roussell Limited), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.
CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND
These are abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to the original products Amaryl Tablets (Hoechst Marion Roussel Limited). Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group.

2. INDICATIONS
Glimepiride is 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.

3. DOSE & DOSE SCHEDULE
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 metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of Glimepiride, concomitant insulin therapy can be initiated 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 lifestyle 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 antidiabetics with a long half life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect. The 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

The dose and dosage schedule are consistent with those for the reference products and are satisfactory.

4.  CLINICAL PHARMACOLOGY
4.1 Bioequivalence
A randomised, open-label, single-dose, two-way, crossover bioequivalence study (with a 10-day washout period) comparing test Glimepiride 4mg Tablets versus reference Amaryl 4mg Tablets (Hoechst Marion Roussel Limited, UK) in healthy volunteers under fasted conditions has been conducted. Samples were taken pre-dose and up to 48 hours post dose.

The pharmacokinetic profile following oral administration of the test and reference products are shown below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>333.51 ± 95.18</td>
<td>390.91 ± 112.04</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.73 ± 1.77</td>
<td>3.37 ± 1.80</td>
</tr>
<tr>
<td>AUC(0-t) (ng.h/mL)</td>
<td>3022.61 ± 2852.92</td>
<td>2942.90 ± 2958.06</td>
</tr>
<tr>
<td>AUC(0-α) (ng.h/mL)</td>
<td>3499.55 ± 5136.99</td>
<td>3775.66 ± 7227.40</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>7.89 ± 5.18</td>
<td>8.35 ± 8.04</td>
</tr>
</tbody>
</table>
Bioequivalence has been demonstrated between the applicant’s Glimepiride 4mg Tablets versus Amaryl 4mg Tablets (Hoechst Marion Roussel Limited, UK), in accordance with the CPMP criteria. These products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). Hence, the results and conclusions of the bioequivalence study on the 4mg strength can be extrapolated to the other strength tablets.

5. EFFICACY
No new data on the efficacy of glimepiride are submitted and none are required for these types of applications.

6. SAFETY
No new data on the safety of glimepiride are submitted and none are required for these types of applications.

7. EXPERT REPORTS
A clinical expert report is provided, written by an appropriately qualified individual. It includes a suitable review of the bioequivalence study.

8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPCs are consistent with the SPCs for the reference products approved in the UK and are satisfactory.

9. PATIENT INFORMATION LEAFLET (PIL)
The PIL is consistent with the PIL for the reference products approved in the UK and is satisfactory.

10. LABELLING
Full colour mock-ups are provided and are satisfactory.

11. APPLICATION FORM (MAA)
The MAA forms are satisfactory.

12. DISCUSSION
Bioequivalence has been satisfactorily demonstrated for the 4mg product, in accordance with CPMP criteria. As these products meet all 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 can be extrapolated to the other strength tablets.

The SPCs and PIL are consistent with those for the UK reference product Amaryl Tablets and are satisfactory.
13. **MEDICAL CONCLUSION**
Marketing authorisations may be granted for these products.
OVERALL CONCLUSION AND RISK BENEFIT 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 Amaryl 4mg Tablets (Hoechst Marion Roussell Limited, UK). As these products meet all 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 can be extrapolated to the other strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the UK comparator product Amaryl Tablets.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with glimepiride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 4\textsuperscript{th} April 2005</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 15\textsuperscript{th} April 2005</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical and quality dossiers on 8\textsuperscript{th} March 2006, 9\textsuperscript{th} October 2006 and 27\textsuperscript{th} July 2007</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information for the clinical and quality dossier on 22\textsuperscript{nd} August 2006, 17\textsuperscript{th} April 2007 and 27\textsuperscript{th} July 2007</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 22\textsuperscript{nd} November 2007</td>
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**GLIMEPIRIDE 1MG TABLETS**  
PL 17907/0106  
**GLIMEPIRIDE 2MG TABLETS**  
PL 17907/0107  
**GLIMEPIRIDE 3MG TABLETS**  
PL 17907/0108  
**GLIMEPIRIDE 4MG TABLETS**  
PL 17907/0109

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Glimepiride 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains glimepiride 1 mg.

Excipients: Contains lactose monohydrate (see section 4.4).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet

Pink coloured, elongated with notch in center, flat bevelled edged, uncoated tablets with “B” & “L” embossing on either side of breakline on one side & only breakline on other side.

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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
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 metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of Glimepiride, concomitant insulin therapy can be initiated 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 antidiabetics with a long half life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect. The 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

### 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.

Glimepiride is contra-indicated in pregnancy and lactation.

### 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 of 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, requires immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycaemia include:
- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- under nutrition, irregular mealtimes or missed meals or periods of fasting,
- alterations in diet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,
- serious liver dysfunction,
- 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 section 4.5).

Treatment with Glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended.

This medicinal 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.

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.

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.

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

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is know to be influenced by concomitant administration of CYP2C9 inducer (e.g. rifampicin) or inhibitors (e.g. fluconazole). Results from an in-vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.
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:

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylbutazone, azapropazon and oxyfenbutazone</td>
<td>Sulphinpyrazone</td>
</tr>
<tr>
<td>Insulin and oral antidiabetic products</td>
<td>Metformin</td>
</tr>
<tr>
<td>Certain long acting sulphonamides</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Salicylates and p-amino-salicylic acid</td>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>Anabolic steroids and male sex hormones</td>
<td>Quinolone antibiotics</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Probenicid</td>
</tr>
<tr>
<td>Coumarin anticoagulants</td>
<td>Miconazol</td>
</tr>
<tr>
<td>Pentoxifylline (high dose parenteral)</td>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Tritoqualine</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Fluoxetine,</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Sympatholytics,</td>
</tr>
<tr>
<td>Cyclo-, tro- and iphosphamides</td>
<td>Fluconazole</td>
</tr>
</tbody>
</table>

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,
- Acetozolamide.

H2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

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

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
4.6 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

The following convention has been used for classification of the frequency of undesirable effects:
Very common:   >1/10
Common:   >1/100 and <1/10
Uncommon:   >1/1000 and <1/100
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Very rare:   <1/10,000 including single reports
<table>
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<tr>
<th><strong>Blood and lymphatic system disorders</strong></th>
<th>Very common</th>
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<th>Rare</th>
<th>Very rare</th>
</tr>
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<tr>
<td></td>
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<td></td>
<td>Changes in hematology 1)</td>
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</tr>
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<table>
<thead>
<tr>
<th><strong>Immune system disorders</strong></th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Mild hypersensitivity reactions 2), leukocytoclastic vasculitis, cross allergenicity with sulfonylureas, sulfonamides or related substances</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Metabolism and nutrition disorders</strong></th>
<th>Very common</th>
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<tr>
<td></td>
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<td></td>
<td>Hypoglycaemia 3)</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Eye disorders</strong></th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual disturbances 4)</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>Gastrointestinal disorders</strong></th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
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<tr>
<td>Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain 5)</td>
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<table>
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<th><strong>Hepatobiliary disorders</strong></th>
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<td>Hepatic enzymes increased</td>
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1) Thrombocytopenia, leukopenia, erythropenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur. These are in general reversible upon discontinuation of medication.

2) Mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.

3) These hypoglycaemic 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 section 4.4).

4) Visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

5) Gastrointestinal complaints seldom lead to discontinuation of therapy.

### 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


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 daily dosage of metformin has been shown in one study.

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

### 5.2 Pharmacokinetic properties

**Absorption:** The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations \( C_{\text{max}} \) 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 \( C_{\text{max}} \) 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 - 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.

### 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 starch glycollate,
Povidone K 30
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Red ferric oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in original package.

6.5 Nature and contents of container
Aluminium / PVC blister. Pack sizes of 10, 20, 30, 60 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside,
Northbridge, Berkhamsted,
Hertfordshire HP4 1EG,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0106

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/11/2007

10 DATE OF REVISION OF THE TEXT
22/11/2007
1 NAME OF THE MEDICINAL PRODUCT
Glimepiride 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains glimepiride 2 mg.

Excipients: Contains lactose monohydrate (see section 4.4).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet

Green coloured, elongated with notch in center, flat bevelled edged, uncoated tablets with “B” & “L” embossing on either side of breakline on one side & only breakline on other side.

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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
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 metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of Glimepiride, concomitant insulin therapy can be initiated 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 lifestyle 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 antidiabetics with a long half life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect. The 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

### 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.

Glimepiride is contra-indicated in pregnancy and lactation.

### 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 of 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, requires immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycaemia include:
- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- under nutrition, irregular mealtimes or missed meals or periods of fasting,
- alterations in diet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,
- serious liver dysfunction,
- 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 section 4.5).

Treatment with Glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended.

This medicinal 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.

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.

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.

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

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is know to be influenced by concomitant administration of CYP2C9 inducer (e.g. rifampicin) or inhibitors (e.g.fluconazole).Results from an in-vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.
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:

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenylbutazone, azapropazon and oxyfenbutazone</td>
<td>sulphinpyrazone</td>
</tr>
<tr>
<td>insulin and oral antidiabetic products</td>
<td>metformin</td>
</tr>
<tr>
<td>certain long acting sulphonamides</td>
<td>tetracyclines</td>
</tr>
<tr>
<td>salicylates and p-aminosalicylic acid</td>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>anabolic steroids and male sex hormones</td>
<td>quinolone antibiotics</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>probenecid</td>
</tr>
<tr>
<td>coumarin anticoagulants</td>
<td>miconazol</td>
</tr>
<tr>
<td>pentoxifylline (high dose parenteral)</td>
<td>fenfluramine</td>
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<tr>
<td>fibrates</td>
<td>tritoqualine</td>
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<tr>
<td>ACE inhibitors</td>
<td>fluoxetine,</td>
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<tr>
<td>allopurinol</td>
<td>sympatholytics,</td>
</tr>
<tr>
<td>Cyclo-, tro- and iphosphamides</td>
<td>fluconazole</td>
</tr>
</tbody>
</table>

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,
- acetozolamide.

H2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

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

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
4.6 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
The following convention has been used for classification of the frequency of undesirable effects:

Very common:  >1/10
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4) Visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.
5) Gastrointestinal complaints seldom lead to discontinuation of therapy.

### 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

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 daily dosage of metformin has been shown in one study.

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

### 5.2 Pharmacokinetic properties

**Absorption:** The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (C\text{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\text{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 - 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.

### 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
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 starch glycollate,
Povidone K 30
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Yellow ferric oxide (E172) and
Indigo carmine lake (E132)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in original package.

6.5 Nature and contents of container
Aluminium / PVC blister. Pack sizes of 10, 20, 30, 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside,
Northbridge, Berkhamsted,
Hertfordshire HP4 1EG,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/11/2007

10 DATE OF REVISION OF THE TEXT
22/11/2007
NAME OF THE MEDICINAL PRODUCT
Glimepiride 3 mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains glimepiride 3 mg.

Excipients: Contains lactose monohydrate (see section 4.4).

For a full list of excipients, see section 6.1

PHARMACEUTICAL FORM
Tablet

Light yellow coloured, elongated with notch in center, flat bevelled edged, uncoated tablets with “B” & “L” embossing on either side of breakline on one side & only breakline on other side.

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

CLINICAL PARTICULARS

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

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

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

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

If control is unsatisfactory the dosage should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3 or 4 mg glimepiride per day.

A dosage of more than 4 mg glimepiride per day gives better results only in exceptional cases. The maximum recommended dose is 6 mg glimepiride per day.

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

In patients not adequately controlled with the maximum daily dose of Glimepiride, concomitant insulin therapy can be initiated 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 antidiabetics with a long half life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect. The 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

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.

Glimepiride is contra-indicated in pregnancy and lactation.

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 of 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, requires immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycaemia include:
- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- under nutrition, irregular mealtimes or missed meals or periods of fasting,
- alterations in diet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,
- serious liver dysfunction,
- 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 section 4.5).

Treatment with Glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended.

This medicinal 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.

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.

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.

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

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducer (e.g. rifampicin) or inhibitors (e.g. fluconazole). Results from an in-vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.
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:

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenylbutazone, azapropazon and oxyfenbutazone</td>
<td>sulphapyrazone</td>
</tr>
<tr>
<td>insulin and oral antidiabetic products</td>
<td>metformin</td>
</tr>
<tr>
<td>certain long acting sulphonamides</td>
<td>tetracyclines</td>
</tr>
<tr>
<td>salicylates and p-aminosalicylic acid</td>
<td>MAO - inhibitors</td>
</tr>
<tr>
<td>anabolic steroids and male sex hormones</td>
<td>quinolone antibiotics</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>probenecid</td>
</tr>
<tr>
<td>coumarin anticoagulants</td>
<td>miconazol</td>
</tr>
<tr>
<td>pentoxifylline (high dose parenteral),</td>
<td>fenfluramine</td>
</tr>
<tr>
<td>fibrates</td>
<td>tritoqualine</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>fluoxetine,</td>
</tr>
<tr>
<td>allopurinol</td>
<td>sympatholytics,</td>
</tr>
<tr>
<td>Cyclo-, tro- and iphosphamides</td>
<td>fluconazole</td>
</tr>
</tbody>
</table>

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,
- acetozolamide.

H2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

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

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

### 4.6 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
The following convention has been used for classification of the frequency of undesirable effects:

- Very common:   >1/10
- Common:   >1/100 and <1/10
- Uncommon:   >1/1000 and <1/100
- Rare:    >1/10,000 and <1/1000
- Very rare:   <1/10,000 including single reports
<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in hematology 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Mild hypersensitivity reactions 2), leukocytoclastic vasculitis, cross allergenicity with sulfonylureas, sulfonamides or related substances</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Hypoglycaemia 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>Visual disturbances 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td>Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain 5)</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Hepatic enzymes increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Hypersensitivity reactions of the skin, pruritus, rash, urticaria and photosensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td>Serum sodium decrease</td>
<td></td>
</tr>
</tbody>
</table>

1) Thrombocytopenia, leukopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur. These are in general reversible upon discontinuation of medication.
2) Mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.
3) These hypoglycaemic 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 section 4.4).
4) Visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.
5) Gastrointestinal complaints seldom lead to discontinuation of therapy.

### 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 amounts have been ingested, it is also advisable to administer anti-diabetic drugs, especially short acting insulin, as a life-saving therapy.
quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdose hospitalisation in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

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

5 PHARMACOLOGICAL PROPERTIES

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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 sulphphonylurea binding site.

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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.

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

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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.

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**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.

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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.

### 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
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Sodium starch glycollate,
Povidone K 30
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Yellow ferric oxide (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in original package.

6.5 Nature and contents of container
Aluminium / PVC blister. Pack sizes of 10, 20, 30, 60 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

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For a full list of excipients, see section 6.1

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The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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
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 metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of Glimepiride, concomitant insulin therapy can be initiated 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 antidiabetics with a long half life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimise the risk of hypoglycaemic reactions due to the additive effect. The 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

### 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.

Glimepiride is contra-indicated in pregnancy and lactation.

### 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 of 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, requires immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycaemia include:
- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- under nutrition, irregular mealtimes or missed meals or periods of fasting,
- alterations in diet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,
- serious liver dysfunction,
- 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 section 4.5).

Treatment with Glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended.

This medicinal 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.

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.

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.

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

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducer (e.g. rifampicin) or inhibitors (e.g. fluconazole). Results from an in-vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.
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:

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylbutazone, azapropazon and oxyfenbutazone</td>
<td>Sulphinpyrazone</td>
</tr>
<tr>
<td>Insulin and oral antidiabetic products</td>
<td>Metformin</td>
</tr>
<tr>
<td>Certain long acting sulphonamides</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Salicylates and p-aminosalicylic acid</td>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>Anabolic steroids and male sex hormones</td>
<td>Quinolone antibiotics</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Probencid</td>
</tr>
<tr>
<td>Coumarin anticoagulants</td>
<td>Miconazol</td>
</tr>
<tr>
<td>Pentoxifylline (high dose parenteral)</td>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Tritoqualine</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Fluoxetine,</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Sympatholytics,</td>
</tr>
<tr>
<td>Cyclo-, tro- and iphosphamides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
</tr>
</tbody>
</table>

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,
- Acetozolamide.

H2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect.

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.

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

Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
4.6 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
The following convention has been used for classification of the frequency of undesirable effects:

- Very common: >1/10
- Common: >1/100 and <1/10
- Uncommon: >1/1000 and <1/100
- Rare: >1/10,000 and <1/1000
- Very rare: <1/10,000 including single reports
<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Changes in hematology 1)</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Mild hypersensitivity reactions 2), leukocytoclastic vasculitis, cross allergenicity with sulfonylureas, sulfonamides or related substances</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Hypoglycaemia 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbances 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Hepatic enzymes increased</td>
<td>Hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Hypersensitivity reactions of the skin as pruritus, rash, urticaria and photosensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>Serum sodium decrease</td>
<td></td>
</tr>
</tbody>
</table>

1) Thrombocytopenia, leukopenia, erythrocytopenia, granulocytopenia, agranulocytosis, haemolytic anaemia and pancytopenia may occur. These are in general reversible upon discontinuation of medication.

2) Mild hypersensitivity reactions may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.

3) These hypoglycaemic 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 section 4.4).

4) Visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

5) Gastrointestinal complaints seldom lead to discontinuation of therapy.

### 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


Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonurea 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 sulphonureas 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 sulphonureas.

**Insulin release:**
Sulphonureas 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 sulphonurea 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 daily dosage of metformin has been shown in one study.

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

### 5.2 Pharmacokinetic properties

#### Absorption:
The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations ($C_{\text{max}}$) 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 $C_{\text{max}}$ 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 - 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.

### 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 starch glycollate,
Povidone K 30
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate
Indigocarmine lake

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in original package.

6.5 Nature and contents of container
Aluminium / PVC blister. Pack sizes of 10, 20, 30, 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside,
Northbridge, Berkhamsted,
Hertfordshire HP4 1EG,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/11/2007

10 DATE OF REVISION OF THE TEXT
22/11/2007
UKPAR Glimepiride 1mg, 2mg, 3mg and 4mg Tablets

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, please ask your doctor or pharmacist.

This medicine has been prescribed for you personally and you should 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 get 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 Tablets are and what they are used for
2. Before you take Glimepiride Tablets
3. How to take Glimepiride Tablets
4. Possible side effects
5. Storing Glimepiride Tablets

WHAT GLIMEPIRIDE TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Glimepiride 1mg, 2mg, 3mg or 4mg Tablets. The active substance is glimepiride and each tablet contains 1mg, 2mg, 3mg or 4mg of the active ingredient glimepiride. The other ingredients are lactose, sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, povidone and magnesium stearate. In addition the tablets contain colouring agents, Glimepiride 1, 2, and 3mg tablets contain ferric oxide (E172), while the 2mg and 4mg tablets contain indigo-carmine lake (E132).

Glimepiride 1mg tablets are pink, elongated with notch in center, flat and bevel-edged, with ‘B’ & ‘L’ embossing on either side of break line on one side & only break line on other side. Glimepiride 2mg tablets are green, elongated with notch in center, flat and bevel-edged, with ‘B’ & ‘L’ embossing on either side of break line on one side & only break line on other side. Glimepiride 3mg tablets are light yellow, elongated with notch in center, flat and bevel-edged, with ‘B’ & ‘L’ embossing on either side of break line on one side & only break line on other side. Glimepiride 4mg tablets are blue, elongated with notch in center, flat and bevel-edged, with ‘B’ & ‘L’ embossing on either side of break line on one side & only break line on other side.

Marketing Authorisation Holder and Manufacturer:
Bristol Laboratories Ltd, Unit 3, Canside, Northbridge Road, Berkhamsted, Hertfordshire, HP4 1EG, UK

Glimepiride tablets are available in blister packs of 10, 20, 30 or 60 tablets. Not all pack sizes may be marketed.

Glimepiride is one of a group of medicines called oral hypoglycaemics, which help to control blood sugar levels.

Glimepiride is used in the treatment of non-insulin dependent (type II) diabetes mellitus. Type II diabetes can sometimes be controlled by a good diet, physical exercise and weight reduction alone, but where this is not possible, glimepiride is used in addition.

BEFORE YOU TAKE GLIMEPIRIDE TABLETS

Do not take Glimepiride Tablets if:
• you have ever had an allergic reaction to glimepiride, any of the ingredients in the tablet, other sulphonylureas (e.g. gliclazide, glipizide, tolbutamide) or sulphonamides (e.g. sulphamethoxazole).

An allergic reaction may include a rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue,
• you are pregnant or planning to become pregnant.
• you are breast-feeding.
• you have insulin dependent (type I) diabetes.
• you have severe liver or kidney problems.
• you have been told by your doctor that you have ‘ketoacidosis’ (your breath may smell of acetic drops).
• you have suffered diabetic coma.

Check with your doctor or pharmacist before taking Glimepiride tablets if:
• you have not been told how often to test your blood sugar levels or discussed with your doctor the need for other blood tests.
• you have had an accident, have an infection or are having an operation. Your doctor may need to review your diabetes treatment.

Taking glimepiride with other medicines
You should seek the advice of your doctor or pharmacist before taking glimepiride if you are taking other medicines, especially the following which are likely to increase or reduce the blood sugar lowering effect of glimepiride:

Medicines which increase the blood sugar lowering effect of glimepiride:
• Other anti-diabetic medicines such as metformin and insulin.
• Alfpirinol, sulfonylurea, sulfonylurea, ascorbixpyrazone or phenylurea (used to treat diabetes or gout).
• Ase inhibitors such as cephalosporin (for high blood pressure or heart conditions).
• Tetracyclines such as tetracycline.
• Steroids and male sex hormones such as nandrolone (for osteoporosis) and testosterone.
• Quinolone antibiotics (for example ciprofloxacin), tetracyclines (for example doxycycline and minocycline), sulphonamides (for example sulmethoxazole), or chloramphenicol.
• Anticoagulants such as warfarin for blood thinning (blood thinning may also be affected).
• Fenfuraline (used for reducing appetite).
• Fluoxetine or MAO inhibitors (such as phenelzine) (medicines used to treat depression and/or certain mental illnesses).
• Anticancer medicines such as cyclophosphamide (used in leukaemia).
• Probenecid (used in the prevention of kidney damage during treatment of HIV infection).
• Anti fungal medicines such as miconazole or fluconazole.
• Pentoxifylline (used to treat conditions resulting from poor peripheral circulation).
• Triptolyl (used to treat anxiety or panic attacks).
• Medicines which reduce the blood sugar lowering effects of glimepiride:
• Ase inhibitors (used to treat diabetes or gout).
• Ase inhibitors (used to treat gout).
• Ase inhibitors (used to treat leukaemia).
• Chlorpromazine or perphenazine or omeprazole or other similar drugs which would generally be administered in hospitals.
• Diabetes agents such as hypoglycaemic.
• Lipid lowering medicines such as niacin or niacin.
• Diazoxide (used to treat severe hypoglycaemia).
• Dexamethasone or prednisolone (used to treat inflammation or allergic reactions).
• Hormones contained in contraceptives or hormone replacement therapy (HRT) such as oestrogen and progesterone.
• Glutagen (a hormone used to raise blood sugar levels).
UKPAR Glimepiride 1mg, 2mg, 3mg and 4mg Tablets

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- Luxatives (used for treating constipation).
- Medications which increase or reduce the blood sugar lowering effects of glimepiride.
- Angiotsin-converting enzyme inhibitors (ACE inhibitors).
- Medications which lower blood pressure or raise blood pressure.
- Medications which increase the amount of fluid retained in the body.
- Medications which affect the way the kidneys work (diuretics).

Taking Glimepiride Tablets with food and drink:
Glimepiride must be taken shortly before or during the main meal of the day.

It is important that you maintain a regular diet when taking Glimepiride tablets. Skipping or delaying meals whilst taking Glimepiride tablets may lead to hypoglycaemia (see section on "Possible side effects for further information.

You are advised NOT to drink alcohol with this medicine. Discuss this with your doctor if you have any questions.

Pregnancy and Breastfeeding:
Do not take Glimepiride tablets if you are pregnant. You may be pregnant or you are planning to become pregnant. Consult your doctor if you are pregnant. Glimepiride tablets are not recommended for use during pregnancy.

Driving and using machines:
Glimepiride may cause hypoglycaemia which may affect your ability to concentrate or cause disorientation of vision. These may affect your ability to drive or use machines. To avoid hypoglycaemia do not miss or delay meals or change your diet or take more Glimepiride tablets than needed, or do a more intense or rigorous physical exercise or more work than normal. Make sure you know how you react to Glimepiride tablets before you drive, use machines or engage in any other activity that could be dangerous if you are not alert.

If you have reduced or absence of awareness of the symptoms of onset of hypoglycaemia, you should seek the advice of your doctor before driving or operating machinery, whilst taking Glimepiride tablets (see section on "Possible side effects for further information.

Other precautions you should take:
If you see another doctor or go into hospital, let them know what medicines you are taking.

Important information about some of the ingredients of Glimepiride Tablets:
Glimepiride tablets contain lactose monohydrate. If you have intolerance to some sugars you should tell your doctor before taking this medicine.

HOW TO TAKE GLIMEPIRIDE TABLETS

Always take Glimepiride exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual starting dose is 1mg glimepiride each day but this may be increased by your doctor at suitable intervals, usually 1 – 2 weeks and depending on your response to treatment, up to a maximum dose of 8mg glimepiride per day.

Glimepiride tablets must be taken shortly before or with the first meal of the day. Glimepiride tablets will not be swallofed whole with some liquid.

Take these tablets until your doctor tells you to stop. Don't stop because you feel better. If you stop taking the tablets too soon, your condition may get worse.

Glimepiride Tablets are meant to be taken in addition to following any advice you have been given on diet, exercise and weight loss. Your doctor may prescribe Glimepiride tablets to take in addition to or instead of other diabetes treatments. Follow instructions given by your doctor carefully.

If you take more Glimepiride tablets than you should:
If you have taken more Glimepiride tablets than you should, consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken.

If you forget to take Glimepiride tablets:
If you forget to take Glimepiride Tablets at the right time, take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dose schedule. Do not take a double dose to make up for forgotten individual doses.

POSSIBLE SIDE EFFECTS

Like all medicines, Glimepiride Tablets can sometimes cause unwanted side effects. If the following happens, STOP taking Glimepiride Tablets and tell your doctor immediately or contact the casualty department at your nearest hospital.

An allergic reaction: skin rash, swelling of the face, lips, tongue or throat, or difficulty breathing or swallowing. This is usually a mild and very rare side effect which may become serious (occurs in less than 1 in 10,000 people). You may need urgent medical attention or hospitalisation.

Other known side effects are:
Rare (occurs in between 1 in 1000 and 1 in 10,000 people): changes in numbers and types of blood cells. Tell your doctor about any strange bruising, repeat nosebleeds or infections such as colds. Glimepiride, temporary visual problems, raised liver enzyme levels (detected in blood tests), allergic skin reactions such as itching, rash or itchy rash.

Very rare (occurs in less than 1 in 10,000 people): feeling or being sick, diarrhoea, bloating, stomach ache, owsensibility of the skin to sunburn, low blood sodium levels (detected in blood test).

Tell your doctor if you notice any of the side effects listed or notice any other effects not listed.

hypoglycaemia (low blood sugar)

Hypoglycaemia may occur if you take meals at irregular hours or skip meals altogether while taking glimepiride. It is important to know what symptoms to expect when hypoglycaemia occurs. These could include headache, severe hunger, feeling and being sick, weakness, sleepiness, restlessness, agitation, 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. Tell your doctor if you notice any such symptoms.

If you notice any of these effects ensure that you immediately take some sugar or carbohydrates. This will help control your symptoms while you go to your doctor or pharmacist.

Ask your doctor or pharmacist for more information if you are not sure how to recognise this.

STORING GLIMEPIRIDE TABLETS

Keep out of the reach and sight of children.

Do not store above 25°C. Store in the original package ( blister carton).

Do not use the tablets after the expiry date as shown on the carton.

Unless your doctor tells you to, do not keep any tablets that you no longer need.

Give them back to your pharmacist.

This leaflet is prepared in November 2007.
UKPAR Glimepiride 1mg, 2mg, 3mg and 4mg Tablets

PL 17907/0106-9
**UKPAR Glimepiride 1mg, 2mg, 3mg and 4mg Tablets**

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**PL 17907/0106-9**

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**Web Direction**
UKPAR Glimepiride 1mg, 2mg, 3mg and 4mg Tablets

PL 17907/0106

Do not store above 25°C.
Keep out of the reach and sight of children.
For further information please see the leaflet.
See section 4.4 for deprotection steps.
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