

**GLIMEPIRIDE 1MG TABLETS
PL 20477/0016
GLIMEPIRIDE 2MG TABLETS
PL 20477/0017
GLIMEPIRIDE 3MG TABLETS
PL 20477/0018
GLIMEPIRIDE 4MG TABLETS
PL 20477/0019**

UKPAR

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 12
Steps taken after authorisation – summary	Page 13
Summary of Product Characteristics	
Product Information Leaflet	
Labelling	

GLIMEPIRIDE 1MG TABLETS

PL 20477/0016

GLIMEPIRIDE 2MG TABLETS

PL 20477/0017

GLIMEPIRIDE 3MG TABLETS

PL 20477/0018

GLIMEPIRIDE 4MG TABLETS

PL 20477/0019

LAY SUMMARY

The MHRA today granted Kohne Pharma GmbH (licences) for the medicinal products Glimepiride 1mg, 2mg, 3mg and 4mg Tablets (PL 20477/0016-19). 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).

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 20477/0016
GLIMEPIRIDE 2MG TABLETS
PL 20477/0017
GLIMEPIRIDE 3MG TABLETS
PL 20477/0018
GLIMEPIRIDE 4MG TABLETS
PL 20477/0019**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 7
Clinical assessment (including statistical assessment)	Page 8
Overall conclusions and risk benefit assessment	Page 11

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Glimpiride 1mg, 2mg, 3mg and 4mg Tablets to Kohne Pharma GmbH (PL 20477/0016-19) on 28th September 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.

Glimpiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group.

Glimpiride 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.

Glimpiride 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. Glimpiride 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: C₂₄H₃₄N₄O₅S

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.

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

Appropriate stability data have been generated to support a retest period for active glimepiride of 3 years.

Other ingredients

Other ingredients consist of lactose monohydrate, microcrystalline cellulose, povidone, indigocarmine lake, magnesium stearate, sodium starch glycolate and purified water. With the exception of indigocarmine lake, all excipients comply with their respective Ph Eur specifications. A satisfactory in-house specification has been provided for Indigocarmine Lake that complies with Commission Directive 95/45 /EC (with regard to specific purity criteria for colours in foodstuffs).

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph/specifications.

Lactose monohydrate and magnesium stearate are the only ingredients that come from animal sources. The lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption, using calf rennet. A satisfactory certificate of suitability has been provided for the stearic acid used to make magnesium stearate showing compliance with current guidelines for the minimising of transmission of animal spongiform encephalopathies.

The commercial packaging consists of (i) Cold form blister pack (structure from outer to inner side: oriented polyamide / aluminium foil / polyvinyl chloride file) with a backing of aluminium foil coated with heat seal laquer enclosed in cardboard boxes (2mg, 3mg and 4mg) and (ii) opaque high-density polyethylene bottles with child-resistant caps (and induction seal), dessicant and absorbent cotton wool (1mg, 2mg, 3mg and 4mg). Both packaging types have pack sizes of 30 tablets. In addition, bulk tablets are stored in polyethylene bags, placed in outer triple laminated bags (with sachets of dessicant in primary packaging, and top and bottom of secondary packaging).

Satisfactory specifications and certificates of analysis have been provided for all packaging components. The aluminium foil, Cold form blister laminate, high-density polyethylene, child resistant cap with induction seal have been shown to comply with relevant guidelines concerning contact with foodstuffs.

Product development, manufacture and finished product specification

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 have been generated for Glimepiride 1, 2, 3 and 4mg Tablets versus various equivalent European products, showing comparable dissolution. Comparative impurity studies have also been undertaken and found to be comparable.

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.

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 has 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.

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 24 months, with storage conditions 'Store in original package' and 'Do not store above 25°C' for all strengths and all finished packaging types.

Data from bulk tablets stored in polyethylene bags support a holding time of 12 months from date of manufacture.

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

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

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.

PRECLINICAL ASSESSMENT

These applications for generic products claim essential similarity to Amaryl 1mg, 2mg, 3mg and 4mg Tablets (Hoechst Marion Roussel 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). Glimpiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group.

2. INDICATIONS

Glimpiride 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 Glimpiride, 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

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

4. CLINICAL PHARMACOLOGY

Absorption:

The bioavailability of glimepiride after oral administration is complete. 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).

Food intake has no relevant influence on absorption, only absorption rate is slightly diminished.

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 radio-labelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites - most probably resulting from hepatic metabolism (major enzyme is CYP2C9) - were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours, respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intraindividual variability was very low. There was no relevant accumulation. Pharmacokinetics was similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall, no additional risk of accumulation is to be expected in such patients. Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Genetic polymorphism of CYP2C9 markedly affects the pharmacokinetics of glimepiride. Niemi M *et al* (2002) investigated the effects of CYP2C9 genetic polymorphism on the pharmacokinetics of glimepiride in 29 healthy volunteers. The pharmacokinetics of glimepiride were not significantly changed among subjects with the CYP2C9*1/*2 genotype. However, in individuals heterozygous for the CYP2C9*3 allele, the median total area under the plasma concentration-time curve of glimepiride was 267 % ($P < 0.01$) of the respective values in subjects with the CYP2C9*1/*1 genotype. The influence of the CYP2C9*3 variant allele on glimepiride pharmacokinetics may be clinically significant. However, the blood glucose responses to glimepiride were not significantly affected by the CYP2C9 genotype.

4.1 Bioequivalence

A randomised, single-dose, two-way, crossover bioequivalence study (with a seven day washout period) comparing Glimepiride 1mg Tablets versus Amarel 1mg Tablets (Aventis, France) has been conducted. The test and reference products were each administered to 36 healthy adult male volunteers following a high-fat breakfast preceded by an overnight fast (of at least 10 hours). Thirty-five volunteers completed the study and there was one withdrawal due to adverse effects.

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

Parameter	Test geometric mean	Reference geometric mean	100% ratio of geometric means	90% confidence interval on log transformed data
AUC _{0-t}	312.771	314.673	99.4	(94.9, 104)
AUC _{0-inf}	327.795	331.782	98.8	(94.3, 103)
C _{max}	47.606	50.679	93.9	(84.8, 104)

Bioequivalence has been demonstrated between the applicant's Glimepiride 1mg Tablets versus Amarel 1mg Tablets (Aventis, France), 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 1mg 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 1mg 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 1mg 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 1mg Tablets and Amarel 1mg Tablets (Aventis, France). 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 1mg 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.

**GLIMEPIRIDE 1MG TABLETS
PL 20477/0016
GLIMEPIRIDE 2MG TABLETS
PL 20477/0017
GLIMEPIRIDE 3MG TABLETS
PL 20477/0018
GLIMEPIRIDE 4MG TABLETS
PL 20477/0019**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 6 th May 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 2 nd June 2005
3	Following assessment of the applications the MHRA requested further information relating to the clinical and quality dossiers on 8 th March 2006 and 17 th January 2007
4	The applicant responded to the MHRA's requests, providing further information for the clinical and quality dossier on 20 th September 2006 and 5 th April 2007
5	The applications were determined on 28 th September 2007

**GLIMEPIRIDE 1MG TABLETS
PL 20477/0016
GLIMEPIRIDE 2MG TABLETS
PL 20477/0017
GLIMEPIRIDE 3MG TABLETS
PL 20477/0018
GLIMEPIRIDE 4MG TABLETS
PL 20477/0019**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Glimpiride 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glimepiride 1 mg.

Excipient(s): contains 35.58mg lactose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Glimpiride 1 mg Tablets comprise of blue coloured, biconvex round uncoated tablets, debossed with 'G 1' on one side and plain on other side.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Glimpiride 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 Glimpiride, 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.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Potential of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

- phenylbutazone, azapropazon and oxyfenbutazone
- sulphinpyrazone
- insulin and oral antidiabetic products
- metformin
- certain long acting sulphonamides
- tetracyclines
- salicylates and p-amino-salicylic acid

- MAO-inhibitors
- anabolic steroids and male sex hormones
- quinolone antibiotics
- chloramphenicol
- probenecid
- coumarin anticoagulants
- miconazol
- pentoxifylline (high dose parenteral)
- fenfluramine
- fibrates
- tritoqualine
- ACE inhibitors
- fluoxetine
- allopurinol
- sympatholytics
- cyclo-, tro- and iphosphamides
- CYP2C9 Inhibitors
- fluconazole

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

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

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

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic 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

	Very common	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders				Changes in hematology ¹⁾	
Immune system disorders					Mild hypersensitivity reactions ²⁾ , leukocytoclastic vasculitis, cross allergenicity with sulfonylureas, sulfonamides or related substances
Metabolism and nutrition disorders				Hypoglycaemia ³⁾	
Eye disorders			Visual disturbances ⁴⁾		
Gastrointestinal disorders					Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain ⁵⁾
Hepatobiliary disorders				Hepatic enzymes increased	Hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure

Skin and subcutaneous tissue disorders					Hypersensitivity reactions of the skin aspruritus, rash, urticaria and photosensitivity
Investigations					Serum sodium decrease

- 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

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives. ATC Code: A10B B12.

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

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release:

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results in 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.

Extrapaneatic 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_{max}) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min).

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

Biotransformation and elimination: Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism - 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
Microcrystalline cellulose
Povidone
Lake colour of indigocarmine (Cl. No. 73015)
Sodium starch glycollate
Magnesium stearate

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

HDPE bottle pack comprises white opaque HDPE bottle with 33 mm / 400 neck finish.

Pack size: 30 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

None

- 7 MARKETING AUTHORISATION HOLDER**
Kohne Pharma GmbH
Schallbruch 1,
D-42781 Haan,
Germany
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 20477 / 0016
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
28/09/2007
- 10 DATE OF REVISION OF THE TEXT**
28/09/2007

1 NAME OF THE MEDICINAL PRODUCT

Glimpiride 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glimepiride 2 mg.

Excipient(s): contains 71.15mg lactose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Glimpiride 2 mg Tablets comprise of blue coloured, dumbbell-shaped uncoated tablets, debossed with 'R' and 'B' on either side of the scoreline on one side and '4' and '9' on either side of scoreline on the other side.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Glimpiride 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 Glimpiride, 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.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Potiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

- phenylbutazone, azapropazon and oxyfenbutazone
- sulphinpyrazone
- insulin and oral antidiabetic products
- metformin
- certain long acting sulphonamides
- tetracyclines
- salicylates and p-amino-salicylic acid

- MAO-inhibitors
- anabolic steroids and male sex hormones
- quinolone antibiotics
- chloramphenicol
- probenecid
- coumarin anticoagulants
- miconazol
- pentoxifylline (high dose parenteral)
- fenfluramine
- fibrates
- tritoqualine
- ACE inhibitors
- fluoxetine
- allopurinol
- sympatholytics
- cyclo-, tro- and iphosphamides
- CYP2C9 Inhibitors
- fluconazole

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

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

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

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic 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

	Very common	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders				Changes in hematology ¹⁾	
Immune system disorders					Mild hypersensitivity reactions ²⁾ , leukocytoclastic vasculitis, cross allergenicity with sulfonylureas, sulfonamides or related substances
Metabolism and nutrition disorders				Hypoglycaemia ³⁾	
Eye disorders			Visual disturbances ⁴⁾		
Gastrointestinal disorders					Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain ⁵⁾
Hepatobiliary disorders				Hepatic enzymes increased	Hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure

Skin and subcutaneous tissue disorders					Hypersensitivity reactions of the skin aspruritus, rash, urticaria and photosensitivity
Investigations					Serum sodium decrease

- 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

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives. ATC Code: A10B B12.

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

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release:

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results in 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_{max}) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min).

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

Biotransformation and elimination: Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism - 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
Microcrystalline cellulose
Povidone
Lake colour of indigocarmine (Cl. No. 73015)
Sodium starch glycollate
Magnesium stearate

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

Cold form blister pack (structure from outer to inner side: oriented polyamide / aluminium foil / polyvinyl chloride file) with a backing of aluminium foil coated with heat seal lacquer.

HDPE bottle pack comprises white opaque HDPE bottle with 33 mm / 400 neck finish.

Pack size: 30 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Kohne Pharma GmbH
Schallbruch 1,
D-42781 Haan,
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 20477 / 0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

28/09/2007

10 DATE OF REVISION OF THE TEXT

28/09/2007

1 NAME OF THE MEDICINAL PRODUCT

Glimpiride 3 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glimepiride 3 mg.

Excipient(s): contains 106.73mg lactose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Glimpiride 3 mg Tablets comprise of blue coloured, dumbbell shaped uncoated tablets, debossed with 'R' and 'E' on either side of scoreline on one side and '1' and '1' on either side of the scoreline on the other side.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Glimpiride 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 Glimpiride, 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.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Potential of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

- phenylbutazone, azapropazon and oxyfenbutazone
- sulphinpyrazone
- insulin and oral antidiabetic products
- metformin
- certain long acting sulphonamides
- tetracyclines
- salicylates and p-amino-salicylic acid

- MAO-inhibitors
- anabolic steroids and male sex hormones
- quinolone antibiotics
- chloramphenicol
- probenecid
- coumarin anticoagulants
- miconazol
- pentoxifylline (high dose parenteral)
- fenfluramine
- fibrates
- tritoqualine
- ACE inhibitors
- fluoxetine
- allopurinol
- sympatholytics
- cyclo-, tro- and iphosphamides
- CYP2C9 Inhibitors
- fluconazole

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

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

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

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic 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

	Very common	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders				Changes in hematology ¹⁾	
Immune system disorders					Mild hypersensitivity reactions ²⁾ , leukocytoclastic vasculitis, cross allergenicity with sulfonylureas, sulfonamides or related substances
Metabolism and nutrition disorders				Hypoglycaemia ³⁾	
Eye disorders			Visual disturbances ⁴⁾		
Gastrointestinal disorders					Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain ⁵⁾
Hepatobiliary disorders				Hepatic enzymes increased	Hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure

Skin and subcutaneous tissue disorders					Hypersensitivity reactions of the skin aspruritus, rash, urticaria and photosensitivity
Investigations					Serum sodium decrease

- 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

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives. ATC Code: A10B B12.

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

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release:

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results in 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.

Extraprocreatic 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_{max}) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min).

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

Biotransformation and elimination: Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism - 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
Microcrystalline cellulose
Povidone
Lake colour of indigocarmine (Cl. No. 73015)
Sodium starch glycollate
Magnesium stearate

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

Cold form blister pack (structure from outer to inner side: oriented polyamide / aluminium foil / polyvinyl chloride file) with a backing of aluminium foil coated with heat seal lacquer.

HDPE bottle pack comprises white opaque HDPE bottle with 33 mm / 400 neck finish.

Pack size: 30 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Kohne Pharma GmbH
Schallbruch 1,
D-42781 Haan,
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 20477 / 0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

28/09/2007

10 DATE OF REVISION OF THE TEXT

28/09/2007

1 NAME OF THE MEDICINAL PRODUCT

Glimpiride 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glimepiride 4 mg.

Excipient(s): contains 142.30mg lactose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Glimpiride 4 mg Tablets comprise of blue coloured, dumbbell shaped uncoated tablets debossed with 'R' and 'B' on either side of the scoreline on one side and '5' and '0' on either side of the scoreline on the other side.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Glimpiride 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 Glimpiride, 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.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Potential of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example:

- phenylbutazone, azapropazon and oxyfenbutazone
- sulphinpyrazone
- insulin and oral antidiabetic products
- metformin
- certain long acting sulphonamides
- tetracyclines
- salicylates and p-amino-salicylic acid

- MAO-inhibitors
- anabolic steroids and male sex hormones
- quinolone antibiotics
- chloramphenicol
- probenecid
- coumarin anticoagulants
- miconazol
- pentoxifylline (high dose parenteral)
- fenfluramine
- fibrates
- tritoqualine
- ACE inhibitors
- fluoxetine
- allopurinol
- sympatholytics
- cyclo-, tro- and iphosphamides
- CYP2C9 Inhibitors
- fluconazole

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

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

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

Under the influence of sympatholytic drugs such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic 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

	Very common	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders				Changes in hematology ¹⁾	
Immune system disorders					Mild hypersensitivity reactions ²⁾ , leukocytoclastic vasculitis, cross allergenicity with sulfonylureas, sulfonamides or related substances
Metabolism and nutrition disorders				Hypoglycaemia ³⁾	
Eye disorders			Visual disturbances ⁴⁾		
Gastrointestinal disorders					Nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain ⁵⁾
Hepatobiliary disorders				Hepatic enzymes increased	Hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure

Skin and subcutaneous tissue disorders					Hypersensitivity reactions of the skin aspruritus, rash, urticaria and photosensitivity
Investigations					Serum sodium decrease

- 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

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives. ATC Code: A10B B12.

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

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release:

Sulphonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results in 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.

Extraprocreatic 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_{max}) are reached approx. 2.5 hours after oral intake (mean 0.3 µg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both C_{max} and AUC (area under the time/concentration curve).

Distribution: Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 48 ml/min).

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

Biotransformation and elimination: Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabelled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites – most probably resulting from hepatic metabolism - 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
Microcrystalline cellulose
Povidone
Lake colour of indigocarmine (Cl. No. 73015)
Sodium starch glycollate
Magnesium stearate

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

Cold form blister pack (structure from outer to inner side: oriented polyamide / aluminium foil / polyvinyl chloride file) with a backing of aluminium foil coated with heat seal lacquer.

HDPE bottle pack comprises white opaque HDPE bottle with 33 mm / 400 neck finish.

Pack size: 30 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Kohne Pharma GmbH
Schallbruch 1,
D-42781 Haan,
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 20477 / 0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/09/2007

10 DATE OF REVISION OF THE TEXT

28/09/2007

PATIENT INFORMATION LEAFLET

GLIMEPIRIDE 1 mg TABLETS
GLIMEPIRIDE 2 mg TABLETS
GLIMEPIRIDE 3 mg TABLETS
GLIMEPIRIDE 4 mg 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 further questions, please ask your doctor or your 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.*

In this leaflet:

1. What Glimepiride tablets are and what are they used for
2. Before you take Glimepiride tablets
3. How to take Glimepiride tablets
4. Possible side effects
5. Storing Glimepiride tablets

1. What Glimepiride tablets are and what are they used for

The name of your medicine is Glimepiride 1 mg, 2 mg, 3 mg or 4 mg Tablets (also referred to as Glimepiride tablets or glimepiride throughout this leaflet). Glimepiride tablets are available in four strengths: 1 mg, 2 mg, 3 mg and 4 mg.

The active substance is glimepiride.

Each Glimepiride 1 mg, 2 mg, 3 mg and 4 mg Tablet contains glimepiride 1 mg, 2 mg, 3 mg and 4 mg respectively.

Glimepiride tablets also contain some other ingredients: lactose monohydrate, microcrystalline cellulose, povidone, sodium starch glycolate and magnesium stearate.

Lake colour of indigocarmine (Cl. No. 73015) is used as colouring agent.

Glimepiride belongs to a group of medicines called sulphonylurea, which are a type of oral hypoglycaemic drugs. Oral hypoglycaemic drugs including sulphonylurea are used for the treatment of type 2 diabetes (a disease also known as Maturity Onset Diabetes, or Non-Insulin Dependent Diabetes, where the body does not produce enough insulin to control the level of blood sugar). Sulphonylureas increase the secretion of insulin and thereby reduce the level of sugar (glucose) in the blood.

The initial treatment of type 2 diabetes involves exercise and diet changes. Sulphonylureas like Glimepiride are to be used as additional therapy in patients whose blood sugar levels are not adequately controlled by exercise and diet changes alone.

Glimepiride 1 mg Tablets are blue coloured, biconvex round uncoated tablets, debossed with 'G1' on one side and plain on other side.

Glimepiride 2 mg Tablets are blue coloured, dumbbell shaped, uncoated tablets debossed with 'R' and 'B' on either side of scoreline on one side and '4' and '9' on either side of the scoreline on the other side.

Glimepiride 3 mg Tablets are blue coloured, dumbbell shaped, uncoated tablets debossed with 'R' and 'E' on either side of score line on one side and '1' and '1' on either side of the scoreline on the other side.

Glimepiride 4 mg Tablets are blue coloured, dumbbell shaped, uncoated tablets debossed with 'R' and 'B' on either side of the score line on one side and '5' and '0' on either side of the scoreline on the other side.

Glimepiride tablets are available as blister packs or bottles of 30 tablets.

2. Before you take Glimepiride Tablets

Do not take Glimepiride tablets if any of the following apply to you.

- You have previously had an allergic reaction to glimepiride or other sulphonylureas or sulphonamides or to any of the ingredients of your medicine (An allergic reaction may include rash, itching, swelling of face, lips, tongue or hands, feet, or breathing difficulties)
- You have type 1 diabetes mellitus (a type of diabetes that usually develops in childhood and requires insulin injection to control the blood sugar levels)
- You have serious liver or kidney problems
- You have had diabetic ketoacidosis (a rare but serious complication of high blood sugar levels that can even be fatal. Deep rapid breathing and a fruity breath odour, with non-specific symptoms such as nausea, vomiting, stomach pain, feeling faint or light-headed may indicate the development of ketoacidosis. Insulin injections would be required to prevent further worsening of the condition)
- You have suffered a coma from having diabetes
- You are pregnant or planning to be pregnant
- You are currently breast-feeding

Take special care and inform your doctor before you start to take Glimepiride Tablets if:

- You have dysfunction of hormone secreting glands (especially an increased or decreased secretion of hormones by thyroid, pituitary and/or adrenal glands)
- You have problems with your kidney(s) or liver
- You have to undergo a surgical operation (you would require insulin injections)
- You have a serious infection or have had a major accident (you would require insulin injections in these conditions)
- You consume large amounts of alcoholic beverages

Pregnancy and Breast-feeding

You should not take Glimepiride tablets if you are pregnant, you think you might be pregnant or you are planning to become pregnant.

Inform your doctor in case you become pregnant during treatment with Glimepiride tablets.

You should not take Glimepiride tablets if you are currently breast-feeding.

If any of these conditions apply to you, ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Glimepiride may cause hypoglycaemia that may affect your ability to concentrate or cause disturbances of vision. These may affect your ability to drive and 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.

Important information about some of the ingredients of Glimepiride Tablets

Your medicine contains lactose. If your doctor has told you that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Taking other medicines

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed but bought/obtained without a prescription.

Care is needed if you are taking any of the following medicines:

- Other antidiabetic medicines (e.g. insulin or metformin)
- Lipid lowering medicines [fibric acid derivatives (e.g. gemfibrozil, fenofibrate, bezafibrate); niacin]
- Antibiotics such as sulphonamides, quinolones (e.g. ciprofloxacin, ofloxacin), tetracyclines (e.g. doxycycline), chloramphenicol, rifampicin
- Antifungal medicines such as fluconazole and miconazole
- Oral hormonal contraceptives ("oral pills")
- Anticancer medicines (e.g. cyclophosphamide, iphosphamide)
- Phenytoin, phenobarbitone (used to treat epilepsy)
- Water tablets (e.g. furosemide, bumetanide, hydrochlorothiazide, acetazolamide)
- Diazoxide (used to treat severe hypoglycaemia)
- Medicines used to treat high blood pressure [ACE inhibitors (e.g. captopril, enalapril); beta blockers (e.g. propranolol, atenolol); reserpine; guanethidine, clonidine]
- Fluoxetine, chlorpromazine, MAO inhibitors (e.g. phenelzine, pimozone, tranylcypromine) (medicines used to treat depression and/or certain mental illnesses)
- Steroids
- Warfarin (a blood thinning medicine)
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (used as pain killers, e.g. aspirin, phenylbutazone, azapropazone and oxyfenbutazone)
- Allopurinol, probenecid, sulphapyrazone (medicines used to treat a condition called gout, probenecid is also used along with other antibiotics for treating severe infections)
- Sympathomimetics (e.g. adrenaline/epinephrine, noradrenaline/epinephrine, dobutamine, dopamine or other similar drugs which would generally be administered in hospital)
- H₂ receptor antagonist (e.g. cimetidine, ranitidine) (used to reduce the amount of acid produced in the stomach)
- Glucagon (a hormone used to raise blood sugar levels)
- Pentoxifylline (used in the treat conditions resulting from poor peripheral circulation)
- Laxatives (used for treating constipation)

3. How to take Glimepiride Tablets

Take your medicine as instructed by your doctor. Do not take more than the doctor told you to. Check the label carefully for how much to take and how often to take. Your pharmacist or doctor can help if you are not sure.

Your doctor would usually start the treatment with Glimepiride 1 mg Tablet taken once daily. This dose may be enough to control your diabetes. Depending on your blood sugar levels, your doctor may decide to increase the dose to 2 mg, 3 mg, or 4 mg. The dose would be increased gradually at intervals of 1 to 2 weeks. The recommended daily dose should not exceed 6 mg.

Make sure you continue with your regular diet, exercise and other lifestyle measures even while taking Glimepiride tablets. These are important to help control your diabetes.

Your doctor may decide to prescribe other medicines, such as metformin or insulin, for use with Glimepiride to control your blood sugar levels.

Glimepiride tablets are to be swallowed whole with a glass of water. You should always take the tablets immediately before or during breakfast. If you are not in the habit of taking breakfast, then take your medicine before or during the first main meal. Do not skip or delay your meals, as this may increase chances of developing hypoglycemia (please see the separate section on 'Hypoglycaemia' below).

To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.

You should continue to take your tablets as directed unless told to stop by your doctor. Do not stop taking your tablets because you feel better as your symptoms may return.

If you have the impression that the effect of Glimepiride tablets is too strong or too weak, talk to your doctor or pharmacist.

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 dosing schedule. Do not take a double dose to make up for forgotten individual doses.

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.

4. Possible side effects

Like all medicines, Glimepiride tablets may cause side effects, although not everybody experiences them.

Based upon frequency of occurrence, side effects can be classified as:

Uncommon: reported by less than 1 in 100, but more than 1 in 1,000 patients treated

Rare: reported by less than 1 in 1,000, but more than 1 in 10,000 patients treated

Very rare: reported by less than 1 in 10,000 patients treated, including isolated reports.

Very serious side effects

If any of the following happen, stop taking Glimepiride tablets and tell your doctor immediately or go to the casualty department at your nearest hospital

- Rash, hives, itching, chest constriction, swelling of face, lips, hands / feet or shortness of breath, fainting, high temperature (very rare).

These are very serious side effects, although reported very rarely. If you have them, you may have had a serious allergic reaction or other type of reaction to glimepiride. You may need urgent medical attention or hospitalization.

Serious side effects

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Unusual bleeding or increased tendency to bleed, persistent sore throat and frequent infections, and/or anaemia (rare)
- Tiredness, uncontrolled shaking, cold sweats, fast heart beat, feeling faint or lightheaded, hunger pangs, anxiety, inability to concentrate, blurred vision, or nervousness. These may be manifestations of hypoglycaemia (see note below). If not treated promptly, may progress to confusion, or coma. If you experience any of these symptoms, you should immediately take sugar (glucose) tablets or sweetened juices. 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 (rare)
- Yellowing of skin and whites of eyes with decreased appetite, abdominal pain and general feeling of being unwell (these may be manifestations of a liver problem) (very rare).

Other side effects

Tell your doctor if you notice any of the following:

- Temporary problems with your vision, especially on initiation of treatment (uncommon).
- Feeling sick (nausea) or being sick (vomiting), diarrhoea (loose stools), abdominal fullness or abdominal pain (very rare)
- Rash, hives, itching (very rare)
- You develop rash or spots on the skin on exposure to light (very rare).

Laboratory tests

There may be changes in the results of certain laboratory tests

- Abnormal liver function tests (rare)
- Decrease in blood sodium levels (very rare)

Hypoglycaemia (low blood sugar):

Lowering of blood sugar levels to below normal values can lead to symptoms of hypoglycaemia such as tiredness, feeling faint or lightheaded, headache, feeling sick, hunger pangs, anxiety, nervousness, inability to concentrate, sleepiness, blurred vision, uncontrolled shaking, cold sweats, a rapid heart beat, chest pain, fits (convulsions). If not treated promptly, it may progress to loss of consciousness (fainting attack) or even coma.

If you develop any of these symptoms, you should immediately take sugar (glucose) or sweetened juices (artificial sweeteners will not help you).

If the symptoms become severe, or you experience them for a prolonged period of time, you must contact your doctor immediately. You may require immediate medical treatment and in some cases you may need to be hospitalized.

Although, hypoglycemia is reported rarely with the use of Glimepiride tablets, the chances of developing hypoglycaemia increase if:

- You miss or delay your meals. Always take your Glimepiride tablet immediately before or during breakfast or your first main meal
- You change your diet without your doctor's advice
- You do more intense or longer physical exercise than usual, or you do more work than what you usually do
- You take more Glimepiride tablets than advised by your doctor
- You consume alcohol while you are on treatment with Glimepiride tablets
- You have severe liver problems
- You have kidney problems
- You have certain hormonal problems such as a thyroid disorder
- You take other medicinal products without your doctor's advice
- You are recovering from an injury, operation, fever or other illness, or from other forms of stress.

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

5 Storing Glimepiride Tablets

Do not take the tablets after the expiry date on the label.

Do not keep the tablets above 25°C. Store in the original package.

Keep all medicines out of the reach and sight of children - preferably in a locked cupboard or medicine cabinet.

If your doctor tells you to stop taking the tablets, please take them back to the pharmacist.

Marketing Authorisation Holder: Kohne Pharma GmbH, Schallbruch 1, D-42781 Haan, Germany.

Manufacturer: Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co-Tipperary, Republic of Ireland.

This leaflet was prepared in July 2007.

RANBAXY

30 TABLETS

1 mg

Glimepiride

1 mg Tablets

Each tablet contains, as the active ingredient: Glimepiride 1 mg
The tablets also contain lactose monohydrate.

For oral use only.
Use as directed by a physician.
Do not store above 25°C. Store in the original package.

POM

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
DO NOT EXCEED THE STATED DOSE.

MA Holder: Kohne Pharma GmbH
Schallbruch 1,
D-42781 Haan, Germany

PL 20477 / 0016

B.N.

Exp.

CODE No. HP/DRUGS/MNB/95/2

PRESS TABLET THROUGH THE FOIL FROM THE OTHER SIDE.

RANBAXY	RANBAXY	RANBAXY
Glimepiride	Glimepiride	Glimepiride
2 mg	2 mg	2 mg
Tablets	Tablets	Tablets
MA Holder: Kohne Pharma GmbH	MA Holder: Kohne Pharma GmbH	MA Holder: Kohne Pharma GmbH

PRESS TABLET THROUGH THE FOIL FROM THE OTHER SIDE.

RANBAXY	RANBAXY	RANBAXY
Glimepiride	Glimepiride	Glimepiride
2 mg	2 mg	2 mg
Tablets	Tablets	Tablets
MA Holder: Kohne Pharma GmbH	MA Holder: Kohne Pharma GmbH	MA Holder: Kohne Pharma GmbH

PRESS TABLET THROUGH THE FOIL FROM THE OTHER SIDE.

RANBAXY	RANBAXY	RANBAXY
Glimepiride	Glimepiride	Glimepiride
2 mg	2 mg	2 mg
Tablets	Tablets	Tablets
MA Holder: Kohne Pharma GmbH	MA Holder: Kohne Pharma GmbH	MA Holder: Kohne Pharma GmbH

Exp.

B.N.

CODE No. HP/DRUGS/MNB/95/2

30 TABLETS

Glimepiride

2 mg Tablets

Each tablet contains, as the active ingredient: Glimepiride 2 mg. The tablets also contain lactose monohydrate.

2 mg

For oral use only. Use as directed by a physician.

Do not store above 25°C. Store in the original package.

POM

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

DO NOT EXCEED THE STATED DOSE.

MA Holder: Kohne Pharma GmbH, Schallbruch 1, D-42781 Haan, Germany

PL 20477 / 0017

B.N. Exp.


CODE No. HP/DRUGS/MNB/95/2

Glimepiride 2 mg Tablets

Each tablet contains, as the active ingredient: Glimepiride 2 mg. The tablets also contain lactose monohydrate.

For oral use only. Use as directed by a physician.

Affix pharmacist label :



2 mg

30 TABLETS

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

POM

B.N. Exp.

MA Holder: Kohne Pharma GmbH, Schallbruch 1, D-42781 Haan, Germany PL 20477 / 0017

Distributor: Ranbaxy (UK) Limited, 20 Balderton Street, London W1K 6TL, United Kingdom

Do not store above 25°C. Store in the original package. DO NOT EXCEED THE STATED DOSE.

30 TABLETS

RANBAXY

Glimepiride

2 mg Tablets

2 mg

R

Please read the enclosed leaflet before taking this medicine

Glimepiride
Size : 124
Market : U
Proof : 27

021

glimepiride
#2 mg
tablets

RANBAXY

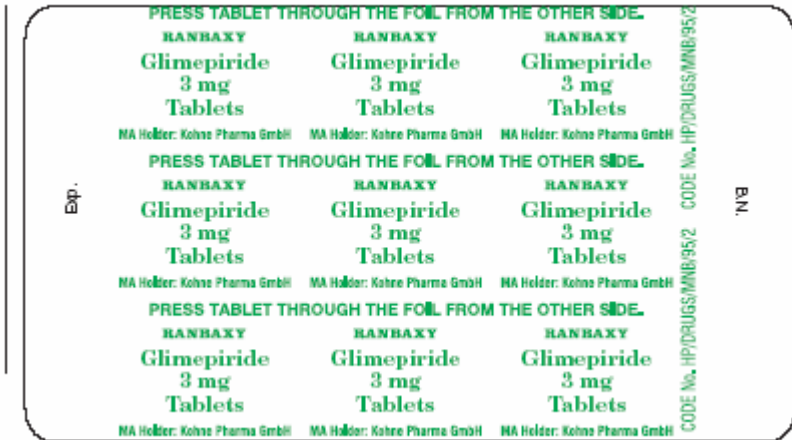
Glimepiride

2 mg Tablets

CODE No. HP/DRUGS/MNB/95/2

2 mg

PACK CONTAINS 30 TABLETS



30 TABLETS

3 mg

Glimepiride

3 mg Tablets

Each tablet contains, as the active ingredient:
Glimepiride 3 mg
The tablets also contain lactose monohydrate.

For oral use only.
Use as directed by a physician.
Do not store above 25°C. Store in the original package.

POM

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
DO NOT EXCEED THE STATED DOSE.

MA Holder:
Kohne Pharma GmbH
Schallbruch 1,
D-42781 Haan, Germany
PL 20477 / 0018

B.N.

Exp.

CODE No. HP/DRUGS/MNB/95/2

<p>Glimepiride 3 mg Tablets</p> <p>Each tablet contains, as the active ingredient: Glimepiride 3 mg The tablets also contain lactose monohydrate. For oral use only. Use as directed by a physician.</p> <p>Affix pharmacist label:</p>  <p>3 mg 30 TABLETS</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p>POM</p> <p>B. N. Exp.</p>	<p>MA Holder: Kohne Pharma GmbH Schallbruch 1, D-42781 Haan, Germany PL 20477 / 0018</p> <p>Distributor: Ranbaxy (UK) Limited, 20 Balderton Street, London W1K 6TL, United Kingdom</p> <p>Do not store above 25°C. Store in the original package. DO NOT EXCEED THE STATED DOSE.</p>	
<p>RANBAXY Glimepiride 3 mg Tablets</p> <p>3 mg PACK CONTAINS 30 TABLETS</p>	<p>30 TABLETS</p> <p>RANBAXY Glimepiride 3 mg Tablets</p>  <p>3 mg</p> <p>Please read the enclosed leaflet before taking this medicine</p>	<p>Glimepiride Size : 12 Market : 1 Proof : 2</p> <p>021</p> <p>glimepiride #3 mg tablets</p>
<p>RANBAXY Glimepiride 3 mg Tablets</p> <p>CODE No. HPDRUGS/MNB/052</p> <p>3 mg PACK CONTAINS 30 TABLETS</p>		



30 TABLETS

Glimepiride

4 mg Tablets

Each tablet contains, as the active ingredient: Glimepiride 4 mg. The tablets also contain lactose monohydrate.

4 mg

For oral use only.

Use as directed by a physician.

Do not store above 25°C. Store in the original package.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

DO NOT EXCEED THE STATED DOSE.

POM





MA Holder:
Kohse Pharma GmbH
Schallbruch 1,
D-42781 Haan, Germany

PL 20477 / 0019

B.N.

Exp.

CODE No. HP/DRUGS/MNB/95/2

<p>Glimepiride 4 mg Tablets</p> <p>Each tablet contains, as the active ingredient: Glimepiride 4 mg The tablets also contain lactose monohydrate. For oral use only. Use as directed by a physician.</p> <p>Affix pharmacist label:</p>  <p>5015525107094511</p>	<p>4 mg 30 TABLETS</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p>POM</p> <p>B.N. Exp.</p>	
<p>MA Holder: Kohne Pharma GmbH Schallbruch 1, D-42781 Haan, Germany PL 20477 / 0019</p>	<p>Distributor: Ranbaxy (UK) Limited, 20 Balderton Street, London W1K 6TL, United Kingdom</p>	<p>Do not store above 25°C. Store in the original package. DO NOT EXCEED THE STATED DOSE.</p>
<p>RANBAXY Glimepiride 4 mg Tablets</p> <p>4 mg PACK CONTAINS 30 TABLETS</p>	<p>30 TABLETS</p> <p>RANBAXY Glimepiride 4 mg Tablets</p>   <p>Please read the enclosed leaflet before taking this medicine</p>	<p>Glimepirid Size : 124 : Market : U Proof : 27-</p> <p>021</p> <p>glimepirid #4 mg tablets</p> 
<p>RANBAXY Glimepiride 4 mg Tablets</p>	<p>CODE No. HP/DRUGS/MNB/862</p>	<p>4 mg PACK CONTAINS 30 TABLETS</p>