

**GLICLAZIDE 40MG TABLETS
(GLICLAZIDE)**

PL 17907/0067

UK Public Assessment Report

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Steps taken after authorisation	Page 15
Summary of Product Characteristics	Page 16
Product Information Leaflet	Page 20
Labelling	Page 22

**GLICLAZIDE 40MG TABLETS
(GLICLAZIDE)**

PL 17907/0067

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Gliclazide 40mg Tablets (PL 17907/0067) on 12th June 2007. This is a prescription-only medicine (POM) used in the treatment of non insulin-dependent diabetes.

Gliclazide 40mg Tablets are used for the treatment of diabetes when insulin is not necessary and when diet alone fails to lower blood glucose (sugar). Gliclazide belongs to a group of medicines called sulphonylureas and works by lowering the sugar level.

Gliclazide 80mg Tablets BP was considered to be a generic version of the reference product Diamicon 80mg Tablets (PL 00093/0024, Servier Laboratories Limited) based on data submitted by Bristol Laboratories Limited. Data from the application for Gliclazide 80mg Tablets (PL 17907/0068) were extrapolated to the Marketing Authorisation applied for, Gliclazide 40mg Tablets.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Gliclazide 40mg Tablets outweigh the risk; hence a Marketing Authorisation has been granted.

**GLICLAZIDE 40MG TABLETS
(GLICLAZIDE)**

PL 17907/0067

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment	Page 9
Overall conclusion and risk benefit assessment	Page 13

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited a Marketing Authorisation for the medicinal product Gliclazide 40mg Tablets (PL 17907/0067) on 12th June 2007. The product is a prescription-only medicine (POM) indicated for the treatment of non insulin-dependent diabetes mellitus.

The application was submitted, at the same time as the application for Gliclazide 80mg Tablets (PL 17907/0068), according to Article 10.3 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Diamicon 80mg Tablets (PL 00093/0024, Servier Laboratories Limited), which was originally granted a UK licence on 21/12/1979.

The innovator UK SPC states “The total daily dose may vary from 40 to 320 mg taken orally. The dose should be adjusted according to the individual patient's response, commencing with 40-80 mg daily (1/2 - 1 tablet) and increasing until adequate control is achieved.”. As the dosage range of the innovator product includes the dose of 40mg, the application for a 40mg strength tablet is acceptable.

Gliclazide 40mg Tablets contain the active ingredient gliclazide, which belongs to the sulphonylurea class of drugs and can control the level of sugar in the blood of patients with non-insulin-dependent diabetes mellitus. Apart from having similar hypoglycaemic effect to the other sulphonylureas, gliclazide has been shown to reduce platelet adhesiveness and aggregation and increase fibrinolytic activity. These factors are thought to be implicated in the pathogenesis of long-term complications of diabetes mellitus.

The application depends upon the bioequivalence study presented by the applicant comparing the Bristol Laboratories Limited product Gliclazide 80mg Tablets (PL 17907/0068) with the reference product Diamicon 80mg Tablets (PL 00093/0024, Servier Laboratories Limited). As the test products, Gliclazide 40mg Tablets and Gliclazide 80mg Tablets BP, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 80mg strength were extrapolated to the 40mg strength tablets.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

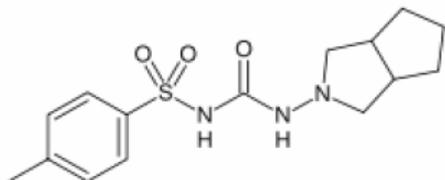
Gliclazide

Nomenclature:

INN: Gliclazide

Chemical name: *N*-[[[(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)amino]carbonyl]-4-methylbenzenesulfonamide

Structure:



Molecular formula: $C_{15}H_{21}N_3O_3S$

Molecular weight: 323.4

CAS No: 21187-98-4

Physical form: A white or almost white powder

Solubility: Insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in alcohol

The active substance, gliclazide, is the subject of a Ph. Eur. monograph.

The manufacture and quality of the active substance, manufactured by the active substance manufacturers, are controlled by Certificates of Suitability. Confirmation has been provided that the materials used in the synthesis of the active substance are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which is in line with the European Pharmacopeia monograph specification and Certificates of Suitability (CEPs).

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Active gliclazide is stored in appropriate packaging. The primary packaging complies with Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

The CEPs state a retest period of 2 years for active substance stored in the proposed packaging.

DRUG PRODUCT

Composition

The drug product is presented as immediate release uncoated tablets containing 40mg of the active substance gliclazide.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, purified talc, croscarmellose sodium, magnesium stearate, and povidone. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as milk collected for human consumption.

There were no novel excipients used and no overages.

Dissolution profiles

Dissolution profiles of Gliclazide 40mg Tablets were shown to be comparable with Diamicon Tablets.

Pharmaceutical development

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

Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification is satisfactory and complies with the requirements of the BP monograph. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification.

Container Closure System

The tablets are packed in PVC (polyvinyl chloride) / PVDC (polyvinylidene chloride) / aluminium foil blisters, which are placed with the PIL into cardboard outer cartons. The product is packaged in carton pack sizes of 20, 28, 56, 60, 84, or 100 tablets. The tablets are also marketed in HDPE containers with HDPE lids in pack sizes of 100, 250, 500 or 1000 tablets. The MA holder has stated that not all pack sizes will be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. The storage instructions are 'Do not store above 25°C' and 'Store in the original package' for the blisters, and 'Do not store above 25°C' and 'Keep the container tightly closed' for the HDPE containers.

Bioequivalence Study

A bioequivalence study was submitted comparing the test product, Gliclazide 80mg Tablets BP, to the innovator product, Diamicron 80mg Tablets (PL 00093/0024, Servier Laboratories Limited).

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

Product Information

The approved SPC, leaflet, and labelling are satisfactory.

Conclusion

Considering the bioequivalence data provided, the applicant's claim that Gliclazide 80mg Tablets BP is a generic medicinal product of Diamicron 80mg Tablets appears justified. The results of the bioequivalence study can be extrapolated to the 40mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation may be granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, complex, hybrid application, according to Article 10.3 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Gliclazide 40mg Tablets are indicated for the treatment of non insulin-dependent (deficient) diabetes mellitus (NIDDM).

The indication is consistent with that for the innovator product and is satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the innovator product.

TOXICOLOGY

No new data has been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

Pharmacodynamics

No additional pharmacodynamic studies have been presented.

Pharmacokinetics

The company have aimed to justify their claim that Gliclazide 40mg Tablets are a hybrid version of Diamicon 80mg Tablets by showing bioequivalence between Gliclazide 80mg Tablets (PL 17907/0068) and the innovator product through a single dose bioequivalence study.

Bioequivalence Study

The applicant has conducted a bioequivalence study in healthy human subjects and in accordance with Good Clinical Practice. The study design was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose crossover comparative oral study in healthy adult male human subjects under fasting conditions.

Following initial screening, 26 eligible volunteers were enrolled into the study to obtain the data from 24 evaluable subjects as required in the study protocol. At the initial screening the health, blood picture and physical measurements were recorded, and the subjects satisfying the inclusion criteria were enrolled onto the study. The inclusion criteria included an age range of 18-55 years of age, a body mass index of 18-25 inclusive, and having to be a healthy male.

Subjects received 1 tablet of either the test product, Gliclazide 80mg tablets BP, or the reference product, Diamicon 80mg Tablets, manufactured by Servier Laboratories Limited. Treatment compliance was confirmed by mouth inspection at the time of dose administration. There was a wash-out period of 6 days between treatments. Blood samples were taken pre-dose and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 28, 32, 36, 48 and 60 hours following oral administration of the test materials. Blood samples were processed and the resultant plasma stored until the measurement of drug concentration. The drug concentration measurements were conducted using a validated HPLC-UV method.

The following pharmacokinetic parameters were calculated from the resulting plasma concentration curve:-

- Maximum plasma concentration [C_{\max}]
- Time point of maximum plasma concentration [T_{\max}]
- Area under the plasma concentration-time curve from 0 hours to the last measurable concentration [AUC_{0-t}]
- Area under the plasma concentration-time curve from 0 hours to infinity [$AUC_{0-\infty}$]
- Elimination rate constant [λ_z]
- Half-life of drug elimination during the terminal phase [$t_{1/2}$]
- AUC % extrapolated [residual area]

The results were statistically analysed using analysis of variance. Bioequivalence was concluded if the 90% confidence interval was within the acceptable range of 0.8-1.25 (80-125%) for ln-transformed pharmacokinetics parameters – C_{\max} , T_{\max} , AUC_{0-t} and $AUC_{0-\infty}$.

It was originally planned to dose 26 subjects and analyse blood samples from the first 24, however, only 23 subjects completed the study. Of the three subjects that did not complete the study, one dropped out before dose administration at the start of the first period and two dropped out on the day of check-in for the second (crossover phase) of the study. The statistical analysis was therefore conducted on data from the 23 who completed the study. The results of the analysis of the blood samples are presented as mean values \pm SD in Table 1

Table 1 Mean pharmacokinetics parameters estimated for gliclazide formulations, test product v reference product.

Parameter (units)	Mean \pm SD	
	Test Product	Reference Product
T_{\max} (hours)	3.6909 \pm 1.1477	4.130 \pm 1.1699
C_{\max} (mcg/ml)	4.889 \pm 1.1892	4.714 \pm 0.9740
AUC_{0-t} (mcg.h/ml)	67.848 \pm 24.5448	67.894 \pm 21.6228
$AUC_{0-\infty}$ (mcg.h/ml)	71.406 \pm 26.7924	72.077 \pm 23.8415
λ_z (1/h)	0.0630 \pm 0.02000	0.0582 \pm 0.02093
$t_{1/2}$ (hours)	11.991 \pm 3.5828	13.126 \pm 3.8210
AUC% extrapolated (%)	4.662 \pm 2.2958	5.475 \pm 2.2840

The confidence intervals are presented in Table 2.

Table 2 In-transformed least square means and 90% confidence interval based on root mean square error obtained from ANOVA and ratio of gliclazide formulations.

Parameter (Unit)	In-transformed least square means			In-transformed Conventional 90% Confidence Interval (Parametric)
	Test Product (A)	Reference Product (B)	B/A %	
C_{\max} (mcg/ml)	4.774	4.625	103.2%	96.63 – 110.27%
AUC_{0-t} (mcg.h/ml)	64.026	64.695	99.0%	94.01 – 104.19%
$AUC_{0-\infty}$ (mcg.h/ml)	67.198	68.438	98.2%	93.38 – 103.25%

It was concluded that none of the values of the parameters in Table 1 of the test material were statistically significantly different from those of the reference product, and that all the parameters stated in Table 2 were well within the acceptable limits of 0.8-1.25 (80-125%).

Bioequivalence has been satisfactorily demonstrated and it can therefore be concluded that the test material Gliclazide 80mg tablets BP, manufactured to be licensed by the applicant, is bioequivalent to the reference product, Diamicon 80mg Tablets, manufactured by Servier Laboratories Limited.

A separate bioequivalence study has not been carried out on the lower strength product and Marketing Authorisation applied for, Gliclazide 40mg Tablets (PL 17907/0067). This was not considered necessary as Gliclazide 40mg Tablets and Gliclazide 80mg Tablets BP meet the specified exemption criteria, detailed in CPMP/EWP/QWP/1401/98, as follows:

- same qualitative composition
- same ratios between active and excipients
- same in-vitro dissolution rates
- drug input linear over therapeutic range
- manufactured by same company on same site

The bioequivalence study submitted is, therefore, sufficient to support the applicants claim that Gliclazide 40mg Tablets are a hybrid version of Diamicon 80mg Tablets.

EFFICACY

No new data are submitted and none are required for this type of application.

Efficacy is reviewed in the clinical expert report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

SAFETY

No new data are submitted and none are required for this type of application.

No new or unexpected safety concerns arose from this application .Safety is reviewed in the clinical expert report. The reference product is established and the main basis of the application depends upon the bioequivalence study.

EXPERT REPORT

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

PRODUCT INFORMATION:**Summary of Product Characteristics**

The final SmPC is consistent with that for the innovator product and is acceptable.

Patient Information Leaflet

The PIL is in line with the approved SPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

DISCUSSION AND CONCLUSION

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Gliclazide 80mg Tablets BP) and reference (Diamicron 80mg Tablets) products within general acceptance limits. It was not necessary for a similar bioequivalence study to be undertaken on the 40mg tablets for the reasons discussed. The bioequivalence study presented supports the applicant's claim that Gliclazide 40mg Tablets are a hybrid version of Diamicron 80mg Tablets.

Sufficient clinical information has been submitted to support this application. A Marketing Authorisation may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Gliclazide 40mg 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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between Gliclazide 80mg tablets BP and the reference product Diamicon 80mg Tablets (Servier Laboratories Limited). This supports the applicant's claim that Gliclazide 40mg Tablets are a hybrid version of Diamicon 80mg Tablets. The results and conclusions of the bioequivalence study on the 80mg strength were extrapolated to the 40mg tablet strength. A separate bioequivalence study was not considered necessary for Gliclazide 40mg Tablets as exemption criteria, detailed in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), have been fulfilled.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory and consistent with that for Diamicon 80mg Tablets.

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

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

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's test product (Gliclazide 80mg tablets BP) and the innovator product (Diamicon 80mg Tablets) are interchangeable. Based on consideration of composition, method of manufacture, supporting development data and pharmacokinetics, Gliclazide 40mg Tablets are approvable as a 'line extension' to introduce an additional strength tablet within the approved posology. Extensive clinical experience with gliclazide is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**GLICLAZIDE 40MG TABLETS
(GLICLAZIDE)**

PL 17907/0067

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application on 24th November 2003
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 8th January 2004
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 26th February 2004 and further information relating to the quality dossier on 2nd December 2004
- 4 The applicant responded to the MHRA's request, providing further information for the clinical sections on 30th March 2005 and for the quality sections on 16th May 2005
- 5 The application was determined on 12th June 2007

**GLICLAZIDE 40MG TABLETS
(GLICLAZIDE)**

PL 17907/0067

STEPS TAKEN AFTER AUTHORISATION

Date submitted	Application type	Scope	Outcome
04/10/2007	Label and leaflet – self certification	Label and leaflet submission for self certification under article 61 (3)	Application granted 12/10/2007
15/11/2007	Variation Pharmaceutical Type 1B National	To increase the shelf life of the product from 2 years to 3 years- section 6.3 (Shelf life) of the SPC is updated	Application granted 07/12/2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Gliclazide 40mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Gliclazide 40mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gliclazide 40mg

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet

White to off-white, circular, flat, bevelled edged, uncoated tablets with "40" on one side, plain on reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Non insulin dependent diabetes mellitus.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral administration.

Adults:

The total daily dose may vary from 40 to 320 mg taken orally. The dose should be adjusted according to the individual patient's response, commencing with 40-80 mg daily (1 - 2 tablets) and increasing until adequate control is achieved. A single dose should not exceed 160 mg (4 tablets). When higher doses are required, gliclazide should be taken twice daily and according to the main meals of the day.

In obese patients or those not showing adequate response to gliclazide alone, additional therapy may be required.

Elderly:

Plasma clearance of gliclazide is not altered in the elderly and steady state plasma levels can therefore be expected to be similar to those in adults under 65 years. Clinical experience in the elderly to date shows that gliclazide is effective and well tolerated. Care should be exercised, however, when prescribing sulphonylureas in the elderly due to a possible age-related increased risk of hypoglycaemia.

Children:

Gliclazide as with other sulphonylureas, is not indicated for the treatment of juvenile onset diabetes mellitus.

4.3 CONTRAINDICATIONS

Gliclazide should not be used in:

- Juvenile onset diabetes.
- Diabetes complicated by ketosis and acidosis.
- Pregnancy.
- Diabetics undergoing surgery, after severe trauma or during infections.
- Patients known to have hypersensitivity to other sulphonylureas and related drugs or any of the other tablet ingredients.

- Diabetic pre-coma and coma.
- Severe renal or hepatic insufficiency.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- Hypoglycaemia: all sulphonylurea drugs are capable of producing moderate or severe hypoglycaemia, particularly in the following conditions:
 - in patients controlled by diet alone,
 - in cases of accidental overdose,
 - when calorie or glucose intake is deficient,
 - in patients with hepatic and/or renal impairment; however, in long-term clinical trials, patients with renal insufficiency have been treated satisfactorily, using gliclazide at reduced doses.

In order to reduce the risk of hypoglycaemia it is therefore recommended:

- to initiate treatment for non-insulin dependent diabetics by diet alone, if this is possible,
- to take into account the age of the patient: blood sugar levels not strictly controlled by diet alone might be acceptable in the elderly,
- to adjust the dose of gliclazide according to the blood glucose response and to the 24 hour urinary glucose during the first days of treatment.

Dosage adjustments may be necessary:

- on the occurrence of mild symptoms of hypoglycaemia (sweating, pallor, hunger pangs, tachycardia, sensation of malaise). Such findings should be treated with oral glucose and adjustments made in drug dosage and/or meal patterns,
- on the occurrence of severe hypoglycaemic reactions (coma or neurological impairment, see overdose),
- loss of control of blood glucose (hyperglycaemia). When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a loss of control may occur. At such times, it may be necessary to increase progressively the dosage of gliclazide and if this is insufficient, to discontinue the treatment with gliclazide and to administer insulin. As with other sulphonylureas, hypoglycaemia will occur if the patients' dietary intake is reduced or if they are receiving a larger dose of gliclazide than required.
- Care should be exercised in patients with hepatic and/or renal impairment and a small starting dose should be used with careful patient monitoring.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Care should be taken when giving gliclazide with drugs which are known to alter the diabetic state or potentiate the drug's action.

The hypoglycaemic effect of gliclazide may be potentiated by phenylbutazone, salicylates, sulphonamides, coumarin derivatives, MAOIs, beta adrenergic blocking agents, tetracycline compounds, chloramphenicol, clofibrate, disopyramide, miconazole (oral forms) and cimetidine.

It may be diminished by corticosteroids, oral contraceptives, thiazide diuretics, phenothiazine derivatives, thyroid hormones and abuse of laxatives.

4.6 PREGNANCY AND LACTATION

Pregnancy:

Gliclazide is contraindicated during pregnancy (see section 4.3 contra-indications).

Lactation:

It has not been established whether gliclazide is transferred to human milk. However, other sulphonylureas have been found in milk and there is no evidence to suggest that gliclazide differs from the group in this respect. Gliclazide should, therefore, not be taken while the mother is breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be informed that their concentration may be affected if their diabetes is not satisfactorily controlled, especially at the beginning of treatment (see special warnings and precautions).

4.8 UNDESIRABLE EFFECTS

- Hypoglycaemia (see special warnings and precautions).
- Abnormalities of hepatic function are not uncommon during gliclazide therapy. There are rare reports of hepatic failure, hepatitis and jaundice following treatment with gliclazide.
- Mild gastro-intestinal disturbances including nausea, dyspepsia, diarrhoea, constipation have been reported but this type of adverse reaction can be avoided if gliclazide is taken during a meal.
- Skin reactions including rash, pruritus, erythema, bullous eruption; blood dyscrasia including anaemia, leukopenia, thrombocytopenia and granulocytopenia have been observed during treatment with gliclazide but are not known to be directly attributable to the drug.

4.9 OVERDOSE

The symptom to be expected of overdose would be hypoglycaemia. The treatment is gastric lavage and correction of the hypoglycaemia by appropriate means with continual monitoring of the patient's blood sugar until the effect of the drug has ceased.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

A10B B09 Oral Blood Glucose Lowering Drugs

Gliclazide is a hypoglycaemic sulphonylurea differing from other related compounds by the addition of an azabicyclo-octane ring.

In man, apart from having similar hypoglycaemic effect to the other sulphonylureas, gliclazide has been shown to reduce platelet adhesiveness and aggregation and increase fibrinolytic activity. These factors are thought to be implicated in the pathogenesis of long-term complications of diabetes mellitus.

Gliclazide primarily enhances the first phase of insulin secretion, but also to a lesser degree its second phase. Both phases are diminished in non-insulin dependent diabetes mellitus.

5.2 PHARMACOKINETIC PROPERTIES

The drug is well absorbed and its half-life in man is approximately 10-12 hours. Gliclazide is metabolised in the liver; less than 5% of the dose is excreted unchanged in the urine.

5.3 PRECLINICAL SAFETY DATA

No data of relevance which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**

Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Purified talc
Croscarmellose sodium
Povidone

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Blisters: Do not store above 25°C. Store in the original package.
Tablet containers: Do not store above 25°C. Keep the container tightly closed.

6.5 NATURE AND CONTENTS OF CONTAINER

Al / PVC/PVDC blister, pack sizes of 20, 28, 56, 60, 84, 100 tablets.
HDPE tablet containers, pack sizes of 100, 250, 500 or 1000 tablets.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted
Hertfordshire
HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0067

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/06/2007

10 DATE OF REVISION OF THE TEXT

03/12/2007

PATIENT INFORMATION LEAFLET**PATIENT INFORMATION LEAFLET**

Please read all of this leaflet carefully before you start taking this medicine.

Keep the leaflet, you may need to read it again.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is
GLICLAZIDE 40mg TABLETS

Gliclazide tablets contains 40mg gliclazide as the active ingredient. The tablets also contain lactose monohydrate, microcrystalline cellulose, magnesium stearate, purified talc, croscarmellose sodium and povidone.

The product licence holder and manufacturer is Bristol Laboratories Ltd., Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG, UK.

What the tablets are and what they are used for

Gliclazide belongs to a group of medicines called sulphonylureas that work by lowering the blood glucose (sugar) level.

Gliclazide 40 mg tablets are round, white or off white coloured, uncoated tablets with '40' on one side.

The tablets are supplied to your pharmacist in packs containing 20, 28, 56, 60, 84, 100, 250, 500 or 1000 tablets who will then provide you with the required number of tablets as prescribed by your doctor (not all pack sizes may be marketed).

Gliclazide Tablets are used in the treatment of diabetes mellitus when insulin is not necessary and when diet alone fails to lower blood glucose (sugar).

Before you take the tablets**DO NOT TAKE THIS MEDICINE IF:**

- You are pregnant, think you may be pregnant or are planning a pregnancy.
- You are breastfeeding.
- You are allergic to gliclazide, sulphonylureas or other related drugs, or to any of the other ingredients in the tablets which are listed above.
- You are undergoing surgery, after trauma or if you have an infection.
- You suffer from severe kidney or liver problems.
- You are suffering from diabetes complicated with ketosis or acidosis.

This medicine should not be given to treat diabetes in children.

CHECK WITH YOUR DOCTOR BEFORE TAKING IF you are taking any other medicines, particularly any of the following:

- Salicylates (e.g. aspirin) used for pain relief.
- Sulphonamide drugs (used to treat infections).
- Coumarin drugs (for e.g. warfarin) used to thin the blood.
- Monoamine oxidase inhibitors, also known as MAOI's (used to treat depression).
- Beta-blockers (used to treat high blood pressure).
- Tetracycline drugs (antibiotics used to treat infections).
- Corticosteroids (used to treat allergic and inflammatory conditions).
- Thiazide diuretics, also known as water tablets (used to increase urine output).
- Phenothiazine derivatives (used as sedatives).
- The drugs phenylbutazone (used to treat arthritis), chloramphenicol (an antibiotic used to treat infection), clofibrate (used to reduce high levels of cholesterol), disopyramide (used to treat an irregular or fast heart beat), miconazole (when taken orally to treat fungal infections), cimetidine (used to treat stomach ulcers), thyroid hormones or if you overuse laxatives.

XXX

If you are taking any other medicines, including any you have bought without a prescription, please check with your doctor before taking these tablets.

As with all diabetic medicines, it is possible that your blood sugar level may become too low (a condition known as hypoglycaemia). This is more likely to occur if your dietary intake is reduced, you suffer from impaired liver or kidney function, you are elderly or if you accidentally take too much of your medicine.

If you suffer from a fever, an infection, trauma or undergo surgery your diabetes may not be controlled. Please ensure you tell your doctor, as your dose or medication may need to be changed.

If your diabetes is not satisfactorily controlled, your concentration and therefore your ability to drive or operate machinery may be affected. Drinking alcohol can alter the control of your treatment for diabetes.

This medicine contains lactose; if you have been told by your doctor that you have an intolerance to lactose, contact your doctor before taking this product.

Taking your medicine

For oral use. Swallow the tablets with a drink of water.

The total daily dose of gliclazide may vary from 40mg to 320mg and the dose required will be adjusted according to your response. Take the tablets exactly as directed by your doctor, this will be written on the pharmacist's label. If you do not understand the directions, ask your pharmacist or doctor to explain them to you.

The usual adult dose is as follows:

Initially, a daily dose of 40-40mg will be prescribed. This dose will gradually be increased by your doctor until adequate control is achieved. A single dose should not exceed 160mg. When higher doses are required, the tablets should be taken twice a day with the main meals of the day.

Gliclazide tablets are not recommended for use in children.

If you miss a dose: Take the missed dose as soon as you remember and then take your next dose when it is due. Do not take a double dose to make up for the missed dose.

If you take too much: If you have taken too many tablets, you must contact your doctor or hospital casualty department IMMEDIATELY. If you take too many tablets it may cause hypoglycaemia (too low a level of blood sugar); symptoms may include weakness, headache, sweating, feelings of hunger, raised pulse rate, breathlessness, tremor, problems with vision, loss of muscle co-ordination or anxiety. This condition can be helped by taking glucose or sweet drinks.

Possible Side-Effects

As with all medicines there is a possibility of unwanted effects whilst taking this medicine, these may include:

- Hypoglycaemia; symptoms may include weakness, headache, sweating, feelings of hunger, raised pulse rate, breathlessness, tremor, problems with vision, loss of muscle co-ordination or anxiety.
- Impaired liver function and rarely liver failure, hepatitis or jaundice (yellowing of the skin/whites of the eyes).
- Gastro-intestinal problems such as nausea, indigestion, diarrhoea or constipation. These may be avoided if the tablets are taken during a meal.
- Skin rash or itching, blood disorders which may result in anaemia, bruising/bleeding under the skin, abnormal bleeding or signs of infection such as sore throat or fever.

If you do notice any of the above effects, or you notice any other unusual or unexpected effects and think your tablets may be causing them, please inform your doctor or pharmacist.

Storing the tablets

Keep out of the reach and sight of children.

Blisters: Do not store above 25°C. Store in the original package to protect from moisture.

Tablet Containers: Do not store above 25°C. Keep the container tightly closed to protect from moisture.

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

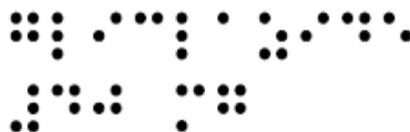
Unless your doctor tells you to, do not keep any tablets that you no longer need. Give them back to the pharmacist.

Date of preparation of leaflet: February 2007.

XXXXXX

LABELLING

Carton for pack size 28, with braille

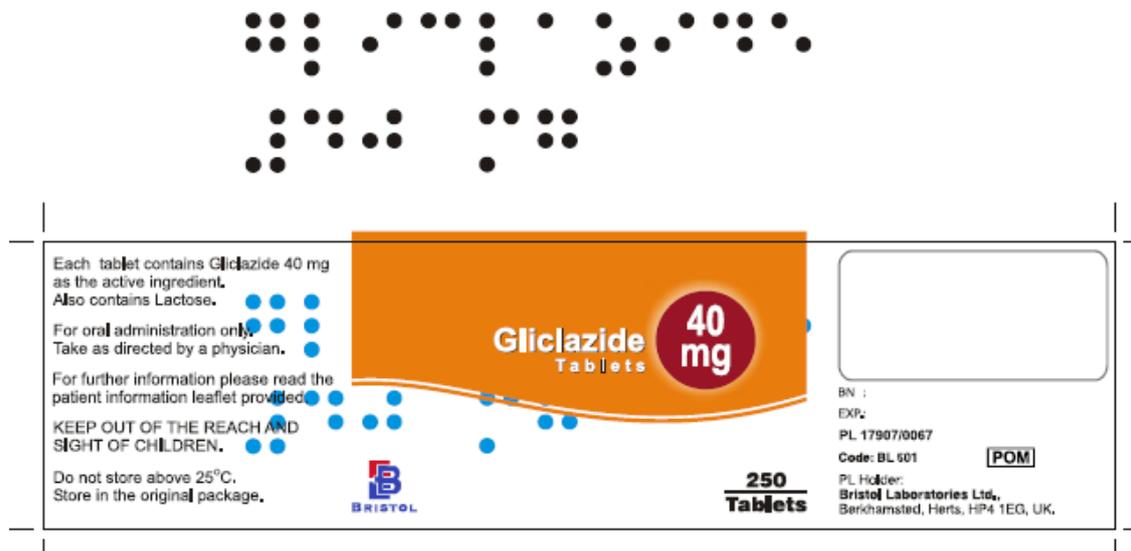


Gliclazide 40 mg Tablets Carton 28's
 Size: 116 x 16 x 50 mm
 Layout No.: 38 09 10 41
 716 C 7427 C 2728 C
 186 C 424 C Black
 Graphic Creations

Carton for pack size 20, with braille



Bottle label for pack size 250, with braille



Blister foil for blisters of 8 tablets

<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>FXXX EXP.</p>
<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>FXXX B.No.</p>
<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>FXXX EXP.</p>
<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>FXXX B.No.</p>

Blister foil for blisters of 10 tablets

<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>
<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>
<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>
<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>
<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>	<p>GLICLAZIDE 40 MG TABLETS PL Holder Bristol Laboratories Ltd. Code: BL 501</p>