

GLICLAZIDE 80 MG TABLETS

PL 17907/0068

UKPAR

TABLE OF CONTENTS

Lay summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 17
Summary of product characteristics	Page 18
Product information leaflet	Page 23
Labelling	Page 25

GLICLAZIDE 80 MG TABLETS

PL 17907/0068

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Bristol Laboratories a Marketing Authorisation (licence) for the medicinal product Gliclazide 80mg Tablets (PL 17907/0068) on 19 July 2006. This product has been granted prescription only status.

Gliclazide 80mg Tablets contain the active ingredient gliclazide, which can control the level of sugar in the blood of patients with non-insulin-dependent diabetes mellitus.

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 80mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

GLICLAZIDE 80 MG TABLETS

PL 17907/0068

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 11
Clinical assessment (including statistical assessment)	Page 12
Overall conclusions and risk benefit assessment	Page 16

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Gliclazide 80mg Tablets (PL 17907/0068) to Bristol Laboratories on 19 July 2006. This tablet is available by prescription only.

This is a national application for Gliclazide 80mg Tablets, submitted under EC Article 10.1, cross-referring to a reference product with a valid UK licence.

Gliclazide acts on the cells of the pancreas, causing it to produce more insulin, which in turn helps the body regulate blood sugar levels in patients with non insulin dependent diabetes mellitus.

PHARMACEUTICAL ASSESSMENT REPORT

1 INTRODUCTION

This application is for Gliclazide 80mg Tablets (PL 17907/0068).

1.1 LEGAL BASIS

This is an abridged application. The applicant claims essential similarity, under article 10.1 of Directive 2001/83/EC, to Diamicron 80mg Tablets (PL 00093/0024, licensed 21 December 1979).

1.2 USE

The product is indicated for “non insulin dependent diabetes mellitus”. This is the same as the innovator.

2 MODULE 2.3 QUALITY OVERALL SUMMARY (QOS)

This is satisfactory.

3 DRUG SUBSTANCE

There is a Ph.Eur monograph for Gliclazide. There are two drug substance manufacturers and actives from both sites have CEP. Letters have been provided confirming that Bristol laboratories are authorised to use the active.

3.1 GENERAL INFORMATION

Description

N-[[[Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl]amino]carbonyl]-4-methylbenzenesulfonamide (gliclazide) is a white solid with a melting point of 181°C and a pKa of 5.8.

Manufactures

Details of the drug product manufacturers have been provided and are satisfactory.

TSE Statement

It is stated that no materials of animal origin are used in the production of the active ingredient.

3.2 CONTROL OF DRUG SUBSTANCE

Specification

Gliclazide is controlled by a Ph.Eur monograph. A CEP is provided for both sources. Particle size and residual solvents are controlled in addition.

Reference Standards or Materials

Example statements:

BP CRS (batch number 2234) reference standards are used as primary reference standards for identification.

Satisfactory copies of IR and UV spectra have been provided for the primary and secondary working standards (WS002).

3.3 BATCH ANALYSES

Satisfactory batch data are provided for three batches from each drug substance supplier. The data comply with the specification and demonstrate consistent manufacture.

3.4 CONTAINER CLOSURE SYSTEM

Gliclazide is stored in a suitable container closure system.

3.5 STABILITY

A re-test of 2 years is stated on the CEPs.

3.6 ESSENTIAL SIMILARITY

As the Drug Substance Specification complies with Ph Eur requirements or is not different from that for the reference material, essential similarity can be considered proven.

3.7 DRUG SUBSTANCE SPECIFICATION USED BY THE FINISHED PRODUCT MANUFACTURER

The drug substance is tested for compliance with the Ph.Eur and is accompanied by a certificate.

3.P.2 DRUG PRODUCT

3.8 DESCRIPTION AND QUALITATIVE COMPOSITION OF THE DRUG PRODUCT

<u>Example Table 1:</u>	Function	Ref. Spec.
Gliclazide	Active	Ph.Eur
Lactose monohydrate	Diluent	Ph.Eur
Microcrystalline cellulose	Diluent, disintegrant	Ph.Eur
Povidone (PVP-K-30)	Binder	Ph.Eur
Croscarmellose sodium	Glidant	Ph.Eur
Purified talc	Glidant	Ph.Eur
Magnesium stearate	Lubricant	Ph.Eur
Purified water	Granulating Vehicle	Ph.Eur
Total weight		

The formulation of batches used in the bioequivalence study are the same as the finalised formulation. Batches manufactured during development were tested against the proposed specification.

Results of the biostudy have been provided and are satisfactory.

Packaging

PVC film PVDC coated/aluminium foil blister packs (20, 28, 56, 60, 84, 100 pack sizes with 1, 2, 3, 4, 8 or 10 blister strips)

HDPE tablet containers with HDPE lids (100, 250, 500, 1000).

PHARMACEUTICAL DEVELOPMENT

Drug Substance

As the drug is not very soluble but extensively absorbed, particle size has been satisfactorily controlled.

Compatibility study

The same excipients as the innovator are used except that pregelatinised starch and maize starch are replaced by microcrystalline cellulose and croscarmellose. Povidone has also been included. Data from mixes of the drug substance with various excipients have been provided. It was concluded that all were compatible.

Manufacturing Process Development

Optimisation batches were used to investigate the effects of mixing, drying, milling, mixing with a lubricant and compression.

Container Closure System

PVDC coated PVC film (of 250µm thickness) with aluminium foil (of 0.020 mm thickness) or HDPE tablet containers with HDPE lids were chosen for this product's packaging. It is stated that the transparent packaging selected is similar to that used for the innovator product. It has been stated that the PVC of the PVC/PVDC film is compliant with various EU directives, including 90/128/EEC, and is in compliance with the Ph.Eur. This is accepted. It is stated that the HDPE tablet container conforms with relevant EU directives. This is accepted.

Excipients

The role of the various excipients is discussed.

Microbiological Attributes

The tablets comply with Ph Eur 5.1.4.

3.9 MANUFACTURE

Manufacturer(s)

Manufacture and assembly and QC are performed at suitable sites. Importation and batch release are carried out by Bristol Laboratories Ltd.

Batch Formula

The batch formula, of a size representative of the product to be marketed, has been presented. This is accepted.

Description of Manufacturing Process and Process Controls

The manufacture of the product is relatively simple and uses conventional pharmaceutical methods. The account of the process is generally satisfactory.

Controls of Critical Steps and Intermediates

Satisfactory controls are in place during tablet manufacture. Mixing times and drying temperatures are controlled. After mixing with lubricants magnesium stearate and talc the granulate is tested for appearance, assay and loss on drying.

Process Validation and/or Evaluation

Process validation was carried out on batches of 10% max production size.

Data for one batch has been provided; LOD, assay and tablet weight hardness are acceptable. Dissolution is shown to be consistent. Data is also provided for a second batch. It is stated that it is the same formulation and is made by the same process as intended for routine production. Active content is within in-process controls and it is stated that results were homogenous. Tablets samples taken at the beginning middle and end of the run show consistent dissolution results at 10mins and 45 mins. Weight, thickness, hardness and friability were also consistent at the beginning middle and end of the run.

3.10 CONTROL OF EXCIPIENTS

All excipients comply with their Ph.Eur. Monographs.

Excipients of Human or Animal Origin

Only lactose is of animal origin. The supplier states that the lactose is made from milk coming from healthy cows from a herd which is officially BSE free. The milk is fit for human consumption. All other excipients and the active have statements from the manufacturers confirming that they do not pose a TSE risk.

3.11 CONTROL OF DRUG PRODUCT

Finished Product Specification

The specification complies with the BP monograph for gliclazide tablets as well as the general Ph.Eur monograph for tablets. Dissolution conditions and limits are as stated in the BP monograph for Gliclazide tablets, and are accepted. The HPLC method used for related substances and assay method is the same as that described in the BP monograph for Gliclazide tablets.

Analytical Procedures and Validation

Analytical methods have been validated by submission of comprehensive validation data.

Batch Data

Satisfactory batch data have been provided for three batches manufactured in September 2002 in the designated facility. These demonstrate compliance with the proposed specification and satisfactory certificates of analysis have been provided.

3.12 CONTAINER CLOSURE SYSTEM

Packaging:

1. PVC (250µm), PVDC coated/aluminium (0.020mm heat sealable VCMH matt finished) blister packs.
2. HDPE containers with HDPE lids.

The PVC/PVDC film is tested for appearance, physical properties and dimensions, including thickness. Identification is by chemical means. This is accepted. It has been confirmed that the PVC/PVDC film complies with the USFDA and BGA requirements and that VCM is below 1ppm. It complies with EC directive 90/128/EEC and UK statutory instrument 1376 (1998) and also complies with Ph.Eur 3.1.11 and 3.2.22.

The foil manufacturer confirms that coated foil conforms to the FDA requirements and EU legislation for food. This is accepted.

3.13 STABILITY

A shelf-life of two years is proposed for Gliclazide Tablets when stored below 25°C. Diamicon has a 5 year shelf life with no special precautions for storage.

A commitment to continue shelf studies to 36 months is provided.

The shelf life specification is similar to the release specification, except that there is no identification, average weight or uniformity of weight as stated in the release specification. This is accepted. The test methods are as detailed in the release specification, which is acceptable.

Three pilot scale batches (10% of maximum) as detailed in batch analysis have been placed on stability.

It is stated that three commercial batches will be placed on stability.

Twenty-four months' data is presented for batches stored at 25 and 30°C and six months' data is presented for batches stored at 40°C. The results obtained showed that there were no significant deviations from initial values and the product remained within the proposed specification at all time points and temperatures.

3.14 BIOEQUIVALENCE / BIOAVAILABILITY

Suitability of the test and reference products

Diamicon 80mg (Gliclazide) is used.

The bioassay

The bioassay has been satisfactorily validated. Plasma did not show interference. Satisfactory chromatograms are provided. Commonly prescribed drugs also did not interfere (ibuprofen, paracetamol and aspirin).

Accuracy was satisfactorily determined over a similar range and found to be within acceptance limits 90-110%.

Precision and recovery were also satisfactory. Stability was demonstrated when samples were frozen for 9 days and then re-refrigerated for 9 days, followed by 17 hours in an autosampler and freeze thawed (although long term frozen stability is still outstanding).

The Test Batch

The test batch is representative of that to be marketed as it is 10% of maximum batch size and made at the intended manufacturing site which is GMP compliant.

3.15 ESSENTIAL SIMILARITY

The following data are provided to support the claim for essential similarity:

- a) Satisfactory bioequivalence is seen between the test and reference products.
- b) Satisfactory comparative dissolution profiles are provided for the test and reference products.
- c) Satisfactory comparative impurity profiles are not provided for the test and reference products but this is not necessary as the FPS complies with the BP monograph and ICH guidelines on impurities.
- d) The active substance complies with the Ph Eur and there are no new impurities.

Essential similarity is considered proven.

4 MODULE 1

4.1 APPEARANCE

The appearance of the product is acceptable.

4.2 SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is in-line with the reference product.

4.3 PATIENT INFORMATION LEAFLET

Pharmaceutically acceptable.

4.4 LABELLING

Acceptable.

4.5 MAA FORM

Acceptable.

4.6 PART I C: ADDITIONAL DATA REQUIREMENTS

Acceptable.

5 CONCLUSION

A product license may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

Gliclazide is a sulphonylurea indicated for the treatment of non insulin dependent (deficient) diabetes mellitus (NIDDM).

2. BACKGROUND

Bristol Laboratories have submitted a Marketing Authorisation Application for generic gliclazide 80mg tablets for the treatment of type II diabetes mellitus (NIDDM). The application is submitted under article 10.1 of Directive 2001/83, claiming essential similarity to Diamicon, manufactured by Servier Laboratories (PL 00093/0024), first licensed in the UK on 21 December 1979.

Approval of this licence will enable the applicant to market the product under the generic name. Once the licence is granted it is the intention of the company to proceed to mutual recognition, though the specific Concerned Member States have not yet been decided.

3. INDICATIONS

These are the same as those for the cross-referred product, namely non insulin dependent diabetes mellitus (NIDDM).

4. DOSE & DOSE SCHEDULE

The total daily dose in adults varies from 40mg to 320mg taken orally. Above 160mg, gliclazide should be taken twice daily. As with all sulphonylureas, care should be taken in the elderly due to a possible age-related increased risk of hypoglycaemia.

5. TOXICOLOGY

No formal data is presented and none is required for this application.

6. CLINICAL PHARMACOLOGY

6.1 PHARMACODYNAMICS

In keeping with an application made under Article 10.1 of Directive 2001/83, no additional pharmacodynamic studies have been presented.

6.2 PHARMACOKINETICS

In accordance with Article 10.1 of Directive 2001/83, the company have aimed to justify the claim of essential similarity by showing bioequivalence between their medicinal product and the authorised product by a single dose bioequivalence study.

6.2.1 Bioavailability

The applicant has conducted a bioequivalence study in healthy human subjects (report no. 049-02, dated 24 February 2003). The study was conducted 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 health, blood picture and physical measurements were recorded, and, providing the subjects satisfied the inclusion and exclusion criteria, they 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, healthy males who gave written informed consent.

Subjects received either one tablet of Diamicon (each tablet containing 80mg gliclazide) manufactured by Servier Laboratories, UK or one gliclazide tablet (containing 80mg gliclazide) manufactured at the intended site of manufacture for this drug product. 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 at -60°C in duplicate until the measurement of drug concentration. The drug concentration measurements were conducted using a validated HPLC-UV method.

The following pharmacokinetics 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 [$\text{AUC}_{0-\infty}$]
- 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 $\text{AUC}_{0-\infty}$.

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.

A total of nine adverse events (all mild in nature) were recorded during the study, four of which were considered possibly related to the test material. These were:-

- 1 incident of yawning (test material)
- 1 incident of vomiting associated with nausea (reference material)
- 2 incidences of diarrhoea (1 subject on test material, 1 subject on reference material)

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)	3.609 \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-∞} (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 (B)	Reference Product (A)	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-∞} (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%).

It is, therefore, reasonable to conclude that the test material, Gliclazide 80mg Tablets, to be licensed by the applicant, is bioequivalent to the reference product, Diamicon tablets (containing 80mg gliclazide), manufactured by Servier Laboratories UK.

7. EFFICACY

No formal data is presented and none is required for this application. An overview of the efficacy of gliclazide is provided in section 2.5.4 of the expert report.

8. SAFETY

No formal data is presented and none is required for this application. An overview of the safety of gliclazide is provided in section 2.5.5 of the expert report.

9. EXPERT REPORTS

There is a full clinical expert report prepared by suitably qualified experts. Their curricula vitae are included, as are those for the preclinical expert and the pharmaceutical expert.

10. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is very close to that of the market leader and is satisfactory.

11. PATIENT INFORMATION LEAFLET (PIL)

The Patient Information Leaflet is satisfactory.

12. LABELLING

The labelling is satisfactory.

13. MAA

The MAA is satisfactory.

14. DISCUSSION

The data presented have shown that the product particulars for Bristol Laboratories' Gliclazide 80mg Tablets are essentially the same as those of the cross-referred Diamicon 80mg tablets from Servier Laboratories.

15. RECOMMENDATION

The efficacy and safety of the product is satisfactory for the granting of a product licence.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. The risk benefit ratio is considered to be positive.

GLICLAZIDE 80 MG TABLETS

PL 17907/0068

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 24 November 2003
2	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 26 February 2004 and the quality dossier on 2 December 2004
3	The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 30 March 2005 and on the quality dossier on 16 May 2005
4	Following assessment of the application the MHRA requested further information relating to the quality dossier on 25 May 2006
5	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 26 May 2006
6	The application was determined on 19 July 2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gliclazide 80mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gliclazide 80mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablet

White to off-white, circular, flat, bevelled edged, uncoated tablets with “80” on one side and a breakline on the 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 - 1 tablet) and increasing until adequate control is achieved. A single dose should not exceed 160 mg (2 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. Interactions 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

2 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. Instruction for use and handling (, and disposal)

No special requirements

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 17907/0068

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

19/07/2006

10. DATE OF REVISION OF THE TEXT

19/07/2006

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 80mg TABLETS

Gliclazide tablets contains 80mg 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 80 mg tablets are round, white or off white coloured, uncoated tablets with '80' on one side and breakline on the other 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.

XXXXXX

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 40-80mg 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.

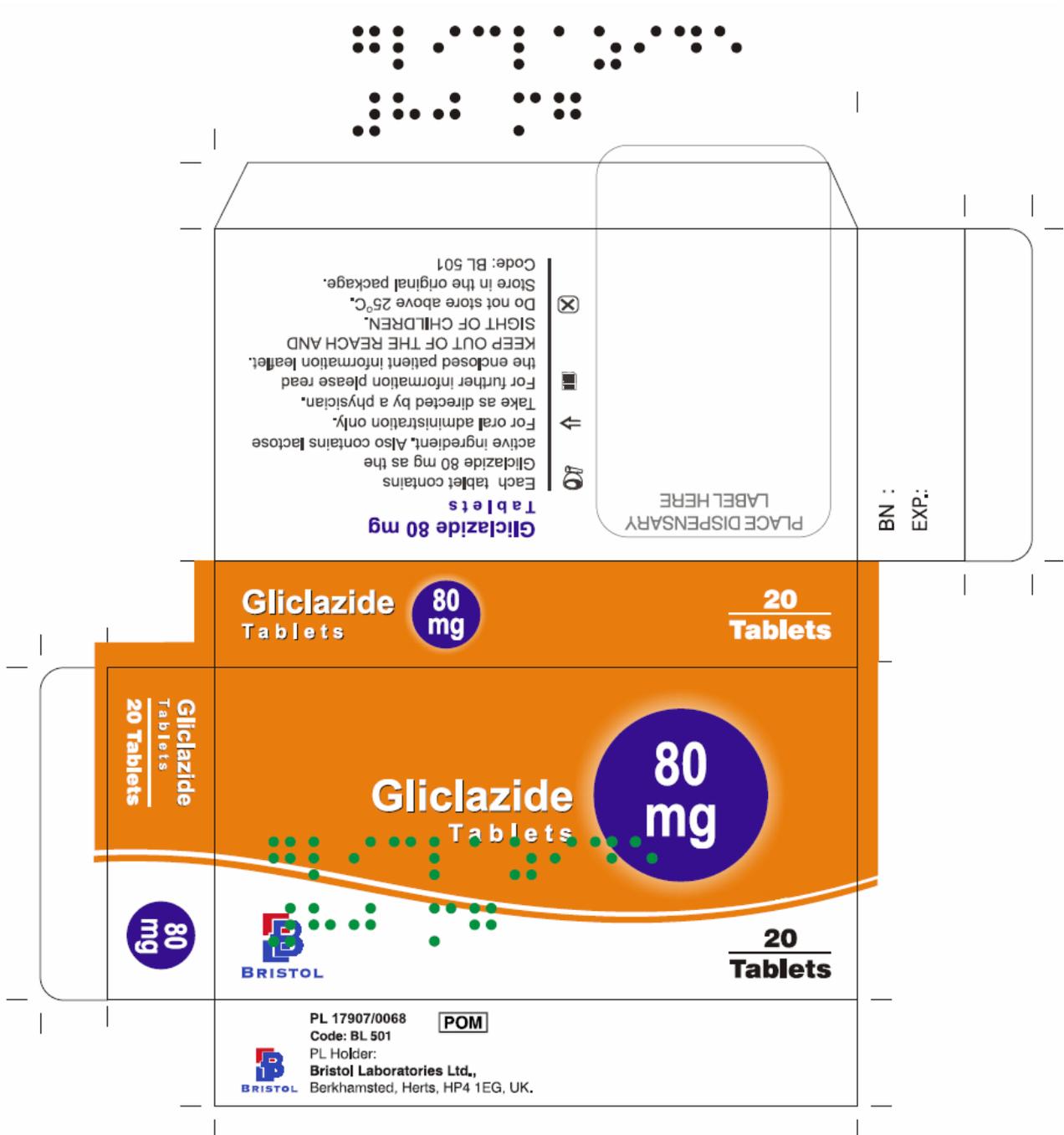
Do not use the tablets after the expiry date shown on the carton or label.

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: January 2005.

XXXXX

LABELLING





Each tablet contains Gliclazide 80 mg as the active ingredient. Also contains Lactose.

For oral administration only. Take as directed by a physician.

For further information please read the patient information leaflet provided.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

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



250
Tablets

BN :
EXP:
PL 17907/0068
Code: BL 501

POM

PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.

Size : 120 X 40 mm

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

GLICLAZIDE
80 MG TABLETS
PL Holder
Bristol Laboratories Ltd.
Code: BL 501

F000X EXP. B.No.

SAME SIZE ARTWORK
224mm
GLICLAZIDE 80 MG 20'S BLISTER