

**GLICLAZIDE 80MG TABLETS BP**

**PL 20532/0038**

**UKPAR**

**TABLE OF CONTENTS**

Lay summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 10
Summary of product characteristics	Page 11
Product information leaflet	Page 17
Labelling	Page 19

## **GLICLAZIDE 80MG TABLETS BP**

**PL 20532/0038**

### **LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aurobindo Pharma Limited a Marketing Authorisation (licence) for the medicinal product Gliclazide 80mg Tablets BP (PL 20532/0038). This prescription only medicine (POM) is indicated for non-insulin-dependent diabetes mellitus.

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

This application is based on the reference product Gliclazide 80mg Tablets BP (PL 18909/0038), which was first granted a UK licence on 12 June 2002.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Gliclazide 80mg Tablets BP outweigh the risks, hence a Marketing Authorisation has been granted.

# **GLICLAZIDE 80MG TABLETS BP**

**PL 20532/0038**

## **SCIENTIFIC DISCUSSION**

### **TABLE OF CONTENTS**

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 7
Clinical assessment	Page 8
Overall conclusions and risk benefit assessment	Page 9

## **INTRODUCTION**

The UK granted marketing authorisation for the medicinal product Gliclazide 80mg Tablets BP (PL 20532/0038) to Aurobindo Pharma Limited on 12 April 2006. This product is a POM.

The application was submitted as an abridged application according to article 10.1(a)(i) of Directive 2001/83/EC, cross-referring to 80mg Gliclazide Tablets BP (PL 18909/0038), approved on 12 June 2002.

No new data was submitted, nor was it necessary for this simple application, as the data is identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.

## **PHARMACEUTICAL ASSESSMENT**

### **1. Introduction**

#### 1.1 Legal basis

This is a simple abridged national application for Gliclazide 80mg Tablets BP under article 10.1(a)(i). The cross-referral product is Gliclazide 80mg Tablets BP, the marketing authorisation for this (PL 18909/0038) is held by Arrow Generics Ltd, and was granted on 12 June 2002. A letter of informed consent (dated 7 April 2004) has been received from the MA holder of the cross-referral product.

#### 1.2 Letters of access

A satisfactory letter of access has been provided stating that the applicant has access to all supporting data, including Part II, relevant for the application (dated 7 April 2004). Confirmation from the manufacturer that they are prepared to manufacture the product on the applicant's behalf is also provided (dated 31 March 2004).

#### 1.3 Cross-referral product

There are no outstanding concerns, or pending variation applications, with the cross-referral product.

#### 1.4 Name of product

The name of the product is acceptable.

#### 1.5 Excipients in the formulation

Details of these have been given and are satisfactory.

#### 1.6 Expert Reports

These have been provided and are satisfactory.

### **2. MAA Form (Part IA)**

#### 2.1 Manufacturing sites and licenses

Details of the manufacturing sites have been provided and are satisfactory and the relevant licences have been supplied.

#### 2.2 Expert CVs

The CVs of relevant experts have been provided and are satisfactory

#### 2.3 Qualitative and quantitative composition

The qualitative and quantitative composition is given and is accurate.

### **3. TSE**

Confirmation has been provided that the magnesium stearate used in the formulation is the same as that used in the cross-referral, i.e. is of vegetable origin.

#### **4. Summary of Product Characteristics (Part IB)**

This is in line with the reference product. Additional text has been included to the new SPC that coincides with current guidelines.

#### **5. Patient Information Leaflet**

A mock up has been provided. The leaflet includes additional warnings about lactose (used as an excipient) that are in line with the Guidelines: *Excipients in the label and package leaflet of medicinal products for human use, Notice to Applicants, July 2003*. All other information is exactly the same as the cross-referral product.

The PIL is satisfactory.

#### **6. Labelling**

Mock ups have been provided of the blister and package labels and are satisfactory.

#### **7. Additional Data Requirements (Part IC)**

The method of manufacture, drug substance specification, and the finished product specification are exactly the same as the cross-referral product.

#### **8. Pharmaceutical Conclusions**

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**

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



## **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 TABLETS 80MG BP**

**PL 20532/0038**

### **STEPS TAKEN FOR ASSESSMENT**

<b>1</b>	The MHRA received the marketing authorisation application on 24 May 2004
<b>2</b>	Following assessment of the application the MHRA requested further information relating to the quality dossier on 23 August 2004
<b>3</b>	The applicant responded to the MHRA's requests, providing further information on 13 October 2004
<b>4</b>	Following assessment of the response the MHRA requested further information relating to the quality dossier on 27 July 2005
<b>5</b>	The applicant responded to the MHRA's requests, providing further information on 22 August 2005
<b>6</b>	Following assessment of the response the MHRA requested further information relating to the quality dossier on 31 January 2006
<b>7</b>	The applicant responded to the MHRA's requests, providing further information on 31 January 2006
<b>8</b>	Following assessment of the response the MHRA requested further information relating to the quality dossier on 1 February 2006
<b>9</b>	The applicant responded to the MHRA's requests, providing further information on 2 February 2006
<b>10</b>	The application was determined on 12 April 2006

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **Product Summary for Gliclazide Tablets 80mg BP (PL 20532/0038):**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Gliclazide Tablets 80mg BP

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Gliclazide 80mg

For excipients see section 6.1

#### **3. PHARMACEUTICAL FORM**

Tablet

Gliclazide Tablets 80mg BP are white, circular tablets with GZ80 and a breakline on one face and blank 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 320mg taken orally. The dose should be adjusted according to the individual patient's response, commencing with 40-80mg daily ( $\frac{1}{2}$  – 1 tablet) and increasing until adequate control is achieved. A single dose should not exceed 160mg (two tablets). When higher doses are required, gliclazide tablets should be taken twice daily 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 show that gliclazide is effective

and well tolerated. However, care should be exercised when prescribing sulphonylureas in the elderly due to a possible age-related increased risk of hypoglycaemia.

*Renal and hepatic impairment.*

The starting dose should be 40mg daily ( $\frac{1}{2}$  tablet) increasing until adequate control is achieved.

*Children*

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

#### **4.3. Contraindications**

Hypersensitivity to the active substance or to any of the excipients, other sulphonylureas and related drugs.

Juvenile onset diabetes

Ketoacidosis.

Severe infection, stress, trauma, surgical procedures or other severe conditions where the drug is unlikely to control the hyperglycaemia.

Severe impairment of renal or hepatic function.

Diabetic coma and pre-coma.

Pregnancy.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### **4.4. Special warnings and precautions for use**

As with other sulphonylureas, gliclazide should be avoided in porphyria.

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 overdose.
- When calorie or glucose intake is insufficient
- 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 with careful patient monitoring.

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 adjustment 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 adjustment made in drug dosage and/or meal patterns.
- On the occurrence of severe hypoglycaemic reactions (coma or neurological impairment, (see overdose).
- On 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 time, it may be necessary to increase progressively the dosage of gliclazide and if this is insufficient, to discontinue 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

#### **4.5. Interactions with other medicinal products and other forms of interaction**

The following may enhance the hypoglycaemic effect of gliclazide: ACE inhibitors, testosterone, alcohol, anabolic steroids, MAOIs, cimetidine, ranitidine, beta-blockers, azapropazone, phenylbutazone, salicylates and possibly other NSAIDs, anticoagulants, disopyramide, chloramphenicol, co-trimoxazole, sulphonamides, tetracyclines, trimethoprim, sulphinpyrazone.

The warning signs of hypoglycaemia (such as tremor) may also be masked by beta-blockers.

Clofibrate group drugs may improve glucose tolerance and have an additive effect. Octreotide possibly reduces antidiabetic drug requirements in diabetes mellitus. Fluconazole and miconazole increase plasma concentrations of sulphonylureas. Rifamycins, phenothiazines, corticosteroids, loop and thiazide diuretics, diazoxide, oestrogens, progesterones, oral contraceptives, aminoglutethimide, thyroid hormones and abuse of laxatives may reduce the effect of sulphonylureas.

The anticoagulant effects of warfarin and other coumarins may be changed.

Nifedipine and lithium may occasionally impair glucose tolerance.

#### **4.6. Pregnancy and lactation**

Gliclazide is contraindicated in pregnancy.

It has not been established whether gliclazide is transferred to human milk. However, some sulphonylureas are excreted in breast milk and this class of drug should be avoided during lactation.

#### **4.7. Effects on ability to drive and use machines**

Gliclazide has influence on the ability to drive and use machines.

Patients should be informed that their concentration might be affected if their diabetes is not satisfactorily controlled, especially at the beginning of treatment. (See Special Warnings and Special Precautions for use.)

#### **4.8. Undesirable effects**

Hypoglycaemia (see Special Warnings and Special 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 gastrointestinal disturbances including nausea, dyspepsia, diarrhoea and constipation have been reported, but this type of adverse reaction can be avoided if gliclazide is taken during a meal.

Hypersensitivity reactions can occur, usually in the first 6-8 weeks of therapy, and they consist mainly of allergic skin reactions including pruritis, erythema and bullous eruption,

Blood disorders including anaemia, leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia and aplastic anaemia and granulocytopenia have been observed during treatment with gliclazide but are not known to be directly attributable to the drug.

#### **4.9. Overdose**

*Symptoms:* hypoglycaemia.

*Treatment:* gastric lavage and correction of hypoglycaemia by appropriate means with continued monitoring of the patient's blood sugar until the effect of the drug has ceased.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Sulfonamides, urea derivatives  
ATC code: A10BB09

Gliclazide is an oral hypoglycaemic sulphonylurea which stimulates the release of insulin from pancreatic  $\beta$ -cells, probably by facilitating  $\text{Ca}^{2+}$  transport across the  $\beta$ -cell membranes. The effect of gliclazide on increasing the secretion of insulin is most marked in the early phases of the response to a rise in plasma glucose. Nevertheless, hypoglycaemic effects can be shown even without any increase in the plasma levels of insulin. Like other sulphonylureas, it exerts an

important hypoglycaemic effect on the cell surface at one or more post-binding sites, although there is evidence that there may sometimes be an increase in insulin receptors. The sulphonylureas also have an important hypoglycaemic action by decreasing hepatic glucose output, and it has recently been shown that the sulphonylureas, including gliclazide, stimulate the most potent activator of liver phosphofructokinase at concentrations which are found in the blood of treated diabetic patients. This would help to explain the extrapancreatic action of the sulphonylureas of inhibiting hepatic gluconeogenesis through phosphofructokinase and fructose diphosphatase activities and also the reduction of insulin resistance in non-insulin dependent diabetes.

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

## **5.2. Pharmacokinetic properties**

The speed of absorption from the gastrointestinal tract varies considerably, and individuals can be classified as slow or fast absorbers, although the apparent difference may depend more on first-pass metabolism than absorption rate. For an 80mg dose in normal volunteers the average time to maximum is four hours and maximum concentration  $3.9\text{mg.l}^{-1}$ . Presystemic metabolism has not been properly studied, but the low plasma clearance ( $13\text{ ml.min}^{-1}$ ) suggests it is not significant. The mean plasma half-life is ten hours and the volume of distribution is about 25L. About 95% (85-97%) of gliclazide is bound to protein in plasma, mostly to albumin. Ethyl alcohol has been shown to reduce the binding to albumin, possibly explaining an enhanced hypoglycaemic effect. It may also be important that non-enzymatic glycolization of human serum albumin induced by chronic hyperglycaemia markedly decreases its binding to sulphonylureas, thus increasing the proportion of free and active drug.

No studies have reported the presence of gliclazide in human breast milk.

## **5.3. Preclinical safety data**

There are no pre-clinical data of relevance to the prescriber that are additional to those included in other sections.

# **6. PHARMACEUTICAL PARTICULARS**

## **6.1. List of excipients**

Maize starch  
Lactose monohydrate  
Polyvinylpyrrolidone  
Magnesium stearate

## **6.2. Incompatibilities**

Not applicable

**6.3. Shelf life**

36 months

**6.4. Special precautions for storage**

Do not store above 25°C.

**6.5. Nature and contents of container**

PVC/aluminium blister packs of 28, 30, 56 or 60 tablets in cartons.  
Not all pack sizes may be marketed.

**6.6. Instruction for use and handling and disposal**

No special requirements

**7. MARKETING AUTHORISATION HOLDER**

Aurobindo Pharma Limited  
Centurion House  
65 Delamere Road  
Hayes  
Middlesex  
UB4 0NN

**8. MARKETING AUTHORISATION NUMBER**

PL 20532/0038

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

12/04/2006

**10 DATE OF REVISION OF THE TEXT**

12/04/2006



## **PATIENT INFORMATION LEAFLET**

### **INFORMATION FOR PATIENTS**

#### **GLICLAZIDE 80mg TABLETS BP**

Please read this leaflet carefully before you start to take this medicine. It gives an outline of the more important things you should know. If you want to know more about this medicine, or you are not sure about anything, ask your doctor or pharmacist. You should keep this leaflet throughout your course of treatment.

#### **The name of your medicine is Gliclazide 80mg Tablets BP**

Gliclazide Tablets BP contain the active ingredient Gliclazide. The tablets come in one strength, 80mg.

Other ingredients in your tablets are maize starch, lactose, polyvinylpyrrolidone and magnesium stearate.

Gliclazide Tablets BP are white, circular tablets marked with GZ 80 with a breakline on one face.

Gliclazide Tablets BP are available in blister packs of 60 tablets.

The Marketing Authorisation Holder is: Aurobindo Pharma Limited, Centurion House, 65 Delamere Road, Hayes, Middlesex UB4 0NN.

Manufacturer: Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, UK.

#### **How does your medicine work?**

Gliclazide belongs to a group of medicines called sulphonylureas, which are used to control the level of sugar in the blood in certain forms of diabetes.

#### **What are Gliclazide Tablets BP for?**

Gliclazide Tablets BP are used for the treatment of diabetes, by diabetics who do not need insulin but who need more than just diet to control their diabetes.

#### **Before taking this medicine**

You should not take Gliclazide Tablets BP if: -

- you have ever had a reaction or been told that you are allergic to gliclazide, other sulphonylureas or any of the other ingredients in the tablets. Check by reading the list of ingredients above.
- you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
- you have seriously low blood sugar levels with loss of consciousness.
- you have juvenile onset diabetes mellitus.
- you have severe liver or kidney problems.
- you are having an operation, or have a severe infection or are suffering from extreme stress or trauma.
- you have ketoacidosis (a complication of diabetes with ketones in the urine).
- you are pregnant.

Taking another medicine while you are taking Gliclazide Tablets BP



can affect how it or the other medicine works. Make sure that your doctor knows what other medicines you are taking. Do not take any other medicines while you are taking Gliclazide Tablets BP unless you have told your doctor or pharmacist and asked their advice. This includes medicines you may have bought yourself.

Examples of medicines that can affect Gliclazide Tablets BP are:

- Hormone drugs such as testosterone, oral contraceptives and steroids and aminoglutethimide (an anti-hormone drug).
- Alcohol.
- Some drugs for high blood pressure and heart trouble such as ACE inhibitors, nifedipine, beta-blockers (for example, atenolol).
- Drugs for stomach ulcers and dyspepsia including cimetidine and ranitidine.
- Some anti-inflammatory drugs (painkillers) such as azapropazone, aspirin and phenylbutazone.
- Drugs which are used to treat infections such as chloramphenicol, cotrimoxazole, sulphonamides, tetracyclines, rifamycins, fluconazole, and miconazole.
- Drugs used to thin the blood such as warfarin and disopyramide.
- Drugs for high cholesterol in the blood such as clofibrate.
- Corticosteroids such as prednisolone.
- Some drugs used for getting rid of excess water in the body (diuretics) such as furosemide and bendroflumazide.
- MAOIs, such as phenelzine, and other drugs used for mental problems such as lithium and phenothiazines.
- Drugs for gout such as sulphinpyrazone.
- Thyroid hormone drugs used to treat an underactive thyroid gland.
- Octreotide, used to treat growth disorders.
- Laxatives, if used excessively.

If you have any doubts about whether you should take this medicine then talk to your doctor.

#### **Advice when taking Gliclazide Tablets BP**

- Make sure your doctor knows if you have been told you have porphyria (a rare metabolic disorder)
- You should test your urine or blood sugar levels regularly, as instructed by your doctor.
- Care is required if you are elderly, very underweight or "run down", or have problems with your adrenal or pituitary glands. Your dosage will be reduced.



- Care should be taken if you are exercising strenuously as this may cause your blood sugar levels to go too low (this is known as hypoglycaemia). Early warning symptoms of low blood sugar include feeling faint, sweating, trembling, confusion or headache. You will need to eat or drink something sugary quickly. Ask your doctor for more information about the symptoms of hypoglycaemia and what you should do if it happens.
- Do not drive or operate machinery if you have signs of low blood sugar.
- Drinking alcohol may cause troublesome flushing in some patients and can affect your blood sugar level.
- If you are exposed to stress such as fever, trauma, infection or surgery, a loss of control of your diabetes may occur. If this happens, your doctor may decide to increase your dose of gliclazide and if this dose not help, to stop giving you gliclazide and give you insulin.

#### Taking this medicine

The usual adult starting dose for Gliclazide Tablets BP is 40 to 80mg (one half to one tablet), adjusted according to your response, up to a maximum of 320mg (four tablets) daily. Up to 160mg (two tablets) can be taken at one time.

Your starting dose will be reduced if you are elderly or have liver or kidney problems.

To obtain a tablet, press on the tablet from the blister (or bubble) side, pushing it through the foil. Do not remove the tablet from the blister until you are ready to take it.

Your doctor will decide the dose that is best for you. Always follow your doctor's instructions completely. Also, follow any instructions or warnings that appear on the label that the pharmacist has put on the pack. If you do not understand, or are in any doubt, ask your doctor or pharmacist.

Unless told otherwise, the tablets should be swallowed with a glass of water before a meal.

You should take your medicine for as long as your doctor tells you to. If you forget to take a dose, do not worry, just wait until it is time for your next dose. Never double the next dose to make up for the one missed. Do not stop taking the medicine without talking to your doctor first.

If you accidentally take too many tablets you may experience hypoglycaemia (low blood sugar) the symptoms of which include feeling faint, sweating, trembling, confusion or headache. You will need to quickly eat or drink something sugary then contact your doctor, pharmacist or nearest hospital casualty department immediately. Take this leaflet and any tablets you have left to show the doctor or pharmacist.

#### Are there any side-effects?

Like many medicines Gliclazide Tablets BP may cause side-effects in some patients, particularly when you first start taking them. The side-effects that some other patients have had with gliclazide include hypoglycaemia (low blood sugar), feeling sick, indigestion, constipation, diarrhoea, skin rash or redness, itching,

painful red eruptions on the skin, blood disorders and anaemia resulting in paleness, prolonged bleeding, bruising sore throat and fever.

There have been rare reports of liver problems and jaundice (yellowing of the skin and whites of the eyes).

If you experience any other side-effects or feel that the medicine is affecting you badly, tell your doctor or pharmacist.

#### Safe keeping for this medicine

Do not take this medicine if the expiry date on the label has passed or if the tablets show signs of "going off" such as discolouration.

Do not store above 25°C. keep the tablets in the package or container in which they were given to you.

Do not transfer your tablets to another container.

**Keep Gliclazide Tablets in a secure place where children cannot get at them.**

Remember this medicine is for you only. Never give it to anyone else. It may harm them, even if their symptoms are the same as yours.

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

Date of preparation: April 2004

P1500275



A/s: 200 x 180 mm

2

## **LABELLING**

### **Carton Mock up for Gliclazide 80mg Tablets BP - 60's Pack**



PANTONE 382 C PANTONE 287 C PANTONE 179 C Process Black

Version : 2

# Foil Mock of Gliclazide 80mg Tablets BP

