SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gliclazide 80mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80mg of Gliclazide

Excipient with known effect: 110mg of Lactose Monohydrate

For the full list of excipients, see section 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.

Renal and hepatic impairment
The starting dose should be 40mg daily increasing until adequate control is achieved

Children:

Gliclazide as with other sulphonylureas, 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 listed in section 6.1, other sulphonylureas, sulphonamides
- Type 1 diabetes
- Diabetes complicated by ketosis and acidosis
- Diabetic pre-coma and coma
- Severe infection, stress, trauma, surgical procedures or other severe conditions where the drug is unlikely to control the hyperglycaemia
- Severe renal or hepatic insufficiency: in these cases the use of insulin is recommended
-Lactation (see section 4.6)
-Treatment with Miconazole (see section 4.5)
- Porphyria

4.4 Special warnings and precautions for use

Hypoglycaemia***:***
This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.
Hypoglycaemia may occur following administration of sulphonylureas (see section 4.8). Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days.
Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

Factors which increase the risk of hypoglycaemia:

- In patients controlled by diet alone, patient refuses or (particularly in

elderly subjects) is unable to co-operate,

- malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes,
- imbalance between physical exercise and carbohydrate intake,
- renal insufficiency,
- severe hepatic insufficiency,
- overdose of Gliclazide Tablets,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- In patients with hepatic and/or renal impairment. However, in long term clinical trials patients with renal insuffiency have been treated satisfactorily using gliclazide at reduced doses with patient monitoring.
- concomitant administration of alcohol or certain other medicines (see section 4.5).
- When calorie or glucose intake is insufficient.

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. This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.
- 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.
- Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

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

Renal and hepatic insufficiency: the pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

Patient information:
The risks of hypoglycaemia, together with its symptoms (see section 4.8), treatment, and conditions that predispose to its development, should be explained to the patient and to family members.
The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Poor blood glucose control: blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic agent, including gliclazide, is attenuated over time in many patients: this may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

Laboratory tests: Measurement of glycated haemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the class of sulphonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

1) The following products are likely to increase the risk of hypoglycaemia

Contra-indicated combination

- **Miconazole** (systemic route, oromucosal gel): increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or

even coma.

Combinations which are not recommended

- **Phenylbutazone** (systemic route): increases the hypoglycaemic effect of sulphonylureas (displaces their binding to plasma proteins and/or reduces their elimination).

  It is preferable to use a different anti-inflammatory agent, or else to warn the patient and emphasise the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.

- **Alcohol:** increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma.

  Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions for use

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is taken:
other antidiabetic agents (insulins, acarbose, biguanides (e.g metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), testosterone, anabolic steroids, beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, trimethoprim, sulphonamides, clarithromycin and nonsteroidal anti-inflammatory agents.
The warning signs of hypoglycaemia (such as tremor) may also be masked by beta blockers.

2) <u>The following products may cause an increase in blood glucose levels</u>

Combination which is not recommended

- **Danazol**: diabetogenic effect of danazol.

  If the use of this active substance cannot be avoided, warn the patient and emphasise the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

Combinations requiring precautions during use

- **Chlorpromazine** (neuroleptic agent): high doses (>100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release).

Warn the patient and emphasise the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.

- **Glucocorticoids** (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood glucose levels with possible ketosis (reduced tolerance to carbohydrates due to glucocorticoids).

  Warn the patient and emphasise the importance of blood glucose

monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with glucocorticoids.

- **Ritodrine, salbutamol, terbutaline**: (I.V.)

  Increased blood glucose levels due to beta-2 agonist effects.
  Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

3) Combination which must be taken into account

- **Anticoagulant therapy** (Warfarin ...):

  Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment.
  Adjustment of the anticoagulant may be necessary.

The hypoglycaemic effect of gliclazide may be potentiated by salicylates, sulphonamides, octreotide, azapropazone, sulfinpyrazone, metabolism of gliclazide may be accelerated by aminoglutethimide, testosterone, tetracycline compounds, chloramphenicol, clofibrate, disopyramide, cimetidine. Co-trimoxazole rarely enhances the effect of gliclazide.

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.

Gliclazide may be diminished by rifamycins, oral contraceptives, thiazide diuretics, diazoxide, phenothiazine derivatives, thyroid hormones, loop diuretics, and abuse of laxatives.

Calcium channel blockers (nifedipine) may occasionally impair glucose tolerance as well as Lithium may occasionally impair glucose tolerance.

4.6 Fertility, pregnancy and lactation

Pregnancy:

For gliclazide, no clinical data on exposed pregnancies are available, even though there are few data with other sulphonylureas.
In animal studies, gliclazide is not teratogenic.

Studies in animals have shown reproductive toxicity (see section 5.3).
Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

Oral hypoglycaemic agents are not suitable, insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycaemic

therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered.

Breast-feeding:

It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, the product is contra-indicated in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Gliclazide 80mg has no known influence on the ability to drive and use machines. However, patients should be informed that their concentration may be affected if their diabetes is not satisfactorily controlled, especially at the beginning of treatment (see section 4.4).

4.8 Undesirable effects

Based on the experience with gliclazide, the following undesirable effects have been reported.

Hypoglycaemia

As for other sulphonylureas, treatment with Gliclazide 80 mg Tablets can cause hypoglycaemia, if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and lethal outcome.

In addition, signs of adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

Usually, symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulphonylureas shows that hypoglycaemia can recur even when measures prove effective initially.

If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation are required.

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.

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting dyspepsia, diarrhoea, and constipation have been reported: if these should occur they can be avoided or minimised if gliclazide is taken with breakfast/meal.

The following undesirable effects have been more rarely reported:

- Skin and subcutaneous tissue disorders: rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), photosensitivity skin reactions.

- Blood and lymphatic system disorders: Changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, aplastic anaemia and granulocytopenia have been observed during treatment with gliclazide but are not known to be directly attributable to the drug. These are in general reversible upon discontinuation of medication.

- Hepato-biliary disorders: raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears.

These symptoms usually disappear after discontinuation of treatment.

- Eye disorders

Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

- Class attribution effects:

As for other sulphonylureas, the following adverse events have been observed: cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, allergic vasculitis, hyponatremia, elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulphonylurea or led to life-threatening liver failure in isolated cases.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard

4.9 Overdose

An overdose of sulphonylureas may cause hypoglycaemia.
Moderate symptoms of hypoglycaemia, without any loss of consciousness or neurological signs, must be corrected by carbohydrate intake, dose adjustment and/or change of diet. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.
Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalisation.
If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50 mL of concentrated glucose solution (20 to 30 %).

This should be followed by continuous infusion of a more dilute glucose solution (10 %) at a rate that will maintain blood glucose levels above 1 g/L. Patients should be monitored closely and, depending on the patient's condition after this time, the doctor will decide if further monitoring is necessary.
Dialysis is of no benefit to patients due to the strong binding of gliclazide to proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeuticgroup: sulphonamides, urea derivatives.
ATC code: A10BB09
Gliclazide is a hypoglycaemic sulphonylurea antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.
Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.
In addition to these metabolic properties, gliclazide has haemovascular properties.

Effects on insulin release

In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose.
Haemovascular properties:
Gliclazide decreases microthrombosis by two mechanisms which may be involved in complications of diabetes:

- a partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B_2).
- an action on the vascular endothelium fibrinolytic activity with an increase in tPA activity

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

Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have not been done. No teratogenic changes have been shown in animal studies, but lower fetal body weight was observed in animals receiving doses 9.4 fold higher than the maximum recommended dose in humans.

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

4 years

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

Al / PVC/PVDC blister, pack sizes of 20, 28, 56, 60, 84, 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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