Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diabrezide 80 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: gliclazide 80 mg.

Excipient(s): each tablet contains lactose monohydrate 33 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, round tablets with a breakline on one side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of type 2 diabetes mellitus, inadequately controlled by non-pharmacological means (balanced diet and regular physical exercise).

4.2 Posology and method of administration

Tablets for oral use.
The desired blood glucose levels and the Diabrezide dosage must be determined individually in relation to the degree of diabetes.

ADULTS: The usual initial dose is 40-80 mg/day (half to one tablet) before breakfast. If necessary, the dosage may be increased by 40-80 mg every 7-14 days, until a satisfactory metabolic control is achieved. The maximum dose is 320 mg/day. The usual maintenance dose is 80-160 mg in two daily administrations (before breakfast and before dinner); higher doses (up to 320 mg/day) may be used, although it has not been demonstrated that the increase of doses over 160 mg/day necessarily leads to an improvement of glycaemic control.

ELDERLY: The usual initial dose is 40 mg (half tablet) before breakfast, increasing the dose of 40 mg every 7-14 days if necessary. Caution should be used when prescribing doses over 160 mg/day, particularly if renal function is impaired.

CHILDREN: Diabrezide is contraindicated in children (see section 4.3)

Gliclazide is not indicated in the treatment of type 1 diabetes mellitus.

Diabrezide tablets must be swallowed without chewing preferably 30 minutes before the meal.

4.3 Contraindications

Gliclazide must not be used in:
- insulin-dependent (type 1) diabetes mellitus,
- diabetic ketoacidosis,
- diabetic pre-coma and coma,
- in patients with complete secondary failure to sulphonylurea-therapy,
- in patients with severe renal and/or hepatic failure,
- in cases where insulin is required, e.g. surgery, and severe trauma or infection,

- in patients hypersensitive to gliclazide, sulphonylureas or sulphonamides, or any of the excipients in the tablets,
- in children,
- in pregnancy and in lactating women.

4.4 Special warnings and precautions for use

Use of sulphonylureas must be limited to the treatment of maturity onset diabetes mellitus, not ketogenic, unable to be controlled by diet, and for which insulin therapy is not appropriate.
Warnings and precautions of use concern:
Hypoglycaemia
All sulphonylureas, taken in too high doses in relation to the requirement, are capable of producing hypoglycaemia, even of severe degree, which may lead to neurological damage and may have a fatal outcome.
Diabrezide can provoke a moderate or severe hypoglycaemia particularly in the following circumstances:
- Insufficient glucose or caloric intake.
- Too high posology or accidental overdoses.
- Prolonged physical activity.
- Patients with uncompensated thyroid function disorders.

In order to lower the risk of hypoglycaemia it is recommended to start the treatment with a low dose of Diabrezide.
Proper patient selection and dosage and instructions are important to avoid hypoglycaemic episodes.
Renal or hepatic insufficiency may cause elevated drug levels and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycaemic reactions.
Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycaemic action of glucose-lowering drugs. Hypoglycaemia may be difficult to recognise in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycaemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Hypoglycaemia can be promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g. in the form of sugar lumps, sugar-sweetened fruit juice or tea, see under 4.9).
So that initial corrective action can be taken immediately, patients should carry a minimum of 1-2 lumps of sugar with them at all times.
To reduce the risk of hypoglycaemia a number of precautions should be taken when Diabrezide is first prescribed, including adjusting the dose according to blood glucose levels during the first few months, and beginning treatment with low doses especially in the elderly and in patients with renal and/or hepatic impairment.
Loss of control of blood glucose
When a patient stabilised on any diabetic regimen is exposed to stress such a fever, trauma infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue gliclazide and administer insulin.
Concomitant administration of Diabrezide with agents that increase blood glucose levels (see under 4.5) should not be considered without careful monitoring of blood glucose levels to avoid hyperglycaemia.
Hepatic disease
Definite hepatic disease should contraindicate the use of Diabrezide, since gliclazide is almost completely metabolised in the liver; in moderate hepatic disease a dosage reduction is advisable.
Renal disease
Although renal disease does not appear significantly to alter the pharmacokinetics of gliclazide, it may be wise to limit the maximum dose when the serum creatinine starts to rise.
Elderly
Some elderly patients may be more sensitive to the drug; although the plasma clearance is not altered so that increased plasma levels are unlikely, it is wise to start the therapy at the lowest dosage.
The physician gives the patient guidance on the frequency of blood glucose measurements, as well as on whether, how often and when urine test for glucose must be performed. In addition, it is recommended that the quality of metabolic control be checked by regular determinations of glycated haemoglobin.

Diabrezide contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

§ Concomitant administration of certain drugs may lead to an increase in the blood glucose lowering effect and susceptibility to hypoglycaemia, and may necessitate dose adjustment.

These drugs include:
- medicinal products used for the same indication, such as insulin, acarbose, other sulphonylureas (not recommended association), biguanides;
- sulphonamides, phenylbutazone, non steroidal anti-inflammatory drugs (NSAID's), aspirin and salicylates, coumarins, allopurinol, miconazole, ketoconazole;
- fibrates (patients stabilised on Diabrezide should be very closely monitored when starting or ending a therapy with fibrates);
- theophylline, caffeine, monoamine oxidase inhibitors;
- beta-adrenoceptor antagonists (they alter recovery from hypoglycaemia and suppress hypoglycaemic symptoms);
- ACE inhibitor;
- anabolic steroids and male sex hormones;
- chloramphenicol;
- cyclophosphamide and derivatives.

§ Other drugs may reduce the blood glucose lowering effect and increase the tendency to hyperglycaemia. Adjustment of the gliclazide dose may become necessary also in such cases.
These drugs include:
- barbiturates, phenytoin, and rifampicin;
- corticosteroids, corticotropin, estrogens, progestogens, oral contraceptives, diazoxide and sympathomimetic drugs, thyroid hormones.
- thiazide diuretics (hyponatremia have been reported when used concomitantly)

§ Alcohol may cause an increase in blood glucose levels. Large amounts of alcohol may, in addition, impair gluconeogenesis and thus increase the risk of hypoglycaemia. The carbohydrate content of alcoholic beverages must also be taken into consideration.
H2-receptor antagonists (as cimetidine, ranitidine) may either increase or reduce the blood glucose lowering effect of sulphonylureas.
§ Patients treated with drugs other than gliclazide should discuss possible interactions with their prescribing physician.

4.6 Fertility, pregnancy and lactation

There is no experience with the use during pregnancy in humans. Oral hypoglycaemic agents are not suitable for the treatment of diabetes during pregnancy, because the blood glucose level can be controlled more tightly by insulin. 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.
It is not known whether gliclazide or its metabolites are excreted in breast milk. Diabrezide is not indicated in nursing mothers.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of a special importance (e.g. driving a car or operating machinery).
Patients should be advised to take precautions to avoid hypoglycaemia whilst driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

At dosages used in the treatment of maturity onset diabetes mellitus, the most frequently reported side effect is hypoglycaemia, which in most cases is the result of overdose or inadequate diet rather than an adverse effect of the drug and therefore can be corrected by dosage reduction.

The following frequencies are used for the description of the occurrence of adverse reactions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000, not known).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders	Rare (≥1/10,000 to <1/1,000):	Leucopoenia, agranulocytosis, thrombocytopoenia, haemolytic anaemia, aplastic anaemia.
Nervous system disorders	Rare (≥1/10,000 to <1/1,000):	Dizzines.
Gastrointestinal disorders	Common (≥1/100 to <1/10):	Gastrointestinal upset (such as abdominal pain, nausea or vomiting, dyspepsia, diarrhoea, constipation). It can

		be avoided or minimised if gliclazide is taken with breakfast.
Skin and subcutaneous tissue disorders	Rare (≥1/10,000 to <1/1,000):	Skin reactions (erythema, pruritus).
Metabolism and nutrition disorders	Common (≥1/100 to <1/10):	Hypoglycemia * (see additional information below).
	Rare (≥1/10,000 to <1/1,000):	Slight disulfiram-like reactions after taking alcohol.
Hepatobiliary disorders	Rare (≥1/10,000 to <1/1,000):	Sulphonylureas can occasionally cause disturbances of liver functions, which rarely may lead to hepatitis.

As per other sulphonylureas, the following skin and subcutaneous tissue disorders have been reported: rash, pruritus, urticaria, angioedema, erythema, rash maculo-papular, dermatitis bullous (as Stevens-Johnson syndrome and Toxic epidermal necrolysis).

***** Hypoglycaemia
All sulphonylureas can produce hypoglycaemia. This can be prolonged by gliclazide and may lead to severe hypoglycaemia with life-threatening coma. In cases of very slow progression of nervous lesion (autonomous neuropathy) or sympatholytic concomitant therapy (see "Special warning and precautions for use" and "Interactions"), typical premonitory symptoms of hypoglycaemia may be weaker or absent.
Hypoglycaemia is characterised by decrease in blood sugar to less than approx. 50 to 40 mg/dl.
The following premonitory simptoms can alert the patient or her/his surroundings of a too great blood sugar decrease: sudden sweating, palpitation, tremor, sensation of hunger, restlessness, tingling sensation in the mouth area, paleness, headache, somnolence, sleep disorder, anxiety, depression, touchiness, altered behaviour, unsteady movements, transient neurological symptoms (e.g. speech and visual disorders, paralytic symptoms or sensitivity disorders). In severe hypoglycaemia the patient may loose self-control and consciousness. In this case the patient's skin is often cool and she/he tends to have cramps.
For treatment of hypoglycaemia see "Overdose".

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Accidental or deliberate overdose of sulphonylureas, including gliclazide, can produce hypoglycaemia (for symptoms see 4.8).

Treatment
Mild hypoglycaemia symptoms, without loss of consciousness or neurological finding, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycaemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalisation. If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more diluted (10%) glucose solution at a rate which will maintain the blood glucose at a level above 100 mg/dl. Patients should be closely monitored for a minimum of 48 h, and, depending on the status of the patient at this time, the physician should decide whether further monitoring is required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: oral blood glucose lowering drugs sulphonylureas; gliclazide. ATC code: A10BB09

Mechanism of action:
1. Hypoglycaemic activity
Gliclazide, like other sulphonylureas, reduces blood glucose levels in healthy volunteers and in patients with non-insulin-dependent diabetes mellitus by correcting both defective insulin secretion and peripheral insulin resistance.

Unstimulated and stimulated insulin secretion from pancreatic beta-cells is increased following administration of gliclazide, with both the first and second phases of secretion being affected.
The extra pancreatic effects restore peripheral insulin sensitivity, such as decreasing hepatic glucose production, and increasing glucose clearance and skeletal muscle glycogen synthase activity. These effects do not appear to be mediated by an effect on insulin receptor numbers, affinity and function.
2. Haemobiological effects
Gliclazide has specific haemobiological effects in that it causes a reduction in platelet adhesiveness and aggregation, it increases the release of plasminogen activator by the vascular walls, and, by increasing the superoxide dismutase activity, reduces free radical levels.
3. Microangiopathy
Clinical data suggest that long-term administration of gliclazide may delay the progression of diabetic retinopathy to a greater extent than other sulphonylureas or diet.

5.2 Pharmacokinetic properties

Gliclazide is extensively absorbed by the gastrointestinal tract, but absorption rate varies considerably, and individuals can be classified as slow or fast absorbers.
Our bioequivalence trial carried out with a 80-mg dose on 20 male healthy volunteers aged 33 ± 7 years, showed a C_{max} of 2.652 ± 0.651 mg/L (test) and 2.647 ± 0.542 mg/L (reference) and t_{max} was 9 h (3-9) and 7.5 h (3-12), respectively. Steady-state concentrations are reached after 2 days' administration.
The mean plasma half life is 10 h and the volume of distribution is about 25L. Renal insufficiency associated to diabetes prolongs the plasma half-life slightly, but not significantly; therefore, dosage alterations are not normally required in patients with renal insufficiency.
About 95% of gliclazide is bound to plasma proteins, mostly to albumin.
^{14}C-labelled tracer studies in rats have shown that gliclazide, given orally or intravenously, tends to concentrate in the liver and kidneys and some was also found in the pancreas and adrenals but very little in the central nervous system. No studies have reported its presence in the human breast milk.
Gliclazide is extensively metabolised by oxidation (its metabolites have no hypoglycaemic activity), and less than 20% is excreted in the urine unchanged.
The major route of elimination of gliclazide and its metabolites is via the urine.

5.3 Preclinical safety data

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans.
Furthermore, *in vivo* and *in vitro* studies did not yield any indication of potential mutagenicity. Carcinogenicity studies have not been done.
No teratogenic changes have been shown in animal studies, but foetotoxic effects were present under treatment with gliclazide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose PH101
Povidone K30
Sodium starch glycollate type A
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Al/PVC+PE+PVDC strip (aluminium foil: thickness 20 ± 1.6 μm; plastic sheet: PVC, thickness 200 ± 10 μm – PE, thickness 30 ± 3 μm; spreading of PVDC: 90 g/m^2 ± 5%).

Pack sizes:
- Carton box with 28 tablets (2 x 14).
- Carton box with 30 tablets (2 x 15).
- Carton box with 60 tablets (3 x 20).
- Carton box with 100 tablets (5 x 20).
- Carton box with 120 tablets (6 x 20).
- Carton box with 180 tablets (9 x 20).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

L. Molteni & C. dei F.lli Alitti
Strada Statale 67
Localita Granatieri
Scandicci
Firenze
Italy

8 MARKETING AUTHORISATION NUMBER

PA0925/001/001

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