IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1380/075/001
Case No: 2061102

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Gliclazide Actavis 80mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **21/05/2010** until **20/05/2015**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gliclazide Actavis 80mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains gliclazide 80 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, flat, round 8.0 mm tablet with bevelled-edges and a central break line on both faces. On one face, “GZ” is engraved on either side of the break line.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

4.2 Posology and method of administration

Tablets for oral use.
As with any hypoglycaemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbA_{lc}).
Gliclazide Actavis tablets should be swallowed with a glass of water preferably 30 minutes before a meal.

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, until a satisfactory metabolic control is achieved. A single dose should not exceed 160 mg (2 tablets). When higher doses are required, Gliclazide Actavis should be taken twice daily and in connection with the main meals of the day. 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.
For obese patients or those not showing adequate response to gliclazide alone, additional therapy may be required.

Elderly
The usual initial dose is 40 mg (half a tablet) before breakfast, increasing the dose of 40 mg if necessary. Caution should be used when prescribing doses over 160 mg/day, particularly if renal function is impaired. 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. However, care should be exercised when prescribing sulfonylureas in the elderly due to a possible age-related increased risk of hypoglycaemia.

Patients with renal or hepatic insufficiency
A small starting dose and careful patient monitoring is recommended for these patients, in order to reduce the risk of hypoglycaemia (see section 4.4).

Children
Gliclazide Actavis should not be used in children due to a lack of data on safety and efficacy.

4.3 Contraindications

- known hypersensitivity to gliclazide, other sulfonylureas, sulfonamides or to any of the excipients
- type 1 diabetes
- diabetic pre-coma and coma, diabetic keto-acidosis
- severe renal or hepatic insufficiency: in these cases the use of insulin is recommended
- treatment with miconazole (see section 4.5)
- lactation (see section 4.6).

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 sulfonylureas (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:
- 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 Actavis tablets
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency
- concomitant administration of alcohol or certain other medicines (see section 4.5).

Renal and hepatic insufficiency
The pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe 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, 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 discontinue gliclazide treatment and 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 a medicinal product 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.

Glucose-6 phosphate (G6PD)-deficiency
Treatment of patients with glucose-6-phosphate (G6PD)-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

<u>The following products are likely to increase the risk of hypoglycaemia</u>

Contraindicated 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 sulfonylureas (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. Intolerance to alcohol (disulfiram-like reaction: flushing, sensation of warmth, giddiness, nausea and occasionally tachycardia) may occur in patients treated with a sulfonylurea. This reaction can be prevented by avoiding the use of 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, for example:
Other antidiabetic agents (insulins, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulfonamides, and nonsteroidal anti-inflammatory agents.

<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 danazol 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 agent 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 agent during and after treatment with glucocorticoids.

- ***Ritodrine, salbutamol, terbutaline****: Intravenous use*

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

Rifampicin: reduces the glucose-lowering effects of gliclazide by induction of the cytochrome P450 2C9 enzyme. Monitor blood glucose carefully. Dosage adjustments of the antidiabetic agent may be necessary.

Combination which must be taken into account

- ***Anticoagulant therapy*** *(e.g. warfarin):*
  Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment.
  Adjustment of the anticoagulant may be necessary.

4.6 Pregnancy and lactation

Pregnancy
There is no experience with the use of gliclazide during pregnancy in humans, even though there are few data with other sulfonylureas.
In animal studies, gliclazide is not teratogenic.
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.

Lactation
It is not known whether gliclazide or its metabolites are excreted in breast milk. Other sulfonylureas have been found in 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

Patients should be made aware of the symptoms of hypoglycaemia and should be careful if driving or operating machinery, especially at the beginning of treatment.

4.8 Undesirable effects

Based on the experience with gliclazide and with other sulfonylureas, the following undesirable effects have been reported.
The frequency is defined using the following conventions:

- 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 (cannot be estimated from the available data).

Common: Hypoglycaemia
As for other sulfonylureas, treatment with Gliclazide Actavis 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: intense 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 sulfonylureas 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, is required.

Other undesirable effects
Uncommon: *Gastrointestinal disorders:* abdominal discomfort, nausea, vomiting, dyspepsia, diarrhoea, and constipation. These can be avoided or minimised if gliclazide is taken with a meal.

Frequency not known (cannot be estimated from the available data):
- *Blood and lymphatic system disorders:* Changes in haematology which may include anaemia, leukopenia, thrombocytopenia and granulocytopenia. These are in general reversible upon discontinuation of gliclazide.
- *Eye disorders:* Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.
- *Gastrointestinal disorders:* Abdominal distension.
  Hepatobiliary disorders: Raised hepatic enzyme levels (ASAT, ALAT, alkaline phosphatase), hepatitis. Discontinue treatment if cholestatic jaundice appears.
- *Skin and subcutaneous tissue disorders*: Rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions.

Class attribution effects
Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, allergic vasculitis, non-acute porphyria, photosensitivity reactions and alcohol intolerance have been described for other sulfonylureas.
With sulfonylureas cases were also observed of elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases.

4.9 Overdose

An overdose of sulfonylureas 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

Pharmacotherapeutic group: Sulfonamides, urea derivaties, ATC code: A10BB09

Gliclazide is a hypoglycaemic sulfonylurea oral 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, which may be involved in complications of diabetes, by two mechanisms:

- 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

Gliclazide is extensively absorbed by the gastrointestinal tract, but absorption rate varies considerably, and individuals can be classified as slow or fast absorbers.
A 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 25 l.
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 mainly metabolised in the liver and excreted in the urine: less than 1% of the unchanged form is found in the urine. No active metabolites have been detected in plasma.

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 foetal body weight was observed in animals receiving doses 25-fold higher than the maximum recommended dose in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (type 101)
Pregelatinised maize starch
Maize starch
Stearic acid
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Opaque PVC/Aluminium blisters.

Pack sizes:
Blisters: 10, 30, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.

Reykjavíkurvegi 76-78

220 Hafnarfjordur

Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/75/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 2010

10 DATE OF REVISION OF THE TEXT