SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gliclazide 80 mg Tablets
Almus Gliclazide 80mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of gliclazide.

Excipient(s) with known effect:
This product contains lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, flat, round tablets marked with a double score line on one side and 3G5 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gliclazide tablets are indicated for the treatment of non insulin dependent diabetes mellitus.

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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 (½-1 tablets) 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.

Children

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

Older people
Plasma clearance of gliclazide is not altered in the older people and steady state plasma levels can therefore be expected to be similar to those in adults under 65 years. Clinical experience in the older people to date shows that gliclazide is effective and well tolerated. Care should be exercised, however, when prescribing sulphonylureas in the older people due to a possible age-related risk of hypoglycaemia.

In patients with mild to moderate renal impairment

In these patients, the same dosing regimen can be used as in patients with normal renal function with careful patient monitoring. These data have been confirmed in clinical trials.

In patients at risk of hypoglycaemia

Higher risk of hypoglycaemia exists in following patients:
- undernourished or malnourished,
- severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic insufficiency),
- withdrawal of prolonged and/or high dose corticosteroid therapy,
- severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease).

It is recommended that the minimum daily starting dose of 30 mg is used.

Paediatric population

There are no data and clinical studies available in children and adolescents under 18 years of age.

4.3 Contraindications

- known hypersensitivity to gliclazide or to any of the excipients listed in section 6.1, other sulphonylureas, sulphonamides,
- 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 sulphonylureas (see 4.8. Undesirable effects). 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 80 mg Tablets,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- concomitant administration of 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 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.

Gliclazide should be avoided, where possible, in patients with acute porphyria.

4.5 Interaction with other medicinal products and other forms of interaction

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

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, for example: Other antidiabetic agents (insulins, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulphonamides, and nonsteroidal anti-inflammatory agents.

2) The following products may cause an increase in blood glucose levels

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.

4.6 Fertility, 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 sulphonylureas. 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.

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

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

4.8 Undesirable effects

Based on experience with gliclazide and other sulphonylureas the following undesirable effects have to be mentioned.
Frequencies are defined as follows:
- 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)

Hypoglycaemia
As for other sulphonylureas, treatment with Gliclazide tablets can commonly 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 or 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 is required.

Other undesirable effects
Gastrointestinal disturbances, including abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, and constipation are uncommon: if these should occur, they can be avoided or minimised if gliclazide is taken with breakfast.
The following undesirable effects have been more rarely reported:

- *Skin and subcutaneous tissue disorders*: Rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions.
- *Blood and lymphatic system disorders*: Changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of gliclazide.
- *Hepato-biliary disorders*: Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears.
- *Eye disorders:* Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

Class attribution effects
Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for other sulphonylureas.

With other sulphonylureas, 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 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 professional are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 intravenous 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

ATC Code: A10B B09 (Sulfonamides, urea derivatives).

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 to inactive metabolites; less than 5% of the dose is excreted unchanged in the urine.

5.3 Preclinical safety data

Preclinical information has not been included because the safety profile of gliclazide has been established after many years of clinical use. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Silicon dioxide (E551)
Pregelatinised maize starch
Talc (E553b)
Magnesium stearate (E572)

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

250 μm polyvinyl chloride (PVC) film with 20 μm aluminium foil blister strips in packs of 28 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point, Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0480

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF (PARTIAL) REVISION OF TEXT

27/09/2021

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