SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gliclazide Teva 30 mg Modified-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 30 mg gliclazide.

Excipient(s) with known effect

Each modified-release tablet contains 73.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet

The modified-release tablets are white, oval, biconvex.

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

Posology

The daily dose may vary from 1 to 4 tablets per day, *i.e*. from 30 to 120 mg taken orally in a single intake at breakfast time.

It is recommended that the tablet(s) be swallowed whole.

If a dose is forgotten, there must be no increase in the dose taken the next day.

As with any hypoglycaemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbA_{1C}).

Initial dose

The recommended starting dose is 30 mg daily.

If blood glucose is effectively controlled, this dose may be used for maintenance treatment.

If blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120 mg daily, in successive steps. The interval between each dose increment should be at least 1 month except in patients whose blood glucose has not reduced after two weeks of treatment. In such cases, the dose may be increased at the end of the second week of treatment.

The maximum recommended daily dose is 120 mg.

Switching from gliclazide 80 mg tablets (immediate release formulation) to Gliclazide Teva 30 mg Modified-release Tablets

1 tablet of gliclazide 80 mg is comparable to 1 modified-release tablet of Gliclazide Teva 30 mg. Consequently, the switch can be performed provided a careful blood glucose monitoring.

Switching from another oral antidiabetic agent to Gliclazide Teva Modified-release Tablets

Gliclazide Teva Modified-release Tablets can be used to replace other oral antidiabetic agents.

The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to Gliclazide Teva Modified-release Tablets.

A transitional period is not generally necessary. A starting dose of 30 mg should be used and this should be adjusted to suit the patient's blood glucose response, as described above.

When switching from a hypoglycaemic sulfonylurea with a prolonged half-life, a treatment free period of a few days may be necessary to avoid an additive effect of the two products, which might cause hypoglycaemia. The procedure described for initiating treatment should also be used when switching to treatment with Gliclazide Teva Modified-release Tablets, *i.e*. a starting dose of 30 mg/day, followed by a stepwise increase in dose, depending on the metabolic response.

Combination treatment with other antidiabetic agents

Gliclazide Teva Modified-release Tablets can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

In patients not adequately controlled with Gliclazide Teva Modified-release Tablets, concomitant insulin therapy can be initiated under close medical supervision.

Special populations

Elderly

Gliclazide Teva Modified-release Tablets should be prescribed using the same dosing regimen recommended for patients under 65 years of age.

Renal impairment

In patients with mild to moderate renal insufficiency, 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.

Patients at risk of hypoglycaemia

Higher risk of hypoglycemia 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

The safety and efficacy of gliclazide in children and adolescents have not been established. No data are available.

4.3 Contraindications

- Hypersensitivity to the active substance, other sulfonylureas, sulfonamides or to any of the excipients listed in section 6.1
- 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,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- concomitant administration of certain other medicinal products (see section 4.5).

Renal and hepatic impairment

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 (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: St. John's Wort (*Hypericum perforatum*) preparations (see section 4.5), 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.

Dysglycaemia

Disturbances in blood glucose, including hypoglycaemia and hyperglycaemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Indeed, careful monitoring of blood glucose is recommended in all patients receiving at the same time gliclazide and a fluoroquinolone.

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.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the chemical class of sulfonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Porphyric patients

Cases of acute porphyria have been described with some other sulfonylurea drugs, in patients who have porphyria.

Excipients

Gliclazide Teva contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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 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.

  Alcohol or medicinal products containing alcohol should be avoided.

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, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H_2-receptor antagonists, MAOIs, sulfonamides, clarithromycin and nonsteroidal anti-inflammatory agents.

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**: intravenously.

  Increased blood glucose levels due to beta-2 agonist effects.

  Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

- **Saint John's Wort (Hypericum perforatum) preparations:**

  Gliclazide exposure is decreased by Saint John's Wort-Hypericum perforatum. Emphasize the importance of blood glucose levels monitoring.

  The following products may cause dysglycaemia

Combinations requiring precautions during use

- **Fluoroquinolones:** in case of a concomitant use of gliclazide and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasized.

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 Fertility, pregnancy and lactation

Pregnancy

There is no or limited amount of data (less than 300 pregnancy outcomes) from the use of gliclazide in pregnant women, even though there are few data with other sulfonylureas.

In animal studies, gliclazide is not teratogenic (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of gliclazide during pregnancy.

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 unknown whether gliclazide or its metabolites are excreted in human milk. Given the risk of neonatal hypoglycaemia, the medicinal product is therefore contra-indicated in breast-feeding mothers. A risk to the newborns/infants cannot be excluded.

Fertility

No effect on fertility or reproductive performance was noted in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Gliclazide has no or negligible influence on the ability to drive and use machines. However , 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 sulfonylureas 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)

Blood and lymphatic system disorders

Rare: Changes in haematology. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of gliclazide.

Metabolism and nutrition disorders

Common: The most frequent adverse reaction with gliclazide is hypoglycaemia

As for other sulfonylureas, treatment with gliclazide 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 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 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.

Eye disorders
Rare: Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels

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

Hepatobiliary disorders
Rare: 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.

Skin and subcutaneous tissue disorders
Rare: Rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions (such as Steven-Johnson syndrome and toxic epidermal necrolysis) and autoimmune bullous disorders), and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).
Class attribution effects

As for other sulfonylureas, the following adverse events have been observed:

Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, allergic vasculitis, hyponatraemia, 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.

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 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 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

Pharmacotherapeutic group: blood glucose lowering drugs, excl. insulins: sulfonylureas

ATC code: A10BB09

Mechanism of action

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.

Pharmacodynamic effects

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

Absorption

Plasma levels increase progressively during the first 6 hours, reaching a plateau, which is maintained from the sixth to the twelfth hour after administration.

Intra-individual variability is low.

Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption.

Distribution

Plasma protein binding is approximately 95%. The volume of distribution is around 30 litres. A single daily intake of gliclazide 30 mg modified-release tablets maintains effective gliclazide plasma concentrations over 24 hours.

Biotransformation

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.

Elimination

The elimination half-life of gliclazide varies between 12 and 20 hours.

Linearity/non linearity

The relationship between the dose administered ranging up to 120 mg and the area under the concentration time curve is linear.

Special populations

Elderly

No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients.

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. Fertility and reproductive performance were unaffected after gliclazide administration in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose
Calcium carbonate
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Gliclazide Teva is available in PVC/Al blister (10, 14 or 15 tablets/blister) in boxes of 10, 14, 20, 28, 30, 56, 60, 84, 90, 100, 120 or 180 tablets and in tablet containers (HDPE with a tamper evident PP screw-cap) of 90, 120 or 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/2513

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

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