1. NAME OF THE MEDICINAL PRODUCT

Gliclazide Krka 60 mg modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 60 mg gliclazide.

Excipient(s) with known effect:

Each modified-release tablet contains 88.7 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet

White to almost white, oval, biconvex tablets with a length 13 mm and a thickness 3.5 mm - 4.9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-insulin dependent Diabetes mellitus (Type II) 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 of Gliclazide Krka may vary from 30 to 120 mg taken orally in a single intake at breakfast time.

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

As with any hypoglycaemic agent, the dose should be adjusted according to the individual patient's

metabolic response (blood glucose, HbAlc).

Initial dose

The recommended initial 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.

One Gliclazide Krka 60 mg modified-release tablet corresponds to two Gliclazide Krka 30 mg modified-release tablets.

Switching from gliclazide (80 mg) tablets (immediate release formulation) to Gliclazide Krka 60 mg tablets with modified release

One tablet of gliclazide (80 mg) is comparable to one modified-release tablet 30 mg. Consequently, the switch can be performed with careful blood monitoring.

Switchover from another oral antidiabetic medicinal product to Gliclazide Krka 60 mg:
Gliclazide Krka modified-release tablets can be used to replace another oral antidiabetic medicinal product.
The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to Gliclazide Krka 60 mg 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 Krka 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 with other antidiabetic medicines
Gliclazide Krka modified-release tablets can be given in combination with biguanides, alpha-glucosidase inhibitors or insulin. In patients not adequately controlled with Gliclazide Krka 60 mg modified-release tablets, concomitant insulin therapy can be initiated under close medical supervision.

Special populations

Elderly
Gliclazide Krka 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 impairment 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
- undernourishment or malnourishment,
- severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic insufficiency),
- withdrawal of a prolonged and/or high-dose corticoid therapy,
- severe vascular disease (serious coronary heart disease, severe carotid impairment, diffuse vascular disease).

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

Paediatric population
The safety and efficacy of Gliclazide Krka in children and adolescents have not been established. No data are available in children.

Method of administration

Gliclazide Krka is to be taken as a single dose at breakfast time.

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

4.3 Contraindications

- Hypersensitivity to gliclazide or to any of the excipients listed in section 6.1, other sulphonylureas or sulfonamides,
- Insulin-dependent diabetes (Type I),
- Diabetic pre-coma and coma, diabetic ketoacidosis,
- 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 caloric 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 cooperate
- malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes
- imbalance between physical exercise and of carbohydrates intake

- renal insufficiency
- severe hepatic insufficiency
- overdose of Gliclazide Krka modified-release tablet
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency
- concomitant administration with 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 risk 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 sugar controls
The 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.

Lactose
Gliclazide Krka modified release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

1) The following medicines can increase the risk of hypoglycaemia:

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. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the anti-inflammatory agent.

Alcohol: increases in the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma. Alcohol and alcoholic medicinal products should be avoided.

Combinations requiring precautions for use
Potentiation of the blood glucose lowering effect and thus in some instances hypoglycaemia may also occur when one of the following medicinal products is taken:
other antidiabetics (insulins, acarbose, metformin, thiazolidinediones, dipeptidylpeptidase-4 inhibitors, GLP-1 receptor agonists), beta blockers, fluconazole, ACE inhibitors (captopril, enalapril), H_2-receptor antagonists, MAO inhibitors, sulfonamides, clarithromycin and non-steroidal anti-inflammatory agents.

2) <u>The following medicinal 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 the patient must be warned and informed of the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with danazol.

Combinations requiring precautions during use
Chlorpromazine (neuroleptic agent): High doses (>100 mg per day of chlorpromazine) increase in blood glucose levels (reduction of insulin release).
The patient must be warned and informed of 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 the glucocorticoids). The patient must be warned and informed of 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 sugar level due to beta-2-agonist effects. The patient must be informed of the importance of blood glucose monitoring. A switch to insulin treatment may be necessary.

Saint John's Wort (*Hypericum perforatum*) preparations:
Gliclazide exposure is decreased by Saint John's Wort. Emphasize the importance of blood glucose levels monitoring.

<u>The following products may cause dysglycaemia</u>
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.

3) Combination which has to be taken into account:
Anticoagulant therapy (e.g. warfarin, etc.):
Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the dose 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 during pregnancy in humans, 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 is excreted in human milk. Given the risk of neonatal hypoglycaemia the product is contraindicated in breast-feeding mother.
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 Krka 60 mg modified-release tablet has or negligible influence on the ability to drive and use machines. However, patients must 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 the following undesirable effects have been reported.

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)

Description of selected adverse reactions

Hypoglycaemia

The most frequent adverse reaction with gliclazide is hypoglycaemia.
As with other sulfonylureas, treatment with Gliclazide Krka modified-release tablets can commonly cause hypoglycaemia if meals are taken irregularly, and, in particular, if they 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 the 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 are required.

Other undesirable effects

Gastrointestinal disorders
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, angioedema, erythema, maculopapular rashes, bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis and autoimmune bullous disorders) and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).

Blood and lymphatic system disorders
Changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia and granulocytopenia. These are generally reversible upon discontinuation of the medication.

Hepatobiliary disorders
Raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports); Discontinuation of therapy if cholestatic jaundice appears.
These undesirable effects normally 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 sulfonylureas, the following undesirable effects 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 sulfoonylurea 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 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 a 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 a 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 closely monitored 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 derivatives, ATC code: A10BB09.

Mechanism of action

Gliclazide is a hypoglycaemic sulphonylurea oral antidiabetic 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 Krka 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 is 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 relevant changes in the 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 fœtal 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

Hypromellose
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes: 14, 15, 28, 30, 56, 60, 84, 90, 120 or 180 tablets in blisters (OPA/Alu/PVC foil//Alu foil)

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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

PL 01656/0182

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/1/2013

10 DATE OF REVISION OF THE TEXT

11/02/2025