SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bilxona 60mg Modified-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 60 mg gliclazide.

Excipient with known effect:

Each modified-release tablet contains 108 mg lactose (as the monohydrate) (see section 4.4)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet.

Bilxona 60 mg modified-release tablets are white, oval, biconvex 7 x 15 mm tablets scored on both sides, marked with “G” on one side of the score and “60” on the other side of the score. The tablet can be divided into equal doses.

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 one half to 2 tablets per day, i.e. 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 the 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 starting dose is 30 mg daily (half a 60 mg tablet).

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.

The breakability of the Bilxona 60 mg modified-release tablet enables flexibility of dosing to be achieved. One Bilxona 60 mg modified release tablet corresponds to two Bilxona 30 mg modified release tablets.

Switching from gliclazide 80 mg tablets to Bilxona 30mg modified-release tablets

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

Switching from gliclazide 80 mg tablets to Bilxona 60 mg modified-release tablets

1 tablet of gliclazide 80 mg is comparable to 1 tablet of *Bilxona* 30 mg modified-release (i.e. half a tablet of 60 mg). Consequently, the switch can be performed provided careful blood monitoring is undertaken.

Switching from another oral anti-diabetic agent to Bilxona

Bilxona can be used to replace other oral anti-diabetic agents. The dosage and the half-life of the previous anti-diabetic agent should be taken into account when switching to Bilxona.

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 sulphonylurea 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 Bilxona, 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 anti-diabetic agents

Bilxona can be given in combination with biguanides, alpha glucosidase inhibitors or insulin. In patients not adequately controlled with Bilxona. concomitant insulin therapy can be initiated under close medical supervision.

Special Populations

Older people (over 65 years of age)

Bilxona should be prescribed using the same dosing regimen recommended for patients under 65 years of age.

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

There is an increased risk of hypoglycaemia in the following circumstances:

- Undernourished or malnourished patients
- Patients with severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic insufficiency)
- Following withdrawal of prolonged and/or high dose corticosteroid therapy
- Patients with severe vascular disease (severe coronary heart disease, severe carotid impairment or diffuse vascular disease)

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

Paediatric population

The safety and efficacy of Bilxona in children and adolescents has not been established. No data and clinical studies are available in children.

Method of administration

Oral use.

It is recommended that the tablet(s) (whole or half tablet) be swallowed in one piece without chewing or crushing.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to other sulphonylureas or 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 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 Bilxona
- 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, along 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 anti-diabetic 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 anti-diabetic 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.

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

Excipients

Bilxona should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

1) 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 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: Other anti-diabetic agents (insulins, acarbose, biguanides (e.g. metformin), thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists); beta-blockers; fluconazole; angiotensin converting enzyme inhibitors (captopril, enalapril); H2-receptor antagonists; monoamine oxidase inhibitors (MAOIs); sulphonamides; clarithromycin; and non-steroidal anti-inflammatory agents.

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

Combination which is not recommended

-*Danazol:* has a diabetogenic effect. 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 anti-diabetic 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 anti-diabetic active substance during and after treatment with the neuroleptic agent.

- *Glucocorticoids (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin:* increase 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 anti-diabetic active substance during and after treatment with glucocorticoids.

-*Ritodrine, salbutamol and terbutaline (I.V. administration):* 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* (e.g. 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, although there is some data available for 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

Bilxona has no known 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 machinery, especially at the beginning of treatment.

4.8 Undesirable effects

Based on the experience with gliclazide and with other sulphonylureas, the following undesirable effects have to be mentioned.

Hypoglycaemia

As for other sulphonylureas, treatment with gliclazide can cause hypoglycaemia, if meal times 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 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 have been reported. These can be avoided or minimised if gliclazide is taken with a meal.

The following undesirable effects have been more rarely reported.

Skin and subcutaneous tissue disorders

Rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, and bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis)

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) and hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears. These symptoms usually 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

The following adverse events have been described for other sulphonylureas: 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 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 professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

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 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: Blood glucose lowering drugs, excl. insulins: Sulfonylureas, ATC code: A10BB09

Gliclazide is a hypoglycaemic, sulphonylurea, oral anti-diabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.

Mechanism of action

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 Bilxona 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

Older people

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Hypromellose

Cellulose, microcrystalline

Silica, colloidal anhydrous

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

PVC/PVDC/Al blisters.

PVC/PVDC/PVC/Al blisters.

White HDPE containers closed with LDPE caps (for Duma) or PP caps (for Duma Twist-off).

Pack sizes:

Blisters: 10, 14, 28, 30, 56, 60, 90, 120, 180 modified-release tablets.

Containers: 90, 120, 180 modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.

Reykjavíkurvegi 76-78

220 Hafnarfjörður

Iceland

8 MARKETING AUTHORISATION NUMBER(S)

PL 30306/0578

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2015

10 DATE OF REVISION OF THE TEXT

29/06/2016