SUMMARY OF PRODUCTS CHARACTERISTICS

1. Name of the medicinal product

Gliza - 2 tablets

2. Qualitative and quantitative composition

Each Uncoated Tablet Contains: Glimepiride BP 2mg.

Excipients with known effect:

Lactose, Sodium and Propylene glycol.

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets.

4. Clinical Particulars

4.1 Therapeutic Indications

Glimepiride is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate

4.2 Posology and method of administration Route of administration:

Oral.

Posology

The basis for successful treatment of diabetes is a good diet, regular physical activity, as well as routine checks of blood and urine. Tablets or insulin cannot compensate if the patient does not keep to the recommended diet.

The dosage is determined by the results of blood and urinary glucose determinations.

The starting dose is 1 mg glimepiride per day. If good control is achieved, this dosage should be used for maintenance therapy. For the different dosage regimens appropriate strengths are available. If control is unsatisfactory, the dosage should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3, or 4 mg glimepiride per day. A dosage of more than 4 mg glimepiride per day gives better results only in exceptional cases.The maximum recommended dose is 6 mg glimepiride per day.In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, the glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the

glimepiride dose, insulin treatment is started at a low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or - if none is taken - shortly before or during the first main meal. If a dose is forgotten, this should not be corrected by increasing the next dose.

If a patient has a hypoglycemic reaction on 1 mg glimepiride daily, this indicates that they can be controlled by diet alone. In the course of treatment, as an improvement in control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycemia timely dose reduction or cessation of therapy must therefore be considered. Change in dosage may also be necessary if there are changes in weight or life style of the patient, or other factors that increase the risk of hypo- or hyperglycemia.

Switch over from other oral hypoglycemic agents to glimepiride

A switch over from other oral hypoglycemic agents to glimepiride can generally be done. For the switch over to glimepiride the strength and the half-life of the previous medicinal product have to be taken into account. In some cases, especially in ant diabetics with a long half-life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimize the risk of hypoglycemic reactions due to the additive effect.

The recommended starting dose is 1 mg glimepiride per day. Based on the response the glimepiride dosage may be increased stepwise, as ind**icated earlier.**

Switch over from insulin to glimepiride

In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to glimepiride may be indicated. The changeover should be undertaken under close medical supervision.

Pediatrics population

There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as immunotherapy

4.3 Contraindications.

Glimepiride is contraindicated in patients with the following conditions:

-Hypersensitivity to glimepiride, other sulfonylureas or sulfonamides or to any of the Excipients listed in section 6.1.

-Insulin dependent diabetes

-Diabetic coma

-Ketoacidosis

-Severe renal or hepatic function disorders.

In case of severe renal or hepatic function disorders, a change over to insulin is required

4.4 Special Warnings and Precautions for Use

Glimepiride must be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with" Glimepiride Tablets" may lead to hypoglycemia. Possible symptoms of hypoglycemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias.

The clinical picture of a severe hypoglycemic attack may resemble that of a stroke.

Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect.

Factors favoring hypoglycemia include:

-Unwillingness or (more commonly in older patients) incapacity of the patient to cooperate

-Under nutrition, irregular mealtimes or missed meals or periods of fasting

-Alterations in diet

-Imbalance between physical exertion and carbohydrate intake

-Consumption of alcohol, especially in combination with skipped meals

-impaired renal function

-Serious liver dysfunction

-Over dosage with Glimepiride Tablets

-Certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter regulation of hypoglycemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency)

-concurrent administration of certain other medicinal products (see section 4.5)

Treatment with glimepiride tablets requires regular monitoring of glucose levels in blood and urine. In addition, determination of the proportion of glycosylated hemoglobin is recommended.

Regular hepatic and hematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride tablets

In stress-situations (e.g. accidents, acute operations, infections with fever etc) a temporary switch to insulin may be indicated.

No experience has been gained concerning the use of glimepiride tablets in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency, and a non-sulfonylurea alternative should be considered.

Glimepiride Tablets contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of Interaction

glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).

Results from an in-vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with glimepiride and with other sulfonylureas, the following interactions have to be mentioned.

Potentiating of the blood-glucose-lowering effect and, thus in some instances hypoglycemia may occur when one of the following medicinal products is taken, for example:

-Phenylbutazone, azapropazone and oxyfenbutazone,

-Insulin and oral ant diabetic products, such as Metformin,

-Salicylates and p-amino-salicylic acid,

-Anabolic steroids and male sex hormones,

-Chloramphenicol, certain long-acting sulfonamides, tetracyclines, quinolone antibiotics and clarithromycin,

-Coumarin anticoagulants,

-Fenfluramine,

-Disopyramide,

-Fibrates,

-ACE inhibitors,

-Fluoxetine, MAO-inhibitors,

-Allopurinol, probenecid sulfinpyrazone,

- Sympatholytics,

-Cyclophosphamide, trophosphamide and iphosphamides,

-miconazole, fluconazole,

-pentoxifylline (high dose parenteral),

-tritoqualine

Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Risk related to the diabetes

Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

Risk related to glimepiride

There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycemia) of glimepiride (see section 5.3).

Consequently, glimepiride should not be used during the whole pregnancy. In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Lactation

The excretion in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or have frequent episodes of hypoglycemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

4.8 Undesirable Effects

Blood and lymphatic system disorders

Rare: thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, erythropenia, hemolytic anemia and pancytopenia, which are in general reversible upon discontinuation of medication.

Not known severe thrombocytopenia with platelet counts less than 10,000/µl and thrombocytopenic purpura.

Immune system disorders

Very rare: leukocytoclastic vacuities, mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.

Not known cross-allergen city with sulfonylureas, sulfonamides or related substances is possible.

Metabolism and nutrition disorders

Rare: hypoglycemia.

These hypoglycemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycemic therapies, on individual factors such as dietary habits and dosage (see further under section 4.4).

Eye disorders

Not known visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.

Gastrointestinal disorders

Very rare*:* nausea, vomiting, diarrhea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.

Hepato-biliary disorders

Very rare*:* hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis

and hepatic failure. Not known hepatic enzymes increased.

Skin and subcutaneous tissue disorders

Not known hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.

Investigations

Very rare: blood sodium decrease.

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

Pharmacovigilance Electronic Reporting System (PvERS)
https://pv.pharmacyboardkenya.org/

4.9 Overdose and treatment

Symptoms

After ingestion of an overdue sage hypoglycemia may occur, lasting from 12 to 72 hours, and may recur
after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastria pain may occur. The hypoglycemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Management

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) over dosage hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary, by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Blood glucose lowering drugs, excl. insulins: Sulphonamides, urea derivatives

ATC Code : A10B B12

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent (type 2) diabetes mellitus.

Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extra pancreatic effects also postulated for other sulfonylureas.

Insulin release:

Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarization of the beta cell and results -by opening of calcium channels - in an increased influx of calcium into the cell. This leads to insulin release through exocytose.

Glimepiride binds with a high exchange rate to a beta cell membrane protein which is

associated with the ATP-sensitive potassium channel, but which is different from the usual sulfonylureas binding site.

Extra pancreatic activity

The extra pancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver.

The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins, located in the cell's membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Special populations

Pediatrics population:

An active controlled clinical trial (glimepiride up to 8 mg daily or Metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.

Both glimepiride and metformin exhibited a significant decrease from baseline in HbA_{1c} (glimepiride -0.95 (se 0.41); Metformin -1.39 (se 0.40)). However, glimepiride did not achieve the criteria of non-inferiority to Metformin in mean change from baseline of HbA_{1c}. The difference between treatments was 0.44% in favour of Metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin.

Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in pediatric patients.

5.2. Pharmacokinetic properties

Absorption

The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only the absorption rate is slightly diminished. Maximum serum concentrations (Cmax) are reached approx 2.5 hours after oral intake (mean 0.3 μg/ml during multiple dosing of 4 mg/daily) and there is a linear relationship between dose and both Cmax and AUC (area under the time concentration curve).

Distribution

Glimepiride has a very low distribution volume (approx. 8.8 litres), which is roughly equal to the albumin distribution space, high protein binding (>99%) and a low clearance (approx. 48 ml/min).

In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood-brain barrier is low.

Biotransformation and elimination

Mean dominant serum half-life, which is of relevance for the serum concentrations

under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted.

After a single dose of radiolabel led glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faces. No unchanged substance was detected in the urine. Two metabolites most probably resulting from hepatic metabolism (major enzyme is CYP2C9) were identified both in urine and faces: the hydroxyl derivative and the carboxyl derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intra individual variability was very low. There was no relevant accumulation.

Special populations

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding.

Renal elimination of the two metabolites was impaired. Overall, no additional risk of accumulation is to be assumed in such patients.

Pharmacokinetics in five non-diabetic patients after bile duct surgery were similar to those in healthy persons.

Pediatrics population

A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 pediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last) , Cmax and t1/2 similar to that previously observed in adults.

5.3 Preclinical safety data

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use or were due to the pharmacodynamic action (hypoglycemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryo toxicity, teratogenicity and developmental toxicity), adverse effects observed were considered to be secondary to the hypoglycemic effects induced by the compound in dams and in offspring.

6. Pharmaceutical Particulars

6.1 List ofExcipients

Microcrystalline cellulose BP, Lactose BP, Polyethylene glycol USP-NF, Sodium lauryl sulphate BP, Methylene dichloride BP, Microcrystalline cellulose BP, Purified talc BP, Magnesium stearate BP, Sodium starch Glycolate BP

6.2 Incompatibilities

None.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and Contents of Container

Alu-Alu blister packs of 3 x 10's

6.6 Special precaution for disposal and other handling

No special requirements

7 Marketing Authorization Holder

NBS PHARMACEUTICAL
DIVISON OF NORTHLAND BIOSCIENCE
545, LANSING AVANUE, STE 2JACKSON
MICHIGAN 49201.

8 Marketing Authorization Number:

H2025/CTD11308/24887

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