MECURE INDUSTRIES PLC

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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1. NAME OF THE MEDICINAL PRODUCT
MeCure's Glibenclamide 5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Glibenclamide 5mg

Composition:

Each Film coated Tablet Contains:
Glibenclamide 5mg
Excipients: q.s.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:
Film coated Tablet

DESCRIPTION:
A white circular biconvex uncoated tablet, having embossed with "MECURE" on one side and "GB/5" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Glibenclamide is a sulphonylurea hypoglycaemic agent indicated for the oral treatment of patients with non-insulin dependent diabetes who respond inadequately to dietary measures alone.

4.2 Posology and method of administration

The dosage of glibenclamide is governed by the desired blood glucose level.

The dosage of glibenclamide must be the lowest possible dose which is effective.

Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose.

The usual total daily dosage is 2.5 to 15 mg daily with a usual initial dose of 5 mg daily. Weekly adjustments can be made to increase the dosage to the optimal level. Doses of 10 mg or less may be taken as a single dose immediately before/after breakfast, but should the daily dose exceed 10 mg, the remainder should be taken immediately before/after the evening meal.

Patients aged 65 years and older: starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia. Treatment should be started with the lowest available dose and increased gradually if necessary (see section 4.4).

Paediatric population The safety of Glibenclamide in the paediatric population has not been established.

Currently avaible data are described in sections 4.8 but no recommendations on a posolgy can be made.

Dose Omission

A physician should be consulted in the event that a dose has not been taken at the prescribed time, a meal has been skipped or an extra dose has been taken.

It is very important not to skip meals after the tablets have been taken.

Secondary dosage adjustment

As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glibenclamide requirements may fall as treatment proceeds. To avoid hypoglycaemia, timely dose reduction or cessation of Glibenclamide therapy must therefore be considered.

Correction of dosage must also be considered, whenever:

- the patients weight changes
- the patients life-style changes
- other factors arise, which cause an increased susceptibility to hypoglycaemia or hyperglycaemia

Changeover from other oral antidiabetics to Glibenclamide

Changeover from other oral antidiabetic agents to Glibenclamide should be done under the supervision of a specialist, and due to the potential summation of effects of both medications, entails a risk of hypoglycaemia. A break from medication may therefore be required when changing over medications. This should be decided by the attending physician.

4.3 Contraindications

Glibenclamide should not be used in patients who have or ever had diabetic ketoacidosis or diabetic coma/precoma or in patients who have insulin-dependent diabetes mellitus, serious impairment of renal, hepatic or adrenocortical function, in patients who are hypersensitive to glibenclamide or any of the excipients or in circumstances of unusual stress, e.g. surgical operations or during pregnancy, when dietary measures and insulin are essential.

Glibenclamide should not be used in the following:

- Patients with sulphonylurea or sulphonamide intolerance.
- ’Brittle’ or juvenile diabetes
- Pregnancy
- Breast feeding women
- Children
- In patients treated with bosentan

4.4 Special warnings and precautions for use

Epidemiological studies suggest that the administration of glibenclamide is associated with an increased risk of cardiovascular mortality, when compared to treatment with metformin or gliclazide. This risk was especially observed in patients with diagnosed coronary diseases.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucosegalactose malabsorption should not take this medicine.

Persons allergic to other sulphonamide derivatives may develop an allergic reaction to glibenclamide as well.

During treatment with glibenclamide, glucose levels in blood and urine must be measured regularly.

Adjustment of the dosage of hypoglycaemic agents may be required in patients suffering from intercurrent infections, trauma, shock or anaesthesia.

For major surgery, insulin therapy should be substituted for oral hypoglycaemics.

Hepatic or renal dysfunction may require reduction in dosage.

Patients for whom sulphonylurea therapy is intended should be carefully selected, and limited to those who cannot be controlled on dietary measures alone, do not require insulin, and do not suffer from those disorders, the course of which might be affected by this therapy.

Elderly, debilitated patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycaemic action of glucose lowering drugs. Hypoglycemia may be difficult to recognize in the elderly. The initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.

In exceptional stress situations (e.g. trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

As is necessary during treatment with any blood-glucose-lowering drug, the patient and the doctor must be aware of the risk of hypoglycaemia.

Factors favouring hypoglycaemia include:

- unwillingness or incapacity of the patient to co-operate
- undernourishment, irregular mealtimes or missed meals
- imbalance between physical exertion and carbohydrate intake
- alterations of diet
- impaired renal function
- elderly patients: Age 65 years and older has been identified as a risk factor for hypoglycemia in patients treated with sulfonylureas. Hypoglycemia can be difficult to recognize in the elderly. Starting and maintenance doses of glibenclamide must be carefully adjusted to reduce the risk of hypoglycaemia (see section 4.2)
- serious liver dysfunction
- overdosage with glibenclamide
- uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counterregulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or adrenocortical insufficiency)
- concurrent administration of certain other medicines.

If such risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of glibenclamide or the entire therapy. This also applies whenever illness occurs during therapy or the patients lifestyle changes.

Those symptoms of hypoglycaemia, which reflect the body's adrenergic counter-regulation may be milder or absent where hypoglycaemia develops gradually, where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine, or other sympatholytic drugs.

Hypoglycaemia can, almost always, be promptly controlled by immediate intake of carbohydrates.

Despite initially successful counter-measures, hypoglycaemia may recur. Patients must, therefore, remain under close observation.

Severe hypoglycaemia, or a protracted episode, which can only be temporarily controlled by usual amounts of sugar, further requires immediate treatment and follow-up by a doctor and, in some circumstances, in-patient hospital care.

Treatment of patients with G-6-phosphate-dehydrogenase deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since Glibenclamide 5mg Tablets belongs to the class of sulfonylurea agents, caution should be used in patients with G-6-phosphate-dehydrogenase deficiency and a non-sulfonylurea alternative should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Glibenclamide is mainly metabolised by CYP 2C9 and to a lesser extent by CYP 3A4. This should be taken into account when glibenclamide is coadministered with inducers or inhibitors of CYP 2C9.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when taking other drugs, including:

Insulin and other, oral antidiabetics, ACE inhibitors, anabolic steroids and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, ifosfamide, MAO inhibitors, miconazole, para-aminosalicyclic acid, pentoxifylline, phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamides, sympatholytic agents such as beta-blockers and guanethidine, clarithromycin, tetracyclines, tritoqualine, trosfosfamide.

Weakening of the blood-glucose-lowering effect and, thus, raised blood glucose levels may occur when taking other drugs, including:

Acetazolamide, barbiturates, corticosteroids, diazoxide, diuretics, epinephrine and other sympathomimetic agents, glucagon, laxatives, nicotinic acid, oestrogens and progestogens, phenothiazines, phenytoin, thyroid hormones, rifampicin.

H2-receptor antagonists, clonadine, and resperine may lead to either potentiation or weakening of the blood-glucoselowering effect.

Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and resperine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent.

Glibenclamide may increase cyclosporine plasma concentration and potentially lead to its increased toxicity.

Both acute and chronic alcohol intake may potentiate or weaken the blood glucose lowering action of glibenclamide in an unpredicted fashion.

Glibenclamide may either potentiate or weaken the effect of coumarin derivatives.

Bosentan: An increased incidence of elevated liver enzymes was observed in patients receiving glibenclamide concomitantly with bosentan.

Both glibenclamide and bosentan inhibit the bile salt export pump, leading to intracellular accumulation of cytotoxic bile salts. Therefore, this combination should not be used.

4.6 Fertility, pregnancy and lactation

Pregnancy

Glibenclamide must not be taken during pregnancy. The patient must change over to insulin during pregnancy.

Animal studies showed some teratogenic effects.

Fertility

Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

Breast-feeding

Glibenclamide must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

4.7 Effects on ability to drive and use machines

Alertness and reactions may be impaired by hypo- or hyperglycaemic episodes, especially when beginning or after

altering treatment, or when Glibenclamide is not taken regularly. This may affect the ability to drive or operate machinery.

4.8 Undesirable effects

- Hypoglycaemia

Hypoglycaemia, sometimes prolonged and even life-threatening, may occur as a result of the blood glucose lowering action of glibenclamide tablets.

Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness, and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, pareses, sensory disturbances, dizziness, helplessness, loss of self control, delirium, cerebral convulsions, somnolence and loss of consciousness up to an including coma, shallow respiration and bradycardia.

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 hypoglycaemic attack may resemble that of a stroke. The symptoms of hypoglycaemia nearly always subside when hypoglycaemia is corrected.

- Eyes

Temporary visual impairment.

- Digestive tract

Gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur. In isolated cases, there may be elevation of liver enzyme levels and even impairment of liver function (e.g. with cholestatsis and jaundice and hepatitis which can regress after withdrawal of glibenclamide tablets, although they may lead to life-threatening liver failure). Treatment with sulphonylureas has been associated with occasional disturbances of liver function and cholestatic jaundice.

- Blood

Potentially life-threatening changes in the blood picture may occur. They may include – rarely – mild to severe thrombopenia (e.g. presenting as purpura) - isolated cases – haemolytic anaemia, erythrocytopenia, leucopenia, granulocytopenia, agranulocytosis and (e.g. due to myelosupression) pancytopenia.

- General disorder

Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form itching or rashes. In isolated cases, mild reactions in the form of urticaria may develop into serious and even life-threatening reactions with dyspnoea and fall in in blood pressure, sometimes progressing to shock. In the event of urticaria, a physician must therefore be notified immediately.

A hypersensitivity reaction may be directed against glibenclamide itself, but may alternatively be triggered by bexcipients. Allergy to sulphonamide derivatives may also be responsible for an allergic reaction to glibenclamide.

In isolated cases, allergic vasculitis may arise and, in some circumstances, may be life- threatening. In isolated cases, hypersensitivity of the skin to light may occur, and sodium concentration in the serum may 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.

4.9 Overdose

Signs and Symptoms

Acute overdose as well as long-term treatment with too high a dose of glibenclamide may lead to severe, protracted, life-threatening hypoglycaemia.

Management

As soon as an overdose of glibenclamide has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose.

Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycaemia and its clinical signs may recur after initial recovery.

Admission to hospital may sometimes be necessary even as a precautionary measure. In particular, significant overdoses and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital.

If, for example, the patient is unconscious, an intravenous injection of concentrated glucose solution is indicated (for adults starting with 40 ml of 20% solution, for example). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1 mg i.v., s.c. or i.m., may be considered.

In particular when treating hypoglycaemia in infants and young children, the dose of glucose given must be very carefully adjusted in view of the possibility of producing dangerous hyperglycaemia, and must be controlled by close monitoring of blood glucose.

Patients who have ingested life-threatening amounts of Glibenclamide require detoxification (e.g. by gastric lavage and medicinal charcoal).

After acute glucose replacement has been completed, it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, hypoglycaemia, or the danger of slipping back into hypoglycaemia, may persist for several days.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulphonamides, urea derivatives

ATC Code: A10B B01

The pharmacodynamic effect of glibenclamide is to lower blood glucose levels.

Mechanisms proposed for this effect include:

- Stimulation of insulin release from pancreatic beta-cells
- Increasing insulin binding receptor density in peripheral tissues

Plasma glucose levels affect the insulin-releasing response to glibenclamide, (a high glucose level increases the response). The minimum active concentration for effect is considered to be 30 - 50 nanograms/ml glibenclamide.

Investigations of the relationship between insulin, glucose levels and glibenclamide in the hypoglycaemic effect continue.

5.2 Pharmacokinetic properties

A sulphonylurea hypoglycaemic agent rapidly absorbed and inducing its effect within 3 hours with a duration of up to 15 hours although the T½ of drug is 5 to 10 hours. The drug is metabolised extensively in the liver and excreted via bile and urine. It is strongly protein-bound.

5.3 Preclinical safety data

Non of clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate
- Microcrystalline Cellulose
- Talc
- Colloidal anhydrous Silica
- Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf

life

36 months.

6.4 Special precautions for storage

Store in a cool dry place at temperature below 30 °C. Store in the original packaging.

6.5 Nature and contents of container

Aluminum-PVC Blister Pack of 2 x 14’s tablets

6.6 Special precautions for disposal and other handling

No special requirements

ADMINISTRATIVE DATA

7 MARKETING AUTHORISATION HOLDER

7.1 Manufacturer/Marketing Authorisation Holder

Me Cure Industries PLC,

Plot 6, Block H, Oshodi Industrial Scheme,

Oshodi,

Lagos,

Nigeria.