

## **1. NAME OF THE MEDICINAL PRODUCT**

GLUBEN

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Glibenclamide 5mg.

Excipients : contains lactose monohydrate 133.00mg.

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Tablet.

White, biconvex tablets, scored on one side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Control of hyperglycemia in stable, mild, nonketosis prone Glibenclamide responsive type II diabetes mellitus, which cannot be controlled by proper dietary management or when insulin therapy is inappropriate

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

The elderly usually require lower dosage.

#### **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 GLUBEN 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 GLUBEN**

Change over from other oral antidiabetic agents to GLUBEN 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**

GLUBEN should not be used in patients who have or have 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.

GLUBEN should not be used in the following groups:

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**

#### **SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY**

**The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term**

prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes 19 (supp. 2): 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUBEN and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

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

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

During treatment with GLUBEN, 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.

Severe renal or hepatic insufficiency may cause elevated blood levels of GLUBEN and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious, prolonged hypoglycemic reactions. Hepatic or renal dysfunction may require reduction in dosage.

Patients for whom sulfonylurea 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, malnourished 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 patients with autonomic neuropathy, the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. The initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

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. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes.

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
- serious liver dysfunction
- alcohol ingestion
- more than one glucose-lowering drug is used
- overdosage with GLUBEN
- uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation 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.

The effectiveness of any oral hypoglycemic drug, including GLUBEN, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

Treatment of patients with G-6-phosphate-dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since GLUBEN 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. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

**Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glibenclamide or any other anti-diabetic drug.

#### **Laboratory Tests**

**Periodic fasting blood glucose measurements should be performed to monitor therapeutic response. A glycosylated hemoglobin determination should also be performed periodically.**

#### **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. Rifampicin may worsen glucose control of glibenclamide because rifampicin can significantly induce metabolic isozymes of glibenclamide such as CYP2C9 and 3A4.

Potential of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when taking other drugs, including: nonsteroidal anti-inflammatory agents, Insulin and other, oral antidiabetics, ACE inhibitors, disopyramide, fluoxetine, clarithromycin, and other drugs that are highly protein bound, anabolic steroids and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide, fenfluramine, fenylamidol, fibrates, ifosfamide, MAO inhibitors, miconazole, para-aminosalicylic acid, pentoxifylline, phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfapyrazone, sulfonamides, sympatholytic agents such as beta-blockers and guanethidine, tetracyclines, tritoqualine, trosfosfamide. When such drugs are administered to a patient receiving GLUBEN, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving GLUBEN, the patient should be observed closely for loss of control.

Weakening of the blood-glucose-lowering effect and, thus, raised blood glucose

levels may occur when taking other drugs, including: acetazolamide, barbiturates, corticosteroids, diazoxide, thiazides and other diuretics, epinephrine and other sympathomimetic agents, glucagon, laxatives, nicotinic acid, oestrogens and progestogens (oral contraceptives), calcium channel blocking drugs, isoniazid, phenothiazines, phenytoin, thyroid hormones, rifampicin. When such drugs are administered to a patient receiving GLUBEN, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving GLUBEN, the patient should be observed closely for hypoglycemia.

H<sub>2</sub>-receptor antagonists, clonidine, and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

Under the influence of sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine, 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. Monitoring and dosage adjustment of cyclosporine are therefore recommended when both drugs are coadministered.

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

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

A possible interaction between glybenclamide and fluoroquinolone antibiotics has been reported resulting in a potentiation of the hypoglycemic action of glibenclamide. The mechanism for this interaction is not known.

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. The mechanism of these interactions is not known.

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**

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

Animal studies showed some teratogenic effects (see section 5.3).

**Nonteratogenic Effects:** Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives.

#### Fertility

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

#### Breast-feeding

Although it is not known whether glibenclamide is excreted in human milk, some sulfonylureas are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, GLUBEN 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 GLUBEN 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 GLUBEN. 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 and 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, changes in accommodation and/or blurred vision. These are thought to be related to fluctuation in glucose levels.

##### - Digestive tract

Gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or

fullness in the epigastrium, abdominal pain, heartburn, and diarrhoea are the most common reactions and may occur in 1.8% of treated patients. They tend to be dose-related and may disappear when dosage is reduced. In isolated cases, there may be elevation of liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice and hepatitis which can regress after withdrawal of GLUBEN, although they may lead to life-threatening liver failure). GLUBEN should be discontinued if this occurs. Treatment with sulphonylureas has been associated with occasional disturbances of liver function and cholestatic jaundice.

#### - Metabolic Reactions

Hepatic porphyria reactions have been reported with sulphonylureas; however, these have not been reported with glibenclamide. Disulfiram-like reactions have been reported very rarely with glibenclamide. Cases of hyponatremia have been reported with glibenclamide and all other sulphonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulphonylureas, and it has been suggested that these sulphonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

#### - 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, aplastic anemia, erythrocytopenia, leucopenia, granulocytopenia, agranulocytosis and (e.g. due to myelosuppression) pancytopenia have been reported with sulphonylureas.

#### - General disorders

Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching or rashes. Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in 1.5% of treated patients. These may be transient and may disappear despite continued use of GLUBEN; if skin reactions persist, the drug should be discontinued.

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

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulphonylureas.

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

In addition to dermatologic reactions, allergic reactions such as angioedema,

arthralgia, myalgia and vasculitis have been reported.

In isolated cases, allergic vasculitis may arise and, in some circumstance, may be life threatening.

#### **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**

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 in 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 T<sub>1/2</sub> 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**

Glibenclamide is non-mutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay. Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects.

No drug related effects were noted in any of the criteria evaluated in the two year oncogenicity study of glibenclamide in mice.

Animal studies showed some teratogenic effects.

GLUBEN has been shown to affect the maturation of the long bones (humerus and femur) in rat pups when given in doses 6250 times the maximum recommended human dose. These effects, which were seen during the period of lactation and not during organogenesis, are a shortening of the bones with effects to various structures of the long bones, especially in humerus and femur.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipient(s)**

Lactose Monohydrate  
Microcrystalline cellulose  
Sodium starch glycolate  
Carmellose sodium  
Magnesium stearate  
Silica colloidal anhydrous

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Do not store above 25°C. Store in the original package.

**6.5 Nature and contents of container**

PVC/Aluminium blister packs of 10, 28, 30, 50, 100, 1000 tablets

Not all pack sizes maybe marketed

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7. LICENSE HOLDER**

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

**8. MANUFACTURER**

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The format of this leaflet was determined by the Ministry of Health (MOH) and its content was checked and approved by the MOH in 04/2015