**Glimel**

**Glibenclamide**

**PRODUCT INFORMATION**

**Name of the medicine**

The active ingredient of Glimel is glibenclamide. Glibenclamide is 1-{4-[2-(5-chloro-2-methoxybenzamido) ethyl]benzene-sulphonyl}-3-cyclohexylurea.

![Chemical structure of glibenclamide](image)

Molecular formula: C_{23}H_{28}ClIN_{3}O_{5}S  
Molecular weight: 494  
Cas number: 10238-21-8

**Description**

Glibenclamide is a white or almost white, crystalline powder; odourless or almost odourless. It is practically insoluble in water and in ether; soluble in 330 parts of ethanol (96%), in 36 parts of chloroform, and in 250 parts of methanol.

Each Glimel tablet contains 5 mg of glibenclamide. The tablets also contain the following inactive excipients: microcrystalline cellulose, pregelatinised maize starch, purified talc, colloidal anhydrous silica, magnesium stearate.

**Pharmacology**

**Site and Mode of Action**

Glibenclamide, a sulphonylurea, is an orally active hypoglycaemic agent. It appears to acutely lower the blood glucose in both healthy individuals and type 2 diabetic patients by stimulating the release of insulin from the pancreas. Therefore, the pancreatic beta cells must be functional for glibenclamide to be effective. Glibenclamide acts together with glucose (improved sensitivity of beta cells to physiological glucose stimulus), leading to secretion of insulin in the rhythm of meals. The hypoglycaemic action associated with short-term therapy may also include a reduction in basal hepatic glucose production and enhancement of peripheral insulin action at post-receptor (probably intracellular) sites.

Despite a gradual decline in glucose or meal-stimulated secretion of insulin towards pretreatment levels, the improvement in glucose tolerance persists in type 2 diabetic patients with chronic administration of glibenclamide. During long-term administration, the hypoglycaemic action of the drug can be attributed to extra-pancreatic effects. These effects are similar to those observed with short-term therapy and involve enhanced peripheral sensitivity to insulin (via an increase in insulin receptor number and/or an increase in insulin binding to peripheral receptors) and reduction of basal hepatic glucose production.

Glibenclamide also inhibits glucagon production by the pancreatic alpha cells and increases somatostatin release. These two pancreatic non-beta cell actions may however play only a minor clinical role.

Glibenclamide also has a mild diuretic action, increasing free water clearance from the body, in addition to its blood glucose lowering effect.
Pharmacokinetics

**Absorption.** Glibenclamide is almost completely absorbed (84±9%) from the gastrointestinal tract and is extensively bound (99%) to plasma proteins. The peak serum concentration is reached in two to six hours after taking one tablet and falls within 24 hours to less than 5% of the peak value. The area under the serum concentration-time curve (AUC) increases in proportion to increasing doses. Food appears to have no effect on the rate or extent of glibenclamide absorption.

Glibenclamide does not build-up in tissue depots, as shown by similar drug level concentration-time curves in multiple and single dose studies with diabetic patients. The hypoglycaemic action of a single morning dose of glibenclamide persists for 24 hours in non-fasting diabetic patients.

**Metabolism.** Glibenclamide serum levels appear to decline in a biphasic manner. After intravenous administration, the elimination half-life of glibenclamide is approximately two hours, and two to five hours after oral dosage, although some reports indicate a longer half-life of eight to ten hours in diabetic patients.

Glibenclamide appears to be completely metabolised by hydroxylation of the cyclohexyl group, probably in the liver. The principal metabolite is a 4-trans-hydroxy derivative, with a second metabolite, the 3-cis-hydroxy derivative, also occurring. As they are only weakly active (0.25% and 2.5%, respectively, as glibenclamide in rabbits) these metabolites contribute no significant hypoglycaemic action.

**Excretion.** Glibenclamide, in the form of its metabolites is excreted in equal proportions in urine and bile. In patients with renal insufficiency, depending on the degree of the renal excretion disorder, there is increased excretion via the bile. This dual excretory pathway is different from that of other sulfonylureas, which are excreted primarily in the urine. Haemodialysis only has a minimal effect on glibenclamide removal.

Indications

Glibenclamide is used to treat non-insulin dependent diabetes mellitus (type 2), as an adjunct to diet, in patients whose hyperglycaemia cannot be controlled by diet alone. Glibenclamide is often suitable for the management of patients who have failed to respond to other oral antidiabetics because of its broad and predictable action.

Diet should be emphasised as the primary form of treatment when initiating treatment for non-insulin dependent diabetes. It is essential that obese diabetic patients reduce caloric intake and lose weight. Blood glucose levels and symptoms of hyperglycaemia may be effectively controlled by proper dietary management alone. Regular physical exercise is also an important part of diabetic therapy. Cardiovascular risk factors should be identified and corrective measures taken where possible. Upon failure of this treatment program to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered. Glibenclamide should be viewed as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

Contraindications

1. Known hypersensitivity or allergy to glibenclamide or any of the excipients.
2. Insulin dependent diabetes mellitus (type 1 or juvenile onset diabetes).
3. Diabetes complicated by ketosis.
4. Serious metabolic decompensation with acidosis, in particular precoma and coma.
5. Severe impairment of renal function.
6. Severe hepatic dysfunction.

7. Pregnancy (see **Precautions, Use in pregnancy**).

8. Lactation (see **Precautions, Use in lactation**).

9. Patients treated with bosentan (see **Interactions with other medicines**)

**Precautions**

Diabetes treatment should be closely regulated. Until optimal control is achieved, when changing from one product to another or when tablets are not taken regularly, the patient may not be fit to drive or to operate machinery due to impaired alertness reaction time.

A temporary change to insulin may become necessary, when situations of unusual stress arise (e.g. emergency or elective surgery, febrile infections).

Cross sensitivity to sulfonamides and their derivatives is possible. Persons allergic to other sulfonamide derivatives may develop an allergic reaction to glibenclamide as well.

**Hypoglycaemic reactions**

All sulfonylureas can induce severe hypoglycaemia, which may be prolonged and is potentially lethal.

Debilitated, malnourished or elderly patients and patients with mild disease or impaired hepatic or renal function should be carefully monitored. As they may be predisposed to developing hypoglycaemia, the dosage of glibenclamide should be carefully adjusted in these patients. Increased serum concentrations of glibenclamide may be caused by renal or hepatic insufficiency and glyconeogenic capacity may also diminish with hepatic insufficiency, thus increasing the risk of severe hypoglycaemic reactions.

Patients may also develop hypoglycaemia after alcohol ingestion, severe or prolonged exercise, deficient caloric intake, use of more than one antidiabetic agent, severe endocrine disorders or with adrenal and pituitary insufficiency.

Patients should undergo regular clinical and laboratory evaluations, including blood and urine glucose determinations, to determine the minimum effective dosage of glibenclamide and to detect primary failure (inadequate lowering of blood glucose concentration at the maximum recommended dosage) or secondary failure (loss of control of blood glucose concentration following an initial period of effectiveness) to the drug. The patient's response to glibenclamide therapy may also be determined by the measurement of glycosylated haemoglobin. Patients replacing insulin with glibenclamide should be instructed to test their urine for glucose and ketones at least three times daily during the withdrawal period. Patient or laboratory monitoring of blood glucose concentration is preferable when possible. Patients should be careful to avoid ketosis, acidosis and coma during the withdrawal period when switching from insulin to glibenclamide. If blood glucose concentration is no longer lowered during maintenance therapy with glibenclamide, the drug should be discontinued.

Patients and family members should be aware of the signs and symptoms of hyperglycaemia (severe thirst, dry mouth, frequent micturition, dry skin) and hypoglycaemia (intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep or transient neurological disorders) and know how to respond promptly to such occurrences.
The elimination half-life of glibenclamide may be prolonged by a genetic metabolic defect. Because of its broad and predictable hypoglycaemic effect, Glimel should be taken immediately before breakfast. Patients who eat only a light breakfast should defer the first of the day until lunchtime.

Glucose tolerance may improve after a few weeks' treatment with glibenclamide. The clinical status should be checked within the first four to eight weeks and then at regular intervals, to ascertain whether a dose reduction is possible. Correction of dosage must also be considered whenever the patient’s weight changes, the patient’s lifestyle changes or other factors arise that cause an increased susceptibility to hypoglycaemia or hyperglycaemia.

Open Haemolytic anaemia

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glibenclamide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.

Carcinogenicity and mutagenicity

Glibenclamide was not genotoxic in a limited set of assays for gene mutations (Salmonella microsome test (Ames test)) and other genotoxic effects (DNA damage/alkaline elution assay). The clastogenic potential of glibenclamide has not been investigated.

Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects.

Impairment of fertility

The effects of glibenclamide on fertility have not been investigated.

Use in pregnancy (Category C)

It is important to ensure that glucose levels are normal during pregnancy. Oral hypoglycaemic agents should be replaced by insulin because sulfonylureas may enter the fetal circulation and cause neonatal hypoglycaemia. Embryotoxicity and/or birth defects have been demonstrated in animal studies.

Use in lactation

Although it is not known whether glibenclamide is excreted in human milk, some sulfonylureas are known to be excreted in human milk. Because of the potential for hypoglycaemia in nursing infants, glibenclamide is not recommended for use in breast feeding women.

Use in children

Glibenclamide is not recommended for use in children as the safety and efficacy have not been established.

Interactions with other medicines

An increased incidence of elevated liver enzymes was observed in patients receiving glibenclamide concomitantly with bosentan. Both bosentan and glibenclamide inhibit the bile salts export pump, leading to intracellular accumulation of cytotoxic bile salts. Therefore, this combination should not be used (see Contraindications).

Other drugs given at the same time as sulfonylureas may cause undesirable depression or elevation of blood sugar levels.
Drugs which may potentiate the hypoglycaemic action of Glimel include insulin, other antidiabetics, alcohol, ACE inhibitors, aminosalicylic acid, anabolic steroids and male sex hormones, azapropazone, beta-receptor blockers, bezafibrate, biguanides, chloramphenicol, clofibrate, clonidine, co-trimoxazole, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidal, fbrates, fluoxetine, gemfibrozil, guanethidin, heparin, ifosfamide, MAO-inhibitors, miconazole, oxpentiniflyringe (parenteral, in high doses), oxyphenbutazone, para-aminosalicylic acid, phenylbutazone, phenyramidal, phosphamides, probenecid, quinolone antibiotics, ranitidine, reserpine, salicylates, sulphinpyrazone, certain long-acting sulphonamides, tetracycline compounds, tritoqualine and trophosphamid. Highly protein-bound drugs, which may also potentiate the hypoglycaemic action of Glimel due to glibenclamide displacement from plasma proteins, include oral anticoagulants, hydantoin, salicylates and other non-steroidal anti-inflammatory agents.

Drugs which may cause an attenuation of the hypoglycaemic action of Glimel include adrenaline (epinephrine) and other sympathomimetic agents, alcohol, acetazolamide, barbiturates, calcium channel blockers, cimetidine, clonidine, corticosteroids, diazoxide, diuretics, glucagon, isoniazid, large doses of laxatives, nicotinic acid (high dosage), oestrogens, progestogens, phenothiazine derivatives, phentoin, ranitidine, rifampicin, ritodrine and thyroid hormones.

Concomitant treatment with beta-receptor blockers, clonidine, reserpine, guanethidin or other sympatholytic drugs may mask the warning symptoms of a hypoglycaemic attack. The symptoms of hypoglycaemia may also be milder or absent where hypoglycaemia develops gradually or where there is autonomic neuropathy. In rare instances, potentiation or attenuation of the blood-sugar-lowering effect of glibenclamide have been observed during concomitant treatment with H₂ receptor antagonists, clonidine or reserpine.

In very rare cases, an intolerance to alcohol may occur. Both acute and chronic alcohol intake, or excessive alcohol ingestion by people who drink occasionally, may attenuate the hypoglycaemic effect of glibenclamide or dangerously potentiate it by delaying its metabolic inactivation. Disulfiram-like reactions have occurred very rarely following the concomitant use of alcohol and glibenclamide.

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

Glibenclamide may increase cyclosporin plasma concentration and potentially lead to its increased toxicity. Monitoring and dosage adjustment of cyclosporin are therefore recommended when both drugs are co-administered.

Food does not alter the bioavailability or other pharmacokinetic parameters of glibenclamide.

**Effects on laboratory tests**

It is unknown whether glibenclamide has any effect on laboratory tests.

**Adverse Effects**

Clinical experience in the use of glibenclamide has shown that side effects serious enough to compel discontinuation of therapy are uncommon, even during long-term therapy. However, if adverse reactions persist, the drug should be discontinued.

**Hypoglycaemia**

May be not only severe, but also prolonged and fatal (see Precautions - Hypoglycaemic reactions and Overdosage).

**Eye disorders**

Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependent on blood glucose level.
Gastrointestinal
Adverse gastrointestinal effects such as nausea, vomiting, epigastric fullness or sensation of pressure, abdominal pain, anorexia, heartburn, dyspepsia and diarrhoea are common reactions to glibenclamide, occurring in about 1 to 2% of patients. Glibenclamide-induced adverse gastrointestinal effects appear to be dose related and may subside following a reduction in dosage. Pancreatitis has been reported rarely.

Dermatological
Allergic reactions such as pruritus, erythema, urticaria, and erythematous, maculopapular and bullous skin eruptions or psoriasiform drug eruption occur in 1.5% of treated patients. These reactions may only be transient and disappear despite continued use of glibenclamide. However, 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.

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 isolated cases, allergic vasculitis may arise and, in some circumstances, may be lifethreatening. In isolated cases, hypersensitivity of the skin to light may occur, and sodium concentration in the serum may decrease. Porphyria cutanea tarda and pellagra-like changes have been reported with sulphonylureas.

Haematological
Anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis, pancytopenia, eosinophilia, haemolytic anaemia, aplastic anaemia, bone marrow aplasia, eosinophilia and coagulation disorders have been reported with sulphonylureas. Potentially lifethreatening changes in the blood picture may occur. They may include, rarely, mild to severe thrombocytopenia (e.g. presenting as purpura) and, in isolated cases, haemolytic anaemia, erythrocytopenia, leucopenia, granulocytopenia, agranulocytosis and (for example, due to myelosuppression) pancytopenia. In principle, these reactions are reversible once glibenclamide has been withdrawn.

Hepatic
Increased hepatic enzymes (AST, ALT), abnormal hepatic function, cholestasis, cholestatic hepatitis, granulomatous hepatitis and bilirubinaemia have been reported with sulphonylureas. In isolated cases there may be hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice which may progress to lifethreatening liver failure but can regress after withdrawal of glibenclamide.

Other
Although a causal relationship with glibenclamide has not been established, the following adverse effects have been reported: paraesthesia, blindness, deafness, diplopia, visual disturbances, tremor, convulsions (other than withdrawal), encephalopathy, confusion, acute psychosis, abnormal renal function, acute renal failure, ocular disturbances (accommodation changes, crystalline lens changes), lactic acidosis, alopecia/hypotrichosis, hyponatraemia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), arthralgia, arthritis, cerebrovascular disorders, headache, facial oedema, angioedema, hypersensitivity vasculitis and increased sweating.

Dosage and Administration
The dosage of glibenclamide must be individualised based on the patients blood and urine glucose determinations. If appropriate glibenclamide dosage regimens are not followed, hypoglycaemia may be precipitated.

In newly treated diabetic patients, stabilisation should be commenced with glibenclamide 2.5 mg daily, taken immediately before breakfast. Patients who eat only a light breakfast should defer the first dose of the day until lunchtime. After three to five days the blood sugar and urine sugar should be checked. If good control has been achieved, the daily dose of 2.5 mg is continued as maintenance therapy. If control is unsatisfactory, the daily dose is elevated in steps of 2.5 mg at intervals of seven days, up to a maximum of 15 mg or, in exceptional cases, glibenclamide 20 mg daily.
Daily allotments of up to 10 mg can be taken as a single dose before breakfast; daily dosage in excess of 10 mg should be taken before the evening meal.

Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose. Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal), or in the event a dose cannot be taken at the prescribed time, must be discussed and agreed between the doctor and patient beforehand.

For the management of type 2 diabetes mellitus, oral hypoglycaemic administration is not a substitute for appropriate dietary control.

When transferring patients from other oral antidiabetic drugs, it is recommended to begin with the usual starting dose (2.5 to 5 mg/day). A drug free transition period may be necessary, depending on the pharmacokinetic and pharmacodynamic characteristics of the previous medication, in order to avoid overlapping drug effects, possibly resulting in hypoglycaemia.

In general, patients who were previously maintained on insulin dosages up to 40 IU daily may be transferred directly to glibenclamide and administration of insulin may be abruptly discontinued. The initial glibenclamide dosage is 2.5 to 5 mg daily in patients whose insulin dosage was less than 20 IU daily and 5 mg daily in patients whose insulin dosage was 20 to 40 IU daily. Patients requiring insulin dosages greater than 40 IU daily, should be started on an initial glibenclamide dosage of 5 mg daily and the insulin dosage reduced by 50%. Insulin is then gradually withdrawn and the glibenclamide dosage increased in increments of 1.25 to 2.5 mg daily every two to ten days, according to the patient's tolerance and therapeutic response. During insulin withdrawal, patients should test their urine at least three times daily for glucose and acetone, and should report the results to their doctor so that appropriate adjustments in therapy may be made. Patient or laboratory monitoring of blood glucose concentration is preferable. The presence of persistent ketonuria with glycosuria, ketosis and/or inadequate lowering or persistent elevation of blood glucose concentration is indicative that the patient requires insulin therapy.

If adequate control is no longer possible with diet and glibenclamide (maximum 20 mg daily), good results may be obtained by combined administration of glibenclamide and a biguanide derivative.

**Overdosage**

Acute glibenclamide toxicity may be caused by excessive dosage, and numerous conditions may predispose patients to the development of glibenclamide induced hypoglycaemia (see **Precautions**). Accidental and intentional overdose of glibenclamide may cause severe and prolonged hypoglycaemia. Fatal hypoglycaemia has occurred with ingestion of as little as 2.5 to 5 mg of the drug.

**Signs and symptoms**

Acute glibenclamide overdosage is manifested principally as hypoglycaemia, which may be severe and has occasionally been fatal. Severe hypoglycaemia may result in loss of consciousness and seizures, with resultant neurological sequelae.

**Treatment**

Treatment of acute glibenclamide overdosage consists principally of administration of glucose and supportive therapy. The patient should be monitored closely until complete recovery is assured.

Mild hypoglycaemic symptoms without loss of consciousness or neurological findings should be treated aggressively with oral glucose and adjustments in glibenclamide dosage and/or meal patterns.

Since hypoglycaemia and its clinical symptoms may recur after apparent clinical recovery (even after several days), close and continued medical supervision and possibly referral to a hospital are indicated. In particular, significant overdosage and severe reactions, e.g. with unconsciousness or other neurological dysfunction, are emergency cases and require immediate care and hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, administer glucagon (adults: 0.5 to 1 mg) intravenously,
subcutaneously or intramuscularly, or an intravenous infusion of a 20% glucose solution (adults: 40 to 100 mL), until the patient recovers consciousness. In infants, glucose must be dosed very carefully, accompanied by close monitoring of blood glucose, taking into account the risk of potentially severe hyperglycaemia. Other symptomatic therapy (e.g. anticonvulsants) should be administered as necessary.

In cases of acute intake of large amounts of glibenclamide, detoxification, e.g. by gastric lavage or medicinal charcoal as an absorbent, is indicated.

After acute glucose replacement has been completed, it is usually necessary to give an intravenous glucose infusion in lower concentration 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.

In cases of overdosage, it is advisable to contact the Poisons Information Centre (131126) for recommendation on the management and treatment of overdosage.

**Presentation and Storage Conditions**

*Glimel*, glibenclamide 5 mg tablet: white, marked GE/5 on one side, α on the reverse; 100's.

Store below 30°C.

**Poisons Schedule of the Medicine**

S4 – Prescription Only Medicine

**Name and Address of Sponsor**

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**Date of Approval**

Approved by the Therapeutic Goods Administration on 18 January 2007.
Date of most recent amendment: 19 August 2008.