**4.6 Pregnancy and lactation**

*Pregnancy*

Glibenclamide must not be used during pregnancy. Since oral antidiabetics do not control blood glucose levels as reliably as insulin, they are on principle unsuitable for the treatment of diabetes during pregnancy. During pregnancy the optimum choice of treatment is insulin. If possible oral antidiabetics should be discontinued and replaced by insulin before a planned pregnancy.

*Lactation*

Glibenclamide must not be used during lactation, since it is unknown whether glibenclamide passes into human breast milk. For diabetic control nursing mothers should either be treated with insulin or nursing should be stopped.

**4.7 Effects on ability to drive and use machines**

Hypoglycaemia may reduce concentration and the ability to react. This could become dangerous in situations where these abilities are of special importance (e.g. when driving a car or operating machines). The patient should be advised to take precautions to avoid hypoglycaemia when driving an automobile. This is especially important in patients with frequent hypoglycaemic episodes or reduced or missing perception of hypoglycaemic warning symptoms. In these cases it should be considered, whether driving a car is advisable.

**4.8 Undesirable effects**

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

In this section frequencies of undesirable effects are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

***Blood and the lymphatic system disorders***

Rare: Thrombocytopenia

Very rare: Leukocytopenia, erythrocytopenia, granulocytopenia to the point of agranulocytosis.

Isolated cases of pancytopenia, haemolytic anaemia.

These changes in blood picture are usually reversible upon discontinuation, can, however, very rarely also become life-threatening.

***Eye disorders***

Very rare: Especially when treatment is first started, transient visual and accommodation disturbances through the change in blood glucose levels may occur.

***Gastrointestinal disorders***

Uncommon: Nausea, gastric discomfort, sensation of pressure or fullness in the epigastrium, vomiting, abdominal pain, diarrhoea, eructation, metallic taste. These disorders are often transient and usually do not require discontinuation of medication.

***Skin and subcutaneous tissue disorders***

Uncommon: Pruritus, urticaria, erythema nodosum, morbilliforme or maculopapular exanthema, increased photosensitivity, purpura. These disorders are transient hypersensitivity reactions, can, however, very rarely develop into life-threatening situations with breathing difficulties and drop in blood pressure to the point of life-threatening shock.

Very rare: Generalised hypersensitivity reactions including skin rash, arthralgia, fever, proteinuria and icterus.

Very rare: Life-threatening allergic vasculitis.

If skin reactions occur the doctor must be contacted immediately.

***Metabolism and nutrition disorders***
Common: The most common adverse effect of glibenclamide therapy is hypoglycaemia. Low blood sugars may be protracted with glibenclamide, leading to severe hypoglycaemia, which may cause the patient to lapse into a life-threatening coma.

The typical warning symptoms of hypoglycaemia may be attenuated or absent in case of very insidious onset, in patients with autonomic neuropathy or in patients receiving concurrent treatment with sympatholytic drugs (see section 4.5). Possible reasons for hypoglycaemia are described in section 4.4.

Hypoglycaemia is characterised by blood glucose levels dropping approximately below 50 mg/dl. The following symptoms may warn the patient or his surrounding that the patient's blood sugar levels are dropping too low: sudden sweating, rapid heartbeat, trembling, feeling hungry, restlessness, tingling sensation in the mouth area, paleness, headache, sleepiness, insomnia, anxiety, instability in movements, transient neurological deficits (e.g. speech and vision problems, paralysis or abnormal sensations).

As hypoglycaemia progresses, the patient may lose self-control and consciousness, will usually have a cold, clammy skin, and develop a tendency for seizures.

A mild hypoglycaemic episode can easily be abolished by taking in sugar or highly sugared food or drinks. Diabetics should therefore always have 20 g dextrose readily available. If hypoglycaemia cannot be abolished promptly, emergency medical help is immediately necessary.

***Further metabolic or nutritional disorders***
Common: Weight gain.

***Hepatobiliary disorders***
Very rare: Transient elevation of SGOT, SGPT, alkaline phosphatase, drug-induced hepatitis, intrahepatic cholestasis, perhaps due to an allergic/hyperergic hepatic tissue response. These liver function disorders are reversible on discontinuation of glibenclamide, may, however, also lead to life-threatening liver failure.

***Other side effects***
Very rare: Weak diuretic effect, transient proteinuria, hyponatraemia, a disulfiram-like reaction, cross-reactions to sulphonamides, sulphonamide derivatives and probenecid are possible.

**4.9 Overdose**
Both significant acute glibenclamide overdosage and prolonged use of slightly too-high doses of glibenclamide may produce severe, protracted and life-threatening hypoglycaemia.

Symptoms of intoxication
An overdose with abuse in mind is likely to produce protracted hypoglycaemia that may tend to recur over several days after successful initial therapy.

Patients with clouding of consciousness may rapidly progress to hypoglycaemic shock characterised by loss of consciousness, tachycardia, clammy skin, hyperthermia, motoric restlessness, hyperreflexia, paresis with positive Babinski reflex.

Therapy of intoxication
For the management of mild hypoglycaemia, see section 4.8.

Apart from intravenous glucose, the management of accidental poisoning should include initial induction of emesis or gastric lavage in conscious patients with no tendency for seizures.

In unconscious patients, intravenous glucose should be given immediately (injection of 40-80 ml of 40% glucose solution, followed by infusion of 5-10% glucose solution). 1 mg of intramuscular or intravenous glucagon may be administered in addition. If the patient's consciousness has not changed after this treatment, it can be repeated, and further intensive care measures may become necessary.

The management of protracted hypoglycaemia calls for close monitoring over several days including regular blood glucose controls and, if necessary, infusion therapy.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidiabetics, excluding insulin, sulphonylurea derivatives
ATC code: A10B B01

Glibenclamide lowers blood glucose in both metabolically healthy individuals and patients with non-insulin-dependent diabetes mellitus (type 2, NIDDM) by increasing insulin secretion by the beta cells of the islets of the pancreas. This effect is dependent upon the glucose concentration in the vicinity of the beta cell islets.

At very high blood glucose concentrations, where stimulation of insulin secretion by glucose is maximal, glibenclamide is unlikely to induce significant additional insulin release. Clinical significance of this observation in healthy test candidates for diabetic patients treated with glibenclamide is unclear.

Inhibition of glucagon secretion by the pancreatic alpha cells and extrapancreatic effects (increase in the number of insulin receptors, increased insulin sensitivity of peripheral tissues) have been described as well, but the clinical significance of these effects is still unclear.

### 5.2 Pharmacokinetic properties

After oral intake glibenclamide is rapidly and nearly completely absorbed. Food intake has little influence on absorption of glibenclamide.

Plasma albumin binding of glibenclamide is greater than 98%. Maximum serum concentration is reached after 1-2 hours and is approximately 100 ng/ml after intake of 1.75 mg glibenclamide. After 8-10 hours, depending on the given dose, the serum concentration drops to 5-10 ng/ml. Mean elimination half-life after intravenous injection is approximately 2 hours, after oral application mean half-life is 2-5 hours. Some studies indicated, however, that mean half-life is prolonged to 8-10 hours in diabetics. Glibenclamide is completely metabolised in the liver. The main metabolite is 4-trans-hydroxyglibenclamide; another is 3-cis-hydroxyglibenclamide. The metabolites do not significantly contribute to the blood glucose lowering activity of glibenclamide. Excretion of the metabolites is in equal proportions in urine and bile and is completed after 45-72 hours.

The elimination of the active substance from plasma is delayed in patients with impaired hepatic function.

Biliary elimination of the metabolites rises compensatively depending on the degree of function impairment in patients with renal insufficiency. In moderate renal insufficiency (creatinine clearance ≥ 30 ml/min) total elimination is unchanged; in severe renal insufficiency accumulation is possible.

### 5.3 Preclinical safety data

Studies on chronic toxicity have revealed no findings that led to the assumption that to date unknown adverse effects could occur in humans. *In vitro* studies to date further revealed no indication for mutagenic potential of glibenclamide.