SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tolbutamide 500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Tolbutamide 500 mg

Excipient with known effect

Each tablet contains 100 mg of lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Flat, white, bevelled odourless tablets. Engraved MP43 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of non-insulin dependent diabetes where control cannot be achieved by diet alone. It should not be used to replace dietetic therapy in the obese diabetic patient.

4.2 Posology and method of administration

Posology

The tablets may be taken as a single dose with, or immediately after, the first main meal of the day, or as a divided dose for optimum control of blood sugar.

Treatment of previously untreated diabetics: Stabilisation can be achieved by commencing with 2 tablets (1g) daily. The subsequent dosage must depend on the patient's individual response. The average daily dose is 1-3 tablets (0.5–1.5 g) which can be taken as a single dose or divided doses as required. Generally, patients who do not respond to 4 tablets (2g) daily will not respond to higher doses.

Change-over from other oral hypoglycaemics: It is possible to freely interchange hypoglycaemic agents (including chlorpropamide) without a break in treatment. Stabilisation can initially be achieved with 2 tablets (1g) daily, followed by a maintenance dose depending on response.

Combination with biguanides: If adequate control is not achieved through diet and 4 tablets (2g) of tolbutamide daily, the concurrent use of a biguanide derivative can often re-establish control.

Change-over from insulin: Some patients with non-insulin dependent diabetes, and who are already taking insulin, may be changed to tolbutamide. Low insulin doses (less than 20 units) can be replaced immediately. With higher doses, a gradual change is advisable by giving insulin and tolbutamide concurrently and gradually reducing the dose of insulin.

Paediatric population:

There is insufficient data on the efficacy and safety of tolbutamide in children and adolescents and therefore its use in this age group is not recommended.

Elderly:

Tolbutamide is particularly suitable for elderly patients as the risk of hypoglycaemia is lower with Tolbutamide than with other sulphonylureas. However, treatment should be initiated at a lower dose.

Method of Administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to tolbutamide or to any of the excipients listed in section 6.1
- Patients who have, or have ever had, diabetic ketoacidosis
- Patients with insulin-dependent diabetes mellitus
- Patients with serious impairment of renal, hepatic, adrenocorticoid or thyroid function.

- Patients in circumstances of unusual stress (e.g. surgical operations or during pregnancy) when dietary treatment and insulin are essential.
- Patients with porphyria
- Women who are breast feeding

4.4 Special warnings and precautions for use

- Debilitated, aged, or those patients who have difficulty in metabolising the drug are more likely to become hypoglycaemic.
- Elderly patients are especially sensitive to sulfonylurea-induced hypoglycaemia and the onset may be insidious and the impaired performance prolonged.
- Tolbutamide should not be used as a substitute for dietary treatment in obese diabetics.
- If fever or sore throat occurs, a white cell count should be performed and repeated after five days as blood abnormalities may develop slowly.
- The possibility of thrombocytopenia should be borne in mind and a platelet count performed if indicated.

Patients with mild to moderate renal impairment should start with lower doses and have careful monitoring of the blood glucose levels.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since tolbutamide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.

Tolbutamide contains lactose

This product contains lactose. 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

The hypoglycaemic effect of tolbutamide may be enhanced by coumarin antico-agulants (e.g. dicoumarol and warfarin), MAOIs, beta-adrenergic blocking agents, sulphonamides, phenylbutazone, chloramphenicol,

cyclophosphamide and salicylates or diminished by adrenaline, lithium, rifampicin, corticosteroids, oral contraceptives or thiazide diuretics.

Alcohol should be avoided since it may cause a disulfiram-like reaction.

Tolbutamide should not be co-administered with sulfafurazole or coumarins as severe hypoglycaemic reactions have occurred.

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4.6 Fertility, pregnancy and lactation

Pregnancy:

Oral hypoglycaemics are not indicated for use by the pregnant diabetic as they will not provide good control of plasma glucose levels in patients that cannot be controlled by diet alone. Insulin should be used to control gestational diabetes if dietary control is not sufficient. Tolbutamide should not be used during the first trimester of pregnancy. There is some evidence of harmful effects in pregnancy in animals and isolated reports which suggest a hazard in human pregnancy. Placental transfer of tolbutamide may result in prolonged hypoglycaemia in the neonate. If tolbutamide is to be used during pregnancy, treatment should be changed to insulin at least 4 days prior to delivery to lessen the risk of prolonged hypoglycaemia in the infant.

Breast-feeding:

Tolbutamide has been detected in small quantities in breast milk. The effect on the neonate is unknown but there is a theoretical risk of hypoglycaemia. Breast feeding is best avoided in mothers taking tolbutamide.

4.7 Effects on ability to drive and use machines

Whilst tolbutamide does not cause any adverse effects that may affect a patient's ability to drive or operate machinery the patient should ensure their blood glucose levels are adequately controlled before driving or operating machinery.

4.8 Undesirable effects

Based on the experience with tolbutamide and with other sulfonylureas, the following undesirable effects have to be mentioned.

Blood and the lymphatic system disorders

Blood disorders are also rare but may include leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia and aplastic anaemia.

Immune system disorders

Hypersensitivity reactions may develop usually in the first 6–8 weeks of starting treatment with tolbutamide. Allergic skin reactions may occur which progress rarely to erythema multiforme and exfoliative dermatitis and fever. Photosensitivity may occur.

Metabolism and nutrition disorders

Hypoglycaemia and hypoglycaemic symptoms have occasionally been reported when tolbutamide has been administered without due regard to the dietary habits of the patient

Nervous system disorders

Paraesthesia and headache have been reported. Patients may become intolerant to alcohol (see section 4.5).

Ear and labyrinth disorders

Tinnitus has been reported.

Gastrointestinal disorders

Nausea, vomiting, diarrhea, anorexia, increased appetite, weight gain and constipation have been reported in patients taking tolbutamide.

Hepato-biliary disorders

Disturbance in liver function and cholestatic jaundice have been reported in patients taking tolbutamide.

Class attribution effects

As of other sulfonylureas, the following adverse events have been observed:

Common or very common:- Abdominal pain

Rare or very rare :- erythropenia

Not known :- visual impairment

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 the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:

The features are those of hypoglycaemia and include nausea, vomiting, sweating, hyperventilation, tachycardia, hypotension, bizarre behaviour and drowsiness leading to coma with increased muscle tone, hyperreflexia and extensor planatar responses. Convulsions and cerebral oedema may occur.

The duration of the risk of hypoglycaemia varies according to the plasma half-life of the drug. As the half-life of tolbutamide is generally 4-8 hours a minimum observation period of 24 hours is recommended.

Treatment:

1. If the patient is conscious give activated charcoal (50g) or consider gastric lavage in adults within 1 hour of the overdose, provided the airway can be protected.
2. Correct hypoglycaemia as quickly as possible.
3. If the patient is awake give oral glucose followed by a carbohydrate meal.
4. If the patient is drowsy or unconscious give up to 500ml 5% or 250 ml 10% dextrose IV. 50 ml 50% dextrose IV may be given but is irritant to veins and can cause skin necrosis in cases of extravasation.
5. Glucagon 1-2 mg IM may also be used if IV access is difficult or the patient is combative but its effects are dependent on available glycogen stores.

6. Maintenance treatment with 10% dextrose infusion will be required to prevent persistent hypoglycaemia.
7. Check blood sugar hourly and adjust rate of infusion accordingly.
8. Check urea and electrolytes regularly. Potassium supplements may be necessary.
9. If the patient is persistently hypoglycaemic despite receiving 10% dextrose infusion increase the concentration to 20% dextrose. This is irritant to veins and ideally should be given through a central venous line. Additional potassium may also be required.

In cases of severe refractory hypoglycaemia contact NPIS.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonylureas ATC Code A10BB03

Tolbutamide is an oral sulfonylurea hypoglycaemic agent from the sulfonamide, urea derivative group. Tolbutamide is used to treat type II diabetes when diet modification is not effective on its own.

Mechanism of action

Tolbutamide has several mechanisms of action which appear to be mediated by the inhibition of ATP sensitive potassium channels. Initially, secretion of insulin by functioning islet beta cells is increased. However, insulin secretion subsequently falls again but the hypoglycaemic effect persists and may be due to inhibition of hepatic glucose production and increased sensitivity to any available insulin.

5.2 Pharmacokinetic properties

Absorption: Tolbutamide is readily absorbed from the gastro-intestinal tract. Peak plasma levels are reached within 3-4 hours.

Distribution: The half-life is generally within the range of 4-8 hours but may be considerably longer. Tolbutamide is 97% bound to plasma proteins.

Metabolism: Tolbutamide is metabolised in the liver and involves the cytochrome P450 isoenzyme (CYP2C9).

Elimination: Excretion via the urine, chiefly as metabolites with little hypoglycaemic activity. Tolbutamide has been detected in breast milk.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Methylcellulose
Starch, pregelatinised
Sodium starch glycollate type A
Magnesium stearate
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Containers: 36 months

Blister packs: 36 months

6.4 Special precautions for storage

Store in the original package in order to protect from light

6.5 Nature and contents of container

Containers: Polypropylene tablet containers with polyethylene lids and polyurethane wads or polyethylene inserts.
Pack sizes: 100, 112 and 500 tablets

Blister packs: Blister packs of 250 µm PVC/ 20 µm Aluminium
Pack size: 28 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Genethics Europe Limited

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Nicosia 1061

Cyprus

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PL 42976/0062

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20/02/2009

10 DATE OF REVISION OF THE TEXT

14/01/2025