SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TOLBUTAMIDE TABLETS BP 500mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Tolbutamide PhEur 500mg.

3 PHARMACEUTICAL FORM

White tablets.

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 (0.5g-1.5g) 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 inter-change 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 sulfonylureas**.** However, treatment should be initiated at a lower dose.

Method of Administration
For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or 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 (*eg* 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 a 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 non-sulfonylurea alternative should be considered.

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, sulfonamides, 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.

4.6 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 breast milk in small quantities. 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 patients 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

- *Blood and lymphatic system disorders*

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

- *Immune system disorders*

Hypersensitivity reactions may develop, usually within 6 to 8 weeks of starting treatment with tolbutamide. Allergic skin reactions may occur which progress rarely to erythema multiforme, 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, diarrhoea, anorexia, increased appetite, weight gain and constipation have been reported in patients taking tolbutamide.

- *Hepato-biliary disorders*

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

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 plantar 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 250ml 10% dextrose IV. 50ml 50% dextrose IV may be given but is irritant to veins and can cause skin necrosis in cases of extravasation.
5. Glucagon 1-2mg 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.
10. In cases of severe refractory hypoglycaemia contact NPIS.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonylureas
ATC code: A10B B03

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.

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 gastrointestinal 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: It 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

Also contains: magnesium stearate, maize starch, pregelatinised maize starch, dried maize starch, stearic acid, microcrystalline cellulose (E460), water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life
12 months.
Shelf-life after dilution/reconstitution
Not applicable.
Shelf-life after first opening
Not applicable.

6.4 Special precautions for storage

Store below 25°C in a dry place.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:
a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack size: 28s, 30s, 56s, 60s, 84s, 90s, 100s, 112s, 250s, 500s, 1000s.

Product may also be supplied in bulk packs for reassembly, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 25,000

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0378

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th January 1994
Date of latest renewal: 26th April 2004

10 DATE OF REVISION OF THE TEXT

12/12/2019