Product Name: Proglicem 25 mg	Component: English Professional Information MCC Approval: 23 November 2017 Date Approved: 01 October 1974

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PROGLICEM® 25 mg Capsules

COMPOSITION

Each capsule contains 25 mg diazoxide, a non-diuretic thiazide.

Excipients: lactose monohydrate, magnesium stearate, gelatin.

Contains 194,45 mg lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION

A.21.11 Hyperglycaemic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Orally administered diazoxide produces an increase in blood glucose level, due primarily to an inhibition of pancreatic release of insulin, and also to an extra-pancreatic effect possibly stemming from catecholamine enhancement.

Diazoxide decreases sodium and water excretion, resulting in fluid retention, which may be clinically significant.

Other pharmacologic actions of diazoxide include increased pulse rate and blood pressure, increased serum uric acid levels due to decreased excretion, decreased chloride excretion, increased serum free fatty acid levels and decreased para-aminohippuric acid (PAH) clearance with no appreciable effect on glomerular filtration rate.

Pharmacokinetic properties

Diazoxide is extensively bound (more than 90 %) to serum protein and is excreted by the kidneys. The plasma half-life following intravenous administration is 28 ± 8,3 hours. Limited data on oral administration revealed a plasma half-life of 24 and 36 hours in adults, and in children, aged 4 months to 6 years, the half-life varied from 9,5 to 24 hours on long-term oral administration. The half-life may be prolonged in patients with impaired renal function (see **WARNINGS AND SPECIAL PRECAUTIONS**).

INDICATIONS

PROGLICEM Capsules is useful in the management of intractable hypoglycaemia such as idiopathic hypoglycaemia of infancy or the hypoglycaemia resulting from inoperable tumours of the pancreas.

CONTRAINDICATIONS

The use of PROGLICEM Capsules is contraindicated in patients with functional hypoglycaemia and in patients hypersensitive to diazoxide or to other thiazides (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

PROGLICEM Capsules should be used with care in patients with impaired cardiac or cerebral circulation.

The antidiuretic property of PROGLICEM Capsules may lead to significant fluid retention, which in patients with compromised cardiac reserve, may precipitate congestive heart failure.

Patients should be under close clinical observation when treated with PROGLICEM Capsules. During prolonged therapy, blood-glucose concentrations should be monitored and the blood should be examined regularly for signs of leucopenia and thrombocytopenia. Regular monitoring of urine for sugar and ketones is also recommended (see **SIDE EFFECTS**). In children, bone and psychological maturation and growth should be regularly assessed.

The effects of PROGLICEM Capsules on the level of serum uric acid should be kept in mind. Blood tests should be conducted periodically (see **SIDE EFFECTS**).

Keto-acidosis and non-ketotic hyperosmolar coma have been reported in patients treated with recommended doses of PROGLICEM Capsules, usually during intercurrent illnesses. Prompt recognition and treatment are essential.

Since plasma half-life of diazoxide is prolonged in patients with impaired renal function, a reduced dosage should be considered and serum electrolyte levels should be evaluated.

Lactose

Patients with the rare hereditary problems of galactose intolerance e.g. the Lapp lactase deficiency or glucose-galactose malabsorption should not take PROGLICEM Capsules.

Effects on ability to drive and use machines

Certain side effects that have been reported with PROGLICEM Capsules may affect some patients' ability to drive or operate machinery. Individual responses to PROGLICEM Capsules may vary (see **SIDE EFFECTS**).

INTERACTIONS

These potential interactions must be considered when administering PROGLICEM Capsules.

Since diazoxide is highly bound to serum protein, it may displace other substances which are also protein-bound, such as bilirubin or warfarin, resulting in higher blood levels of these substances. Accordingly, anticoagulant dosage reduction may be required when administered with PROGLICEM Capsules. The possible displacement of bilirubin should be kept in mind, particularly when treating newborns with increased bilirubinaemia.

Medicine interaction has been reported for PROGLICEM Capsules and diphenylhydantoin and their concomitant administration may result in a loss of seizure control.

Concomitant administration of thiazides or other commonly used potent diuretics may potentiate the hyperglycaemic and hyperuricaemic effects of PROGLICEM Capsules. In the presence of hypokalaemia, hyperglycaemic effects are also potentiated.

Diazoxide induced hyperglycaemia is reversed by the administration of insulin and discontinuation of PROGLICEM Capsules.

The inhibition of insulin release by PROGLICEM Capsules is antagonised by alpha-adrenergic blocking agents.

The antihypertensive effect of other medicines may be enhanced by concurrent PROGLICEM Capsules.

PREGNANCY AND LACTATION

Safety and efficacy have not been established.

DOSAGE AND DIRECTIONS FOR USE

Patients should be under close clinical observation when treatment with PROGLICEM Capsules is initiated. Clinical response and blood glucose levels should be carefully monitored until the patient's condition has stabilised satisfactorily; in most instances this may be accomplished in several days. If administration of PROGLICEM Capsules is not effective after 2 or 3 weeks the medicine should be discontinued.

Dosage must be individualised based on the severity of the hypoglycaemic condition, the blood glucose level and the clinical response of the patient. The dosage should be adjusted until the desired clinical and laboratory effects are produced with the least amount of drug.

Adults and children: The usual dose is 3 to 8 mg/kg divided into 2 or 3 equal doses every 8 or 12 hours. In certain instances, patients with refractory hypoglycaemia may require higher doses.

The starting dosage is 3 mg/kg/day, divided into 3 equal doses every 8 hours. Thus, an average adult would receive a starting dosage of approximately 200 mg daily.

Infants and newborns: The usual dosage is 8 to 15 mg/kg divided into 2 or 3 equal doses every 8 or 12 hours. An appropriate starting dose is 10 mg/kg/day, divided into 3 equal doses every 8 hours.

SIDE EFFECTS

Cardiac disorders

Common and severe side effects: Sodium and fluid retention is most common in young infants and adults and may precipitate congestive heart failure in patients with compromised cardiac reserve

Common: Tachycardia, palpitations and increased levels of serum uric acid are common; hypotension, which may be augmented by concurrent thiazide diuretic administration

Rare: Chest pain

Frequency not known: Transient hypertension has been noted. Pulmonary hypertension in neonates, infants, and children has also been noted; in most reported cases, pulmonary hypertension improved upon discontinuation of PROGLICEM Capsules.

Metabolism and nutrition disorders

Frequency not known but severe side effects: Diabetic ketoacidosis and hyperosmolar non-ketotic coma may develop very rapidly

Common: Hyperglycaemia or glycosuria may require dosage reduction to avoid progression to ketoacidosis or hyperosmolar coma

Frequency not known: Gout.

Gastrointestinal disorders

Common: Gastrointestinal intolerance may include anorexia, nausea, vomiting, abdominal pain, and transient loss of taste

Uncommon: Diarrhoea

Rare: Ileus, acute pancreatitis

Frequency not known: Pancreatic necrosis.

Blood and lymphatic system disorders

Common: Thrombocytopenia, with or without purpura, may require discontinuation of the medicine (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Neutropenia is usually transient, and does not ordinarily require discontinuation of the medicine.

Frequency not known: Eosinophilia, decreased haemoglobin/haematocrit, excessive bleeding and decreased IgG, lymphadenopathy.

Investigations

Frequency not known: Increased serum AST, alkaline phosphatase, decreased creatinine clearance, reversible, and decreased urinary output.

Renal and urinary disorders

Frequency not known: Uraemia, nephrotic syndrome, haematuria and albuminuria.

Psychiatric disorders

Frequency not known: Anxiety, insomnia.

Nervous system disorders

Common: Dizziness, headache, extrapyramidal signs, polyneuropathy, paraesthesia.

Skin and subcutaneous tissue disorders

Common: Hirsutism of the lanugo type, mainly on the forehead, back and limbs, occurs most commonly in children and women and may be cosmetically unacceptable. It subsides on discontinuation of the medicine

Frequency not known: Pruritus, skin rash, loss of scalp hair.

Eye disorders

Common: Blurred vision

Frequency not known: Cataracts, subconjunctival haemorrhage, ring scotoma, diplopia, lacrimation.

Musculoskeletal and connective tissue disorders

Frequency not known: Osteoporosis.

General disorders and administration site conditions

Frequency not known: Fever, malaise.

Infections and infestations

Frequency not known: Herpes simplex.

Reproductive system and breast disorders

Frequency not known: Galactorrhoea.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

An overdosage of PROGLICEM Capsules causes marked hyperglycaemia which may be associated with ketoacidosis.

It will respond to prompt insulin administration and restoration of fluid and electrolyte balance. Because of the long half-life of this product, symptoms of overdosage require prolonged surveillance for periods up to 7 days, until the blood sugar level stabilises within the normal range. Successful lowering of diazoxide blood levels by peritoneal dialysis and by haemodialysis has been reported.

IDENTIFICATION

A hard gelatin capsule, having a clear cap and body containing a fine, white to off-white powder.

PRESENTATION

Cartons of 100 capsules, packed as 4 blisters of 25 capsules.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Keep out of reach of children.

REFERENCE NUMBER

G3217 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE APPLICANT

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