APPROVED PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

AUSTELL-GLIMEPIRIDE 1 mg TABLETS

AUSTELL-GLIMEPIRIDE 2 mg TABLETS

AUSTELL-GLIMEPIRIDE 3 mg TABLETS

AUSTELL-GLIMEPIRIDE 4 mg TABLETS

COMPOSITION

AUSTELL-GLIMEPIRIDE 1 mg: Each tablet contains glimepiride 1 mg.

AUSTELL-GLIMEPIRIDE 2 mg: Each tablet contains glimepiride 2 mg.

AUSTELL-GLIMEPIRIDE 3 mg: Each tablet contains glimepiride 3 mg.

AUSTELL-GLIMEPIRIDE 4 mg: Each tablet contains glimepiride 4 mg.

PHARMACOLOGICAL CLASSIFICATION

A.21.2 Oral Hypoglycaemics

PHARMACOLOGICAL ACTION

Glimepiride, a second-generation sulphonylurea, lowers blood glucose concentrations by stimulating insulin release from pancreatic beta cells.

Pharmacokinetics:

Following oral administration, glimepiride is completely absorbed from the gastrointestinal tract. Food can reduce the absorption of glimepiride.

Maximum serum concentrations of glimepiride are reached approximately 2-3 hours after oral administration and its effect is dose-dependant over the dosage range of 1 to 6 mg. The mean plasma half-life is about 5 to 9 hours.

Glimepiride is highly plasma protein bound (>99%) and elimination is both renal (approximately 60%) and fecal (approximately 40%).

INDICATIONS

AUSTELL-GLIMEPIRIDE is indicated as an adjunct to exercise and diet, to lower the blood glucose, in patients with type 2 diabetes mellitus whose hyperglycaemia cannot be controlled by diet and exercise alone.

CONTRA-INDICATIONS

- Hypersensitivity to glimepiride or to any ingredients of **AUSTELL-GLIMEPIRIDE.**
- Hypersensitivity to other sulphonylureas and sulfonamides.
- Pregnancy and Lactation.
- Impaired liver function.
- Moderate to severe impaired renal function.
- Children.
- Treatment of Type 1 diabetes mellitus.

WARNINGS

SPECIAL WARNING: INCREASED RISK OF CARDIOVASCULAR MORTALITY

Results from a large multicenter trial (the University Group Diabetes Program) (UGDP) have shown that the sulphonylurea antidiabetic agent tolbutamide may be associated with an increased cardiovascular mortality in patients with type 2 diabetes mellitus. Although other studies have failed to reach a similar conclusion and have suggested that control of hyperglycaemia with oral sulphonylureas may in fact lessen cardiovascular mortality, the UGDP study provides an adequate basis for caution, especially for patients at high risk for myocardial ischaemia (coronary artery disease, angina pectoris, congestive cardiac failure).

Patients should be informed of the potential risks and advantages of sulphonylurea antidiabetic agents and of alternative modes of therapy.

INTERACTIONS

Hypoglycaemia may occur with concomitant use of **AUSTELL-GLIMEPIRIDE** and the following agents:

- Allopurinol.
- Anabolic steroids and androgens.
- Angiotensin-converting enzyme inhibitors.
- Anti-arrhythmics: disopyramide.
- Antibacterials: chloramphenicol, sulphonamides, quinolones, tetracyclines.
- Anticoagulants: coumarin derivatives.
- Antidepressants: fluoxetine.

- Antimetabolites: cyclophosphamide, ifosfamide, trofosfamide.
- Appetite suppressants: fenfluramine.
- Azole antifungals: miconazole, ketoconazole, fluconazole, itraconazole.
- Beta-blockers.
- Fenyramidol.
- Fibrates: clofibrate.
- Guanethidine.
- Insulin and other oral antidiabetic agents.
- Monoamine-oxidase inhibitors.
- Para-aminosalicyclic acid.
- Pentoxyphylline (high dose parenteral).
- Phenylbutazone, azapropazone, oxyphenbutazone.
- Probenecid.
- Sulphinpyrazone.
- Tritoqualine.

Hyperglycaemia may occur with concomitant use of **AUSTELL-GLIMEPIRIDE** with the following:

- Acetazolamide.
- Adrenaline and other symphathomimetic agents.
- Barbiturates.
- Corticosteroids.
- Diazoxide.
- Diuretics.

- Glucagon.
- Isoniazid.
- Laxatives (protracted use).
- Nicotinic acid (high doses).
- Oestrogens and progesterones.
- Phenothiazines.
- Phenytoin.
- Rifampicin.
- Thyroid hormones.

The effect of coumarin derivatives may be weakened or potentiated. Concomitant use of **AUSTELL-GLIMEPIRIDE** with alcohol, beta-blockers, clonidine, reserpine and H_2-receptor antagonists may either weaken or potentiate the hypoglycemic effect of **AUSTELL-GLIMEPIRIDE.** Sympatholytic medicines (e.g. beta-blockers, clonidine, reserpine, guanethidine) may blunt the signs of adrenergic response to hypoglycaemia.

PREGNANCY AND LACTATION

Safety and efficacy in pregnancy and lactation have not been established. (See **CONTRA-INDICATIONS**)

DOSAGE AND DIRECTIONS FOR USE

The dosage of **AUSTELL-GLIMEPIRIDE** is determined by the desired blood glucose level and it should be the lowest dose sufficient to achieve the desired metabolic

control. The distribution and timing of doses should be decided upon by a medical practitioner.

Blood and urine glucose levels must be measured regularly during therapy with **AUSTELL-GLIMEPIRIDE**, with regular determinations of the proportion of glycosylated haemoglobin.

AUSTELL-GLIMEPIRIDE must be swallowed whole with a glass of water and should be taken immediately before a substantial breakfast or the first main meal of the day. Meals should not be missed after the tablets have been taken. **AUSTELL-GLIMEPIRIDE** should be taken at the same time each day.

A single daily dose of **AUSTELL-GLIMEPIRIDE** is usually adequate to provide metabolic control over 24 hours.

Treatment with **AUSTELL-GLIMEPIRIDE** is considered a long-term commitment.

If a patient forgets to take a dose, this must not be corrected by taking a larger dose. Measures for dealing with such situations, especially skipping a dose or forgetting a meal, where a dose cannot be taken at the prescribed time must be discussed and agreed upon between the medical practitioner and patient beforehand. If the recommended dose is exceeded or an extra dose has been taken, a medical practitioner should be contacted immediately.

<u>Initial dose and dose titration:</u>

1 mg **AUSTELL-GLIMEPIRIDE** once daily, which can be increased gradually at one or two weekly intervals to a maximum of 8 mg daily. The recommended increments are 1

mg/2 mg/3 mg/4 mg/6 mg, with daily doses of higher than 6 mg seldom being more effective.

Dose range in patients with well controlled diabetes:

Usual doses in patients with well controlled diabetes are 1 mg to 4 mg daily.

Secondary dosage adjustment:

An improvement in the control of diabetes is associated with improved sensitivity to insulin. As a result, the dose of **AUSTELL-GLIMEPIRIDE** required for adequate glucose control may decrease over time. This needs to be monitored and appropriate dosage adjustments made in order to prevent hypoglycaemia. Dosage adjustments may also need to be considered with changes in the patient's weight, lifestyle or medication that may place them at increased risk of hyper-or hypoglycaemia (See **INTERACTIONS** and **SPECIAL WARNING).**

Change-over from other oral antidiabetics to **AUSTELL-GLIMEPIRIDE:**

When substituting **AUSTELL-GLIMEPIRIDE** for other oral antidiabetic medicines, it is recommended that the procedure be the same as for the initial dosage, starting with daily doses of 1 mg. This applies to any oral regimen, even if maximum doses of another oral agent are being used. There is no exact dosage relationship between **AUSTELL-GLIMEPIRIDE** and other oral antidiabetic agents.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Haematological

Less frequent: Eosinophilia, haemolytic anaemia, thrombocytopenia, erythrocytopenia, granulocytopenia, agranulocytosis, leukopenia, pancytopenia. Blood dyscrasias may occur within the first six weeks of therapy and are thought to be hypersensitivity reactions.

Central nervous system

Less frequent: Headache, dizziness, drowsiness.

Endocrine/Metabolic

Less frequent:

Hypoglycaemia (including nocturnal hypoglycaemia) may range from mild to severe and life-threatening. Symptoms and signs of hypoglycaemia are varied and include aggression, apathy, behavioural changes that can mimic drunkenness, poor concentration, confusion, delirium, nightmares, sleepiness, sleep disorders, restlessness, depression, dizziness, seizures, paresis, blurred vision, slurred speech, aphasia, excessive hunger, nausea, vomiting, shallow respiration, coma, bradycardia. In addition, signs of adrenergic excess may be present such as anxiety, cold sweats, tremor, tachycardia, palpitations, hypertension, angina pectoris, cardiac arrhythymias (See **Special Precautions**).

Gastro-intestinal

Less frequent: Constipation, diarrhoea, flatulence, heartburn, loss or increase of appetite, nausea, stomach pain, fullness or discomfort, vomiting, alterations in sense of taste.

Kidney/Genitourinary

Less frequent: Polyuria.

Liver

Less frequent: Cholestasis, cholestatic jaundice, hepatic functional impairment, hepatitis which may complicate with liver failure.

Ocular

Less frequent: Blurred vision and/or changes in accommodation, which may be more pronounced when therapy is initiated.

Skin

Less frequent: Erythema multiforme, photosensitivity, allergic vasculitis. Itching, urticaria or rashes may herald the onset of a life-threatening anaphylactoid response.

Special precautions:

Alertness and reactions may be impaired by hypo- or hyperglycaemia, especially when initiating treatment of altering doses. This may affect the ability to drive or operate machinery.

Clinical signs of a still insufficiently lowered glucose (i.e. hyperglycaemia, polyuria, polydipsia, dry mouth) may require dose adjustment of **AUSTELL-GLIMEPIRIDE**.

In the initial weeks of treatment, the risk of hypoglycaemia may be increased and careful monitoring is necessary. Factors that predispose a patient to the development of hypoglycaemia that need to be carefully considered are the following:

- Impaired renal function.
- The elderly.
- Poor nutrition, alteration of diet, skipped meals, irregular meal times.
- Imbalance between energy expenditure and carbohydrate intake.

- Consumption of alcohol, especially with skipped meals.
- Severe impairment of hepatic function.
- Overdosage with **AUSTELL-GLIMEPIRIDE.**
- Endocrine disorders involving the thyroid, anterior pituitary or adrenal glands.

Patients and their family members must be educated about the symptoms of hypoglycaemia and how to treat them. Hypoglycaemia can, in most cases be promptly treated with ingestion of carbohydrates in the form of sugar lumps, sugar sweetened fruit juice, sugar sweetened tea. Despite being easily treated, hypoglycaemia may recur with oral antidiabetic agents and patients must be closely observed. Severe or persistent hypoglycaemia will need immediate treatment, follow-up by a medical doctor and may even require urgent hospital admission. If hypoglycaemia has persisted for a protracted period of time, neurological damage may not be reversible. Symptoms of hypoglycaemia are mediated by the counter-regulatory hormonal response to low blood glucose (See **SIDE-EFFECTS).** In certain conditions, these symptoms are blunted or attenuated; for example in gradually developing hypoglycaemia, in the elderly, in diabetic autonomic neuropathy and during administration of beta-adrenergic blockers, clonidine, reserpine, guanethidine or other sympatholytic medicines. (See **INTERACTIONS**). Blood glucose control may deteriorate under certain conditions, despite compliance from the patient. This occurs with exceptional stressors like trauma, surgery and febrile illness. Under these circumstances, it is prudent to convert the patient to insulin therapy temporarily to maintain good metabolic control.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Treatment is symptomatic and supportive.

IDENTIFICATION

AUSTELL-GLIMEPIRIDE 1 mg:

Pink coloured, elongated with notch in center, flat bevelled edged, uncoated tablets with “B” and “L” embossing on either side of breakline on one side and only breakline on other side.

AUSTELL-GLIMEPIRIDE 2 mg:

Green coloured, elongated with notch in center, flat bevelled edged, uncoated tablets with “B” and “L” embossing on either side of breakline on one side and only breakline on other side.

AUSTELL-GLIMEPIRIDE 3 mg:

Light yellow coloured, elongated with notch in center, flat bevelled edged, uncoated tablets with “B” and “L” embossing on either side of breakline on one side and only breakline on other side.

AUSTELL-GLIMEPIRIDE 4 mg:

Blue coloured, elongated with notch in center, flat bevelled edged, uncoated tablets with “B” and “L” embossing on either side of breakline on one side and only breakline on other side.

PRESENTATION

AUSTELL-GLIMEPIRIDE 1 mg:

Blister packs (Clear PVC film and Aluminium foil) of 2x14, 3x10, 6x10 tablets.

AUSTELL-GLIMEPIRIDE 2 mg:

Blister packs (Clear PVC film and Aluminium foil) of 2x14, 3x10, 6x10 tablets.

AUSTELL-GLIMEPIRIDE 3 mg:

Blister packs (Clear PVC film and Aluminium foil) of 2x14, 3x10, 6x10 tablets.

AUSTELL-GLIMEPIRIDE 4 mg:

Blister packs (Clear PVC film and Aluminium foil) of 2x14, 3x10, 6x10 tablets.

STORAGE INSTRUCTIONS

Store in a dry place at or below 25 ˚C. Protect from light.

Keep blister packs in carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

AUSTELL-GLIMEPIRIDE 1 mg: A40/21.2/0193

AUSTELL-GLIMEPIRIDE 2 mg: A40/21.2/0194

AUSTELL-GLIMEPIRIDE 3 mg: A40/21.2/0195

AUSTELL-GLIMEPIRIDE 4 mg: A40/21.2/0196

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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