SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

GLIMEPIRIDE 1 UNIMED (Tablets)

GLIMEPIRIDE 2 UNIMED (Tablets)

GLIMEPIRIDE 4 UNIMED (Tablets)

COMPOSITION:

GLIMEPIRIDE 1 UNIMED

Each tablet contains glimepiride 1 mg.

Contains sugar: Lactose monohydrate 35,58 mg/tablet.

GLIMEPIRIDE 2 UNIMED

Each tablet contains glimepiride 2 mg.

Contains sugar**:** Lactose monohydrate 71,15 mg/tablet.

GLIMEPIRIDE 4 UNIMED

Each tablet contains glimepiride 4 mg.

Contains sugar: Lactose monohydrate 142,30 mg/tablet.

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-dependent 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 faecal (approximately 40 %).

INDICATIONS:

GLIMEPIRIDE UNIMED 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 of the ingredients of **GLIMEPIRIDE UNIMED**.
- 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 **GLIMEPIRIDE UNIMED** and the following agents:

- Allopurinol
- Anabolic steroids and androgens
- Angiotensin-converting enzyme inhibitors
- Antiarrhythmics: 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-aminosalicylic acid

- Pentoxyphylline (high dose parenteral)
- Phenylbutazone, azapropazone, oxyphenbutazone
- Probenecid
- Sulphinpyrazone
- Tritoqualine

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

- Acetazolamide
- Adrenaline and other sympathomimetic 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 **GLIMEPIRIDE UNIMED** with alcohol, beta-blockers, clonidine, reserpine and H_2-receptor antagonists may either weaken or potentiate the hypoglycaemic effect of **GLIMEPIRIDE**

UNIMED. 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 **GLIMEPIRIDE UNIMED** 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 **GLIMEPIRIDE UNIMED**, with regular determinations of the proportion of glycosylated haemoglobin.

GLIMEPIRIDE UNIMED must be swallowed whole with half 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. **GLIMEPIRIDE UNIMED** should be taken at the same time each day. A single dose of **GLIMEPIRIDE UNIMED** is usually adequate to provide metabolic control over 24 hours. Treatment with **GLIMEPIRIDE UNIMED** 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.

Initial dose and dose titration

1 mg **GLIMEPIRIDE UNIMED** 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 dose in patients with well controlled diabetes is 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 **GLIMEPIRIDE UNIMED** 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 GLIMEPIRIDE UNIMED

When substituting **GLIMEPIRIDE UNIMED** 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 **GLIMEPIRIDE UNIMED** and other oral antidiabetic agents.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects

Frequency estimate: Very common ≥ 10 %; common ≥ 1 % to < 10 %; uncommon ≥ 0,1 % to < 1 %; rare ≥ 0,01 % to < 0,1 %; very rare < 0,01 %.

Blood and lymphatic system disorders

Rare: 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.

Endocrine disorders

More 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 arrhythmias (see **SPECIAL PRECAUTIONS**).

Nervous system disorders

More frequent: Headache, dizziness, drowsiness

Eye disorders

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

Gastrointestinal disorders

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

Hepato-biliary disorders

Rare: Cholestasis, cholestatic jaundice, hepatic function impairment, hepatitis which may complicate with liver failure.

Skin and subcutaneous tissue disorders

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

Renal and urinary disorders

More frequent: Polyuria.

Special Precautions

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

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

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 **GLIMEPIRIDE UNIMED**
- 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 by the patient. This occurs with exceptional stressors like trauma, surgery and febrile illnesses. 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:

See **SIDE-EFFECTS AND SPECIAL PRECAUTIONS**. Treatment is symptomatic and supportive.

IDENTIFICATION:

GLIMEPIRIDE 1 UNIMED: Blue coloured, biconvex, round, uncoated tablets, plain on both sides.

GLIMEPIRIDE 2 UNIMED: Blue coloured, dumbbell shaped, uncoated tablets, scored both sides ; debossed with "2" adjacent to the score line on only one side of the tablet and plain on the other side of the tablet.

GLIMEPIRIDE 4 UNIMED: Blue coloured, dumbbell shaped, uncoated tablets, scored both sides ; debossed with "4" adjacent to the score line on only one side of the tablet and plain on the other side of the tablet.

PRESENTATION:

GLIMEPIRIDE 1 UNIMED: A white HDPE bottle containing 30 tablets with a desiccant sachet.

GLIMEPIRIDE 2 UNIMED: Cartons contain 10, 28, 30 or 60 tablets packed in cold form blister strips comprising of a cold form laminate with a backing of aluminium foil sealed with a heat seal lacquer or packed in transparent PVDC coated PVC blister strips having a backing layer of aluminium foil coated with a heat seal lacquer. Alternatively 30 tablets are packed in a white HDPE bottle with a desiccant sachet.

GLIMEPIRIDE 4 UNIMED: Cartons contain 10, 30 or 60 tablets packed in cold form blister strips comprising of a cold form laminate with a backing of aluminium foil sealed with a heat seal lacquer. Alternatively 30 tablets are packed in a white HDPE bottle with a desiccant sachet.

STORAGE INSTRUCTIONS:

Store at or below 25 °C, protected from light and moisture in the original container. Do not remove the blisters from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

GLIMEPIRIDE 1 UNIMED: A40/21.2/0132

GLIMEPIRIDE 2 UNIMED: A40/21.2/0133

GLIMEPIRIDE 4 UNIMED: A40/21.2/0134

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

Unimed Healthcare (Pty) Ltd.

Cnr Birch Road and Bluegum Avenue

Anchorville

Lenasia

1827

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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