PACKAGE INSERT FOR GLIMEPIRIDE 1, 2, AND 4 OETHMAAN TABLETS:

Scheduling Status: S3

Proprietary names and dosage forms:

GLIMEPIRIDE 1 OETHMAAN Tablets

GLIMEPIRIDE 2 OETHMAAN Tablets

GLIMEPIRIDE 4 OETHMAAN Tablets

Composition:

Each GLIMEPIRIDE 1 OETHMAAN tablet contains: 1 mg glimepiride.

Each GLIMEPIRIDE 2 OETHMAAN tablet contains: 2 mg glimepiride.

Each GLIMEPIRIDE 4 OETHMAAN tablet contains: 4 mg glimepiride.

Sugar free

Inactive ingredients: Iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycollate.

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 to 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 faecal (approximately 40 %).

Indications:

GLIMEPIRIDE 1, 2, AND 4 OETHMAAN 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 1, 2, AND 4 OETHMAAN
- Hypersensitivity to other sulphonylureas and sulfonamides
- Pregnancy and lactation
- Impaired liver function
- Moderate to severe impaired renal function
- Children
- Treatment of Type1 Diabetes mellitus

Warnings:

Special warning: Increased risk of cardiovascular mortality:

Results from a large multi-centre 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.

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

Interactions:

Hypoglycaemia may occur with concomitant use of* GLIMEPIRIDE 1, 2, AND 4 OETHMAAN *and the following agents:

- Allopurinol
- Anabolic steroids and androgens
- Angiotensin-converting enzyme inhibitors
- Antidysrhythmics: disopyramide
- Antibacterials: chloramphenicol, sulphonamides, quinolones, tetracyclines, clarithromycin
- Anticoagulants: warfarin

- 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 **GLIMEPIRIDE 1, 2, AND 4 OETHMAAN** ***with the following:***

- Acetazolamide
- Epinephrine (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 warfarin may be weakened or potentiated. Concomitant use of GLIMEPIRIDE 1, 2, AND 4 OETHMAAN with alcohol, beta-blockers, clonidine, reserpine and H_2-receptor antagonists may either weaken or potentiate the hypoglycemic effect of GLIMEPIRIDE 1, 2, AND 4 OETHMAAN. 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 1, 2, AND 4 OETHMAAN 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 1, 2, AND 4 OETHMAAN, with regular determinations of the proportion of glycosylated haemoglobin.

GLIMEPIRIDE 1, 2, AND 4 OETHMAAN 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 1, 2, AND 4 OETHMAAN should be taken at the same time each day.

A single daily dose of GLIMEPIRIDE 1, 2, AND 4 OETHMAAN is usually adequate to provide metabolic control over 24 hours.

Treatment with GLIMEPIRIDE 1, 2, AND 4 OETHMAAN 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 1 OETHMAAN 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 to 2 mg to 3 mg to 4 mg to 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 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 1, 2, AND 4 OETHMAAN 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 1, 2, and 4 Oethmaan*:

When substituting GLIMEPIRIDE 1, 2, AND 4 OETHMAAN 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 1, 2, AND 4 OETHMAAN and other oral antidiabetic agents.

Side-effects and special precautions:

Side-effects:

Blood and the lymphatic system disorders:

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.

Endocrine disorders:

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”).

Nervous system disorders:

Frequent: Headache, dizziness, drowsiness.

Eye disorders:

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

Gastrointestinal disorders:

Frequent: Constipation, diarrhoea, flatulence, heartburn, loss or increase of appetite, nausea, stomach pain, abdominal distension, abdominal discomfort, vomiting, alterations in sense of taste.

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

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

Renal and urinary disorders:

Frequent: Polyuria.

Special precautions:

Clinical signs of a still insufficiently lowered blood glucose (i.e. hyperglycaemia, polyuria, polydipsia, dry mouth) may require dose adjustment of GLIMEPIRIDE 1, 2, AND 4 OETHMAAN.

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 1, 2, AND 4 OETHMAAN
- 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 or 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 illnesses. Under these circumstances, it is prudent to convert the patient to insulin therapy temporarily to maintain good metabolic control.

Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Lactose intolerance:

GLIMEPIRIDE 1, 2, AND 4 OETHMAAN contains lactose; thus patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take GLIMEPIRIDE 1, 2, AND 4 OETHMAAN.

Known symptoms of overdosage and particulars of its treatment:

(See “Side-effects and special precautions”).

After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended.

Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalisation in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50 % solution, followed by an infusion of a 10 % solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In particular when treating hypoglycaemia due to accidental intake of glimepiride in infants

and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

Identification:

GLIMEPIRIDE 1 OETHMAAN Tablets: Light red, flat, modified oblong, scored tablet, encoded G/1 on one side.

GLIMEPIRIDE 2 OETHMAAN Tablets: Light green, flat, modified oblong, scored tablet, encoded G/2 on one side.

GLIMEPIRIDE 4 OETHMAAN Tablets: Light blue, flat, modified oblong, scored tablet, encoded G/4 on one side.

Presentations:

GLIMEPIRIDE 1 OETHMAAN Tablets: Transparent or white opaque PVC/Aluminium foil blisters containing 10 tables each.

3 (10) blister strips to be packed into a carton i.e. 30 tablets per carton or 10 (10) blister strips to be packed into a carton i.e. 100 tablets per carton, or 28 tablets packed in a blister to be packed in a carton.

GLIMEPIRIDE 2 OETHMAAN Tablets: Transparent or white opaque PVC/Aluminium foil blisters containing 10 tables each.

3 (10) blister strips to be packed into a carton i.e. 30 tablets per carton or 10 (10) blister strips to be packed into a carton i.e. 100 tablets per carton, . or 28 tablets packed in a blister to be packed in a carton.

GLIMEPIRIDE 4 OETHMAAN Tablets: Transparent or white opaque PVC/Aluminium foil blisters containing 10 tables each.

3 (10) blister strips to be packed into a carton i.e. 30 tablets per carton or 10 (10) blister strips to be packed into a carton i.e. 100 tablets per carton, . or 28 tablets packed in a blister to be packed in a carton.

Storage instructions:

Store below 25 °C.

Keep the blisters in the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

Registration numbers:

GLIMEPIRIDE 1 OETHMAAN: 39/21.2/0023

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GLIMEPIRIDE 4 OETHMAAN: 39/21.2/0025

Name and business address of the holder of the certificates of registration:

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