AMENDED PROPOSED PACKAGE INSERT (CLEAN COPY)

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

ACCORD GLIMEPIRIDE 1 mg (tablets)

ACCORD GLIMEPIRIDE 2 mg (tablets)

ACCORD GLIMEPIRIDE 4 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

ACCORD GLIMEPIRIDE 1 mg: Each tablet contains glimepiride 1 mg.

ACCORD GLIMEPIRIDE 2 mg: Each tablet contains glimepiride 2 mg.

ACCORD GLIMEPIRIDE 4 mg: Each tablet contains glimepiride 4 mg.

Contains sugar (lactose monohydrate):

Each 1 mg tablet contains 78,4 mg lactose monohydrate.

Each 2 mg tablet contains 156,8 mg lactose monohydrate.

Each 4 mg tablet contains 154,8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

ACCORD GLIMEPIRIDE 1 mg: Pink coloured, round, flat, uncoated tablets with bevelled edges and a score line on one side and plain on the other side.

ACCORD GLIMEPIRIDE 2 mg: Light pink coloured, oval shaped, uncoated tablets, with a score line on one side and plain on the other side.

ACCORD GLIMEPIRIDE 4 mg: White, oval shaped, uncoated tablets, with a score line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

ACCORD GLIMEPIRIDE is indicated as an adjunct to diet and exercise, to lower the blood glucose, in patients with non-insulin-dependent (Type 2) diabetes mellitus (NIDDM) whose hyperglycaemia cannot be controlled by diet and exercise alone.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The dosage of **ACCORD GLIMEPIRIDE** is determined by the desired blood glucose level.

The dosage of **ACCORD GLIMEPIRIDE** must be the lowest which is sufficient to achieve the desired metabolic control.

During treatment with **ACCORD GLIMEPIRIDE**, glucose levels in blood and urine must be measured regularly. In addition, it is recommended that regular determinations of the proportion of glycated haemoglobin be carried out.

If a patient forgets to take a dose, this must never be corrected by subsequently taking a larger dose. Measures for dealing with such situations (in particular forgetting a dose or skipping a meal) where a dose cannot be taken at the prescribed time must be discussed and agreed between ~~physician~~ doctor and patient beforehand.

If it is discovered that too high a dose or an extra dose of **ACCORD GLIMEPIRIDE** has been taken, a ~~physician~~ doctor must be notified immediately.

Initial dose and dose titration:

The usual initial dose is 1 mg **ACCORD GLIMEPIRIDE** once daily.

If necessary, the daily dose can be increased. It is recommended that the increase be guided by regular blood glucose monitoring, and that the dose be increased gradually, i.e. at intervals of one to two weeks and according to the following dose steps: 1 mg - 2 mg - 3 mg - 4 mg - 6 mg. Daily doses of more than 6 mg are more effective only in a minority of patients. A maximum of 8 mg per day may not be exceeded.

Dose range in patients with well controlled diabetes:

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

Distribution of doses:

Timing and distribution of doses are to be decided by the ~~physician~~ doctor, taking into consideration the patient's current life-style.

Normally a single daily dose of **ACCORD GLIMEPIRIDE** is sufficient to provide metabolic control over 24 hours.

It is recommended that this dose be taken immediately before a substantial breakfast or, if none is taken, immediately before the first main meal.

It is very important not to skip meals after the tablet(s) have been taken.

Secondary dosage adjustment:

An improvement in the control of diabetes is associated with higher insulin sensitivity, therefore glimepiride requirements may fall as treatment proceeds.

To avoid hypoglycaemia, dose reduction or cessation of **ACCORD GLIMEPIRIDE** therapy must therefore be considered, in time.

Correction of dosage must also be considered, whenever the patient's weight changes, the patient's lifestyle changes or other factors arise which cause an increased susceptibility to hypoglycaemia or hyperglycaemia (see section 4.4).

Duration of treatment:

Treatment with **ACCORD GLIMEPIRIDE** is normally long-term therapy.

Change-over from other oral antidiabetics to ACCORD GLIMEPIRIDE:

There is no exact dosage relationship between **ACCORD GLIMEPIRIDE** and other oral antidiabetics.

When substituting **ACCORD GLIMEPIRIDE** for other oral antidiabetics, it is recommended that the procedure be the same as for initial dosage, starting with daily doses of 1 mg. This applies even in cases where the patient is being switched from the maximum dose of another oral antidiabetic.

Special populations

Renal insufficiency: There is limited information available on the use of glimepiride in renal insufficiency. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of **ACCORD GLIMEPIRIDE.**

Paediatric population: There is insufficient data to recommend paediatric use of **ACCORD GLIMEPIRIDE.**

Method of administration:

ACCORD GLIMEPIRIDE tablets must be swallowed whole with approximately half a glass of water.

4.3 CONTRA-INDICATIONS:

ACCORD GLIMEPIRIDE must not be used:

- In patients hypersensitive to glimepiride, other sulphonylureas, other sulfonamides, or any of the excipients listed in section 6.1 (risk of hypersensitivity reactions);
- In pregnant or breastfeeding women as safety has not been shown;
- In patients with impaired liver function and moderate to severe impaired renal function and
- In children.

ACCORD GLIMEPIRIDE is not suitable for the treatment of insulin-dependent (Type 1) diabetes mellitus.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY.

The administration of oral hypoglycaemic medicines has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. The patient should be informed of the potential risks and advantages of glimepiride tablets and of alternative modes of therapy.

Treatment with **ACCORD GLIMEPIRIDE** must be initiated and monitored by a doctor. The patient must take **ACCORD GLIMEPIRIDE** at the times and in the doses prescribed by the doctor, normally at the same time every day. To achieve the goal of treatment with **ACCORD GLIMEPIRIDE,** optimal control of blood glucose,

adherence to correct diet, regular and sufficient physical exercise and, if necessary, reduction of body weight are just as necessary as regular ingestion of **ACCORD GLIMEPIRIDE**.

Clinical signs of a still insufficiently lowered blood glucose (hyperglycaemia) are e.g. increased urinary frequency (polyuria), intense thirst, dryness of the mouth and dry skin.
In the initial weeks of treatment, the risk of hypoglycaemia may be increased and necessitates especially careful monitoring.

Factors favouring hypoglycaemia include:

- Unwillingness or (more commonly in older patients) incapacity of the patient to co-operate.
- Undernourishment, irregular meal times or skipped meals.
- Imbalance between physical exertion and carbohydrate intake.
- Alteration of diet.
- Consumption of alcohol, especially in combination with skipped meals.
- Impaired renal function.
- Severe impairment of liver function.
- Overdosage with **ACCORD GLIMEPIRIDE**.
- Certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or corticoadrenal insufficiency).
- Concurrent administration of certain other medicines (see section 4.5).
- Treatment with **ACCORD GLIMEPIRIDE** in the absence of any indication.

The patient must inform the doctor about such factors and about hypoglycaemic episodes since they may indicate the need for particularly careful monitoring. If such risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of **ACCORD GLIMEPIRIDE** or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life-style changes.

Those symptoms of hypoglycaemia which reflect the body's adrenergic counter-regulation (see section 4.8) may be milder or absent where hypoglycaemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine or other sympatholytic medicines.

When meals are taken at irregular hours or skipped altogether, treatment with glimepiride may lead to hypoglycaemia. Possible symptoms of hypoglycaemia include: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac dysrhythmias.

The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke.

Hypoglycaemia can almost always be promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g. in the form of sugar lumps, sugar sweetened fruit juice or sugar sweetened tea). For this purpose, patients must carry a minimum of 20 grams of glucose with them at all times. They may require the assistance of other persons to avoid complications. Artificial sweeteners are ineffective in controlling hypoglycaemia. It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation.

Severe hypoglycaemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.

In exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Insulin is the treatment of choice for non-insulin-dependent diabetes mellitus (NIDDM) with renal and hepatic dysfunction. No experience has been gained concerning the use of **ACCORD GLIMEPIRIDE** in patients with

impairment of liver function. In patients with severe impairment of renal function, change-over to insulin is indicated, to achieve optimal metabolic control (see section 4.3).

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

ACCORD GLIMEPIRIDE tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Patients who take or discontinue taking certain other medicines while undergoing treatment with **ACCORD GLIMEPIRIDE** may experience changes in blood glucose control. For this reason, other medicines should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole).

The following interactions must be considered:

Potentiation of the blood-glucose-lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following medicines is taken:

- insulin and other oral antidiabetics
- MAO inhibitors
- ACE inhibitors
- Miconazole, fluconazole
- anabolic steroids and male sex hormones
- para-aminosalicyclic acid
- chloramphenicol
- pentoxifylline (high dose parenteral)

- tritoqualine
- coumarin derivatives
- phenylbutazone, azapropazone, oxyphenbutazone
- cyclophosphamide, trophosphamide and iphosphamides
- probenecid, allopurinol
- disopyramide
- quinolones
- fenfluramine
- disopyramide
- salicylates and p-amino-salicylic acid
- sulphinpyrazone
- fibrates
- sulfonamide antibiotics
- fluoxetine
- tetracyclines

Weakening of the blood-glucose-lowering effect and thus, raised glucose levels may occur when one of the following medicines are taken:

- acetazolamide
- laxatives (after protracted use)
- barbiturates
- nicotinic acid (in high doses) and nicotinic acid derivatives
- corticosteroids
- oestrogens and progestogens
- diazoxide
- phenothiazine derivatives, chlorpromazine
- saluretics, thiazide diuretics
- phenytoin
- epinephrine (adrenaline) and other sympathomimetic medicines

- rifampicin
- glucagon
- thyroid stimulating medicines, glucocorticoids

H_2-receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect. Under the influence of sympatholytic medicines such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of **ACCORD GLIMEPIRIDE** in an unpredictable fashion. The effect of coumarin derivatives may be potentiated or weakened.

4.6 FERTILITY, PREGNANCY AND LACTATION

ACCORD GLIMEPIRIDE must not be used in pregnant and breastfeeding women as safety and efficacy have not been established.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Alertness and reactions may be impaired due to hypo- or hyperglycaemia, especially when beginning or after altering treatment, or when **ACCORD GLIMEPIRIDE** is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.

4.8 UNDESIRABLE EFFECTS

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and the lymphatic system disorders	Less frequent	Thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis (e.g. due to myelosuppression), erythropenia, haemolytic anaemia and

		pancytopenia, which are in general reversible upon discontinuation of medicine
	Frequency unknown	Severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura.
Immune system disorders	Less frequent	Leukocytoclastic vasculitis, mild hypersensitivity reactions (itching, urticaria or rashes) that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimes shock.
	Frequency unknown	Cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible
Metabolism and nutrition disorders	Frequent	Hypoglycaemia
Nervous system disorders	Less frequent	Dizziness and drowsiness
Eye disorders	Less frequent	Temporary visual impairment (due to change in blood glucose level)

Gastrointestinal disorders	Frequent	Nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea, metallic taste, anorexia, increased appetite and weight gain.
Hepato-biliary disorders	Less frequent	Elevation of liver enzyme levels, impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which may also lead to life-threatening liver failure.
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rashes, erythema multiforme, Stevens-Johnson Syndrome, exfoliative dermatitis and erythema nodosum
	Frequency unknown	Hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.
Investigations	Less frequent	Blood sodium decrease

Description of selected adverse reactions

Allergic and pseudo-allergic reactions:

Allergic or pseudo-allergic reactions may occur such as itching, urticaria or rashes. These reactions may develop into serious and even life-threatening reactions with dyspnoea and a fall in blood pressure, sometimes progressing to shock. Therefore in the event of urticaria a doctor must be notified immediately. A decrease

in serum sodium concentration has been seen and allergic vasculitis or hypersensitivity of the skin to light may occur. If any of these reactions occur a doctor should be consulted.

Hypoglycaemia

Hypoglycaemia (sometimes life-threatening) may occur as a result of the blood-glucose-lowering action of **ACCORD GLIMEPIRIDE**. This happens when there is an imbalance between **ACCORD GLIMEPIRIDE** dosage, carbohydrate intake (diet), physical exercise and other factors influencing metabolism.

Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, sleep disorders, restlessness, aggressiveness, impaired concentration, impaired alertness and reactions, depression, confusion, speech disorders, aphasia, visual disorders, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia.

In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and cardiac dysrhythmias.

The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke.

The symptoms of hypoglycaemia may persist if hypoglycaemia is corrected.

Visual impairment

Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity and hence the refractive index of the lens, this being dependent on blood glucose level.

4.9 OVERDOSE

Please refer to sections 4.4 and 4.8.

Treatment is symptomatic and supportive.

After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose/dextrose infusion in lower concentration so as to ensure that the hypoglycaemia does not recur. The patient's blood glucose level should be carefully monitored for at least 24 hours. In severe cases with a protracted course, the danger of ongoing or recurring hypoglycaemia, may persist for several days.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological classification: A 21.2 Oral hypoglycaemic

Glimepiride is a sulfonylurea. Glimepiride decreases blood glucose concentrations mainly by stimulating insulin release from pancreatic beta cells. This effect is based predominantly on an improved responsiveness of the pancreatic beta cells to the physiological glucose stimulus. Glimepiride also has extra pancreatic (insulin-sensitizing and insulin-mimetic) effects. The effect of glimepiride is dose-dependent over the dose range of 1 to 6 mg. The physiological response to acute physical exercise, i.e. reduction of insulin secretion, is still present with glimepiride.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

There was no significant difference in effect regardless of whether glimepiride was given 30 minutes or immediately before a meal. The absolute bioavailability of glimepiride is complete. Food intake has no relevant influence on absorption. Maximum serum concentrations are reached approximately 2,5 hours after oral intake and there is a linear relationship between dose and both maximum concentrations and area under the time/concentration curve.

Distribution

Glimepiride has a high protein binding (>99 %) and a low clearance (approximately 48 ml/min). It has a low distribution volume (approximately 8,8 L), which is roughly equal to the albumin distribution space.

Biotransformation and elimination

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After single-dose radiolabelled glimepiride, 58 % of the radioactivity was recovered in the urine, and 35 % in the faeces. No unchanged substance was detected in the urine.

Two metabolites most probably resulting from hepatic metabolism (major enzyme is CYP2C9) were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively.

Special populations

Pharmacokinetics were similar in males and females, as well as in young and elderly patients.

In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding.

Renal elimination of the two metabolites was impaired. Overall, no additional risk of accumulation is to be assumed in such patients.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Sodium starch glycolate

Iron oxide red E172 (1 mg & 2 mg only)

Povidone (K-30)

Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 °C.

Keep blister strips in original outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 NATURE AND CONTENTS OF CONTAINER

ACCORD GLIMEPIRIDE 1 mg: Blister Strips of clear PVC/PVDC Aluminium Foil with 10 tablets per blister.

Marketed in packs of 30's.

ACCORD GLIMEPIRIDE 2 mg: Blister Strips of clear PVC/PVDC Aluminium Foil with 10 tablets per blister.

Marketed in packs of 30's.

ACCORD GLIMEPIRIDE 4 mg: Blister Strips of clear PVC/PVDC Aluminium Foil with 10 tablets per blister.

Marketed in packs of 30's.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd.

Tuscany Office Park

6 Coombe Place

Rivonia,

Gauteng

South Africa

8. REGISTRATION NUMBER:

ACCORD GLIMEPIRIDE 1 mg: 41/21.2/0656

ACCORD GLIMEPIRIDE 2 mg: 41/21.2/0657

ACCORD GLIMEPIRIDE 4 mg: 41/21.2/0658

9. DATE OF FIRST AUTHORISATION

5 August 2011

10. DATE OF REVISION OF THE TEXT

05 February 2015