PROFESSIONAL INFORMATION FOR

GLYGARD

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

GLYGARD gliclazide 80 mg, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of gliclazide.

Contains sugar: Lactose monohydrate 73,5 mg per tablet.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Tablets

White, circular, flat, bevelled tablets with a break line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLYGARD is indicated for the control of hyperglycaemia in non-insulin-dependent diabetes mellitus or Type II diabetes mellitus, when appropriate control cannot be achieved by diet alone. Continued dietary restrictions should be observed.

4.2 Posology and method of administration

Posology

Take GLYGARD tablets 30 minutes before a meal or with a meal.

The dose must be guided by the individual patient's response and must be carefully monitored.

Initial dose:	40 to 80 mg per day, taken in divided doses, at breakfast and at dinner.
Maximum dose:	320 mg per day, taken in divided doses, at breakfast and at dinner.
General dosage:	2 tablets per day taken with meals. Take 1 tablet with breakfast and one tablet with dinner.

Method of administration

GLYGARD is for oral administration.

4.3 Contraindications

GLYGARD is contraindicated in:

- Patients with known hypersensitivity to gliclazide or other sulphonylureas or to any of the excipients in GLYGARD (see **section 6.1**).
- Cross-sensitivity to other sulphonamide or thiamine-type medications may occur.
- Patients with insulin-dependent diabetes mellitus.
- Patients with significant hepatic or renal insufficiency.
- The presence of keto-acidosis.
- Patients with hepatic impairment and adrenal or thyroid dysfunction.
- Pregnancy and lactation has not been established.
- Paediatrics: safety and efficacy have not been proven.
- Patients with 'Brittle' or unstable diabetes.

- Acidosis, severe burns, coma, major surgery, trauma or in conditions where the blood glucose level may be severely influenced or when the need for insulin changes rapidly.
- Treatment with miconazole (see **section 4.5**).

4.4 Special warnings and precautions for use

The administration of oral hypoglycaemics may be associated with increased cardiovascular mortality compared to treatment with diet alone or diet with insulin. Dose reduction may be necessary in patients with renal dysfunction.

GLYGARD should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia, if a meal is taken late, if an inadequate amount of food is consumed or, if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic medicine is being used.

Hypoglycaemia

Hypoglycaemia may occur following administration of sulphonylureas including GLYGARD (see **section 4.8**). Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

Treatment with GLYGARD can cause hypoglycaemia if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycaemia are:
headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, aphasia, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, bradycardia, drowsiness, and loss of consciousness, possibly resulting in coma and lethal outcome.
In addition, signs of adrenergic counter-regulation may be observed, sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac dysrhythmia.
Usually, symptoms disappear after intake of carbohydrates (sugar), however, artificial sweeteners have no effect. Experience with other sulphonylureas shows that hypoglycaemia can recur even when measures prove effective initially.

If a hypoglycaemic episode is severe, or is prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation is required.

In the initial weeks of treatment, the risk of hypoglycaemia may increase, and careful monitoring is necessary. At risk patients and/or factors favouring hypoglycaemia include:

- patients (particularly elderly patients) refusing or unable to co-operate,
- malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes,
- imbalance between physical exercise and carbohydrate intake,
- withdrawal of prolonged and/or high dose corticosteroid treatment,
- severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease),
- renal insufficiency,

- severe hepatic insufficiency,
- overdose of GLYGARD,
- concomitant administration of alcohol or certain other medicines (see **section 4.5**).

The risk benefit should be considered in the following conditions: severe diarrhoea, intestinal obstruction, prolonged vomiting and gastro paresis. Because of its shorter half-life, gliclazide may be prescribed to patients with renal impairment, but with caution and under close supervision (see boxed "**Warnings**").

GLYGARD should be used with caution in patients with renal or hepatic insufficiency, especially the elderly (see **section 4.2** and **4.4**).

Severe hypoglycaemia in the elderly may present as an acute neurological emergency. It is therefore advised that the plasma glucose level be checked in any elderly patient with acute neurological symptoms (headache, mental confusion, unusual tiredness, irritability, drowsiness).

The blood glucose concentration should be monitored whenever there is a need to administer any medication that may affect the metabolic or glycaemic control of the diabetes mellitus.

In an exceptional stress situation e.g. trauma, fever, infection or surgical intervention, blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

Gastrointestinal side effects can be avoided if GLYGARD is taken with breakfast.

Hepatobiliary symptoms may disappear after discontinuation of treatment. Discontinue treatment if cholestatic jaundice appears.

Beta-blockers may decrease the efficacy of GLYGARD by impairing the release of insulin. Beta-blockers may mask the typical sympathomimetic warning signs and symptoms of hypoglycaemia and may inhibit the normal physiological response to hypoglycaemia.

Patient information

The risks of hypoglycaemia, together with its symptoms (see **section 4.8**), treatment, and conditions that predispose to its development, should be explained to the patient and to family members. The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

Poor blood glucose control

Blood glucose control may deteriorate under certain conditions, despite compliance from the patient. This occurs with exceptional stressors like fever, trauma, infection, surgery and febrile illnesses as well as St. John's wort (*Hypericum perforatum*) preparations (see **section 4.5**). Under these circumstances, it is prudent to convert the patient to insulin therapy temporarily to maintain good metabolic control.

The hypoglycaemic efficacy of GLYGARD, including gliclazide, is attenuated over time in many patients: this may be due to progression in the severity of the diabetes, or to a reduced response to treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure, which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

Dysglycaemia

Disturbances in blood glucose, including hypoglycaemia and hyperglycaemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Careful monitoring of blood glucose is recommended in all patients receiving GLYGARD and a fluoroquinolone together.

Renal and hepatic insufficiency

The pharmacokinetic and/or pharmacodynamic properties of GLYGARD may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

Skin reactions

There is a potential for the occurrence of erythema multiforme, toxic dermal necrolysis and allergic vasculitis.

Laboratory tests

Measurement of glycated haemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

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

Paediatric population

Safety and efficacy have not been proven (see **section 4.3**).

Lactose monohydrate

GLYGARD contains 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

Hypoglycaemia may occur with concomitant use of GLYGARD and the following medicines

Combination which is contraindicated

Miconazole (systemic route, oromucosal gel) — increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma and is therefore contraindicated (see **section** 4.3).

Combinations which are not recommended

Phenylbutazone (systemic route) – increases the hypoglycaemic effect of sulphonureas (displaces their binding to plasma proteins and/or reduces their elimination).

It is preferable to use a different anti-inflammatory medicine, or else to warn the patient and emphasise the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory medicine.

Alcohol — increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma. Avoid alcohol or medicines containing alcohol.

Combinations requiring precautions during use

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

- allopurinol
- anabolic steroids and androgens
- angiotensin-converting enzyme inhibitors: captopril and enalapril
- antidysrhythmic: disopyramide

- antibacterials: chloramphenicol, sulphonamides, fluoroquinolone antibiotics, tetracyclines, clarithromycin
- antidepressants and monoamine-oxidase inhibitors: fluoxetine
- appetite suppressants: fenfluramine
- azole antifungals: ketoconazole, itraconazole, voriconazole, fluconazole (systemic route, oral gel)
- H2 receptor antagonists – cimetidine and ranitidine
- fibrates: clofibrate
- insulin and other oral antidiabetic medicines (acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists)
- salicylates or nonsteroidal anti-inflammatory medicines (NSAIDs)
- probenecid or sulphinpyrazone
- sulphonamides.

Sympatholytic medicines (e.g. beta-blockers, clonidine) may blunt the signs of adrenergic response to hypoglycaemia, as well as impair mechanisms that control the normal physiological response to a fall in blood glucose, thereby increasing the risk of a severe hypoglycaemic reaction.

Hyperglycaemia may occur with concomitant use of GLYGARD with the following:

Combination which is not recommended:

Danazol — diabetogenic effect of danazol. If the use of gliclazide, as in GLYGARD, cannot be avoided, warn the patient and emphasise the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of GLYGARD during and after treatment with danazol.

Combinations requiring precautions during use

- epinephrine (adrenaline) and other sympathomimetic medicines

- corticosteroids
- calcium channel blocking medicines
- phenothiazines, chlorpromazine (neuroleptic medicine): high doses (> 100 mg/day) increase blood glucose levels (reduced insulin release).
- clonidine
- diazoxide, parenteral
- diuretics
- ephedrine, pseudoephedrine and common cold products
- glucagon
- glucocorticoids (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin: increase in blood glucose levels with possible ketosis
- isoniazid
- lithium
- oestrogens and progesterone's
- phenytoin
- rifampicin
- thyroid hormones
- St. John's wort (*Hypericum performatum*) preparations: Gliclazide exposure is decreased by St. John's wort. Emphasise the importance of blood glucose level monitoring
- ritodrine, salbutamol, terbutaline (I.V.) and other beta-adrenergic medicines: increased blood glucose levels due to beta-2 agonist effects. Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

Combinations which must be taken into account

- barbiturates may prolong the effect of GLYGARD.

The following products may cause dysglycaemia

Combinations requiring precautions during use

Fluoroquinolones: in case of a concomitant use of GLYGARD and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.

Anticoagulant therapy (coumarin derivatives such as warfarin): GLYGARD may lead to weakening or potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary, and INR should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see **section 4.3**).

Breastfeeding

Safety in lactation has not been established (see **section 4.3**).

4.7 Effects on ability to drive and use machines

GLYGARD has no or negligible influence on the ability to drive and use machines, however, 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.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reaction with GLYGARD is hypoglycaemia – especially if mealtimes are irregular and, in particular, if meals are skipped.

Hypoglycaemia may range from mild to severe and life threatening with possible symptoms that may include:

headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, sleepiness, nightmares, agitation, aggression, poor concentration, reduced awareness and slowed reactions, restlessness, depression, delirium, apathy, confusion, visual and speech disorders, slurred speech, aphasia, seizures, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, behavioural changes that mimic drunkenness, loss of self-control, convulsions, shallow respiration, bradycardia, drowsiness, loss of consciousness, coma, adrenergic counter-regulation (cold sweats, sweating, clammy skin, anxiety, tremor, tachycardia, hypertension, palpitations, angina pectoris, cardiac dysrhythmia).

Usually, symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulfonylureas shows that hypoglycaemia can recur even when measures prove effective initially (see **section 4.4**).

If a hypoglycaemic episode is severe or prolonged, even if temporarily controlled by the intake of sugar, immediate medical treatment or hospitalisation is required.

Tabulated list of adverse reactions

MedDRA system organ class	Frequency	Side effects
Blood and lymphatic system disorders	*Less Frequent*	Blood disorders, such as aplastic anaemia, granulocytopenia, agranulocytosis, thrombocytopenia, haemolytic anaemia and leukopenia, erythrocytopenia, pancytopenia, dyscrasias.
Immune system disorders	*Less Frequent*	Rash, allergic vasculitis.
Endocrine disorders	*Less Frequent*	Hypoglycaemia.
Metabolism and nutrition disorders	*Less Frequent*	Hypoglycaemic reactions including coma, may occur, especially in the elderly patient. Weight changes - most studies indicate no significant overall weight changes. hyponatraemia, anorexia.
Nervous system disorders	*Frequent*	Headache, dizziness, drowsiness.
Eye disorders	*Less Frequent*	Blurred vision and/or changes in accommodation.

Gastrointestinal disorders	*Frequent*	Gastro-intestinal disturbances such as nausea and vomiting, epigastric pain, anorexia, diarrhoea, metallic taste. Constipation, dyspepsia, flatulence, loss of or increase in appetite, weight gain, stomach pain, fullness or discomfort.
Hepato-biliary disorders:	*Less frequent*	Increased levels of hepatic enzymes (alanine amino-transferase, aspartate amino transferase, alkaline phosphatase), hepatitis, cholestasis, cholestatic jaundice, hepatic function impairment, hepatic porphyria, porphyria cutanea tarda, liver failure.
Skin and subcutaneous tissue disorders	*Frequency Not known*	Dermatological reactions: skin rashes, pruritus, photosensitivity, urticaria, maculopapular rashes. Generalized hypersensitivity reactions, such as fever, erythema multiforme or Stevens-Johnson syndrome and toxic epidermal necrolysis, exfoliative dermatitis and erythema nodosum, angioedema, drug rash with eosinophilia and systemic symptoms (DRESS).
Renal and urinary disorders	*Frequent*	Polyuria.

Description of selected adverse reactions

Hypoglycaemia may be prevented if mealtimes are regular and, in particular, if no meals are skipped.

Usually, symptoms disappear after intake of carbohydrates (sugar).

If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation are required.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

The blood sugar levels should be corrected by intravenous glucose administration. The blood sugar levels should be monitored continuously, until the effects of the overdosage has ceased. This may be necessary for several days. Should the patient develop hypoglycaemia, it should be treated with urgency and the general management for hypoglycaemia followed. Hypoglycaemic reactions may indicate possible renal dysfunction.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.2. Oral hypoglycaemics.

Pharmacotherapeutic group: Sulphonamides, urea derivative

ATC code: A10BB09

Mechanism of action

Gliclazide is a second generation hypoglycaemic sulphonylurea. Sulphonylureas stimulate insulin release from the pancreatic β- cells and are therefore only effective when the pancreas is capable of producing insulin.

In addition, gliclazide may have a direct influence on the intracellular transport of calcium, that specifically improves the biphasic response of the β-cells after food ingestion. This includes the immediate first phase insulin release, as well as the delayed, second phase insulin release. In addition, it has been demonstrated that the metabolic utilisation of glucose may be improved at a peripheral level by the administration of gliclazide.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, gliclazide is rapidly absorbed from the gastro-intestinal tract.

Distribution

Gliclazide is extensively bound to the plasma proteins (85 to 97 %).

Biotransformation

Gliclazide is metabolised by the liver and the metabolites excreted through the kidneys and in the faeces.

Elimination

The half-life is approximately 10 to 12 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Lactose

Magnesium stearate

Microcrystalline cellulose (Pharma grade)

Povidone (PVK K30)

Purified talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C, in a dry place.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

GLYGARD is packed in an Alu foil-Alu film blister with 10 tablets, packed in 60’s and 500’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

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Mispel Street

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Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

34/21.2/0070

Namibia: NS2 06/21.2/0317

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 07 August 2002.

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

09 December 2025