SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

MINIDIAB® tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glipizide 5 mg.

Contains sugar (lactose).

Excipients with known effect

Each MINIDIAB 5 mg tablet contains 153 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

A white to whitish, round, biconvex tablet, scored on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MINIDIAB is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with Type II diabetes mellitus.

4.2 Posology and method of administration

There is no fixed dosage regimen for the management of diabetes mellitus with MINIDIAB or any other oral

hypoglycaemic medicine.

In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically. Glycosylated haemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short term administration of MINIDIAB may be sufficient during periods of transient loss of control in patients usually well-controlled on diet.

Posology

Initial Dose

The recommended starting dose is 2,5 mg given 30 minutes before breakfast or midday meal.

Titration

Dosage adjustments should ordinarily be in increments of 2,5 - 5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended single dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate kilojoule content.

Maintenance

Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should be divided into two doses daily. The maximum recommended dosage is 30 mg.

Patients receiving other oral hypoglycaemic medicines

No transition period is necessary when transferring patients to MINIDIAB from other sulphonylureas, metformin or insulin, except with chlorpropamide. Patients should be observed carefully (1 - 2 weeks) for

hypoglycaemia when being transferred from longer half-life sulphonylureas (e.g. chlorpropamide) to MINIDIAB due to potential overlapping of medicine effect.

Special populations

Use in elderly and in high risk patients

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycaemic reactions.

Paediatric population

Safety and efficacy in children have not been established.

Method of administration

For oral use

4.3 Contraindications

- Hypersensitivity to glipizide, other sulphonylureas or sulphonamides, or to any of the excipients in the tablets (listed in section 6.1)
- Insulin-dependent diabetes, diabetic ketoacidosis, diabetic coma
- Severe hepatic or renal insufficiency
- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

The administration of oral hypoglycaemics, such as MINIDIAB, may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin.

G6PD-deficiency

Since MINIDIAB belongs to the class of sulphonylurea medicines, caution should be used in patients

with G6PD-deficiency. Treatment of patients with G6PD-deficiency with sulphonylurea medicines, such as MINIDIAB, can lead to haemolytic anaemia and a non-sulphonylurea alternative should be considered.

Hypoglycaemia

MINIDIAB can produce severe hypoglycaemia which may result in coma, and may require hospitalisation. Proper patient selection, dosage and instructions are important to avoid hypoglycaemic episodes. Regular, timely carbohydrate intake is important to prevent hypoglycaemic events occurring when a meal is delayed or insufficient food is eaten or carbohydrate intake is unbalanced. Patients experiencing severe hypoglycaemia should be managed with appropriate glucose therapy and be monitored for a minimum of 24 to 48 hours.

Renal or hepatic insufficiency may cause elevated blood levels of MINIDIAB and may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycaemic reactions. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycaemic action of MINIDIAB. Hypoglycaemia may be difficult to recognise in elderly and in people taking beta-adrenergic blocking medicines (see section 4.5). Hypoglycaemia is more likely to occur when caloric intake is deficient after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering medicine is used.

Loss of control of blood glucose

When a patient stabilised on a diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue MINIDIAB and administer insulin.

The effectiveness of MINIDIAB in lowering blood glucose to a desired level decreases in many patients

over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the medicine. This phenomenon is known as secondary failure, to distinguish it from primary failure, in which the medicine is ineffective in an individual patient when first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Renal and hepatic disease

The pharmacokinetics and/or pharmacodynamics of MINIDIAB may be affected in patients with impaired renal or hepatic function. If hypoglycaemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

Laboratory tests

Blood and urine glucose should be monitored periodically. Measurement of glycosylated haemoglobin should be performed and goals assessed by the current standard of care.

Metabolic reactions

Hepatic porphyria and porphyria cutanea tarda have been reported.

Information for patients

The risks of hypoglycaemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

MINIDIAB tablets contain lactose. 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

The following medications are likely to increase the hypoglycaemic effect

Antifungals

Miconazole

Increase in hypoglycaemic effect, possibly leading to symptoms of hypoglycaemia or even coma.

Fluconazole

There have been reports of hypoglycaemia following the co-administration of MINIDIAB and fluconazole, possibly the result of an increased half-life of glipizide.

Voriconazole

Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during co-administration.

Nonsteroidal anti-inflammatory drugs (NSAIDS)

Increase in hypoglycaemic effect of MINIDIAB (displacement of MINIDIAB binding to plasma proteins and/or decrease in MINIDIAB elimination).

Alcohol

Increase in hypoglycaemic reaction which can lead to hypoglycaemic coma.

Salicylates (acetylsalicylic acid)

Increase in hypoglycaemic effect by high doses of acetylsalicylic acid (hypoglycaemic reaction of acetylsalicylic acid).

Beta-blockers

All beta-blockers mask some of the symptoms of hypoglycaemia, i.e. palpitations and tachycardia. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia.

Angiotensin-converting enzyme inhibitors

The use of angiotensin converting enzyme inhibitors may lead to an increased hypoglycaemic effect in diabetic patients treated with MINIDIAB. Therefore, a reduction in MINIDIAB dosage may be required.

H_2 receptor antagonists

The use of H_2 receptor antagonists (i.e. cimetidine) may potentiate the hypoglycaemic effects of MINIDIAB.

The hypoglycaemic action of MINIDIAB may also be potentiated by monoamine oxidase inhibitors and medicines that are highly protein bound, such as sulphonylureas, sulphonamides, warfarin, chloramphenicol, probenecid,-fibrates and coumarins.

When such medications are administered to (or withdrawn from) a patient receiving MINIDIAB, the patient should be observed closely for hypoglycaemia (or loss of control).

In vitro binding studies with human serum proteins indicate that MINIDIAB binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of MINIDIAB with these medicines.

The following medications could lead to hyperglycaemia

Danazol

Diabetogenic effect of danazol – if it cannot be avoided, warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of MINIDIAB during treatment with danazol and after its discontinuation.

Phenothiazines, e.g. chlorpromazine, at high doses > 100 mg per day of chlorpromazine

Elevation in blood glucose (reduction in insulin release).

Corticosteroids

Elevation in blood glucose.

Sympathomimetics, e.g. ritodrine, salbutamol, terbutaline

Elevation in blood glucose due to beta-2-adrenoceptor stimulation.

Progestogens

Diabetogenic effects of high-dose progestogens. Warn the patients and step up self-monitoring of blood glucose and urine. Possibly adjust the dosage of antidiabetic medication during treatment with the neuroleptics, corticoids or progestogen and after discontinuation.

Other medications that may produce hyperglycaemia and lead to a loss of control include the thiazides and other diuretics, thyroid medication, oestrogens, oral contraceptives, phenytoin, nicotinic acid (niacin), calcium channel blocking medication and isoniazid.

When such medications are withdrawn from (or administered to) a patient receiving MINIDIAB, the patient should be observed closely for hypoglycaemia (or loss of control).

4.6 Fertility, pregnancy and lactation

MINIDIAB is contraindicated during pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

The effect of MINIDIAB on the ability to drive or operate machinery has not been studied; however

there is no evidence to suggest that MINIDIAB may affect these abilities. Patients should be aware of the symptoms of hypoglycaemia and if affected should not drive or operate machinery.

4.8 Undesirable effects

The majority of adverse events have been dose-related, transient and have responded to dose reduction or withdrawal of MINIDIAB. However, clinical experience has shown that some side effects associated with hypersensitivity may be severe and deaths have been reported in some instances.

Tabulated summary of adverse reactions

The table below contains side effects categorized as follows utilizing the incidence rates: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

System organ class	Frequency	Adverse effect
Blood and lymphatic system disorders	Very rare	Aplastic anaemia
Immune system disorders	Very rare	Some side effects associated with hypersensitivity may be severe and deaths have been reported in some instances
Metabolism and nutrition disorders	Common	Hypoglycaemia
	Uncommon	Disulfiram-like reactions (see section 4.5)
Nervous system disorders	Uncommon	Dizziness[#], somnolence[#]
Eye disorders	Uncommon	Blurred vision[#]

Gastrointestinal disorders	Common	Nausea[$], diarrhoea, upper abdominal pain, abdominal pain, heartburn
	Uncommon	Vomiting
Hepato-biliary disorders	Uncommon	Cholestatic jaundice[†]
Skin and subcutaneous tissue disorders	Uncommon	Eczema
Congenital familial and genetic disorders	Very rare	Non-acute porphyria

[#] This is usually transient and does not require discontinuance of therapy; however, it may also be a symptom of hypoglycaemia.

[$] Appear to be dose related and generally disappear when the dose is divided or reduced

[†] Discontinue treatment if cholestatic jaundice occurs

[‡] They frequently disappear with continued therapy. However, if they persist, MINIDIAB should be discontinued

[§] The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

Post-marketing side effects

System organ class	**Side effect**
Blood and lymphatic system disorders	Agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia, pancytopenia
Metabolism and nutrition disorders	Hyponatraemia
Psychiatric Disorders	Confusion[#]
Nervous system disorders	Headache
Eye disorders	Diplopia[#], visual impairment, visual acuity

	reduced[#]
Gastrointestinal disorders	Constipation[$]
Hepato-biliary disorders	Abnormal hepatic function, hepatitis
Skin and subcutaneous tissue disorders	Allergic dermatitis[‡], erythema[‡], morbilliform rash[‡], maculopapular rash[‡], urticaria[‡], pruritus[‡], photosensitivity reactions
General Disorders and Administration Site Conditions	Malaise[#]
Investigations	Aspartate amino transferase increase[§], blood lactate dehydrogenase increase[§], blood alkaline phosphatase increase[§], blood urea increase[§] and blood creatinine increase[§]

[#] This is usually transient and does not require discontinuance of therapy; however, it may also be a symptom of hypoglycaemia.

[$] Appear to be dose related and generally disappear when the dose is divided or reduced

[†] Discontinue treatment if cholestatic jaundice occurs

[‡] They frequently disappear with continued therapy. However, if they persist, MINIDIAB should be discontinued

[§] The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

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 asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**,

found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In overdose, side effects will be exacerbated and exaggerated (see section 4.8).

Overdosage of MINIDIAB can produce hypoglycaemia and hypoglycaemic coma.

Treatment is symptomatic. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated actively with oral sugar (e.g. glucose tablets, fruit juice, corn syrup, honey, table sugar dissolved in water, orange juice) and adjustments in MINIDIAB dosage and/or meal patterns. Close monitoring should continue until the medical practitioner is assured that the patient is out of danger. Severe hypoglycaemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalisation and IV glucose/dextrose administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.2 Oral hypoglycaemics

Glipizide, a sulphonylurea, is an orally active hypoglycaemic medicine which reduces the blood sugar concentration.

It acts by stimulating the pancreatic β-cells to produce insulin, with consequent increase in insulin plasma levels. Since the preparation is rapidly absorbed, an evident lowering of blood sugar is already observed half an hour after the oral administration of a 2,5 mg dose.

The following pharmacological actions have been attributed to glipizide, namely:

i) Enhancement of in vivo insulin action by extra-pancreatic mechanism(s);

ii) Reduction of both fasting (basal) and postprandial plasma glucose concentrations

5.2 Pharmacokinetic properties

Absorption

Absorption of glipizide is rapid and complete. Peak plasma concentrations occur 1 - 3 hours after a single oral dose and the half-life ranges from 2 - 4. Glipizide does not accumulate in plasma on repeated oral administration. Total absorption of an oral dose is not affected by food but is delayed by about 40 minutes. Glipizide was more effective when administered about 30 minutes before a meal in diabetic patients.

Distribution

Protein binding is 98 - 99 % and volume of distribution is 11 litres, indicative of localization within the extracellular fluid compartment.

Biotransformation

The metabolism of glipizide is extensive and occurs mainly in the liver.

Elimination

The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10 % unchanged glipizide is found in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Maize starch

Stearic acid

Lactose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

6.5 Nature and contents of the pack

Cartons with 100 and 500 blister-packed tablets.

Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27 (0)11) 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

L/21.2/248

9. DATE OF FIRST AUTHORISATION

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