AUSTRALIAN PRODUCT INFORMATION – MINIDIAB (GLIPIZIDE)

1. NAME OF THE MEDICINE

Glipizide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of glipizide.

Excipient(s) with known effect

lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

White, round, biconvex, scored tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MINIDIAB is indicated as an adjunct to diet and exercise for the control of hyperglycaemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory. In initiating treatment for non-insulin-dependent diabetes, diet should be emphasised as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycaemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified, and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose the use of an oral sulphonylurea or insulin should be considered. Use of MINIDIAB must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone also may be transient, thus requiring only short-term administration of MINIDIAB. During maintenance programs, MINIDIAB should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

4.2 Dose and method of administration

Dosage

Generally speaking, the drug should be taken about 30 minutes before meals in order to achieve the greatest reduction in postprandial hyperglycaemia. There is no fixed dosage regimen for

the management of diabetes mellitus with MINIDIAB or any other hypoglycaemic agent. In addition to the usual monitoring of urinary glucose the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient to detect primary failure, i.e. inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e. loss of an adequate blood glucose lowering response after an initial period of effectiveness. Monitoring of glycosylated haemoglobin levels may also be of value.

Initial dose:

The recommended starting dose is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

Dosage titration:

Dosage adjustments should ordinarily be in increments of 2.5 mg – 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 once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

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 ordinarily be divided. Total daily doses above 30 mg have been safely given on a twice daily basis to long-term 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 (see section 4.4 Special precautions and warnings for use).

Patients receiving insulin agents:

As with other sulphonylurea class hypoglycaemics, many stable non-insulin-dependent diabetic patients receiving insulin may be safely placed on MINIDIAB.

Patients receiving other oral hypoglycaemic agents:

As with other sulphonylurea class hypoglycaemics, no transition period is necessary when transferring patients to MINIDIAB. 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 drug effect.

4.3 Contraindications

MINIDIAB is contraindicated in patients with:

- Known hypersensitivity to glipizide or to other sulphonylurea derivatives
- Allergy to sulphonamides
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

- Juvenile, Growth Onset or Brittle Diabetes Mellitus
- Severe renal or hepatic insufficiency
- Severe thyroid dysfunction
- Pregnancy
- Severe or unstable diabetes
- Infections and febrile conditions
- Gangrene
- Severe trauma
- Major surgical procedures.

MINIDIAB is also contraindicated in children.

4.4 Special warnings and precautions for use

General

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. Patients should be informed of the potential risks and advantages of MINIDIAB and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

Glucose-6-phosphate dehydrogenase (G6PD)-deficiency

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

Hypoglycaemia

All sulphonylurea agents are capable of producing severe hypoglycaemia. Proper patient selection, dosage, and instruction are important to avoid hypoglycaemic episodes. 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 glucose-lowering drugs. Hypoglycaemia may be difficult to recognise in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycaemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of control of blood glucose

When a patient stabilised on any 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.

Secondary failure

The effectiveness of any oral hypoglycaemic drug, including 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 due to diminished responsiveness to the drug. The phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

Use in hepatic and renal impairment

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

Use in the elderly

In elderly patients, the initial and maintenance dosing should be conservative to avoid hypoglycaemic reactions

See section 4.4 Special warnings and precautions, Hypoglycaemia and section 4.2 Dose and method of administration.

Paediatric use

Not for use in children (see section 4.3 Contraindications).

Effects on laboratory tests

Blood and urine glucose should be monitored periodically. Measurement of glycosylated haemoglobin and/or fructosamine levels may be useful.

The pattern of laboratory test abnormalities observed with MINIDIAB was similar to that for other sulphonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to MINIDIAB is uncertain, and they have rarely been associated with clinical symptoms.

4.5 Interactions with other medicines and other forms of interactions

The hypoglycaemic action of sulphonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, quinolone antibiotics, and drugs that are highly protein bound, salicylates, sulphonamides, clofibrate, biguanides, diazoxide, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents.

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

***Alcohol*:** Alcohol may increase the hypoglycaemic effect of MINIDIAB, which could lead to hypoglycaemic coma.

***Angiotensin-converting Enzyme Inhibitors*:** The use of angiotensin converting enzyme inhibitors may lead to an increased hypoglycaemic effect in diabetic patients treated with sulphonylureas, including 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 sulphonylureas, including MINIDIAB.

***Voriconazole*:** Although not studied, voriconazole may increase plasma level of sulfonylureas (e.g. tolbutamide, glipizide and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during co-administration.

When such drugs are administered to a patient receiving MINIDIAB, the patient should be observed closely for hypoglycaemia. When such drugs are withdrawn from a patient receiving MINIDIAB, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicated that MINIDIAB binds differently than tolbutamide and does not interact with salicylate or dicoumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of MINIDIAB with these drugs.

Certain drugs tend to produce hyperglycaemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, progestogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, alcohol (chronic abuse), glucagon, and isoniazid. When such drugs are administered to a patient receiving MINIDIAB, the patient should be closely observed for loss of control. When such drugs are administered to (or withdrawn from) a patient receiving MINIDIAB, the patient should be observed closely for hypoglycaemia.

A potential interaction between oral miconazole and oral hypoglycaemic agents leading to severe hypoglycaemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

The risk of increase of effect of barbiturates is extremely low for pharmacokinetic reasons (non-ionic protein binding).

Tetracycline may interfere with determination of urine glucose. Cyclophosphamide and derivatives should also be used with care in diabetic patients since increased and decreased effects of sulphonylureas have been reported.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category C

MINIDIAB (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5 – 50 mg/kg). The fetotoxicity has been similarly noted with other sulphonylureas,

such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycaemic) action of MINIDIAB. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women.

Sulphonylureas are not suitable for the treatment of diabetes mellitus during pregnancy as significant metabolic changes occur during this period, which make control difficult.

Use in lactation

Although it is not known whether MINIDIAB is excreted in human milk, some sulphonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycaemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

4.7 Effects on ability to drive and use machines

The treatment of diabetes with MINIDIAB requires regular check-ups. Until optimum stabilisation has been achieved, for example during the change-over from other medications or during irregular use, the ability to drive and use machines may be impaired.

4.8 Adverse effects (undesirable effects)

In controlled studies, the frequency of serious adverse reactions reported was low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was MINIDIAB discontinued.

Hypoglycaemia: See section 4.4 Special warnings and precautions for use and section 4.8 Overdose.

Gastrointestinal: Gastrointestinal disturbances are the most common reactions. Gastrointestinal complaints were reported with the following approximate incidence: nausea and diarrhoea, (1.4%); constipation and gastralgia, (1%), vomiting (>1%). They appear to be dose-related and may disappear on division or reduction of dosage. Abdominal pain has also been reported. Cholestatic jaundice may occur rarely with sulphonylureas; MINIDIAB should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including rash, erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in seventy patients. These may be transient and may disappear despite continued use of MINIDIAB; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulphonylureas.

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulphonylureas. In the mouse, MINIDIAB pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that MINIDIAB has an extremely low incidence of disulfiram-like alcohol reactions.

Haematologic: Leucopoenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, and pancytopenia have been reported with sulphonylureas.

Endocrine reaction: Cases of hyponatraemia, and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulphonylureas.

Miscellaneous: Dizziness, drowsiness, vertigo and headache have each been reported in about one in fifty patients treated with MINIDIAB. Confusion, tremor and malaise have also been reported. They are usually transient and seldom require discontinuance of therapy. These symptoms together with weakness, clouding of vision etc. may be signs of hypoglycaemia. However, the risk of severe or prolonged hypoglycaemia is low.

Eye Disorders: Visual disturbances such as blurred vision, diplopia, and abnormal vision including visual impairment and decreased vision, have each been reported in patients treated with MINIDIAB. They are usually transient and do not require discontinuance of therapy. However, they may also be symptoms of hypoglycaemia.

Hepatobiliary Disorders: Impaired hepatic function and hepatitis have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

There is no well documented experience with MINIDIAB overdosage. Overdosage of sulphonylureas, including MINIDIAB can produce hypoglycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician 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.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 5.55 mmol/L. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycaemia may recur after apparent clinical recovery.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal may reduce absorption of the medicine if given within one hour after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Clearance of MINIDIAB from plasma would be prolonged in people with liver disease. Because of the extensive protein binding of MINIDIAB, dialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

MINIDIAB is a sulphonylurea hypoglycaemic agent. The primary mode of action of MINIDIAB in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans MINIDIAB appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which MINIDIAB lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by MINIDIAB in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term MINIDIAB administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of MINIDIAB in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulphonylurea hypoglycaemic drugs. Some patients fail to respond initially, or gradually lose their responsiveness to sulphonylureas, including MINIDIAB. Alternatively, MINIDIAB may be effective in some patients who have not responded, or have ceased to respond to other sulphonylureas.

Duration of Action:

Clinical studies show that blood sugar control persists in some patients for up to 24 hours after a single dose of MINIDIAB, even though plasma levels have declined to a small fraction of peak levels by that time.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Gastrointestinal absorption of MINIDIAB in humans is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1 to 3 hours after a single oral dose. The half-life of elimination ranges from 2 to 4 hours in normal subjects, whether given intravenously or orally. Total absorption and disposition of an oral dose were unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus MINIDIAB was more effective when administered about 30 minutes before, rather than with a test meal in diabetic patients.

Distribution

Protein binding was studied in serum from volunteers who received either oral or intravenous MINIDIAB and found to be 92 to 99% one hour after either route of administration. The apparent volume of distribution of MINIDIAB after intravenous administration was 5-11 L, indicative of localisation within the extracellular fluid compartment. In mice neither

MINIDIAB nor metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given the labelled drug.

Metabolism and Excretion

The metabolism of MINIDIAB is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 3.0-4.3% unchanged MINIDIAB is found in the urine. The metabolic and excretory patterns are similar with both oral and IV routes of administration, indicating that first-pass metabolism is not significant. MINIDIAB does not accumulate in plasma on repeated oral administration.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

cellulose,
maize starch,
stearic acid
lactose monohydrate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

The tablets are blister packed and available in pack size of 100 tablets.

6.6 Special precautions for disposal

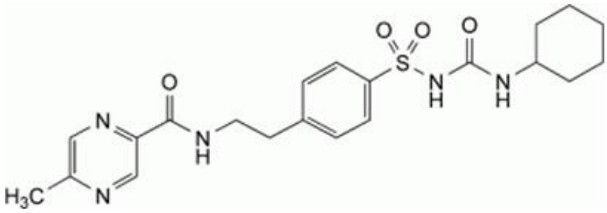
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Glipizide is a whitish, odourless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 N NaOH; it is freely soluble in dimethylformamide.

MINIDIAB (glipizide) is an oral blood-glucose lowering drug of the sulphonylurea class. The chemical name of glipizide is 1-cyclohexyl-3-{4-[2-(5-methylpyrazine-2-carboxamido)ethyl]-benzene-sulphonyl} urea. The molecular formula is $C_{21}H_{27}N_5O_4S$, molecular weight is 445.5, and the structural formula is shown below:

Chemical structure



CAS number

29094-61-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

23 September 1991

10. DATE OF REVISION

20 April 2020

Summary Table of Changes

Section changed	Summary of new information
4.2, 4.4, 4.5, 4.6, 4.9, 5.1, 5.2.	Minor editorial/typographical updates to text.