

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Minidiab 5 mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains glipizide 5 mg

Excipient(s) with known effect

- Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Minidiab is presented as white, biconvex, 8 mm round scored tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Minidiab is an orally active hypoglycaemic sulphonylurea and is indicated as an adjunct to diet and exercise in the treatment of stable, mild to moderate, non-insulin dependent diabetes mellitus (type II diabetes mellitus or NIDDM) without likelihood of ketosis, which cannot be adequately controlled by diet alone. Treatment with Minidiab is indicated only if a satisfactory reduction in blood sugar has not been achieved by other measures, e.g. conscientious adherence to the recommended diet, weight reduction in overweight patients, and adequate exercise. In certain patients receiving insulin, the concurrent use of Minidiab allows a reduction in the daily dose of insulin.

4.2 Dose and method of administration

Dose

The usual dose range of Minidiab is 2.5-30 mg daily but if control is not achieved within this range then it may be increased to a total maximum daily dose of 40 mg, although the additional proportion of patients responding to this higher dosage may not be large.

Patients previously untreated: The initial dose is 2.5-5 mg daily. Doses of 2.5 mg daily should be taken as a single dose before breakfast or the midday meal. Doses of 5 mg daily may be taken as a single dose before breakfast or the midday meal, or as two doses; one in the morning and one in the evening before meals.

Patients changing from other oral antidiabetics: The recommended starting dose is 5 mg daily taken as a single dose or in two divided doses.

Dosage adjustments in all patients, either upwards or downwards, should be in 2.5-5 mg steps at weekly intervals until good control is achieved. The maximum recommended single dose is 15 mg. Doses above 15 mg should ordinarily be taken in two divided doses before meals.

Multiple divided doses (2 or 3 daily) are recommended for patients who experience particularly high post-prandial blood glucose peaks.

Concomitant food intake may delay absorption and administration should therefore be 15-20 minutes before a main meal: therapeutic effects are usually seen within 30 minutes and peak at about 60 minutes. Glipizide is rapidly metabolised and excreted mainly in the urine and therefore it is unlikely that delayed hypoglycaemic episodes will occur.

A biguanide may be added to treatment if control is not achieved with Minidiab.

Paediatric Population

Safety and effectiveness in children have not been established.

Use in Elderly and High Risk Patients

In elderly, debilitated or malnourished patients or patients with an impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycaemic reactions (see sections 4.2 and 4.4).

Patients Receiving Other Oral Hypoglycaemic Agents

As with other sulfonylurea class hypoglycaemic, no transition period is necessary when transferring patients to glipizide. Patients should be observed carefully (1-2 weeks) for hypoglycaemia when being transferred from longer half-life sulfonylureas (e.g. chlorpropamide) to glipizide due to potential overlapping of drug effect.

4.3 Contraindications

Glipizide is contraindicated in patients with:

Hypersensitivity to glipizide, other sulfonylureas or sulphonamides, or any excipients in the tablets;

Insulin-dependent diabetes, diabetic ketoacidosis, diabetic coma;

Severe renal or hepatic insufficiency;

Pregnancy and lactation.

4.4 Special warnings and precautions for use

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 sulfonylurea agents are capable of producing severe hypoglycaemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycaemic episodes. Regular, timely carbohydrate intake is important to avoid hypoglycaemic events occurring when a meal is delayed or insufficient food is eaten or carbohydrate intake is unbalanced. Renal or hepatic insufficiency may cause elevated blood levels of glipizide 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 (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 drug is used.

Loss of Control of Blood Glucose

When a patient stabilized 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 glipizide and administer insulin.

The effectiveness of any oral hypoglycaemic drug, including glipizide, 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. This 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. 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 glipizide 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.

Information for Patients

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

The risk 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.

Laboratory Tests

Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

4.5 Interaction with other medicines and other forms of interaction

The following products are likely to increase the hypoglycaemic effect:

Inadvisable Combinations

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

Nonsteroidal Anti-inflammatory Drugs: Increase in hypoglycaemic effect of sulfonylureas (displacement of sulfonylurea binding to plasma proteins and/or decrease in sulfonylurea elimination).

Alcohol: Increase in hypoglycaemic reaction which can lead to hypoglycaemic coma.

Combinations Requiring Precautions

Fluconazole: Increase in the half-life of the sulfonylurea, possibly giving rise to symptoms of hypoglycaemia.

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.

Salicylates (acetylsalicylic acid): Increase in hypoglycaemic effect by high doses of acetylsalicylic acid (hypoglycaemic action of the 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 sulfonylureas.

H₂ Receptor Antagonists: The use of H₂ receptor antagonists (i.e. cimetidine) may potentiate the hypoglycaemic effects of sulphonylureas, including glipizide.

The hypoglycaemic action of sulfonylureas, in general, may also be potentiated by monoamine oxidase inhibitors, quinolones, and drugs that are highly protein bound, such as sulfonamides, chloramphenicol, probenecid, coumarins and fibrates.

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

In vitro binding studies with human serum proteins indicate that glipizide 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 glipizide with these drugs.

The following products could lead to hyperglycaemia:

Inadvisable Combinations

Danazol : Diabetogenic effect of danazol. If it cannot be avoided, warn the patient and step up self monitoring of blood glucose and urine. Possibly adjust the dosage of antidiabetic agent during treatment with danazol and after its discontinuation.

Combinations Requiring Precautions

Phenothiazines (e.g. chlorpromazine at greater than 100 mg per day): Elevation in blood glucose (reduction in insulin release).

Corticosteroids: Elevation in blood glucose.

Sympathomimetics (e.g. 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 agent during treatment with the neuroleptics corticoids or progestogen and after discontinuation.

Other drugs that may produce hyperglycaemia and lead to a loss of control include the thiazides and other diuretics, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, calcium channel blocking drugs and isoniazid.

When such drugs are administered to (or withdrawn from) a patient receiving glipizide, the patient should be observed closely for hyperglycaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy - Category C

Preclinical reproductive toxicity study in rabbits revealed no teratogenic effects, but glipizide was found to be mildly fetotoxic in rats at doses of 5-50 mg/kg during the perinatal period, probably due to the hypoglycaemic activity of the drug. Sulphonylureas are not suitable for the treatment of diabetes mellitus during pregnancy as significant metabolic changes occur during this period, which may make control difficult.

Breast-feeding

There is no data on the excretion of glipizide in human milk; however, it is known that some sulphonylureas pass into mother's milk. It is therefore recommended that Minidiab should not be administered to mothers who wish to breast feed.

Fertility

No data available.

4.7 Effects on ability to drive and use machinery

The effect of glipizide on the ability to drive or operate machinery has not been studied. However, there is no evidence to suggest that glipizide may affect these abilities. Patients should be aware of the symptoms of hypoglycaemia and be careful about driving and the use of machinery, especially when optimum stabilization has not been achieved, for example during the changeover from other medications or during, irregular use.

4.8 Undesirable effects

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

Hypoglycaemia

See sections 4.4 and 4.9.

Gastrointestinal

Gastrointestinal complaints include nausea, diarrhoea, constipation and gastralgia. They appear to be dose related and usually disappear on division or reduction of dosage. Abdominal pain and vomiting have also been reported.

Dermatologic

Allergic skin reactions including erythema, morbilliform or maculopapular reactions, urticaria, pruritus and eczema have been reported. They frequently disappear with continued therapy. However if they persist, the drug should be discontinued. With other sulfonylureas, photosensitivity reactions have been reported.

Miscellaneous

Confusion, dizziness, drowsiness, headache, tremor, malaise and visual disturbances such as blurred vision, diplopia, and abnormal vision including visual impairment and decreased vision have each been reported in patients treated with glipizide. They are usually transient and do not require discontinuance of therapy; however, they may also be symptoms of hypoglycaemia.

Laboratory Test

The pattern of laboratory test abnormalities observed with glipizide is similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphates. BUN and creatinine were noted. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

Hepatic Disorders

Cholestatic jaundice, impaired hepatic function and hepatitis have been reported. Discontinue treatment if cholestatic jaundice occurs.

Haematological Reactions

Leukopenia, agranulocytosis, thrombocytopenia, haemolytic anaemia, aplastic anaemia and pancytopenia have been reported.

Metabolic Reactions

Hepatic porphyria and porphyria cutanea tarda have been reported. Disulfiram-like reactions have been reported very rarely.

Endocrine Reactions

Hyponatraemia has been reported.

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. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

There is no well documented experience with glipizide overdose.

Overdosage of sulfonylureas, including glipizide can produce hypoglycaemia. Mild hypoglycaemic symptoms without loss of consciousness or neurologic findings should be treated actively 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glipizide is an orally active sulphonylurea having hypoglycaemic action. The hypoglycaemic activity of glipizide is due to its ability to stimulate release of insulin by pancreatic β -cells. It has also been postulated that glipizide potentiates the effect of insulin by increasing the number of insulin receptors, decreasing insulin uptake by peripheral tissues, reducing hepatic glycogenolysis and facilitating the uptake and metabolism of glucose by muscle.

Glipizide has no effect on heart rate, blood pressure, electrocardiogram results, respiration or autonomic function in animal studies, and no pharmacological actions on the cardiovascular respiratory or nervous system have been seen in human studies.

Glipizide could have a beneficial effect on the progress of diabetic microangiopathy. This is based on the clinical evidence of a decrease in the thickness of the muscle capillary basement membrane which is considered to be a sensitive marker of diabetic microangiopathy.

It is believed that there is an increased platelet aggregation and adhesiveness in diabetes, which may also contribute to diabetic angiopathy.

A reduction of platelet aggregation by glipizide was confirmed *in vitro* in normal healthy human platelets, and in 88 patients with diabetes, although only a subgroup in whom the disease had a duration of less than 6 years.

5.2 Pharmacokinetic properties

After oral administration to patients with NIDDM, glipizide is rapidly absorbed with a time to maximum plasma level of about 2 hours.

The volume of distribution at steady state in diabetic patients, after oral administration of 5 mg glipizide was about 11 L.

At pharmacological concentrations, glipizide binds extensively to human plasma (98% to 99% protein binding). The characteristics of the binding indicate non-ionic interactions. Glipizide binding is similar to that of glibenclamide, and therefore it can be predicted that glipizide, like glibenclamide, would be only weakly displaced by anionic drugs such as phenylbutazone, warfarin and salicylates.

The half-life following oral dosing is between 2 and 4 hours.

Glipizide is metabolised primarily by the liver to at least 5 metabolites with first pass metabolism accounting for about 5% of the dose. Between 72% and 85% of the drug present in the plasma is unaltered and the rest exists as metabolites.

Within 24 hours post administration, 65% to 68% of the dose is excreted in the urine and of this, less than 5% is unaltered. Approximately 15% of unaltered drug is eliminated via the faeces, the kidneys playing little or no role in the excretion of the parent compound.

No clinically relevant differences have been found in the pharmacokinetics of glipizide in elderly patients. Many studies in healthy volunteers and patients have shown that glipizide is more effective in reducing fasting blood glucose and post-prandial blood glucose when given 30 minutes before meals.

Ingestion with food leads to a 30-60 minutes delay in absorption and a reduction in absorption, as shown by the AUC and C_{max}, resulting in a reduced efficacy in lowering blood glucose in diabetic patients even though food stimulated insulin secretion is not significantly altered.

There is no significant difference in efficacy when glipizide is given as a single dose or divided into two or three doses over the day although mean blood glucose levels over a 12 hour period were slightly lower after the single dose.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Maize starch,
Microcrystalline cellulose,
Stearic acid.

6.2 Incompatibilities

No data available.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

30, 90, 100 tablets aluminium/PVC blister pack.

Not all presentations are available

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

28 November 1985

10. DATE OF REVISION OF THE TEXT

28 May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance