# NEW ZEALAND DATA SHEET

# GLIZIDE

## 1. Product Name

GLIZIDE, 80 mg tablets.

## 2. Qualitative and Quantitative Composition

Each GLIZIDE tablet contains 80 mg gliclazide.

Excipient with known effect:
Each GLIZIDE tablet contains 110 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

GLIZIDE 80 mg tablets are white to off white, circular, flat, beveled edged, uncoated tablets with a breakline on one side and “80” on the reverse.

The tablet can be divided into equal doses.

## 4. Clinical Particulars

### *4.1 Therapeutic indications*

Diabetes mellitus of the maturity onset type, which cannot be controlled by diet alone.

### *4.2 Dose and method of administration*

The dosage of gliclazide should be carefully titrated to maintain optimal control at the various possible dose levels. Dosage should be initiated at 40 mg (1/2 tablet) daily and may be increased if necessary up to 320 mg (4 tablets) daily. Doses up to 160 mg daily may be taken in a single dose but preferably at the same time each morning. Doses in excess of 160 mg should be taken in divided doses in the morning and evening.

The dosage will depend on the severity of the glycaemia with ongoing adjustments made in order to obtain the optimal response at the lowest dosage.

Treatment with gliclazide does not obviate the necessity of maintaining standard dietary requirements.

### *4.3 Contraindications*

This medication is contraindicated in the following cases:

- Hypersensitivity to gliclazide, other sulfonylureas, sulfonamides, or to any of the excipients listed in section 6.1
- Type I diabetes, diabetic keto-acidosis, diabetic pre-coma and coma
- Severe renal or hepatic impairment: in these cases the use of insulin is recommended

- Treatment with miconazole (see section 4.5)
- Pregnancy and lactation (see section 4.6)

It is generally not recommended to use this agent in combination with phenylbutazone or danazol (see section 4.5).

## *4.4 Special warnings and precautions for use*

### Monitoring of diabetic state

As with other antidiabetic therapies, patients must be under close medical supervision. Particular care must be taken during the initial period of stabilisation. Patients treated with gliclazide should be monitored regularly to ensure optimal control of the diabetic state, and where necessary, for adjustment of dosage.

### Transferring to gliclazide

Patients who have been previously treated with sulfonylureas or biguanides alone or in combination may be transferred to gliclazide. When gliclazide is administered as sole therapy to patients who have previously required combination therapy (e.g. biguanides and sulfonylureas), careful observation is essential during the transitional phase.

It is not generally recommended that insulin treated patients be transferred to gliclazide.

### Patient awareness

Comprehensive instructions must be given to the patient about the nature of the disease and what must be done to detect and prevent complications.

### Acute complications such as severe trauma, fever, infection or surgery

These acute complications provoke additional metabolic stress which accentuates the predisposition to hyperglycaemia and ketosis. Patients presenting with such conditions may require insulin to maintain control. It is not appropriate to increase the dosage of gliclazide.

### Hypoglycaemia

The risks of hypoglycaemia, together with its symptoms, 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.

Hypoglycaemia may occur following administration of sulfonylureas. Rarely cases may be severe and prolonged. This may involve hospitalisation and glucose infusion may need to be continued for several days.

Careful selection of patients and of the dose used, as well as provision of adequate information to the patient are necessary to avoid hypoglycaemic episodes.

The following factors may increase the risk of hypoglycaemia:

- patient does not follow the doctor's treatment advice (particularly elderly patients);
- malnutrition;
- irregular mealtimes, skipping meals, periods of fasting or dietary changes;
- imbalance between physical exercise and carbohydrate intake;
- renal impairment;
- severe hepatic impairment;
- overdose of anti-diabetic agents;
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal impairment, concomitant administration of certain other medicines (see section 4.5).

Gliclazide should only be prescribed 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 delayed, an inadequate amount of food is consumed or the food is low in carbohydrate. Therefore, it is recommended to take GLIZIDE with food at breakfast time. Hypoglycaemia is more likely to occur during periods of low-calorie diet, following prolonged or strenuous exercise, following alcohol intake or during treatment with a combination of hypoglycaemic agents.

If a dose is forgotten, the dose taken on the next day should not be increased.

### Poor blood glucose control

Blood glucose control in treated patients may be affected by St. John's Wort (Hypericum perforatum) preparations (see section 4.5), fever, trauma, infection or surgical intervention. It may be necessary to discontinue treatment and to administer insulin in these cases.

The efficacy of oral antidiabetic agents often decreases in the long term. This may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure and should be distinguished from primary failure, when the drug is ineffective as first-line treatment. However, before classifying the patient as a secondary failure, dose adjustment and reinforcement of dietary measures should be considered.

### Unstable blood glucose level (dysglycaemia)

Disturbances in blood glucose, including hypoglycaemia and hyperglycaemia have been reported, in diabetic patients receiving concomitant treatment with fluoroquinolones, especially in elderly patients. Indeed, careful monitoring of blood glucose is recommended in all patients receiving gliclazide and a fluoroquinolone at the same time.

### Renal and hepatic impairment

Severe renal or hepatic impairment may affect the distribution of gliclazide and hepatic impairment may also reduce the capacity for neoglucogenesis. These two effects increase the risk of severe hypoglycaemic reactions. A hypoglycaemic episode in these patients may be prolonged and appropriate management should be initiated.

### Glucose-6-phosphate dehydrogenase deficiency (G6PD)

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

### Effects on laboratory tests

Glycated haemoglobin should be monitored regularly. Blood glucose measurement may also be useful.

### Lactose intolerance

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

### Patients with porphyria

Cases of acute porphyria have been described with the class of sulfonylurea drugs, in patients who have porphyria.

### Paediatric use

Not recommended for paediatric use.

## *4.5 Interaction with other medicines and other forms of interaction*

Blood glucose monitoring during and after treatment is necessary when GLIZIDE is used with medicines which can interact with gliclazide. It may also be necessary to adjust the dose of GLIZIDE during and after treatment with such medicines.

### Medications likely to increase the risk of hypoglycaemia

***Concomitant use which is contraindicated***

*Miconazole (systemic route, oromucosal gel)*
Increases the hypoglycaemic effect with possible onset of hypoglycaemia symptoms, or even coma.

***Concomitant use which is not recommended***

*Phenylbutazone (systemic route)*
Increases the hypoglycaemic effect of sulfonylureas (displaces their binding to plasma proteins and/or reduces their elimination).

It is preferable to use a different anti-inflammatory agent, 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 agent.

*Alcohol*
Acute alcohol intoxication potentiates the hypoglycaemic action of all sulfonylurea agents by inhibiting compensatory reactions. This can lead to the onset of hypoglycaemic coma. Ingestion of alcohol may cause a disulfiram-like reaction with characteristic flushing of the face, throbbing headache, giddiness, tachypnoea, tachycardia or angina pectoris.

Chronic alcohol abuse may, as a result of liver enzyme induction, increase the metabolism of sulfonylurea drugs, shortening the plasma half-life and duration of action.

Avoid alcohol or medicines containing alcohol.

***Concomitant use which requires special care***

*Potentiation of the blood glucose lowering effect and therefore in some instances, hypoglycaemia may occur when one of the following medications is taken*
Other antidiabetic agents (insulins, acarbose, biguanides, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), sulfonamides, clarithromycin, clofibrate, salicylates (high doses), chloramphenicol, MAOIs, β-blockers, $H_2$-receptor antagonists, ACE inhibitors, fluconazole and nonsteroidal anti-inflammatory agents.

### Medications which may cause an increase in blood glucose levels

Advise the patient and emphasise the importance of glucose monitoring.

***Concomitant use which is not recommended***

*Danazol*
If the use of danazol cannot be avoided, it may be necessary to adjust the dose of GLIZIDE during and after treatment with danazol.

***Concomitant use which requires special care***

*Chlorpromazine*
High doses (> 100 mg per day of chlorpromazine) can increase blood glucose levels (reduced insulin release).

Advise the patient and emphasise the importance of glucose monitoring. It may be necessary to adjust the dose of GLIZIDE during and after treatment with chlorpromazine.

*Glucocorticoids (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin*
Concomitant use may increase blood glucose levels with possible ketosis (glucocorticoids cause reduced tolerance to carbohydrates). Emphasise the importance of blood glucose monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of GLIZIDE during and after treatment with glucocorticoids.

*Salbutamol, terbutaline (intravenous)*
May cause increased blood glucose levels due to beta-2 agonist effects. If necessary, switch to insulin.

*Barbiturates, oestrogens and progestogens*
May adversely affect blood sugar control with hypoglycaemic agents in some patients by causing increased blood glucose levels.

*St John's Wort (Hypericum perforatum) preparations*
Gliclazide exposure is decreased by St John's Wort (Hypericum perforatum).

### Products which may cause unstable blood glucose

#### *Concomitant use which requires special care*

*Fluoroquinolones*
In case of a concomitant use of gliclazide and a fluoroquinolone, the patient should be warned of the risk of unstable blood glucose, and the importance of blood glucose monitoring should be emphasised.

#### *Concomitant use to be taken into consideration*

*Anticoagulant therapy (Warfarin)*
Sulfonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of warfarin may be necessary.

## *4.6 Fertility, pregnancy and lactation*

### Pregnancy

In animal studies embryo-toxicity and/or birth defects have been demonstrated with some sulfonylureas.

Gliclazide should not be used in pregnant women. Animal studies of gliclazide have not shown any teratogenic effect. From a clinical point of view, there are limited data (less than 300 pregnancies) to allow evaluation of the possible malformative or foetotoxic effects of gliclazide, when administered during pregnancy.

GLIZIDE is contraindicated during pregnancy and insulin is the medication of first choice for treatment of diabetes during pregnancy. Treatment should be changed from GLIZIDE to insulin therapy before pregnancy is attempted, or as soon as pregnancy is discovered. Control of diabetes should be achieved before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.

### Breast-feeding

It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, GLIZIDE is contraindicated in women who are breast feeding. A risk to newborns/infants cannot be excluded.

### Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

## *4.7 Effects on ability to drive and use machines*

Patients should be made aware of the symptoms of hypoglycaemia and should be careful if driving or operating machinery, especially at the beginning of treatment.

## *4.8 Undesirable effects*

Adverse reactions have occurred in some 12% of cases in clinical studies. However, approximately 2% of patients were withdrawn from therapy because of adverse reactions, notably hypoglycaemia, gastrointestinal disturbances (constipation, nausea, epigastric discomfort and heartburn), dermatological reactions (rash and transient itching), and biochemical abnormalities (elevated serum creatinine, increased serum alkaline phosphatase, raised serum AST, elevated BUN and raised serum bilirubin). Headache, slight disulfiram like reactions and lassitude have also been reported.

Serious reactions which have been reported with other sulfonylureas are leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, cholestatic jaundice and gastrointestinal haemorrhage. These reactions have not been reported with gliclazide.

### Hypoglycaemia (see sections 4.3, 4.4 and 4.9)

The most frequent adverse reaction with gliclazide is hypoglycaemia.

As is the case with all sulfonylurea drugs, hypoglycaemic reactions have been reported following gliclazide administration. However, a number of studies have shown that hypoglycaemia is less common with gliclazide than with glibenclamide.

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/or death.

In addition, signs of adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

Usually, symptoms disappear after intake of carbohydrate such as sugar (artificial sweeteners have no effect). Experience with other sulfonylureas shows that hypoglycaemia can recur even when these measures are initially effective. 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 is required.

Severe hypoglycaemia, though very rarely reported, may occur in patients receiving gliclazide.

### Other adverse effects reported with gliclazide

Gastrointestinal disturbances (reported with gliclazide), including nausea, dyspepsia, diarrhoea, abdominal pain, vomiting, and constipation may be avoided or minimised if gliclazide is taken with breakfast.

The following adverse effects have been rarely reported:

***Skin and subcutaneous tissue disorders***
Pruritus, urticaria, maculopapular rashes, rash, angioedema, erythema and bullous reactions (such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) (as with other sulfur-containing medications) and autoimmune bullous disorders and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS).

***Blood and lymphatic system disorders (as with other sulfonylurea medications)***
Anaemia, leucopenia, thrombocytopenia and agranulocytosis. These are in general reversible upon discontinuation of medication.

***Hepatobiliary disorders***
Elevations of serum bilirubin and hepatic enzymes (AST, ALT, alkaline phosphatase) levels, and exceptionally, hepatitis (isolated reports). Treatment should be discontinued if cholestatic jaundice appears. These symptoms usually disappear after discontinuation of treatment.

***Investigations***
Occasional elevations of serum creatinine, blood urea nitrogen.

***Eye disorders***
Transient visual disturbances may occur due to changes in blood glucose levels, particularly on initiation of treatment. As with any glucose-lowering medication, transient visual disturbances may occur on initiation of treatment due to changes in blood glucose levels.

### Class effects

***The following adverse events have been observed with sulfonylureas***
Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, hyponatremia, elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases.

### 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*

Overdose of sulfonylureas may cause hypoglycaemia.

Moderate symptoms of hypoglycaemia (without loss of consciousness or neurological signs), should be corrected by carbohydrate intake, dose adjustment and/or modification of diet. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

Severe hypoglycaemic reactions are possible (with coma, convulsions or other neurological disorders) and should be treated as a medical emergency, requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of 50 mL of concentrated glucose solution (20 to 30%). This should be followed by continuous infusion of a more dilute glucose solution (10%) at a rate necessary to maintain blood glucose levels above 5 mmol/L. It is recommended that patients should be monitored closely for a 48 hour period at least.

Plasma clearance of gliclazide may be prolonged in patients with hepatic disease. However, due to the strong binding of gliclazide to proteins, dialysis is not effective in these patients.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group:sulphonamides, urea derivatives

ATC code: A10BB09

### Mechanism of action

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. Gliclazide shows high affinity, strong selectivity and reversible binding to the β-cell $K_{ATP}$ channels with a low affinity for cardiac and vascular $K_{ATP}$ channels. Increased postprandial insulin and C-peptide secretion persists after two years of treatment.

In type II diabetes, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin release is seen in response to stimulation induced by a meal or glucose.

Gliclazide also has extra-pancreatic effects and haemovascular properties.

It has been shown to increase peripheral insulin sensitivity:

- In muscle, euglycaemic hyperinsulinaemic clamp studies with gliclazide have demonstrated significantly increased (35%) insulin mediated glucose uptake which may improve diabetes control. Gliclazide potentiates insulin action on muscle glycogen synthase. These effects are consistent with a post-transcriptional action of gliclazide on GLUT4 glucose transporters.
- Studies on glucose turnover have further shown that gliclazide decreases hepatic glucose production, leading to an improvement in fasting blood glucose levels.

Gliclazide has been shown in some studies to have actions independent of that on glucose levels. These haemovascular effects of gliclazide include:

- Partial inhibition of platelet aggregation and adhesion with a decrease in markers of platelet activation (beta thromboglobulin, thromboxane B2).
- Increased vascular endothelial fibrinolytic activity (increased tPA activity).
- Anti-oxidant properties, notably a reduction in plasma lipid peroxides and increased erythrocyte superoxide dismutase activity.
- Inhibition of the increased adhesiveness of type II diabetic patient's monocytes to endothelial cells *in vitro*.

The anti-oxidant, platelet inhibiting and fibrinolytic actions of gliclazide involve processes which have been implicated in the pathogenesis of vascular complications of type II diabetes. There is no clinical evidence that the haemovascular effects of gliclazide are of therapeutic benefit in type II diabetes patients.

## *5.2 Pharmacokinetic properties*

### Absorption

Gliclazide is absorbed in the gastrointestinal tract reaching peak serum concentrations within 4 to 6 hours.

Single dose studies have demonstrated that maximal falls in blood glucose levels (23% of an 80 mg dose; 30% of a 160 mg dose) occur approximately five hours after drug administration; nine hours after a dose of 160 mg, a reduction of 20% was still in evidence.

The half-life of gliclazide is approximately 12 hours.

### Distribution

Gliclazide is distributed to the extracellular fluid. In animals, high concentrations of the drug were found in the liver, kidneys, skin, lungs, skeletal muscle, intestinal and cardiac tissue. Penetration of gliclazide into the central nervous system was negligible. Gliclazide crosses the placental barrier and penetrates the foetus. The apparent volume of distribution of gliclazide (20 to 40% expressed as a percentage bodyweight) is low and probably reflects the high degree of protein binding (94.2% at a plasma concentration of approximately 8 micrograms/mL).

### Biotransformation

Little information is available in the metabolism of gliclazide. At least eight metabolites (three major) have been identified by thin layer and gas-liquid chromatography. Some of these are glucuronic acid conjugates; only one of the metabolites has been identified (ρ-toluene sulfonamide). The liver is the probable site of metabolism.

### Elimination

Approximately 70% of the administered dose appears to be excreted in the urine and 11% in the faeces. The urinary excretion of the drug is slow and the maximum rates do not occur until 7 to 10 hours after initial administration. The metabolic products are detectable in the urine 120 hours after oral administration. Faecal elimination is usually complete within 144 hours of oral administration.

# 6. Pharmaceutical Particulars

## *6.1 List of excipients*

- Lactose monohydrate
- Microcrystalline cellulose
- Povidone (PVPK 30)
- Croscarmellose sodium
- Purified talc
- Magnesium stearate

GLIZIDE is gluten free.

## *6.2 Incompatibilities*

Not applicable.

## *6.3 Shelf life*

3 years

## *6.4 Special precautions for storage*

Store below 25°C.

## *6.5 Nature and contents of container*

PVC/PVDC/Al blister packs of 20, 60 or 100 tablets.

HDPE bottle with PP cap of 100, 250 or 500 tablets.

Not all pack types and sizes may be marketed.

## *6.6 Special precautions for disposal*

No special requirements.

# 7. Medicines Schedule

Prescription Medicine

# 8. Sponsor Details

Mylan New Zealand Ltd
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Ellerslie
AUCKLAND
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# 9. Date of First Approval

02 November 2006

# 10. Date of Revision of the Text

14 October 2019

**Summary table of changes**

| Section | Summary of new information |
|---|---|
| - | Editorial changes |
| 4.4 | Addition of porphyria and paediatric use |
| 4.8 | Addition of autoimmune bullous disorders |