

AUSTRALIAN PRODUCT INFORMATION GLYADE® TABLET, FILM COATED

1 NAME OF THE MEDICINE

Gliclazide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each GLYADE tablet contains 80 mg of gliclazide.

Gliclazide is an oral hypoglycaemic sulphonylurea which differs from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.

Excipient with known effect: each tablet contains 45 mg of lactose monohydrate.

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

3 PHARMACEUTICAL FORM

Film-coated tablet: white, round, cross-scored on one side.

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

For adult use only.

GLYADE should be taken with food because there is increased risk of hypoglycemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. It is recommended that the medication be taken at breakfast time. If a dose is forgotten, the dose taken on the next day should not be increased.

The daily dose may vary from 40 to 320 mg taken orally. The initial recommended dose is 40 mg (half tablet) daily, even in elderly patients (≥ 65 years) and may be increased if necessary up to 320 mg (four 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.

In general, 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 regulations.

4.3 CONTRAINDICATIONS

This medication is contra-indicated in the following cases:

- hypersensitivity to gliclazide, other sulphonylureas, sulfonamides, or to any of the excipients.
- 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 - *Interactions with other medicines and other forms of interactions*)
- pregnancy and lactation (see section 4.6 - *Fertility, pregnancy and lactation*).

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 sulphonylureas 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 sulphonylureas), 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 accentuate 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 sulphonylureas. 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 - Interactions with other medicines and other forms of interactions*).

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. 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.

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 - Interactions with other medicines and other forms of interactions*), 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 sulphonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the chemical class of sulphonylurea drugs, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

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.

Use in elderly

See *sections 4.2 - Dose and method of administration and 5.2 - Pharmacokinetic properties.*

Paediatric use

Not recommended for paediatric use, see *section 4.2 - Dose and method of administration.*

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

1) The following medications are 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 sulphonylureas (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 sulphonylurea agents by inhibiting compensatory reactions. This can lead to the onset of hypoglycaemic coma. Ingestion of alcohol may also 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 sulphonylurea drugs, shortening the plasma half life and duration of action.

Avoid alcohol or medicines containing alcohol.

Concomitant use which requires special care:

Potential 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, H₂-receptor antagonists, ACE inhibitors, fluconazole and nonsteroidal anti-inflammatory agents.

2) The following medications 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 GLYADE 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 GLYADE 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 GLYADE 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*).

3) The following products 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)

Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of warfarin may be necessary.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Australian Pregnancy Categorisation (Category C).

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

Gliclazide should not be used in pregnant women. 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. Animal studies of gliclazide have not shown any teratogenic effect.

GLYADE is contra-indicated during pregnancy and insulin is the drug of first choice for treatment of diabetes during pregnancy. Treatment should be changed from GLYADE 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.

Use in lactation

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

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

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 sulphonylureas 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 - Contraindications and 4.4 - Special warnings and precautions for use)

The most frequent adverse reaction with gliclazide is hypoglycaemia.

As is the case with all sulphonylurea 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 sulphonylureas 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 sulphonylurea 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 sulphonylureas: 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 sulphonylurea or led to life-threatening liver failure in isolated cases.

4.9 OVERDOSE

Advice on overdose management can be obtained from the national Poisons Information Centre by telephoning 131126.

Overdose of sulphonylureas 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 must 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacodynamics

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 µg/mL).

Metabolism

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 (p-toluene sulfonamide). The liver is the probable site of metabolism.

Excretion

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.

Use in elderly

No clinically significant modifications in the pharmacokinetic parameters have been observed in elderly patients.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate
Magnesium stearate
Maize starch
Pregelatinised maize starch
Purified talc.

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

GLYADE tablets are supplied in aluminium/PVC blister strips containing 100 tablets enclosed in an outer carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

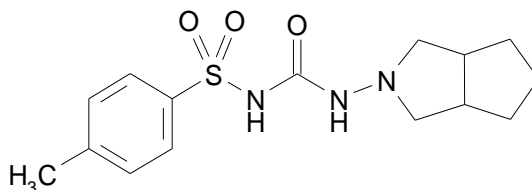
6.7 PHYSICOCHEMICAL PROPERTIES

Gliclazide has the chemical name 1-(3-azabicyclo[3.3.0]oct-3-yl)-3-p-tolylsulphonylurea. It is a white or almost white powder, practically insoluble in water, freely soluble in dichloromethane, sparingly soluble in acetone and slightly soluble in ethanol 96 %. The melting point of gliclazide is approximately 168 °C.

Molecular formula:

C₁₅H₂₁N₃O₃S

Chemical structure



CAS number

21187-98-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 November 1999

10 DATE OF REVISION

30 July 2019

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information
All	Reformatting of the PI in line with the latest TGA requirements for PI
2, 3, 6.1, 6.3 & 6.5. 4.4, 4.6 4.8 & 8	Editorial changes. Warning regarding patients with porphyria, inclusion of new rare AE (autoimmune bullous disorders) & Inclusion of Sponsor website address