AUSTRALIAN PI – APO-GLICLAZIDE (GLICLAZIDE)

1 NAME OF THE MEDICINE

Gliclazide.

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Each tablet contains gliclazide 80 mg, as the active ingredient.

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, lactose monohydrate, microcrystalline cellulose.

80 mg Tablets:

Round, white, flat-sided tablets with bevelled edges, engraved “APO” over “80” on one side, cross-scored on the other 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.

Gliclazide 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 and 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 (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.

In general, the dosage will depend on the severity of the glycaemia with ongoing adjustments should be 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 contraindicated in the following cases:

- Hypersensitivity to gliclazide, other sulphonylureas, sulfonamides, or to any of the excipients (see **2 and 3 Qualitative and Quantitative Composition and Pharmaceuticals Form**).
- Type I diabetes, diabetic keto-acidosis, diabetic pre-coma and coma;
- Severe renal or hepatic insufficiency.

- Treatment with miconazole (See **4.5 Interactions with other medicines and other forms of interactions**)
- Pregnancy and lactation (See **4.6 Fertility, Pregnancy and Lactation, Use in Pregnancy and Use in Lactation**).

It is generally not recommended to use this agent in combination with phenylbutazone or danazol (See **4.5 Interactions with other medicines and other forms of interactions**).

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, and require hospitalisation where 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 medicines (See **4.5 Interactions with other medicines and other forms of interactions**).

This treatment 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 **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.

Renal and Hepatic Impairment

Severe renal or hepatic impairmentmay 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.

Use in the elderly

See **4.2 Dose and method of administration**

Paediatric use

See **4.2 Dose and method of administration.**

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

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:

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
- nonsteroidal anti-inflammatory agents
- quinolone antibiotics.

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 gliclazide 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 gliclazide 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). Emphasize the importance of blood glucose monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of Gliclazide during and after treatment with glucocorticoids.

Salbutamol, terbutaline (intravenous):

May cause increased blood glucose levels due to β_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).

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

Effect on Fertility

No data available.

Use in Pregnancy (Category C)

Gliclazide is contraindicated during pregnancy and insulin is the drug of first choice for treatment of diabetes during pregnancy. Treatment should be changed from gliclazide 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.

The sulphonylureas may enter the foetal circulation and cause neonatal hypoglycaemia.

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.

Use in Lactation

It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, gliclazide 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 signs and symptoms of hypoglycaemia and should be careful if driving or operating machinery, especially at the beginning of treatment.

4.8 ADVERSE EFFECTS (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 sulphonylureas are leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, cholestatic jaundice and gastrointestinal haemorrhage. These reactions have not been reported with gliclazide (see also **Class Effects**).

Hypoglycaemia (see 4.4 Special Warnings and Precautions for Use and 4.9 Overdose)

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.

In long-term comparative studies, the percentage of patients experiencing hypoglycaemic episodes was similar between patients treated with gliclazide MR (11.6%) and those treated with gliclazide 80 mg (11.1%).

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, symptoms of adrenergic counter-regulation may be observed: sweating, clammyskin, 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.

Adverse events that were reported in at least 2.0% of patients, in long-term controlled clinical studies, are presented in the following table. The most frequent adverse events were not specifically related to the disease (such as respiratory infections or back pain).

Treatment emergent adverse events* (listed by body system) occurring in ≥ 2.0% of patients in long-term controlled clinical trials

	Gliclazide 80 mg (n=734) %	Gliclazide MR (n=728) %
Resistance mechanism		
Viral infection	5.6	7.7
Respiratory		
Rhinitis	4.6	4.4
Bronchitis	4.6	4.4
Pharyngitis	3.5	4.3
Upper respiratory infection	3.7	3.3
Coughing	2.0	2.1
Musculo-skeletal		
Back pain	4.1	5.2
Arthralgia	3.5	3.0
Arthrosis	2.2	2.2
Secondary term		
Inflicted injury	4.5	4.3
Body as a whole		
Headache	4.6	3.8
Asthenia	2.6	2.2
Cardiovascular		
Hypertension	3.7	3.2
Angina pectoris	2.2	2.1
Urinary		
Urinary tract infections	3.0	2.6
Gastrointestinal		
Diarrhoea	2.0	2.5
Central, peripheral, nervous system		
Dizziness	2.3	2.2
Metabolism & nutrition		
Hyperglycaemia	2.2	1.9

* whatever the relationship to treatment

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 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, hyponatraemia, 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.

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose of sulphonylureas may cause hypoglycaemia.

Symptoms

Manifestations of severe hypoglycaemia result from overdosage. Hypoglycaemia caused by sulphonylurea agents differs in several aspects from insulin coma. Warning symptoms are often absent, neurological syndromes are frequent and coma is often prolonged.

Treatment

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 50mL 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 5mmol/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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 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.

Clinical trials

No data available.

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 (ρ--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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In animal studies embryotoxicity and/or birth defects have been demonstrated with some sulphonylureas.

Animal studies of gliclazide have not shown any teratogenic effect.

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 INCOMPATIBILITIES

See Section 4.5-Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, the 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 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

80 mg Tablets

Blister pack (PVC/Aclar clear/Aluminium silver foil) in cartons of 100 tablets.

AUST R 80084

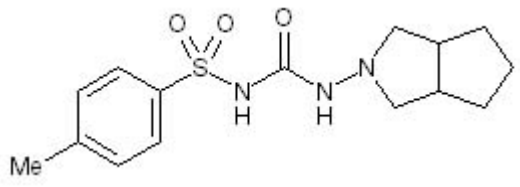
Not all packs sizes and/or pack types may be available.

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

Chemical structure



Chemical Name: 1-(3-azabicyclo[3.3.0]oct-3-yl)-3-*p*-tolylsulphonylurea.

Chemical Formula: $C_{15}H_{21}N_3O_3S$

Molecular Weight: 323.4

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

7 August 2002

10 DATE OF REVISION

06 February 2018.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted product information
2, 3	Minor Editorial Changes