APO-GLICLAZIDE MR 30 MG TABLETS

NAME OF THE MEDICINE
Gliclazide

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

![Chemical Structure of Gliclazide]

Molecular Formula: C_{15}H_{21}N_{3}O_{3}S
Molecular Weight: 323.4
CAS Registry Number: 21187-98-4

DESCRIPTION
Gliclazide is a white or almost white powder which is 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.

Gliclazide MR 30 mg tablets are intended for oral administration. Each tablet contains gliclazide 30 mg.

They are white to off-white, flat faced, beveled edge, capsule shaped tablets, engraved “APO 30” on one side and plain on the other side.

In addition to gliclazide, each tablet contains the following inactive ingredients: hypromellose, stearic acid and silica, colloidal anhydrous.

PHARMACOLOGY
Gliclazide is an oral hypoglycaemic sulfonylurea which differs from other related compounds. It has an N-containing heterocyclic ring with an endocyclic bond.

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the beta-cells of the Islets of Langerhans. Gliclazide shows high affinity, strong selectivity and reversible binding to the β-cell KATP channels with a low affinity for cardiac and vascular KATP channels.

Increased postprandial insulin and C-peptide secretion persists after two years of treatment. Gliclazide also has extra-pancreatic effects and haemovascular properties.

Effects on insulin release
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.

Extra-pancreatic effects
Gliclazide 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.

Other actions
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.

Pharmacokinetics
Absorption
Hydration of the tablets induces formation of a gel to activate drug release. Plasma levels increase progressively, resulting in a plateau-shaped curve from the sixth to the twelfth hour after administration. Intra-individual variability is low. Gliclazide is completely absorbed and food intake does not affect the rate or degree of absorption. The relationship between the dose administered and the area under the concentration curve as a function of time is linear for doses of gliclazide up to 90 mg/day. At the highest evaluated dose (135 mg/day), the AUC increases slightly more than proportionally to the dose.

Distribution
Plasma protein binding is approximately 95%.

Metabolism and Excretion
Gliclazide is mainly metabolised in the liver, the products of which are extensively excreted in the urine. Less than 1% of unchanged drug is recovered in the urine. No active metabolites have been detected in plasma.

The clearance of gliclazide has been found to be slightly reduced with ageing. This reduction, however, is not considered to be clinically significant.

The elimination half-life of gliclazide is approximately 16 hours.

No clinically significant modifications in the pharmacokinetic parameters have been observed in elderly patients.
INDICATIONS
- Type II diabetes in association with dietary measures when dietary measures alone are inadequate to control blood glucose.

During controlled clinical trials in patients with type II diabetes, Gliclazide MR 30 mg Tablets, taken as a single daily dose, was shown to be effective long term in controlling blood glucose levels, based on monitoring of HbA1c.

CONTRAINDICATIONS
This medication is contra-indicated in the following cases:

- Hypersensitivity to gliclazide, other sulfonylureas, sulfonamides, or to any of the excipients,
- Type I diabetes, diabetic keto-acidosis, diabetic pre-coma,
- Severe renal or hepatic insufficiency,
- Treatment with miconazole (refer to INTERACTIONS WITH OTHER MEDICINES),
- Pregnancy and lactation (refer to PRECAUTIONS - Use in pregnancy and Use in lactation).

It is generally not recommended to use this agent in combination with phenylbutazone or danazol (refer to INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

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 prescriber needs to educate the patient to be alert to the signs and symptoms of hypoglycaemia (refer to ADVERSE EFFECTS and OVERDOSE), and discuss prevention/treatment strategies with the patient at consultation.

Hypoglycaemia may occur following administration of sulfonylureas. Rarely, hypoglycaemia may be severe and prolonged, and may require hospitalisation where glucose infusion may need to be continued for several days.

Experience with sulfonylureas shows that hypoglycaemia can recur even when measures such as the intake of carbohydrate such as sugar 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.

Patients must be warned that artificial sweeteners are not recommended in the treatment of hypoglycaemia as they have negligible effect.

Careful selection of patients and of the dose used are necessary to avoid hypoglycaemic episodes.

Patients who may be particularly sensitive to antidiabetic agents include those who are elderly, undernourished or who have poor general health, and patients with adrenal insufficiency or hypopituitarism. Hypoglycaemia may be difficult to recognise in elderly patients and those receiving beta-blockers.

Close observation and careful initiation and adjustment of dosage is mandatory in patients who are elderly and debilitated, malnourished, semistarved or simply neglecting dietary restrictions. In such patients severe hypoglycaemia may occur with all sulfonylureas and may require corrective therapy.
over a period of several days. Certain conditions such as alcoholism, insulinoma, adrenal thyroid and pituitary insufficiency increase the sensitivity to sulfonylureas and may dispose to hypoglycaemia.

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 jeopardised by: 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.

**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.

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

**Renal and hepatic insufficiency**
Severe renal or hepatic insufficiency may affect the distribution of gliclazide and hepatic insufficiency 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.

**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.

**Use in pregnancy (Category C¹)**
It is important to achieve strict normoglycaemia during pregnancy. Oral hypoglycaemic agents should be replaced by insulin. The sulfonylureas may enter the fetal circulation and cause neonatal hypoglycaemia. In animal studies embryo-toxicity and/or birth defects have been demonstrated with some sulfonylureas.
Gliclazide should not be used in pregnant women although animal studies of gliclazide have not shown any teratogenic effect. From a clinical point of view, there are no adequate data to allow evaluation of the possible malformative or foetotoxic effects of gliclazide, when administered during pregnancy.

**Use in lactation**
In the absence of data on the transfer of gliclazide into breast milk, and given the risk of neonatal hypoglycaemia, breast-feeding is contra-indicated during treatment with this product.

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

¹ Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.
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.

INTERACTIONS WITH OTHER MEDICINES
Disturbances of Blood Sugar Control
As with all hypoglycaemics, caution should be observed in administering thiazide diuretics, since
these diuretics have been reported to aggravate the diabetic state. Other drugs which may adversely
affect blood sugar control with hypoglycaemic agents, include barbiturates, chlorpromazine, danazol,
glucocorticoids, oestrogens and progestogens, salbutamol, terbutaline.

Potentiation of Hypoglycaemic Effect
Certain drugs may potentiate the effect of gliclazide and thereby increase the risk of hypoglycaemia.
These include insulin, acarbose, biguanides, sulfonamides, oxyphenbutazone, phenylbutazone,
clofibrate, salicylates (high doses), coumarin derivatives, chloramphenicol, MAOIs, β-blockers,
cimetidine, ACE inhibitors, ethanol, fluconazole and miconazole (Note: miconazole is contra-indicated
with gliclazide), H₂ receptor antagonists and nonsteroidal anti-inflammatory agents.

Warn the patient and emphasise the importance of self-monitoring of blood glucose levels.
It may be necessary to adjust the dose of the antidiabetic agent during treatment with these
substances.

Anticoagulant Therapy
Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment.
Adjustment of the anticoagulant may be necessary

Alcohol
Acute alcohol intoxication potentiates the hypoglycaemic action of all sulfonylurea agents.
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 sulfonylurea
drugs, shortening the plasma half life and duration of action.

ADVERSE EFFECTS
Good clinical acceptability of gliclazide, has been established in many studies as well as in medical
practice.
The safety of gliclazide MR has been evaluated in controlled clinical trials in 955 patients, of which
728 patients were treated in long-term comparative trials, against gliclazide 80 mg tablets, for up to 10
months. In these comparative trials, the overall incidence and type of adverse events were similar in
both gliclazide MR and gliclazide 80mg groups.

Adverse events were generally mild and transient, not requiring discontinuation of therapy.

However, where patients did discontinue due to adverse events, the percentage was lower in the
gliclazide MR group (2.9%) than in the gliclazide 80 mg group (4.5%).

Serious reactions which have been reported with sulfonylureas are pancytopenia and gastrointestinal
haemorrhage. (see also Class attribution effects, near the end of this section).

Hypoglycaemia (refer to PRECAUTIONS and OVERDOSAGE)
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 signs and 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 and symptoms of hypoglycaemic adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

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%). However, the number of hypoglycaemic episodes per 100 patient.months was lower in the gliclazide MR group (3.5) than in the gliclazide 80 mg group (4.8). Analysis of elderly patients (over 65 years old) showed less hypoglycaemia than in the general population, with a prevalence of hypoglycaemic episodes lower in the gliclazide MR group (2.6 hypoglycaemic episodes for 100 patients.months) than in the gliclazide 80 mg group (4.1). The percentage of patients experiencing hypoglycaemic episodes in the sub-population with renal failure, was similar to that observed in the general population.

**Other adverse events**

Adverse events reported during controlled clinical trials with gliclazide MR were those expected in an ageing population with diabetes. 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).

<table>
<thead>
<tr>
<th>Resistance mechanism</th>
<th>Gliclazide MR (n=728) %</th>
<th>Gliclazide 80 mg (n=734) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infection</td>
<td>7.7</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Coughing</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Musculo-skeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>5.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Arthrosis</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Secondary term</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflicted injury</td>
<td>4.3</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Analysis of adverse events in sub-populations showed a similar pattern to that seen in the general population. Gender, age and renal insufficiency had no significant influence on the safety profile of gliclazide MR. Gastrointestinal disturbances (reported with gliclazide), including nausea, dyspepsia, diarrhoea and constipation may be avoided or minimised if gliclazide is taken with breakfast.

The following adverse events have been rarely reported:

- Skin and mucosae reactions: pruritus, urticaria, maculopapular rashes, rash, erythema and bullous reactions
- Haematological disorders (as with other sulfonylurea drugs): a few rare cases of anaemia, leucopenia, thrombocytopenia and agranulocytosis
- Occasional elevations of serum creatinine, blood urea nitrogen, serum bilirubin and hepatic enzymes (AST, ALT, alkaline phosphatase) levels, and exceptionally, hepatitis. **Treatment should be discontinued if cholestatic jaundice appears.**

These symptoms usually disappear after discontinuation of treatment.

Transient visual disturbances may occur on initiation of treatment due to changes in blood glucose levels.

**Class attribution effects**

Cases of erythrocytopenia haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for sulphonylureas.

With sulphonylureas cases were also observed of 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.

**DOSAGE AND ADMINISTRATION**

Gliclazide MR 30 mg Tablets are for adult use only.

The daily dose may vary from 30 to 120 mg taken orally, once daily. Gliclazide MR 30 mg Tablets 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.

Gliclazide MR 30 mg Tablets are modified release tablets and therefore should be neither broken nor chewed.

As with all hypoglycaemic agents, the dose should be titrated according to the individual patient’s response.

**The initial recommended dose is 30 mg daily, even in elderly patients (≥ 65 years).**

Dose titration should be carried out in steps of 30 mg, according to the fasting blood glucose response. Each step should last for at least two weeks. A single daily dose provides an effective
blood glucose control. The single daily dose may be between one and three, or even four, tablets. The daily dose should not exceed 120 mg.

Previously untreated patients should commence with a dose of 30mg and will benefit from dose titration until the appropriate dose is reached.

- Gliclazide MR 30 mg Tablets, can replace gliclazide 80mg tablets, tablet for tablet, for doses of 1 to 4 tablets per day.

- Gliclazide MR 30 mg Tablets, may be used to replace other antidiabetic treatments without any transitional period. If a patient is switched from a hypoglycaemic sulfonylurea with a prolonged half-life he/she should be carefully monitored (for 1 to 2 weeks) in order to avoid hypoglycaemia due to possible residual effects of the previous therapy.

- Gliclazide MR 30 mg Tablets, may be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

- Elderly subjects: The efficacy and tolerance of Gliclazide MR 30 mg Tablets has been confirmed in clinical trials in subjects over 65 years who were given the same dosage regimen as the general population. The dosage is therefore identical to that recommended for adults under the age of 65 years.

- Renal insufficiency: The efficacy and tolerance of Gliclazide MR 30 mg Tablets has been confirmed in clinical trials of subjects with mild to moderate renal failure (creatinine clearance of between 15 and 80mL/min) who were given the same dosage regimen as the general population. No dosage adjustment is therefore required in subjects with impaired renal function.

OVERDOSAGE

Symptoms
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.

Treatment
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.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.
PRESENTATION AND STORAGE CONDITIONS

APO-Gliclazide MR 30 mg Tablets
White to off-white, flat faced, beveled edge, capsule shaped tablets, engraved “APO 30” on one side and plain on the other side.

Blister pack of 100 tablets.
Aust R Number 151303

Bottle of 100 tablets.
Aust R Number 151307

* Not all strengths, pack types and/or pack sizes may be available.

Storage
Store below 30°C. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR
Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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POISONS SCHEDULE OF THE MEDICINE
S4: Prescription Only Medicine.

Date of TGA approval : 13 May 2009

Date of most recent amendment : 14 February 2012