

# DATA SHEET

## NAME OF THE DRUG

**DIAMICRON® MR** gliclazide 30mg tablet blister pack

## DESCRIPTION

DIAMICRON MR 30 mg tablets are a modified release formulation.

### Active Ingredient

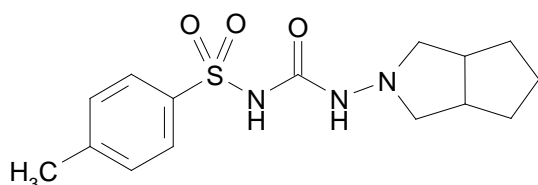
Gliclazide is a white or almost white powder, practically insoluble in water, freely soluble in dichloromethane, sparingly soluble in acetone and slightly soluble in ethanol 96%. The melting point of gliclazide is approximately 168°C.

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

*CAS Registry Number* : 21187-98-4

*Molecular Formula* : C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S

*Chemical Structure* :



### Excipients

Calcium hydrogen phosphate, maltodextrin, hypromellose, magnesium stearate 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 β-cells of the islets of Langerhans. Gliclazide shows high affinity, strong selectivity and reversible binding to the β-cell K<sub>ATP</sub> channels with a low affinity for cardiac and vascular K<sub>ATP</sub> 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

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 90mg/day. At the highest evaluated dose (135mg/day), the AUC increases slightly more than proportionally to the dose.

Plasma protein binding is approximately 95%. 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 as a function of age. 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, DIAMICRON MR, 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),
- Pregnancy and lactation (refer to 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).

## **PRECAUTIONS**

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.

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.

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.

### 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.

### 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.

### **Use in pregnancy (Category C)**

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.

### **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 and terbutaline.

#### **Potential of hypoglycaemic effect**

Certain drugs may potentiate the effect of gliclazide and thereby increase the risk of hypoglycaemia. These include insulin, biguanides, sulfonamides, clofibrate, salicylates (high doses), coumarin derivatives, chloramphenicol, MAOI's,  $\beta$ -blockers, cimetidine, ACE inhibitors, ethanol, fluconazole, miconazole (Note: miconazole is contra-indicated with gliclazide) 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.

#### **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.

### **Laboratory tests**

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

### **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.

## **ADVERSE REACTIONS**

Good clinical acceptability of gliclazide, has been established in many studies as well as in medical practice.

The safety of DIAMICRON MR has been evaluated in controlled clinical trials in 955 patients, of which 728 patients were treated in long-term comparative trials, against gliclazide 80mg tablets, for up to 10 months. In these comparative trials, the overall incidence and type of adverse events were similar in both DIAMICRON 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 DIAMICRON MR group (2.9%) than in the gliclazide 80mg group (4.5%).

### **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.

In long-term comparative studies, the percentage of patients experiencing hypoglycaemic episodes was similar between patients treated with DIAMICRON MR (11.6%) and those treated with gliclazide 80mg (11.1%). However, the number of hypoglycaemic episodes per 100 patients.month was lower in the DIAMICRON MR group (3.5) than in the gliclazide 80mg 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 DIAMICRON MR group (2.6 hypoglycaemic episodes for 100 patients.months) than in the gliclazide 80mg 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 DIAMICRON 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).

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

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

\*whatever the relationship to treatment

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 DIAMICRON 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
- 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.

## **DOSAGE AND ADMINISTRATION**

For adult use only.

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

DIAMICRON MR 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 30mg daily, even in elderly patients ( $\geq 65$  years).

Dose titration should be carried out in steps of 30mg, 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 120mg.

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

- DIAMICRON MR, can replace gliclazide 80mg tablets, tablet for tablet, for doses of 1 to 4 tablets per day.
- DIAMICRON MR, 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.
- DIAMICRON MR, may be given in combination with biguanides, alpha glucosidase inhibitors or insulin.
- Elderly subjects: The efficacy and tolerance of DIAMICRON MR 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 DIAMICRON MR 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**

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 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.

## **PRESENTATION AND STORAGE CONDITIONS**

Modified release tablets, 30mg available in 100's.

The tablets are white oblong tablets with an engraving of "DIA 30" on one face and  on the other face.

Store below 30°C

## **NAME AND ADDRESS OF THE SPONSOR**

### **Australia**

Servier Laboratories (Australia) Pty Ltd  
8 Cato Street  
Hawthorn Victoria 3122  
Australia

### **New Zealand**

Servier Laboratories (New Zealand) Ltd  
12<sup>th</sup> floor, Citibank Building  
23 Customs Street  
Auckland

## **POISONS SCHEDULE**

S4

## **DATE OF PREPARATION**

19 July, 2011