**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

**DIAMICRON MR 60 mg, modified release scored tablet**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One modified release tablet contains 60 mg of gliclazide.

Excipient: lactose.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Modified release tablet.

White, oblong tablet, scored and engraved with 'DIA 60' on both faces.

The tablet can be divided into two equal half doses.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

### 4.2. Posology and method of administration

Oral use.

For adult use only.

The daily dose of DIAMICRON MR 60 mg may vary from ½ to 2 tablets per day, *i.e*.from 30 to 120 mg taken orally in a single intake at breakfast time.

It is recommended to swallow the tablet(s) without crushing or chewing.

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

As with any hypoglycaemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbAlc).

**Initial dose:**

The recommended starting dose is 30 mg daily (half a tablet of DIAMICRON MR 60 mg).

- if blood glucose is adequately controlled, this dose may be used for maintenance treatment,
- if blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120 mg daily, in successive steps. The interval between each dose increment should be at least 1 month, except in patients whose blood glucose has not reduced after two weeks of treatment. In this case, an increase of the dose may be suggested at the end of the second week of treatment.

The maximum recommended dose is 120 mg per day.

One DIAMICRON MR 60 mg modified release tablet is equivalent to two DIAMICRON 30 mg modified release tablets. The breakability of the DIAMICRON MR 60 mg modified release tablet enables flexibility of dosing to be achieved.

*Switching from DIAMICRON 80 mg tablets to DIAMICRON MR 60 mg modified release tablets:*

One tablet of DIAMICRON 80 mg is comparable to 30 mg of the modified release formulation (i.e. ½ tablet of DIAMICRON MR 60 mg). Consequently, the switch can be performed provided that blood glucose is carefully monitored.

*Switching from another oral antidiabetic agent to DIAMICRON MR 60 mg:*

DIAMICRON MR 60 mg can be used to replace another oral antidiabetic treatment.

In that case, the dose and the half-life of the previous antidiabetic agent should be taken into account.

A transitional period is not generally necessary. A starting dose of 30 mg should be used and this should be adjusted to suit the patient's blood glucose response, as described above.

When switching from a hypoglycaemic sulphonylurea with a prolonged half-life, a treatment free period of a few days may be necessary to avoid an additive effect of the two products, which might cause hypoglycaemia.

During this switch, the procedure described for initiating treatment with DIAMICRON MR 60 mg should be used, *i.e*. a starting dose of 30 mg per day, followed by a stepwise increase in dose, depending on the metabolic results.

*Combination with other oral antidiabetic agents:*

DIAMICRON MR 60 mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

In patients not adequately controlled with DIAMICRON MR 60 mg, concomitant insulin therapy can be initiated under close medical supervision.

In subjects over 65 years of age, DIAMICRON MR 60 mg should be prescribed using the same dosing regimen recommended for patients under 65 years of age.

In patients with mild to moderate renal insufficiency the same dosing regimen can be used as in patients with normal renal function with careful patient monitoring.

These data have been confirmed in clinical trials.

*In patients at risk of hypoglycaemia:*

• undernourished or malnourished conditions,

• severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotrophic insufficiency),

• withdrawal of prolonged and/or high dose corticosteroid therapy,

• severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease);

It is recommended to start the treatment systematically with the minimum dose of 30 mg/day.

There are no data or clinical studies available in children.

## 4.3. Contraindications

• known hypersensitivity to gliclazide or to any of the ingredients, to other sulfonylurea, to sulphonamides;

• type 1 diabetes;

• diabetic pre-coma and coma, diabetic keto-acidosis;

• severe renal or hepatic insufficiency: in these cases the use of insulin is recommended;

• treatment with miconazole (see section 4.5);

• lactation (see section 4.6).

## 4.4. Special warnings and precautions for use

**Hypoglycaemia:**

This treatment should be prescribed only 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 taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.

Hypoglycaemia may occur following administration of sulphonylureas (see section 4.8). Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes.

**Factors which increase the risk of hypoglycaemia:**

- patient refuses or (particularly in elderly subjects) is unable to co-operate;
- malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes;
- imbalance between physical exercise and carbohydrate intake;
- renal insufficiency;
- severe hepatic insufficiency;
- overdose of DIAMICRON MR 60mg;
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency;
- concomitant administration of certain other medicines (see section 4.5).
- Renal and hepatic insufficiency: the pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

**Patient information:**

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.

Poor blood glucose control: blood glucose control in a patient receiving oral antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention.

In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic agent, including gliclazide, is attenuated over time in many patients: 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 which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

Laboratory tests: measurement of glycated haemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

Treatment of patients with G6PD (glucose-6-phosphate dehydrogenase) 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.

**Excipients**:

This medicine contains lactose. Its use is not recommended in patients presenting galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases).

### 4.5. Interactions with other medicinal products and other forms of interaction

1) The following products are likely to increase hypoglycaemia

**Contra-indicated combination**

**+ Miconazole** (systemic route, oromucosal gel)

increase of the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma.

**Combinations which are not recommended**

**+ Phenylbutazone** (systemic route)

increase of the hypoglycaemic effect of hypoglycaemic sulphonamides (displaces their binding to plasma proteins and/or reduces their elimination).

It is preferable to use another anti-inflammatory agent, or else to warn the patient and intensify self-monitoring: where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.

**+ Alcohol**

increase of the the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma.

Alcohol beverages or medicinal products containing alcohol should be avoided.

**Combinations requiring precautions for use**

+ Because of the potentiation of the hypoglycaemic effect, in some instances, hypoglycaemia may occur during concomitant treatment with the following drugs:

other antidiabetic agents (insulin, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitor (captopril, enalapril), H2-receptor antagonists, MAOIs, sulphonamides and nonsteroid anti-inflammatory agents.

2) The following products may cause an increase in blood glucose levels.

**Combination which is not recommended**

**+ Danazol**

diabetogenic effect of danazol.

If the combination cannot be avoided, warn the patient and intensify urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

**Combinations requiring precautions during use**

**+ Chlorpromazine** (neuroleptic agents)

at high doses (>100 mg per day of chlorpromazine), increase of blood glucose levels (reduced insulin release).

Warn the patient and intensify blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with the neuroleptic agent.

**+ Glucocorticoids** (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactide:

Increase in blood glucose levels with sometimes ketosis (reduced tolerance to carbohydrates due to glucocorticoids).

Warn the patient and intensify blood glucose monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with glucocorticoids.

**+ Ritodrine, salbutamol, terbutaline:**

(I.V. route)

Increase in blood glucose levels due to beta-2 agonist effects.

Intensify blood glucose monitoring. If necessary, switch to insulin.

3) Combinations which must be taken into account

**+ Anticoagulants** (warfarin, etc.)

Hypoglycaemic sulphonamides may lead to potentiation of anticoagulation during treatment.

Adjustment of the anticoagulant posology may be necessary.

**4.6. Pregnancy and lactation**

**Pregnancy**

There is no clinical data concerning the administration of gliclazide to pregnant women; there are few data with other sulfonylureas.

In animals, gliclazide is not teratogenic.

Control of diabetes should be obtained before the time of conception in order to reduce the risks of congenital abnormalities linked to uncontrolled diabetes.

Oral antidiabetic agents are not suitable during pregnancy, insulin is then the drug of first choice for diabetes. It is recommended that oral antidiabetic therapy is changed to insulin when a pregnancy is considered, or as soon as pregnancy is discovered.

**Lactation**

There is no data on the passage of gliclazide or its metabolites in breast milk. Given the risk of neonatal hypoglycaemia, gliclazide is contra-indicated in breast-feeding women.

**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 and/or operating machinery, especially at the beginning of treatment.

**4.8. Undesirable effects**

Based on the clinical experience with gliclazide and other sulphonylureas, the following undesirable effects have to be reported:

**Hypoglycaemia**

As for other sulphonylureas, treatment with DIAMICRON MR 60mg can cause hypoglycaemia, if mealtimes are irregular and in particular, if meals are skipped.

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 lethal outcome.

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 carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulphonylureas shows that hypoglycaemia can recur even when measures prove effective initially.

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.

**Other undesirable effects**

Gastrointestinal disturbances, including abdominal pain, nausea, vomiting, dyspepsia, diarrhoea and constipation have been reported; if these should occur they can be avoided or minimised if gliclazide is taken with breakfast.

The following undesirable effects have been more rarely reported:

- Skin and subcutaneous tissue disorders: rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions.
- Blood and lymphatic system disorders: changes in haematology are rare. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of medication.
- Hepato-biliary disorders: raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears.

These symptoms usually disappear after discontinuation of treatment.

- Eye disorders: transient visual disorders may occur especially on initiation of treatment, due to changes in blood glucose levels.

**Class attribution effects:**

As for other sulphonylureas, the following adverse events have been observed: cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia, 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.

### 4.9. Overdose

An overdose of hypoglycaemic sulfonylurea may cause hypoglycaemia.

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

Severe hypoglycaemic reactions with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalisation of the patient.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of 50 ml of concentrated glucose solution (20 to 30%), followed by continuous infusion of a more dilute glucose solution (10%) at a rate that will maintain blood glucose levels above 1 g/l.

Patients should be monitored closely and depending on the patient's condition, the doctor will decide if further monitoring is necessary.

Dialysis is unnecessary due to the strong binding of gliclazide to proteins.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

**Pharmacotherapeutic class: HYPOGLYCAEMIC SULPHONAMIDES - UREA DERIVATIVES, ATC code: A10BB09**

Gliclazide is a hypoglycaemic sulphonamide, an oral antidiabetic agent differing from other sulphonamides by 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. Increase in postprandial insulin and C-peptide secretion persists after 2 years of treatment.

In addition to these metabolic properties, gliclazide has haemovascular properties.

**Effects on insulin release**

In type 2 diabetics, 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 response is seen in response to a meal or glucose absorption.

**Haemovascular properties**

Gliclazide decreases the microthrombosis process by two mechanisms which may be involved in complications of diabetes:

• a partial inhibition of platelet aggregation and adhesion, as well as a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane $B_2$);

• an action on the vascular endothelium fibrinolytic activity with an increase in t-PA activity.

**5.2. Pharmacokinetic properties**

Plasma levels increase progressively during the first 6 hours, reaching a plateau from the 6$^{th}$ to the 12$^{th}$ hour after oral administration.

Intra-individual variability is low.

Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption.

The relationship between the dose administered ranging up to 120 mg and the concentration area under the curve (AUC) is linear.

Plasma protein binding is approximately 95%.

Gliclazide is mainly metabolised in the liver. It is excreted in the urine; less than 1% of the unchanged form is found in the urine. No active metabolites have been detected.

The elimination half-life of gliclazide is between 12 and 20 hours.

The volume of distribution is around 30 litres.

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

A single daily intake of DIAMICRON MR 60 mg maintains effective gliclazide plasma concentrations over 24 hours.

**5.3. Preclinical safety data**

Preclinical data reveal no hazards for humans based on studies of chronic toxicity and genotoxicity. Long term carcinogenicity studies have not been performed.

No teratogenic effects have been reported in animals; only lower foetal body weight was observed in animals receiving doses 25 fold higher than the maximum recommended dose in humans.

**6. PHARMACEUTICAL PARTICULARS**

**6.1. List of excipients**

Lactose monohydrate, maltodextrin, hypromellose, magnesium stearate, colloidal anhydrous silica.

**6.2. Incompatibilities**

Not applicable.

**6.3. Shelf life**

3 years.

**6.4. Special precautions for storage**

Store below 30°C.

### 6.5. Nature and content of outer packaging

10, 30 or 300 tablets in heat-sealed blister packs (transparent PVC/Aluminium).

Not all pack sizes may be marketed.

### 6.6. Special instructions for disposal and handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with current requirements.

## 7. MARKETING AUTHORISATION HOLDER

**LES LABORATOIRES SERVIER FRANCE**