Proprietary name:	Gliclazide MR 30 Ascend & Gliclazide MR 60 Ascend
Dosage form:	Modified release tablets
Active Ingredient:	Gliclazide
Strength per dosage unit:	30 mg or 60 mg Gliclazide per tablet

1.3.1.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Gliclazide MR 30 Ascend

Gliclazide MR 60 Ascend

Modified release tablets.

Gliclazide.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gliclazide MR 30 Ascend: Each modified release tablet contains 30 mg of gliclazide.

Gliclazide MR 60 Ascend: Each modified release tablet contains 60 mg of gliclazide.

Contains sugar and mannitol.

Gliclazide MR 30 Ascend: Each tablet contains 39 mg of lactose monohydrate and 27,5 mg of mannitol.

Gliclazide MR 60 Ascend: Each tablet contains 78 mg of lactose monohydrate and 55 mg of mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gliclazide MR 30 Ascend: White to off-white, round tablets, engraved with “G3” on one face and plain on the other face.

Gliclazide MR 60 Ascend: White to off-white, oblong shaped tablets, scored with a break bar on both sides, engraved with “G L” on one face and plain on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gliclazide MR Ascend is indicated in type 2 diabetic patients, in association with dietary measures, lifestyle changes and exercise, when dietary measures, lifestyle and exercise alone are not sufficient to control blood glucose.

4.2 Posology and method of administration

Posology:

For adult use only:

Gliclazide MR 30 Ascend: The daily dose may vary from 1 to 4 tablets a day i.e. 30 mg to 120 mg taken as a single daily dose.

Gliclazide MR 60 Ascend: The daily dose may vary from half to 2 tablets a day i.e. 30 mg to 120 mg taken as a single daily dose.

If a dose is forgotten, the dose taken on the next day should not be increased. The dose should be adjusted according to the individual patient's metabolic response (blood glucose levels and/or glycosylated haemoglobin HbA1C).

Initial dose:

The initial recommended dose is 30 mg once daily, taken with breakfast.

Dose adjustments:

If fasting blood glucose levels have not decreased satisfactorily, the dosage can be increased progressively to 60 mg, 90 mg, or 120 mg per day, by successive increments, respecting an interval of at least one month between each increment, except in patients whose blood glucose levels have

not decreased after 15 days of treatment. In this case, it is possible to propose a dosage increase at the end of the 2nd week of treatment. The daily dose should not exceed 120 mg. Previously untreated patients should commence with a dose of 30 mg.

Replacement of immediate release gliclazide 80 mg with Gliclazide MR Ascend:

In patients stabilised on gliclazide 80 mg, the replacement of gliclazide 80 mg by **Gliclazide MR Ascend** may initially be based on: 1 tablet of immediate release gliclazide 80 mg = 1 tablet of **Gliclazide MR 30 Ascend.**

Replacement of another sulphonylurea with Gliclazide MR Ascend:

Gliclazide MR Ascend can replace other sulphonylurea treatment. For the transition to **Gliclazide MR Ascend**, the dosage and the half-life of the previous oral hypoglycaemic medicine must be considered. If a patient is changed from another oral sulphonylurea with a prolonged half-life, a therapeutic window of a few days may prove to be necessary to avoid the additive effect of the two products and the subsequent risk of hypoglycaemia.

During such a changeover, it is recommended to follow the same procedure as for the initiation of the treatment with **Gliclazide MR Ascend**, i.e. to initiate treatment with a dose of 30 mg per day and then increase the dosage by increments, according to the metabolic evolution of each patient.

Association with other oral antidiabetic medicines:

Gliclazide MR Ascend, can be given in combination with alpha glucosidase inhibitors or insulin, but in that case, diabetic control should be checked with blood sugar readings, because of the possibility of hypoglycaemia. In combined therapy with biguanides, there may be a greater risk of cardiovascular mortality than with the use of **Gliclazide MR Ascend** alone.

Special populations

Elderly patients and patients with renal failure:

The efficacy and tolerance of **Gliclazide MR Ascend**, prescribed using the same therapeutic regimen in subjects over 65 years and patients with mild to moderate renal failure (creatinine clearance 30 – 80 mL/min) has been confirmed in clinical trials. The dosage will therefore be identical to that recommended for adults under the age of 65 years, and for patients with normal renal function, with careful patient monitoring.

Use of **Gliclazide MR Ascend,** is contraindicated in patients with severe renal impairment (see section 4.3).

Patients at risk of hypoglycaemia:

- undernourished or malnourished,
- 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 that the minimum daily starting dose of 30 mg is used.

Paediatric population:

Gliclazide MR Ascend should not be used in children (see section 4.3).

Method of administration

Gliclazide MR Ascend should be given orally, with meals (breakfast).

4.3 Contraindications

Gliclazide MR Ascend is contraindicated in:

- patients with hypersensitivity to gliclazide, other sulphonylureas, sulphonamides, or to any, or to any of the excipients of **Gliclazide MR Ascend**, listed in section 6.1.
- Type 1 diabetes (Juvenile Insulin Dependent Diabetes Mellitus), diabetic keto-acidosis, and diabetic pre-coma and coma,
- Children,
- Severe renal or hepatic insufficiency,
- Treatment with miconazole (see Section 4.5),
- Pregnancy,
- Lactation.

4.4 Special warnings and precautions for use

A reduction in dosage may be necessary in patients with mild to moderate renal dysfunction. (See sections 4.2 and 4.3).

Increased risk of cardiovascular mortality:

The administration of oral hypoglycaemics, including **Gliclazide MR Ascend,** may be associated with increased cardiovascular mortality, as compared to treatment with diet alone or diet with insulin.

Hypoglycaemia:

Hypoglycaemia may occur following administration of sulphonylureas including **Gliclazide MR Ascend** (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 favouring hypoglycaemia include:

- Patient refusing or (particularly elderly patients) being unable to co-operate,
- Malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes,
- Imbalance between physical exercise and carbohydrate intake,
- Certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency. These disorders should be controlled by appropriate therapy before introducing **Gliclazide MR Ascend,**
- Concomitant administration of certain other medicines (see section 4.5),
- Deterioration in renal function.
- Severe hepatic insufficiency

This treatment should only be prescribed if the patient is likely to have a regular food intake (including breakfast). Hypoglycaemia is more likely to occur during periods of low-calorie diet, irregular carbohydrate intake, following prolonged or strenuous exercise, following alcohol intake or during the administration of a combination of hypoglycaemic medicines.

Symptoms of hypoglycaemia usually disappear after absorption of carbohydrates (sugar). However, despite initial effective measures, hypoglycaemia may occur. Artificial sweeteners have no effect on hypoglycaemia. In the case of severe prolonged hypoglycaemia, immediate medical treatment and even hospitalisation is necessary.

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 antidiabetic treatment may be affected by any of the following: St. John's Wort (*Hypericum perforatum*) preparations (see section 4.5), fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic effect of **Gliclazide MR Ascend**, 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.

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, at the same time, **Gliclazide MR Ascend** and a fluoroquinolone.

Renal and hepatic insufficiency:

The pharmacokinetic and/or pharmacodynamic properties of **Gliclazide MR Ascend** 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.

Skin reactions:

There is a potential for the occurrence of erythema multiforme, toxic dermal necrolysis and allergic vasculitis.

Laboratory tests:

Measurement of glycosylated 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-deficiency with sulphonylurea medicines can lead to haemolytic anaemia. Since gliclazide belongs to the chemical class of sulphonylurea medicines, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

Porphyric patients:

Cases of acute porphyria have been described with some other sulfonylurea medicines, in patients who have porphyria.

Gliclazide MR Ascend contains lactose and mannitol.

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take **Gliclazide MR Ascend**.

Mannitol has a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

The following products are likely to increase the risk of hypoglycaemia:

Contraindicated combinations:

- **Miconazole,** (systemic route, oral gel): increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma. (See section 4.3).

Combinations which are not recommended:

- **Phenylbutazone** (systemic route): increases the hypoglycaemic effect of sulphonylureas,
- **Alcohol**: Avoid intake of alcohol or medicine containing alcohol.

Combinations requiring precautions for use:

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following medicines is taken:

Fluconazole, ketoconazole (systemic route, oral gel), beta-blockers, other antidiabetic medicines (insulin, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, biguanides), ACE-inhibitors (captopril, enalapril), sulphonamides, H_2-receptor antagonist (cimetidine, ranitidine), non-steroidal anti-inflammatory medicines (NSAIDS), mono-amine-oxidase (MAO) inhibitors, clarithromycin and chloramphenicol.

The following products may cause an increase in blood glucose level:

Combination which is not recommended:

- **Danazol:** diabetogenic effect of danazol.

Combinations requiring precautions for use:

- **Chlorpromazine**: (neuroleptic agent): high doses (> 100 mg per day of chlorpromazine) increase blood glucose levels (reduced insulin release),
- **Glucocorticoids**: (systemic and local route: intra-articular, cutaneous, and rectal preparations) and tetracosactrin: increase in blood glucose levels with possible ketosis.
- **Salbutamol, terbutaline and other beta-adrenergic agonists**: increased blood glucose levels due to beta-2 agonist effects. Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.
- **Ephedrine, pseudoephedrine and common cold medicines.**
- **Saint John's Wort (*Hypericum perforatum*) preparations:** Gliclazide exposure is decreased by Saint John's Wort (*Hypericum perforatum)*. Emphasise the importance of blood glucose levels monitoring.

The following products may cause dysglycaemia:

Combinations requiring precautions during use:

- **Fluoroquinolones:** in case of concomitant use of **Gliclazide MR Ascend** and a fluoroquinolone, the patient should be warned of the risk of dysglycaemia, and the importance of blood glucose monitoring should be emphasised.,
- **Anticoagulant therapy (warfarin**): sulphonylureas such as **Gliclazide MR Ascend** may lead to potentiation of anticoagulation during concurrent treatment. Regular monitoring of the INR.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of use of **Gliclazide MR Ascend** has not been established. Thus, **Gliclazide MR Ascend** is not recommended during pregnancy (see section 4.3).

Breastfeeding:

Gliclazide MR Ascend must not be used in breastfeeding women as safety has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

Gliclazide MR Ascend has no known influence on the ability to drive and use machines. Patients should be made aware of the symptoms of hypoglycaemia, and should be careful when driving, or operating machinery, especially at the beginning of treatment.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The adverse reactions are sorted by frequencies and be listed by system organ class. Within each frequency grouping, undesirable effects have been presented in order of decreasing seriousness. Frequencies are defined as frequent, less frequent and frequency not known.

Class/ Frequency	***Adverse reaction***
Gastrointestinal disorders:	
Frequent	Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, constipation, metallic taste, increased appetite and weight gain.
Metabolism and nutrition disorders:	
Less frequent	Anorexia
Skin and subcutaneous tissue disorders:	
Frequent	Rash, pruritus

Class/ Frequency	***Adverse reaction***
Less frequent	Urticaria, erythema, maculopapular rashes and bullous reactions, (such as Stevens-Johnson syndrome and toxic epidermal necrolysis), and exceptionally, rash with eosinophilia~~,~~ and systemic symptoms (DRESS)
Frequency unknown	Photosensitivity, facial flushing, exfoliative dermatitis and erythema nodusum
Blood and lymphatic system disorders:	
Less frequent	Changes may include anaemia, leucopenia, thrombocytopenia, granulocytopenia, aplastic anaemia, haemolytic anaemia. These are in general reversible upon discontinuation of medicine.
Hepato-biliary disorders:	
Less frequent	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:	
Less frequent	Transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels

Class attribution effects:

As for other sulfonylureas, the following adverse events have been observed: cases of erythroytopenia, 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 sulfonylurea or led to life-threatening liver failure in isolated cases.

The following side-effects have been reported and the frequencies are unknown:

Hypoglycaemia:

The most frequent adverse reaction with gliclazide is hypoglycaemia. As for other sulfonylureas, treatment with **Gliclazide MR Ascend** 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 dysrhythmia.

Usually, symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulfonylurea 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety

X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website and must also be reported to Ascend Laboratories (Pty) Ltd. vial the e-mail: pharmacist.rsa@alkem.com.

4.9 Overdose

An overdose of **Gliclazide MR Ascend** may cause hypoglycaemia which could be severe and prolonged. Moderate symptoms of hypoglycaemia, without any loss of consciousness or neurological signs, must be corrected by carbohydrate intake, dose adjustment and/or modification of diet.

Strict monitoring should be continued until the patient is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders should be treated as a medical emergency, requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of 50 mL of concentrated glucose solution (20 – 30 %). This should be followed by continuous infusion of a more dilute solution (10 %), at a rate necessary to maintain blood glucose levels above 5,5 mmol/L. Patients should be monitored closely, long enough to be sure that hypoglycaemia will not re-occur, and, depending on the patient's condition, the doctor will decide if further monitoring is necessary.

Dialysis is of no use in these patients due to the strong binding of gliclazide to proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sulfonamides, urea derivatives. ATC code: A10BB09

Pharmacological classification: A.21.2 Oral Hypoglycaemics

Mechanism of action

Gliclazide is a hypoglycaemic sulfonylurea oral antidiabetic active substance differing from other related compounds 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 two years of treatment.

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

Pharmacodynamic effects

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 stimulation induced by a meal or glucose.

Haemovascular properties:

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

- A partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B2).
- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

Pharmacokinetic properties:

Absorption

Plasma levels increase progressively until the sixth hour, resulting in a plateau-shaped curve from the sixth to the twelfth hour after administration. Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption.

Biotransformation

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

Distribution

Plasma protein binding is approximately 95 %. The volume of distribution is around 30 litres.

Elimination

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

Linearity/ Non-linearity

The relationship between the dose administered and the area under the concentration curve, as a function of time, is linear up to 120 mg.

Special populations

Elderly

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other ingredients are colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, mannitol, sodium acetate anhydrous.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

Gliclazide MR 30 Ascend is packed in Aluminium-Aluminium blister pack (with or without dessicant) of 10, 30 and 60 tablets, the strips are packed in a printed cardboard carton and a white, opaque, round HDPE bottle closed with a white, opaque, polypropylene, child-resistant cap with liner, containing 60 or 100 tablets.

Gliclazide MR 60 Ascend is packed in Aluminium-Aluminium blister pack (with or without dessicant) of 10, 30 and 60 tablets, the strips are packed in a printed cardboard carton and a white, opaque, round HDPE bottle closed with a white, opaque, polypropylene, child-resistant cap with liner, containing 60 or 100 tablets.

The blisters are inserted printed cardboard carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ascend Laboratories (Pty) Ltd.

Office 7.6, 7th Floor, Sandton City Office Tower

Corner Rivonia Road and 5th Street

Sandton, 2196, Gauteng

8. REGISTRATION NUMBER(S)

Gliclazide MR 30 Ascend: 59/21.2/0004

Gliclazide MR 60 Ascend: 59/21.2/0005

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

3 February 2026

10. DATE OF REVISION OF THE TEXT