SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT
ATENIGRON – 100-mg + 25-mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains:
Active ingredients:
- Atenolol 100 mg
- Chlorthalidone 25 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
100-mg + 25-mg Tablets

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
ATENIGRON is suitable to treat essential hypertension in patients whose blood pressure is not adequately controlled by a single-agent therapy on atenolol or chlorthalidone alone.

4.2. Posology and method of administration
When clinically appropriate, in patients whose blood pressure is not adequately controlled, direct shifting from a single-agent therapy to the fixed-dose combination can be considered.

Adults:
The usual maintenance dose of Atenolol + Chlorthalidone 50 mg + 12.5 mg is one tablet a day. For patients who do not respond appropriately to Atenolol + Chlorthalidone 50 mg + 12.5 mg, the dose may be increased to one tablet of ATENIGRON 100 mg + 25 mg per day.

ATENIGRON can be combined, if need be, with other hypotensive drugs, e.g. vasodilators.

Special populations:
Elderly
In this group of patients, the lower strength dose is often appropriate.

Children and adolescents (< 18 years old)
There is no experience of using ATENIGRON in children and adolescents. Therefore, it must not be administered to children or adolescents.

Renal impairment
Due to the properties of the chlorthalidone component, ATENIGRON has reduced efficacy in the presence of renal insufficiency. This fixed-dose combination should thus not be administered to patients with severe renal impairment (See section 4.3).

Hepatic impairment
Dosage adjustments are not required in patients with hepatic impairment.

4.3. Contraindications
ATENIGRON should not be used in patients with any of the following:
- known hypersensitivity to atenolol and chlorthalidone (or sulphonamide derived medicinal products) or to any of the excipients
- second- or third-degree heart block

- sick-sinus syndrome
- bradycardia
- uncontrolled heart failure
- cardiogenic shock
- hypotension
- severe peripheral arterial circulatory disturbances
- severe hepatic and/or renal failure
- metabolic acidosis
- untreated pheochromocytoma
- apparent gout
- pregnancy and lactation

4.4. Special warnings and precautions for use

Due to the beta-blocker active ingredient, atenolol:

- Although contraindicated in uncontrolled heart failure (See section 4.3), it may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- It may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. Atenolol is a beta-1 selective beta-blocker; consequently, the use of ATENIGRON may be considered for these patients although utmost caution must be exercised.
- Although contraindicated in severe peripheral arterial circulatory disturbances (See section 4.3), ATENIGRON may also aggravate less severe peripheral arterial circulatory disturbances.
- Due to its negative effect on conduction time, special caution must be exercised if it is given to patients with first-degree heart block.
- May modify warning signs of hypoglycaemia as tachycardia, palpitations and sweating.
- May mask the cardiovascular signs of thyrotoxicosis.
- Will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate, the dose must be reduced.
- Should not be discontinued abruptly in patients suffering from ischemic heart disease.
- May cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction. Such patients may be unresponsive to the usual doses of adrenaline used to treat allergic reactions.
- Patients with bronchospastic disease should, in general, not receive beta blockers due to increase in airways resistance.
  Atenolol is a beta-1 selective beta-blocker; however, this selectivity is not absolute. Therefore, the lowest possible dose of Atenolol + Chlorthalidone should be used and utmost caution must be exercised. If increased airways resistance does occur, ATENIGRON should be discontinued and bronchodilator therapy (such as salbutamol) administered if necessary.
- The systemic effects of oral beta-blockers can be enhanced when used in conjunction with ophthalmic beta-blockers.
- In patients with pheochromocytoma, ATENIGRON must be administered only after alpha-receptor blockade. Blood pressure should be monitored closely.
- Caution must be exercised when using anaesthetic agents with ATENIGRON. The anaesthetist should be informed and the choice of the anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Due to the active ingredient, chlorthalidone:

- Choroidal effusion, acute myopia, and secondary angle-closure glaucoma: Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma.
  Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

- Plasma electrolytes must be measured periodically and at appropriate intervals in order to detect probable electrolyte imbalances, especially hypokaliaemia and hyponatriaemia.
- Hypokaliaemia and hyponatriaemia may occur. Monitoring of serum electrolytes is particularly indicated in the elderly, those receiving treatment with digitalis preparations for cardiac failure, those taking a restricted (low in potassium) diet or those suffering from gastrointestinal problems. Hypokaliaemia may predispose to arrhythmias in patients receiving digitalis.
- Because chlorthalidone may impair glucose tolerance diabetic patients should be aware of the potential for increased glucose levels. Close monitoring of glycaemia is recommended in the initial phase of therapy and in prolonged therapy, test for glucosuria should be carried out at regular intervals.
- In patients with impaired hepatic function or progressive liver disease, minor alterations in hydroelectrolytic balance may precipitate hepatic coma.
- Hyperuricemia may occur. Usually, only a slight increase in uric acid in serum occurs, but in the case of prolonged increases, co-administration of a uricosuric agent will bring hyperuricemia back within normal limits.

Athletes/ sportspeople: The use of this drug for non-therapeutic purposes is regarded as doping, and anti-doping tests may be positive.

4.5. Interaction with other medicinal products and other forms of interaction

Due to atenolol:

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects e.g., verapamil, diltiazem can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia, and cardiac failure. Beta-blockers must not be associated with a calcium antagonist therapy (verapamil, etc.): neither should be administered within 48 hours of discontinuing the other.

Class I antiarrhythmic drugs (e.g. disopyramide) and amiodarone have a potentiating effect on atrial conduction time and induce a negative inotropic effect.

Digitalis glycoside drugs, in association with beta-blockers, may increase the atrioventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Concomitant use of sympathomimetic agents, such as adrenaline, can counteract the effect of beta-blockers.

Concomitant use of prostaglandin synthetase inhibiting drugs (e.g. ibuprofen, indomethacin) may decrease the hypotensive effects of beta-blockers.

Due to chlorthalidone:
The chlorthalidone component may reduce the renal clearance of lithium leading to increased serum concentrations. Dose adjustments of lithium may therefore be necessary.

Due to the combination product:
Concomitant therapy with dihydropyridines e.g., nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of baclofen may increase the antihypertensive effect making dose adjustments necessary.

4.6. Pregnancy and lactation

Pregnancy: ATENIGRON must not be administered during pregnancy.
Lactation: ATENIGRON must not be administered during lactation.

4.7. Effects on ability to drive and use machines

The use of ATENIGRON is unlikely to result in any impairment on the ability to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8. Undesirable effects

In general, they include cold extremities, muscular fatigue, bradycardia, occasionally sleep disturbances. Due to the chlorthalidone component, like other diuretics, gastrointestinal disorders, headache, dizziness, hypokaliaemia, hyperuricaemia and reduced glycide tolerance may occur. In rare cases, allergic skin reactions, thrombocytopenic purpura and alterations in blood cell counts. The beta-blocker may exacerbate pre-existing peripheral vascular disturbances. ATENIGRON may lead to heart rate reduction due to the presence of a beta-blocker: if the rate drops to less than 55 bpm, discontinue treatment and resume it later at a reduced dose. ATENIGRON does not generally cause a pathological increase in uricemia; hyperuricaemia, even if rare, can be solved by using uricosuric drugs or allopurinol.

In clinical studies, the possible adverse reactions are generally attributable to the pharmacological actions of its components.

The following undesirable effects, listed by body system, have been reported with the following frequencies: very common (≥10%), common (1-9.9%), uncommon (0.1-0.9%), rare (0.01-0.09%), very rare (<0.01%), not known (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: purpura, thrombocytopenia, leukopenia (related to chlorthalidone).

Psychiatric disorders
Uncommon: sleep disturbances of the type noted with other beta-blockers.
Rare: mood changes, nightmares, confusion, psychoses and hallucinations.

Nervous system disorders
Rare: dizziness, headache, paraesthesia.

Eye disorders
Rare: dry eyes, visual disturbances.
Not known frequency: choroidal effusion, acute myopia, and secondary angle-closure glaucoma.

Cardiac disorders

Common: bradycardia.
Rare: heart failure deterioration, precipitation of heart block.

Vascular disorders
Common: cold extremities.
Rare: postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders
Rare: bronchospasm may occur in patients with bronchial asthma or a history of asthma complaints.

Gastrointestinal disorders
Common: gastrointestinal disturbances (including nausea related to chlorthalidone).
Rare: dry mouth.
Not known: constipation.

Hepatobiliary disorders
Rarer: hepatic toxicity including intrahepatic cholestasis, pancreatitis (related to chlorthalidone).

Skin and subcutaneous tissue disorders
Rare: alopecia, psoriasiform skin reaction, exacerbation of psoriasis, skin rashes.

Reproductive system and breast disorders
Rare: impotence.

General disorders and administration site conditions
Common: fatigue.

Musculoskeletal system and connective tissue disorders
Not know: Lupus-like syndrome

Investigations
Common (related to chlorthalidone): hyperuricaemia, hyponatraemia, hypokaliaemia, reduced glucose tolerance.
Not common: elevations of transaminase levels.
Very rare: an increase in ANA (Antinuclear Antibodies) has been observed; however, the clinical relevance of this is not clear.

Discontinuation of ATENIGRON should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via the Italian national reporting system at this address https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

4.9. Overdose
The symptoms of overdosage may include bradycardia, hypotension, acute heart failure and bronchospasm.

General treatment should include: close medical supervision; treatment in an intensive care ward; the use of gastric lavage; activated charcoal and a laxative to prevent absorption of any drug still present in the

gastrointestinal tract; the use of plasma or plasma substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia may be countered with atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10-mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effects could be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

Excessive diuresis should be countered by maintaining normal fluid and electrolyte balance.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: ATENIGRON is an association of a hypotensive and a diuretic. The synergic action of these two components results in effective control of hypertension, ATC code: C07CB03.
ATENIGRON is an antihypertensive drug whose two active components exert a synergic hypotensive action. Atenolol has the ability to selectively block and reverse beta-adrenergic receptors. The hypotensive effect of atenolol is fast acting and seen in the diastolic and systolic blood pressure when at rest and after exercise. Chlorthalidone is a sulfonamide diuretic, effective agent, well tolerated and not subject to develop addiction. The synergic action of its two components results in effective control of hypertension. The pharmacokinetic properties of its components allow for a very simple posology scheme. In fact, taking one tablet daily keeps an active level of 24 hours.

5.2. Pharmacokinetic properties

Pharmacokinetic studies show that plasma peaks occur 2-4 hours after administration. The plasma half life is 6-7 hours but it may rise in patients with renal impairment. Atenolol is poorly bound to plasma protein, less than 5% of the amount in blood; since it is hydrophilic, its distribution volume is very low, almost no liver metabolism, and is excreted unchanged in the urine. Slow rate of diffusion in the central nervous system too.

5.3. Preclinical safety data

Acute and chronic toxicity tests conducted on different animal species showed the product has low toxicity. Fertility and teratogenicity studies showed no pathological changes.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Magnesium stearate, maize starch, pregelatinised maize starch, magnesium carbonate, gelatin, sodium lauryl sulphate.

6.2. Incompatibilities

Refer to point 4.5.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25°C
Tablets must be kept in their original container to protect them from light and moisture.

6.5. Nature and contents of container
Aluminium and PVC lithographed blisters.
Tablets: 28 tablets

6.6. Special precautions for disposal and other handling
Medicines no longer used and its medical waste should be disposed of in compliance with the local regulations in force.

7. MARKETING AUTHORISATION HOLDER
MAGIS FARMACEUTICI S.r.l. - Via Cefalonia, 70 - 25124 BRESCIA.

8. MARKETING AUTHORISATION NUMBER
100-MG + 25-MG TABLETS - 28 TABLETS – MA No. 025987037

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION
Date of renewal: June 2010

10. DATE OF REVISION OF THE TEXT
May 2022