SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BLOKIUM 50 mg Tablets

BLOKIUM 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet of BLOKIUM 50 mg contains:

Atenolol (INN) ..... 50 mg

For a full list of excipients, see section 6.1.

One tablet of BLOKIUM 100 mg contains:

Atenolol (INN) ..... 100 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of essential hypertension. Angina pectoris. Cardiac arrhythmias. Acute myocardial infarction.

4.2. Posology and method of administration

Hypertension

Most patients respond to a 100 mg dose, taken once daily. A certain number of people may be maintained on a 50 mg dose once daily.

An assessment of the response should only be performed after 1 to 2 weeks of continued treatment.

In the case that the reduction in blood pressure is insufficient, atenolol may be combined with a diuretic or another antihypertensive agent.

Angina pectoris

The effective dose is generally 100 mg taken in a single dose or in two doses of 50 mg daily. Efficacy tends not to increase if this dose is exceeded.

Cardiac arrhythmias

After initial treatment with atenolol i.v., a maintenance regimen may be established with 50 or 100 mg of atenolol by oral route taken once daily.

Acute myocardial infarction

For patients in whom intravenous beta blocker treatment is indicated, within the 12 hours following onset of chest pain, administer 5-10 mg of atenolol immediately in a slow intravenous injection (1 mg/minute), followed by 50 mg of oral atenolol approximately 15 minutes afterward, assuming no adverse effect has occurred from the intravenous dose.

Subsequently, 50 mg of atenolol are orally administered 12 hours after the intravenous dose, and then 100 mg, orally, after another 12 hours; this will be the daily dose. If bradycardia and/or hypotension require treatment, or any other undesirable effect occurs related to atenolol, treatment should be suspended. (See section 4.4., *Special warnings and precautions for use*).

Patients with renal insufficiency

Given that atenolol elimination occurs primarily via urinary excretion, the posology should be adjusted in cases of renal insufficiency.

The table below shows the recommended doses:

Creatinine clearance	*Serum creatinine*	*Atenolol dose*
125-35 (ml/min/1.73 m^2)	70-300 (µmol/litre)	Normal
35-15 (ml/min/1.73 m^2)	300-600 (µmol/litre)	50 mg/day or 100 mg every other day
<15 (ml/min/1.73 m^2)	>600 (µmol/litre)	50 mg every other day or 100 mg every 4 days

Patients on haemodialysis should receive 50 mg after every dialysis session. The administration must take place in a hospital given that abrupt drops in blood pressure may occur.

The elderly

Beta blockers can be used safely and effectively in the elderly. However, unpredictable responses to beta blockers may occur in these patients and they are more susceptible to adverse reactions, especially headache, drowsiness, bradycardia, hypotension and hypothermia. Therefore, the dose should be chosen carefully and specifically for each patient. Cardioselective beta blockers with a short half-life are the best choice in these patients.

Children

There is no experience in paediatric use and, therefore, Blokium should not be used in children.

4.3. Contraindications

BLOKIUM is contraindicated in patients who present any of the following situations:

- known hypersensitivity to atenolol or to any of its components, or to beta blockers in general

- bradycardia, cardiogenic shock, hypotension, severe peripheral arterial circulatory disorders, uncontrolled heart failure
- second- or third-degree AV block, sick sinus syndrome
- metabolic acidosis
- untreated phaeochromocytoma

4.4. Special warnings and precautions for use

Atenolol may be used with precaution in patients with controlled heart failure. If congestive heart failure occurs during treatment, the drug may be temporarily suspended until the heart failure is controlled.

As with other beta blockers, treatment should not be suspended abruptly in patients with ischaemic heart disease (gradual withdrawal over a 2-week period). Cases have been described of exacerbation of angina pectoris with or without by myocardial infarction, severe hypertension and ventricular arrhythmias in patients in whom beta blocker treatment has been suspended abruptly. If angina pectoris worsens or if acute coronary insufficiency develops, treatment with atenolol should be quickly restored, at least temporarily. However, treatment should be suspended if severe heart failure or severe bradycardia occurs.

The number and duration of angina pectoris attacks may increase in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. BLOKIUM is a beta-1 selective beta blocker; therefore, its use may be considered although the patient should duly monitored.

Due to its negative effect on conduction time, care should be taken if administered to patients with first degree heart block.

One of the pharmacological actions of atenolol is reduction in heart rate. In the case that excessive bradycardia occurs and can be attributed to the drug, the dose should be reduced and, if necessary, withdrawn completely.

Although contraindicated in severe peripheral arterial circulatory disorders (see section 4.3, *Contraindications*), BLOKIUM may also aggravate said disorders even if they are less severe.

In patients, particularly those with impaired ventricular function and/or sinoatrial or atrioventricular conduction disorders, the combined administration of beta blockers and calcium channel blockers with negative inotropic effects (for example, verapamil and diltiazem), may cause a prolongation of these effects, causing severe hypotension, bradycardia and heart failure (see section 4.5., *Interaction with other medicinal products and other forms of interaction*).

In patients with Raynaud's phenomenon or depression, treatment with atenolol should be strictly monitored.

As it is a cardioselective beta blocker, it may be used with precaution in patients with chronic obstructive airway diseases. However, in asthma patients it may cause an increase in the resistance of the airways. In general, this bronchospasm can be reversed with normal-use bronchodilators, such as salbutamol or isoprenaline.

In diabetic patients, it should be kept in mind that beta blockers can mask tachycardia, one of the first symptoms of a hypoglycaemic reaction.

For the same reason, it may mask the signs of hyperthyroidism or thyrotoxicosis.

In the case of severe impaired liver function, an individual dose adjustment of atenolol should be made.

It may cause a more serious reaction to a variety of allergens when administered in patients with a history of anaphylactic reactions to said allergens. These patients may not respond to the normal doses of adrenaline used in the treatment of allergic reactions.

Anaesthesia: if it is decided to suspend the medication before a surgical intervention, the withdrawal should take place 48 hours before the surgery. If vagal preponderance occurs, it can be corrected with atropine (1-2 mg i.v.).

Renal insufficiency: special care should be taken in patients with impaired renal function (see section 4.2., *Posology and method of administration*).

There is no experience in paediatric use and, therefore, it should not be used in children.

Beta blockers can be used in the elderly although their response to treatment can be unpredictable, with a greater risk of adverse events; therefore, precaution is required and the best choice is cardioselective beta blockers with a short half-life.

Warning for sportsmen and sportswomen: it should be kept in mind that this medicinal product contains a component that may lead to a positive doping test result.

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

In patients, particularly those with impaired ventricular function and/or sinoatrial or atrioventricular conduction disorders, the combined administration of beta blockers and calcium channel blockers with negative inotropic effects (for example, verapamil and diltiazem), may cause a prolongation of these effects, causing severe hypotension, bradycardia and heart failure. Therefore, oral treatment with one of the previously mentioned medicinal products should not be started until 7 days after suspending oral treatment with the other (see section 4.4., *Special warnings and precautions for use*).

Concomitant therapy with dihydropyridines (for example, nifedipine) may increase the risk of hypotension and may cause heart failure in patients who present the latent form.

Digitalis glycosides (such as digoxin) in association with beta blockers may increase atrioventricular conduction time.

Beta blockers may exacerbate rebound hypertension secondary to the withdrawal of clonidine. If clonidine is administered concurrently with beta blockers, treatment with beta blockers should be stopped several days before suspending treatment with clonidine, but if clonidine is substituted by beta blockers, starting treatment with beta blockers should be delayed several days after suspending treatment with clonidine.

Precaution should be taken when prescribing a beta blocker with class I anti-arrhythmics, such as disopyramide, as it may lead to decreased cardiac output.

The concomitant use of sympathomimetics, such as adrenaline, may counteract the effect of beta blockers. The administration of atenolol together with reserpine may enhance the effects of atenolol.

Concomitant use of prostaglandin synthetase inhibitors, such as ibuprofen and indometacin, may decrease the hypotensive effects of beta blockers.

Caution must be exercised when using anaesthetic agents with BLOKIUM; the anaesthesiologist should be informed and the choice of 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 that cause myocardial depression should be avoided.

The concomitant administration of atenolol with other beta blockers, such as celiprolol, propranolol, metoprolol, timolol, bisoprolol, carvedilol, oxprenolol or nebivolol may increase the cardiac depression effect of atenolol.

4.6. Pregnancy and lactation

Pregnancy

Atenolol crosses the placenta and appears in umbilical cord blood. No studies have been conducted regarding the use of atenolol during the first trimester of pregnancy, and therefore the possibility of foetal damage cannot be ruled out. However, this drug has been used in individual cases under strict supervision for the treatment of hypertension during the third trimester, with no evidence of foetal damage. Administration to pregnant women for the treatment of mild to moderate hypertension during the second trimester of pregnancy has been associated to intrauterine growth retardation and signs of foetal block. The use of atenolol in pregnant women or women who think they may be pregnant requires that anticipated benefits be weighed against possible risks, especially during the first and second trimester of pregnancy.

Lactation

There is significant accumulation of atenolol in human milk and, therefore, caution should be exercised when this drug is administered to breastfeeding women, as it may cause signs/symptoms of beta blockages (bradycardia, hypotension, respiratory insufficiency and hypoglycaemia) in infants, especially in premature infants and those with impaired renal function.

4.7. Effects on ability to drive and use machines

It is unlikely that the use of atenolol negatively affects these abilities; however, it should be considered that occasionally dizziness or fatigue may occur. Driving, using machines or performing any other activity that requires alertness is not recommended during the first few weeks of treatment.

4.8. Undesirable effects

The undesirable effects associated with atenolol are more frequent at the start of treatment and tend to disappear after 1-2 weeks. The most characteristic undesirable effects are, in order of frequency:

- Very Common (>1/10): fatigue, sleepiness, headache, insomnia, depression, bronchospasm, peripheral vasoconstriction with coldness of extremities and tingling sensation.

- Common (>1/100, <1/10): severe cardiovascular disorders (bradycardia, AV block, heart failure and hypotension), hallucinations, drowsiness, confusion, paraesthesia, peripheral neuropathy, myopathy, visual damage or disorder.
- Uncommon (>1/1000, <1/100): diarrhoea, constipation, nausea, vomiting, abdominal cramps, hypersensitivity, exanthema, pruritus, reversible alopecia, thrombocytopenia, agranulocytosis, nonthrombocytopenic purpura, transient eosinophilia, impotence, decrease in libido, pulmonary fibrosis and pleural effusion.

Occasionally, the following laboratory test abnormalities have been described with the use of atenolol: decrease in HDL cholesterol, hypoglycaemia.

Withdrawal of treatment should be considered if, based on clinical judgement, the well-being of the patient is adversely affected by any of the abovementioned effects.

4.9. Overdose

The symptoms of overdose may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment consists of: close monitoring; use of gastric lavage, activated charcoal and a laxative to prevent absorption of the drug still present in the gastrointestinal tract; use of plasma or plasma substitutes to treat hypotension and shock. The use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia may be treated with 1-2 mg of intravenous atropine and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of 10 mg of glucagon intravenously. If required, this may be repeated or followed by an intravenous infusion of 1-10 mg/hour of glucagon, depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as prenalterol (5 mg/h i.v.) should be administered followed by dobutamine by intravenous infusion.

Excessive hypotension may occur after the administration of a beta agonist, but it may be corrected by using another more selective drug, such as prenalterol or dobutamine.

If the intoxication was serious, the dose of dobutamine should be increased to obtain the required response according to the clinical condition of the patient. Bronchospasm can usually be reversed with bronchodilators.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-adrenoceptor blocking agent (atenolol), ATC code: C07A B03

Atenolol is a cardioselective $beta_1$ blocking agent (it acts preferably on the cardiac $beta_1$ adrenergic receptors). Selectivity decreases with an increase in dose.

Atenolol lacks intrinsic sympathomimetic activity and membrane stabilisation and, like other beta blockers, has negative inotropic effects and therefore is contraindicated in uncontrolled heart failure.

As with other beta blockers, the mechanism of action of atenolol in the treatment of hypertension is not completely understood.

It is likely that the action of atenolol on the reduction of heart rate and contractility is what makes it effective in eliminating or reducing symptoms in patients with angina pectoris.

It is unlikely that the additional secondary properties that S(-) atenolol has, in comparison to the racemic mixture, will give rise to different therapeutic effects.

Atenolol is effective and adequately tolerated in most ethnic populations; however the response may be lower in black patients.

Atenolol is compatible with diuretics, other hypotensive agents and antianginals (see section 4.5., *Interaction with other medicinal products and other forms of interaction).*

5.2. Pharmacokinetic properties

The absorption of atenolol after oral administration is consistent but incomplete (approximately 40-50%), with peak plasma concentrations occurring 2-4 hours after the dose. Blood concentrations of atenolol are consistent and undergo very little variability. It undergoes little or no hepatic metabolism and more than 90% of that absorbed reaches systemic circulation unaltered. The plasma half-life is 6 hours, but this may increase in severe renal impairment as the kidney is the primary route of elimination. Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is also minimal, approximately 3%.

BLOKIUM is effective for at least 24 hours after a single oral daily dose. This pharmacological simplicity facilitates compliance because of patient acceptability.

5.3. Preclinical safety data

In acute toxicity studies, atenolol was well tolerated in all species and there were no significant differences between oral and intravenous administration. The LD_{50} data observed were as follows:
LD_{50} p.o. mice = 2.0 g/kg

LD_{50} i.v. mice = 98.7 g/kg

LD_{50} p.o. rats = 3.0 g/kg

LD50 i.v. rats = 59.24 g/kg

LD50 i.v. rabbits = 50.0 g/kg

Atenolol presents weaker acute toxicity than propranolol, another beta blocker from the same group. Thus, the LD_{50} of atenolol by oral route in mice is almost four times higher than that of propranolol, in the same conditions (2000 mg/kg vs. 565 mg/kg).

The effects observed in the subacute and chronic toxicity studies, administering high doses of atenolol, are the desirable effects pursued for this substance, e.g., reduction in heart rate and reduction in blood pressure.

In rats, the studies on fertility and reproductive function, administering oral doses of 200 mg/kg, did not show undesirable effects in males, females or offspring. There were no effects on growth or reproductive function in offspring.

In rats and rabbits, teratological studies on atenolol did not show any teratogenic capacity.

It has also been demonstrated that atenolol does not have mutagenic capacity; the demonstrative studies included the dominant-lethal test, the *in vivo* cytogenetic test of Chinese hamster bone marrow and the *Salmonella typhimurium* reverse mutation assay with and without *in vitro* metabolic activation in the liver and homogenised thymus tissue of rats and mice.

The oncogenic/carcinogenic potential was studied in rats and mice, administering doses of up to 300 mg/kg of atenolol, for a maximum period of two years, with no tumourigenic activity or biological abnormalities found in the clinical-pathological exams, and no significant mortality differences between the treated and control groups.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose
Magnesium stearate
Sodium starch glycolate
Povidone

6.2. Incompatibilities

None described.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Do not store above 30ºC.

6.5. Nature and contents of container

Packs containing 30 or 15 tablets, in PVC-PVDC/aluminium blisters.

6.6. Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF REVISION OF THE TEXT

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