

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Atenolol Actavis[®]. (Atenolol Actavis[®] is marketed under the trade name Tensol[®] in Malta.)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenolol INN 25 mg, 50 mg or 100 mg.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of hypertension.
Management of angina pectoris.

4.2 Posology and method of administration

Dosage for adults:

Hypertension: 50-100 mg daily, rarely 200 mg daily. The drug can be administered as a single daily dose. In case of impaired renal function, lower doses should be used.

Angina pectoris: 50 mg twice daily; can be increased with caution to 100 mg twice daily.

Dosage for children: There is no information available regarding dosage for children.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled heart failure. Cardiogenic shock. Second or third degree atrioventricular heart block or sick sinus syndrome. Severe bradycardia, hypotension or metabolic acidosis.
Pulmonary diseases with bronchial contraction. Uncontrolled phaeochromocytoma. Severe peripheral vasoconstriction. Insulin dependant diabetes. Pregnancy.

4.4 Special warnings and special precautions for use

- Abrupt discontinuation of the drug in patients with coronary disease should be avoided. Atenolol reduces the contractility of the heart and heart failure may deteriorate. Patients with underlying or confirmed heart failure can only receive this medicine if they receive concomitant treatment for heart failure.
- The drug may cause symptoms of obstructive pulmonary disease. Atenolol should be administered with caution to patients with bronchial asthma and patients with chronic obstructive pulmonary disease. These patients should receive bronchodilators concomitantly. In rare cases there is an increased airway resistance in asthmatic patients and therefore it might be necessary to increase the dosage of β_2 receptor stimulating drug.
- The drug can mask the signs of hypoglycaemia and thyrotoxicosis.
- In case of renal impairment, the dosage of atenolol must be reduced.
- Peripheral vasoconstriction can deteriorate with the use of atenolol.

- Raynaud's syndrome. Atenolol should be administered with caution to patients with intermittent claudication, Prinzmetal's angina and first degree atrioventricular heart block.
- If there are signs of hypotension the dosage should be adjusted. Caution should be exercised in case of severe diabetes.
- Treatment should be discontinued in patients, with coronary thrombosis or a probable coronary thrombosis if respiratory difficulties or cold sweats get worse.
- Beta blockers can increase anaphylactic reactions, treatment with adrenaline in standard doses could then be insufficient.
- The treatment should be discontinued gradually over a period of 1-2 weeks and at least 24 hours before surgery.

4.5 Interaction with other medicaments and other forms of interaction

Beta-adrenoceptor blocking agents and calcium channel blockers may cause atrioventricular heart block and cardiac failure if administered concomitantly. This particularly applies to verapamil and to a lesser extent, diltiazem. Digitalis and beta-adrenoceptor blockers may cause bradycardia or heart block. Cimetidine increases the effects of atenolol. Aluminium hydroxide reduces the effects of the drug. Atenolol may mask and prolong the signs of hyperglycaemia in diabetic patients.

- If Class I anti-dysrhythmic agents such as disopyramide and Beta-blockers are given concomitantly, the cardiac output decreases which can have serious effect on the activity of the left ventricle. Also avoid this combination if the patient has impaired sinoatrial node and impaired AV-conduction. The most studied interaction is the interaction with disopyramide. Atenolol can decrease the clearance of disopyramide, which has shown to decrease heart rate.
- Epinephrine. Hypertension and hypotension have occurred in healthy individuals who took non-selective Beta-blockers, the risk is less if selective Beta-blockers are used.
- If treatment with clonidine is withdrawn suddenly in patients concomitantly treated with Beta-blockers, hypertension can increase.
- Non-steroid anti-inflammatory drugs (NSAID) counterweight the effects of Beta-blockers. Indometacin has been studied the most. It doesn't seem to occur with sulindac and in one study there was no such interaction with diclofenac.
- Nifedipine. Concomitant use in patients with impaired cardiac function can cause hypotension and heart failure. This interaction with atenolol has not occurred in healthy individuals.
- Insulin and analogues, Sulphonamides, urea derivatives. An enhanced hypoglycaemic effect with concomitant use of Beta-blockers can occur when patients glycogen supply is fixed, e.g. malnutrition and fasting. This interaction is less likely when beta₁-blocks like atenolol are used. Atenolol can mask the signs of hypoglycaemia.
- Anaesthetics, inhalant (including chloroform). Concomitant use of Beta-blockers and anaesthetics can lead to blood pressure drop requiring a treatment with atropine. Therefore, it is recommended that the administration of Beta-blockers should be stopped 24 hours prior to the administration of an anaesthetic. This may increase the risk of irregular heartbeat from catecholamines if patients have suddenly stopped using the drug before being administered an anaesthetic. Another possible result of suddenly stopping Beta-blockers is coronary thrombosis. It is not recommended to suddenly discontinue the use of Beta-blockers before anaesthesia; thus, very high dosages should be lowered gradually.
- Ergotamine: Concomitant use of ergotalkaloids and Beta-blockers has a negative effect on the blood circulation in peripheral tissue, rare isolated incidents of severe peripheral ischaemia have occurred with concomitant use of propranolol and oxprenolol with migraine patients.
- Phenylpropanolamine (norephedrine). Beta-blockers can cause hypertension in patients using high doses of phenylpropanolamine.

4.6 Pregnancy and lactation

Pregnancy: Atenolol is contra-indicated on the third trimester of pregnancy because of the risk in delivery. The safety of atenolol during pregnancy has not been established and its use should be avoided unless the benefit is considered to be greater than the risk. The drug should not be used during the last trimester because of complications during delivery

Lactation: Atenolol is excreted into breast milk but at therapeutic doses it is not considered to have effects on the breast-fed child.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Very common (>1%):

General: Fatigue and muscle fatigue, cold extremities.

Cardiovascular disorders: Hypotension (resting heartbeat less than 50 beats a minute).

Gastrointestinal disorders: Discomforts like nausea and diarrhoea

Common (<1%, >0,1%):

Nervous system disorders: Insomnia

Hepatobiliary disorders: Increased transaminases.

Uncommon (<0,1%, >0,01%):

General: Dizziness, increased hydrophoresis, headache.

Blood: Thrombocytopenic purpura.

Cardiovascular disorders: Deteriorated heart failure, AV-block, orthostatic hypotension, sometimes with fainting, Raynaud's syndrome.

Central nervous system disorders: Nightmares, hallucinations, depression, emotional disorder, delirium.

Gastrointestinal disorders: Dry mouth (xerostomia).

Skin: Baldness, rash, psoriasis, purpura.

Hepatobiliary disorders: Toxic effect on the liver, including cholestasis

Respiratory disorders: Bronchospasm in patients with bronchial asthma or who have a history of asthma.

Nervous system disorders: Changes in skin sensation.

Eye disorders: Dry eyes and impaired vision.

4.9 Overdose

Toxicosis: A 1½ year old child took 50 mg and a 5 year old took 100 mg (given activated charcoal) and they showed no symptoms of toxic effects. An adult who took 300-350 mg developed mild toxic effects. A 15 year old teenager took 500 mg and got moderate toxic effects. Symptoms are mainly from the cardiovascular system but in certain cases, especially in children and teenagers, symptoms from the central nervous system and respiratory distress can be overwhelming.

Symptoms: Bradycardia, AV-block, asystole, blood pressure drop, poor peripheral blood flow, cardiopathy, possibly shock. Respiratory insufficiency and respiratory arrest.

Other symptoms: Fatigue, lethargy, unconsciousness, subtle tremor, convulsions (even oesophageal spasm), sweat, numbness, bronchospasm, nausea, vomiting, hyperglycaemia or hypoglycaemia (especially with children), hypercalcaemia. Effect on renal function. Reversible myasthenic syndrome.

Treatment: Gastric lavage and activated charcoal. NB! To avoid vagus nerve stimulation the patient has to be given atropine before gastric lavage is performed, adults 0,25-0,5 mg i.v. but children 10-20 µg/kg.

Severe cases: Tracheal intubation and treatment in a respirator, transfusion, glucose infusion, heart electrocardiogram, atropine 1-2 mg i.v., even repeated, especially if there are vagal nerve symptoms.

Bradycardia can be treated with atropine 1-2 mg intravenously for adults and 50 µg for infants. This may be followed by glucagon 10 mg intravenously followed by an intravenous infusion of glucagon 1-10 mg/hour. If no response to glucagon occurs or if glucagon is not available, prenalterol 5 mg intravenously, prenalterol infusion 5 mg/hour or dobutamine infusion 2.5-10 micrograms/kg/minute may be administered.

In case of myocardial depression: Dobutamine or dopamine infusion with calcium gluconate (9 mg/ml), 10-20 ml. 50-150 µg/kg i.v. for one minute, followed up with an infusion can be tried. Adding epinephrine has helped in some cases.

In case of irregular heartbeat and a longer QRS-interval: Sodium (chloride- or bicarbonate) infusion.

In case of disturbed blood circulation it can be justified to perform resuscitation for hours.

In case of bronchospasm: Terbutaline (i.v. or inhaled) can be administered.

In case of severe poisoning, where other treatment did not work, haemodialysis can be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-adrenoceptor blocking agents, not in combination, selective.

ATC code: C07AB03

Selective beta-adrenoceptor blocking agent, selective for beta₁- receptors, without intrinsic adrenergic activity (ISA). Atenolol acts on beta₁-receptors in the heart in lower doses than on beta₂-receptors in peripheral veins and bronchus. Selectivity decreases with increasing dose. Beta-blockers have negative effect on heart contractility and heart rate. The S-isomer of atenolol is the active form. Atenolol is without intrinsic sympathomimetic and membrane stabilising activities and does not exert any beta-stimulating effect nor does it increase membrane stability. Atenolol is a water soluble Beta-blocker and therefore it does not aggregate in brain tissue like lipid-soluble Beta-blockers.

Treatment with atenolol inhibits catecholamine activity in mental or physical stress and reduces heart rate, heart input per minute and blood pressure. Treatment with atenolol causes a small resistance in peripheral veins at first. Atenolol does not inhibit normal vasodilatation on exertion, because of increased epinephrine release from adrenal glands. In therapeutic doses atenolol has lesser contraction effect on bronchus muscle than Beta-blockers that are not beta₁ selective. This makes the drug suitable for treatment for patients who have bronchial asthma or other constricting respiratory diseases, concomitantly with beta₂-adrenergic drugs. Diabetic patients can take the drug since it has negligible effect on insulin release and glucose metabolism.

The drug causes substantial reduction of blood pressure in treatment of hypertension, in both the standing and lying position and does not produce orthostatic hypotension nor disturbance in electrolyte balance.

Concomitant use of other antihypertensive drugs is possible and preferably with thiazides and other drugs that cause peripheral vasodilatation.

5.2 Pharmacokinetic properties

Bioavailability following oral administration is about 45%, but with individual variation this can triple or quadruple. Peak plasma concentrations occur 2-4 hours after oral administration and the duration of therapeutic effect is up to 24 hours. Plasma concentration increases comparatively with the patient's age. If taken with food, the absorption is reduced by approximately 20%. Protein binding is approximately 3% and the volume of distribution is 0,7 l/kg. Atenolol has low lipid solubility. Hepatic metabolism is negligible and the drug is eliminated, almost always unchanged, through the kidneys. Only 10% of atenolol is eliminated as metabolite, none of which have any pharmaceutical activity in man. Plasma half-life is 6-9 hours. In case of impaired renal function half-life is prolonged, but impaired hepatic function has no effect on half-life.

5.3 Preclinical safety data

No relevant data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin *B.P.*

Heavy magnesium carbonate *Ph. Eur.*

Magnesium stearate *Ph. Eur.*

Microcrystalline cellulose *Ph. Eur.*

Maize starch *Ph. Eur.*

Sodium lauryl sulphate *Ph. Eur.*

Talc *Ph. Eur.*

Purified Water *Ph. Eur.*

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Atenolol 25 mg: 2 years.

Atenolol 50 mg: 4 years.

Atenolol 100 mg: 4 years.

6.4 Special precautions for storage

Do not store above 25°C.

Keep out of reach and sight of children.

6.5 Nature and contents of container

Plastic containers.

Tablets 25 mg: 30 and 100 tablets.

Tablets 50 mg: 30 and 100 tablets.

Tablets 100 mg: 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling/disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis hf.
Reykjavíkurvegur 76-78
IS-220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

Atenolol Delta[®] 25mg: 860128 (IS)
Atenolol Delta[®] 50mg: 843408 (IS)
Atenolol Delta[®] 10mg: 843409 (IS)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Atenolol Delta[®] 25mg: 1st April 1987
Atenolol Delta[®] 50mg: 25th July 1985
Atenolol Delta[®] 10mg: 25th July 1985

Renewal: 12th January 2004 – 12th January 2009

10. DATE OF (PARTIAL) REVISION OF THE TEXT

13 May 2005