

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atenolol 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg of Atenolol B.P.

3. PHARMACEUTICAL FORM

Orange, film-coated tablets, marked AT/100 on one side and the Company logo on the reverse, intended for oral administration to human beings.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Management of hypertension.

Management of angina pectoris.

Management of cardiac arrhythmias.

Early intervention in the acute phase of myocardial infarction.

4.2. Posology and Method of Administration

Adults: Hypertension: One tablet (50 mg) daily. Higher doses rarely necessary. A further reduction in blood pressure may be achieved by combining atenolol with other antihypertensive agents. For example, co-administration of atenolol with a diuretic provides a highly effective and convenient antihypertensive therapy.

Angina: Most patients with angina pectoris will respond to 100mg daily given orally once daily or 50mg given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

Dysrhythmias: A suitable initial dose of atenolol is 2.5mg (5ml) injected intravenously over a 2.5 minute period (i.e. 1mg/minute). This may be repeated at 5 minute intervals until a response is observed up to a maximum

dosage of 10mg. If atenolol is given by infusion, 0.15mg/kg bodyweight may be administered over a 20 minute period. If required, the injection or infusion may be repeated every 12 hours. Having controlled the dysrhythmias with intravenous 'atenolol' a suitable oral maintenance dosage is 50-100mg daily, given as a single dose.

Myocardial infarction: For patients suitable for treatment with intravenous beta-blockade and presenting within 12 hours of the onset of chest pain, atenolol 5-10mg should be given by slow intravenous injection (1mg/minute) followed by atenolol 50mg orally about 15 minutes later provided no untoward effects occur from the intravenous dose. This should be followed by a further 50mg orally 12 hours after the intravenous dose and then 12 hours later by 100mg orally to be given once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, atenolol should be discontinued.

Elderly patients: Dosage requirements may be reduced, especially in patients with impaired renal function.

Children: There is no paediatric experience with atenolol and for this reason it is not recommended for use in children.

Renal failure: No significant accumulation of atenolol occurs in patients with a creatinine clearance greater than 35ml/min/1.73m² (normal range is 100-150ml/min/1.73²). For patients with a creatinine clearance of 15-35ml/min/1.73m² (equivalent to serum creatinine of 300-600mcmol/litre) the oral dose should be 50mg daily and the intravenous dose should be 10mg once every two days. For patients with a creatinine clearance of <15ml/min/1.73m² (equivalent to serum creatinine of >600mcmol/litre) the oral dose should be 25mg daily or 50mg on alternate days and the intravenous dose should be 10mg once every four days.

Patients on haemodialysis should be given 50mg orally after each dialysis. This should be done under hospital supervision as marked falls in blood pressure can occur.

Route of administration: Oral

4.3 Contraindications

As with other beta-blocking drugs, atenolol should not be used in patients with any of the following conditions: known hypersensitivity to atenolol or any of the excipients, bradycardia, cardiogenic shock, hypotension, metabolic acidosis, severe peripheral arterial circulatory disturbances, second or third degree heart block, sick sinus syndrome, untreated phaeochromocytoma or uncontrolled heart failure.

4.4 Special warnings and precautions for use

Atenolol as with other beta-blocking drugs:

- Should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7–14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease.

- When a patient is scheduled for surgery, and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk-benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.

-although contra-indicated in uncontrolled heart failure (see Contra-indications above), may be used in patients whose signs of heart failure has been controlled. Caution must be exercised in patients with poor cardiac reserve.

-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 beta1-selective beta-blocking drug, therefore, its use may be considered although utmost caution must be exercised.

-although contra-indicated in severe peripheral arterial circulatory disturbances (see Contra-indications above), may also aggravate less severe peripheral arterial circulatory disturbances.

-because of its negative effect on conduction time, must be used with caution in patients with first degree heart block.

-May mask the symptoms of hypoglycaemia, in particular, tachycardia.

-may mask the 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, and the pulse rate drops to less than 50–55 bpm at rest, the dose may be reduced.

-may cause a more severe reaction to various allergens when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

-should be used only after careful consideration in patients with anamnesticly known psoriasis.

- May cause a hypersensitivity reaction including angioedema and urticaria.
- Should be used with caution in the elderly, starting with a lesser dose (see Section 4.2).

Since Atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73 m².

Although cardioselective (beta1) beta-blocking drugs may have less effect on lung function than non-selective beta-blockers, these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. If such reasons exist, atenolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients. However, this may usually be reversed by commonly used dosage of a bronchodilator such as

salbutamol or isoprenaline.

As with other beta-blockers, in patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.

The label shall contain the following statement:

‘Do not take this medicine if you have a history of wheezing or asthma’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Combined use of beta-adrenoceptor blocking drugs 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 SA or AV conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-adrenoceptor blocking drug nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

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

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

Digitalis glycosides, in association with beta-blocking drugs may increase AV conduction time.

Concomitant use of sympathomimetics e.g. adrenaline, may counteract the effect of beta-blocking drugs.

Concomitant use of alcohol with a beta-blocker may increase the risk of hypotension.

Beta-blockers (especially non-selective ones) may intensify the blood sugar-lowering effects of insulin and oral antidiabetic drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see section 4.4).

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

Anaesthesia: Care should be taken when using anaesthetic agents with atenolol. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible. Concomitant use of beta-adrenoceptor blocking drugs with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

4.6 Pregnancy and lactation

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent.

Breast-feeding is therefore not recommended.

Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol for longer periods to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation. The use of atenolol in women who are, or may become pregnant, requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters.

Neonates born to mothers who are receiving Atenolol at parturition or breast-feeding may be at risk of hypoglycaemia and bradycardia

4.7. Effects on Ability to Drive and Use Machines

Atenolol is unlikely to impair the ability of patients to drive or to operate machinery. However, it should be taken into account that occasional dizziness or fatigue may occur.

4.8 Undesirable effects

Atenolol is well tolerated. The undesirable effects reported in clinical studies are usually attributable to the pharmacological actions of atenolol

The following undesired events, listed by body system, have been reported with the following frequencies: very common ($\geq 10\%$), common (1–9.9%), uncommon (0.1–0.9%), rare (0.01–0.09%), very rare ($< 0.01\%$) including isolated reports, not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Rare: Purpura, thrombocytopenia.

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.

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 asthmatic complaints.

Gastrointestinal disorders:

Common: Gastrointestinal disturbances.

Rare: Dry mouth.

Hepato-biliary disorders:

Uncommon: Elevations of transaminase levels.

Rare: Hepatic toxicity including intrahepatic cholestasis.

Skin and subcutaneous tissue disorders:

Rare: Alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Not known: Hypersensitivity reactions, including angioedema and urticaria.

Reproductive system and breast disorders:

Rare: Sexual dysfunction (Impotence).

General disorders and administration site conditions:

Common: Fatigue.

Investigations:

Very rare: An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

Discontinuance of the drug should be considered if it is the clinical judgement that the well-being of the patient is adversely affected by any of the above reactions.

4.9 Overdose

Symptoms of overdose may include bradycardia, hypotension, acute cardiac insufficiency, cardiovascular collapse and bronchospasm.

General treatment should include close supervision, treatment in an intensive care ward, gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the GI tract, 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 1-2mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously.

If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/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. Because of its inotropic effect, dobutamine could also 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-adrenoceptor 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Atenolol is a beta-adrenoceptor blocking drug which is beta¹ selective (i.e. acts preferentially on beta¹ adrenergic receptors in the heart). Selectivity decreases with increasing dose. It does not possess intrinsic sympathomimetic activity nor membrane stabilising properties. As with other beta-adrenoceptor blocking drugs, atenolol has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

Like other beta-adrenoceptor blocking drugs, the mode of action of atenolol in the treatment of hypertension is unclear. Atenolol reduces cardiac rate and contractility and these actions probably account for its effectiveness in the symptomatic relief of angina.

Atenolol is effective and well tolerated in most ethnic populations, although the response may be less in black patients.

Atenolol is compatible with diuretics, other anti-hypertensive drugs and anti-anginal agents (see Interactions section).

5.2. Pharmacokinetic Properties

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40-50%) with peak plasma concentrations occurring 2-4 hours after dosing.

There is no significant hepatic metabolism of atenolol and more than 90% of the absorbed drug reaches the systemic circulation. The plasma half life is about six hours but this may rise in severe renal impairment since the kidney is the major route of elimination. Due to its hydrophilic structure atenolol penetrates tissues poorly and its concentration in brain tissue is low. Plasma protein binding is also low (approximately 3%).

5.3. Pre-clinical Safety Data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose

Microcrystalline Cellulose

Sodium Lauryl Sulphate

Sodium Starch Glycollate

Maize Starch

Gelatin

Purified Water

Magnesium Stearate

Tablet coat

Opadry OY-I-7000

6.2. Incompatibilities

Nil

6.3. Shelf-Life

36 months.

6.4. Special Precautions for Storage

Store below 25°C.
Protect from light.

6.5. Nature and Content of Container

Blister packs which consist of strips made from hard PVC with a foil back packed in cardboard cartons to contain 2 x 14 tablets or 4 x 14 tablets.

6.6. Instructions for Use, Handling and Disposal

Use as directed by the physician.
Keep out of reach of children.

7. MARKETING AUTHORISATION HOLDER

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CR0 0XT,
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