SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atenolol Tablets 25 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenolol Ph. Eur. 25.00 mg

Excipients with known effect:

Each tablet also contains 10 mg of lactose monohydrate and 35 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White bi-convex film-coated unscored tablet, marked 'ATEN 25' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atenolol is indicated in the:

1. Management of hypertension
2. Management of angina pectoris
3. Management of cardiac arrhythmias
4. Management of myocardial infarction: early intervention in acute phase

4.2 Posology and method of administration

Posology

The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage. The following are guidelines;

Adult Dose:

I. Hypertension

Most patients respond to 100 mg daily given orally as a single dose. Some patients, however, will respond to 50 mg given as a single daily dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining Atenolol with other anti-hypertensive agents. For example,

co-administration of Atenolol with a diuretic provides a highly effective and convenient anti-hypertensive therapy.

II. Angina

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

III. Cardiac Arrhythmias

Having controlled the arrhythmia with intravenous atenolol, a suitable oral maintenance dosage of 50 to 100 mg daily may be given as a single dose.

IV. Myocardial Infarction

For patients suitable for treatment with intravenous beta-blockade and presenting within 12 hours of the onset of the chest pain, atenolol 5-10 mg should be given by slow intravenous injection (1 mg/minute) followed by Atenolol 50 mg orally about 15 minutes later, provided no untoward effects occur from the intravenous dose. This should be followed by a further 50 mg orally 12 hours after the intravenous dose and then 12 hours later by 100 mg orally 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.

Paediatric population:

Atenolol is not recommended for use in children.

Dosage in renal failure:

Since atenolol is excreted via the kidneys, the dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73m^2 (normal range is 100-150 ml/min/1.73m^2). For patients with a creatinine clearance of 15-35 ml/min./1.73m^2 (equivalent to serum creatinine of 300-600 micromol/litre), the oral dose should be 50 mg daily and the intravenous dose should be 10 mg once every two days. For patients with a creatinine clearance of < 15 ml/min/1.73m^2 (equivalent to serum creatinine of > 600 micromol/litre) the oral dose should be 25 mg daily or 50 mg on alternate days and the intravenous dose should be 10 mg once every four days.

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

Method of Administration:

Oral

4.3 Contraindications

Atenolol, as with other beta-blockers should not be used in patients with any of the following:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- second or third degree heart block
- uncontrolled heart failure
- bradycardia (<45 bpm)
- hypotension
- sick sinus syndrome
- cardiogenic shock
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- untreated phaeochromocytoma

4.4 Special warnings and precautions for use

Atenolol should not be taken if there is a history of wheezing or asthma, until a doctor or pharmacist has been consulted.
Although cardioselective beta-adrenoceptor blocking drugs may have less effect on lung function than non-selective beta-adrenoceptor blocking drugs, as with all betaadrenoceptor blocking drugs, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, Atenolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients, however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline. The label and patient information leaflet for this product state the following warning: “Tell your doctor before you take this medicine if you have asthma, wheezing or any other similar breathing problems. If you have ever had asthma or wheezing, do not take this medicine without first checking with your doctor.”
Although contraindicated in uncontrolled heart failure (see section 4.3), Atenolol may be used in patients whose signs of heart failure have been controlled. Special care should be taken with patients whose cardiac reserve is poor.
Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first-degree heart block.
One of the pharmacological actions of atenolol is to reduce heart rate. In rare instances when symptoms may be attributable to the slow heart rate and the pulse rate drops to less than 50–55 bpm at rest, the dose may be reduced.
Atenolol may mask the symptoms of hypoglycaemia, in particular, tachycardia. Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels. (see Section 4.5).
As with other beta-blocking drugs, treatment should not be discontinued 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.
Atenolol 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, its use may be considered although utmost caution must be exercised.
Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), Atenolol may also aggravate less severe peripheral arterial circulatory disorders.
Atenolol may cause a hypersensitivity reaction including angioedema and urticaria.
While taking beta-adrenoceptor blocking drugs patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.
Atenolol may mask the signs of thyrotoxicosis.
As with other beta-blockers, in patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.
When a patient is scheduled for surgery, and a decision is made to discontinue betablocker therapy, this should be done at least 24 hours prior to the procedure. The riskbenefit 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.
Atenolol 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 m^2 (see section 4.2).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium channel blockers

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects, e.g. verapamil and diltiazem, can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sinoatrial or atrioventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta blocker 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.

Cardiac glycosides

Concomitant use with digitalis glycosides may increase atrio-ventricular conduction time.

Anti-hypertensives

Beta-adrenoceptor blocking drugs may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered the betaadrenoceptor 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 (see also prescribing information on clonidine). Generally the hypotensive effect is enhanced when β-blockers are given with other antihypertensive drugs (including ACE inhibitors, adrenergic neurone blockers, αblockers and diuretics).

Vasodilators

Severe postural hypotension is possible when β-blockers are given with moxisylyte.

Anti-arrhythmics

Care should be taken in prescribing a beta-adrenoceptor blocking drug with amiodarone and Class 1 anti-arrhythmic agents such as disopyramide and quinidine due to the potentiating effect on atrial-conduction time, induced negative inotropic effect, increased risk of bradycardia, AV block and myocardial depression.

Sympathomimetcs

In general, beta-adrenoceptor blocking agents should not be given concomitantly with amphetamines and sympathomimetic amines. Risk of severe hypertension and bradycardia with concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine).

Anti-diabetics

Concomitant use with insulin and oral antidiabetic drugs may enhance their hypoglycaemic effects. The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see section 4.4).

Bronchodilators

Atenolol antagonises the bronchodilator effect of Theophylline.

NSAIDs

In general, beta-adrenoceptor blocking agents should not be given concomitantly with non-steroidal anti-inflammatory drugs. Concomitant use of prostaglandin synthetaseinhibiting drugs, e.g. ibuprofen and indometacin, may decrease the hypotensive effects of beta-blockers.

Anti-psychotics

Beta-blockers have additive hypotensive effects if used together with phenothiazines.

Anti-depressants

Enhanced hypotensive effect may occur when beta-blockers given with MAOIs

Hypnotics and anxiolytics

Enhanced hypotensive effect with when β-blockers given with hypnotics and anxiolytics.

Anaesthetics

Care should be taken when using anaesthetic agents with atenolol. The anaesthetist should be informed and the choice of the anaesthetic should be the agent with as little negative inotropic activity as possible. Use of beta-blockers 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.

Antacids

Reduced bioavailability may occur if calcium or aluminium hydroxide is administered concurrently.

4.6 Fertility, pregnancy and lactation

Caution should be exercised when atenolol is administered during pregnancy or to a nursing woman.

Pregnancy:

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 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 trimester, since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in growth retardation, intra-uterine deaths, abortion, immature and premature deliveries.

Breast-feeding:

There is a significant accumulation of atenolol in breast milk. 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

Since there are only rare reports of beta-adrenoceptor blocking drugs causing symptomatic hypotension and bradycardia, the use of Atenolol is unlikely to result in the impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

In clinical studies, the side effects reported 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), 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,

Not known: depression

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

Not known: conduction disorders

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

Not known: hypotension

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 urticarial

Musculoskeletal and connective tissue disorders:

Not known: Lupus-like syndrome

Reproductive system and breast disorders:

Rare: 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, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

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

General treatment should include: close 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 uses of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia may be countered with atropine 1-2 mg intravenously, and/or a cardiac pacemaker, followed, if necessary, 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 or isoprenaline 10 to 25 micrograms given as an infusion at a rate not exceeding 5 micrograms/minute may be given. Dobutamine, because of its positive inotropic effect 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 or isoprenaline 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

Pharmacotherapeutic group: Beta-blocking agents, selective, ATC code: CO7AB03

Mechanism of action:

Atenolol is a beta-adrenoceptor blocking drug which is $beta_1$-selective (i.e. acts preferentially on $beta_1$-adrenergic receptors in the heart). Selectivity decreases with increasing dose. It is without intrinsic sympathomimetic and membrane stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure). Human studies indicate that it crosses the blood brain barrier only to a negligible extent. As with other beta-adrenoceptor blocking drugs, its mode of action in the treatment of hypertension is unclear. It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

It is unlikely that any additional ancillary properties possessed by S(-)atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Clinical efficacy and safety:

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

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Atenolol is compatible with diuretics, other hypotensive agents and antianginals (see section 4.5). Since it acts preferentially on beta-receptors in the heart, Atenolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

Early intervention with atenolol in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to frank infarction; the incidence of ventricular arrhythmias is decreased and marked pain relief may result in reduced need of opiate analgesics. Early mortality is decreased. Atenolol is an additional treatment to standard coronary care.

5.2 Pharmacokinetic properties

Absorption:

Absorption of atenolol following oral dosing is consistent but incomplete (approx. 40-50%), peak plasma concentrations occurring after 2-4 hours. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Distribution:

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Elimination:

The plasma half-life is about 6-7 hours; this may be increased in patients with renal impairment, as the kidney is the major route of elimination. Atenolol diffuses across the placenta and is excreted in breast milk.

5.3 Preclinical safety data

There are no preclinical safety data relevant to this application.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycollate

Magnesium stearate

Lactose monohydrate

Lactose anhydrous

Talc

Maize starch

Sodium lauryl sulphate

Povidone

Microcrystalline cellulose

Stearic acid

Colloidal silicon dioxide

Titanium dioxide

Dibutyl phthalate

Hypromellose (HPMC)

6.2 Incompatibilities

None other than those reported above.

6.3 Shelf life

1. PVC/Aluminium foil blister strips: 60 months
2. “Securitainer” type container - Polypropylene body with a polyethylene (LDPE) cap with a tamper evident tear-strip closure: 48 months

6.4 Special precautions for storage

Store below 25°C. Store in the original container. Keep bulk pack container tightly closed.

6.5 Nature and contents of container

PVC/Aluminium foil blister strips: 28
“Securitainer” type container - Polypropylene body with a polyethylene (LDPE) cap with a tamper evident tear-strip closure: 100

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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