SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Atenolol 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains atenolol 50 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

Plain, white, round, flat tablets 10 mm in diameter, scored on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. The management of hypertension
2. The management of angina pectoris
3. The management of cardiac dysrhythmias
4. The management of myocardial infarction: early intervention in the acute phase and long term prophylaxis after recovery from myocardial infarction.

4.2 Posology and method of administration
For oral administration.

Adults:

Hypertension:
One tablet daily. Most patients respond to 100mg daily given as a single dose. Some patients, however, will respond to 50mg 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 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 given orally once daily or 50mg given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

**Dysrhythmias:**
Having controlled the dysrhythmias with intravenous atenolol a suitable maintenance dosage is 50mg – 100mg daily, given as a single dose.

**Myocardial infarction:**
15 minutes after the administration of the intravenous dose an oral dose of 50mg may be given provided that 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 for up to ten days. If bradycardia and/or hypotension require treatment, or other untoward effects occur, atenolol should be discontinued.

**Renal failure:**
Atenolol is excreted via the kidneys, dosage adjustment should therefore be considered in patients with severe impairment of renal function. As a guide, for patients with a serum creatinine of 300 – 600 μmol/L, the atenolol oral dose should be 50 mg daily or 100 mg once every two days, for patients with a serum creatinine of > 600 μmol/L, the oral dose of atenolol should be 50 mg on alternate days or 100 mg once every four days.

Patients on haemodialysis should be given 50 mg atenolol orally following each dialysis. Because of the possibility of marked falls in blood pressure, this should be carried out under hospital supervision.

**Elderly:**
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.
4.3 Contraindications

Atenolol, as with other beta-blockers should not be used in patients with any of the following:
- Second or third degree heart block.
- Cardiogenic shock.
- Uncontrolled heart failure.
- Sick sinus syndrome (including sino-atrial block).
- Untreated phaeochromocytoma.
- Metabolic acidosis
- Bradycardia (less than 45-50 beats per minute)
- Hypotension
- Hypersensitivity to atenolol or any of the excipients listed in section 6.1.
- Severe peripheral circulatory disturbances.

4.4 Special warnings and precautions for use

*Heart Failure:* care must be exercised in patients with heart failure because of the negative inotropic effects of atenolol. Such patients should be well controlled on digitalis before therapy commences. Close monitoring for progressive failure is essential. Similarly, care must be taken with patients with poor cardiac reserve.

*Ischaemic Heart disease:* especially in patients with ischaemic heart disease, treatment should not be discontinued suddenly. The dosage should be gradually reduced, i.e. over 1-2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris.

*Untreated Congestive Heart disease:* beta-blockers should not be used in such patients. The condition should be stabilised first.

*First Degree Heart Block:* due to its negative effect on conduction time, beta-blockers should only be given with caution to such patients.

*Bradycardia:* beta-blockers may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

*Prinzmetal's angina:* beta-blockers may increase the number and duration of anginal attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers should not be used for these patients, and beta-1 selective blockers only with the utmost care.

*Peripheral Circulatory Disease:* In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta-
blockers should be used with great caution as aggravation of these disorders may occur.

**Respiratory Disorders:** atenolol is cardioselective but not totally cardiospecific. Therefore, if it is necessary to use atenolol in patients with a history of asthma, bronchospasm or reversible obstructive airways disease, it should be introduced carefully. If an increase in airways resistance occurs, this can usually be reversed by bronchodilators such as salbutamol or terbutaline.

Patient information leaflets and labels will carry the following warnings:
**Patient Information Leaflet:** Do not take this medicine if you have a history of wheezing or asthma. Consult your doctor or pharmacist first.
**Labels:** Do not take this medicine if you have a history of wheezing or asthma.

**Liver or Kidney Insufficiency:** patients with liver or kidney insufficiency may need a lower dosage, depending on the pharmacokinetic profile of the compound.

**Phaeochromocytoma:** atenolol should not be administered to patients with phaeochromocytoma without concurrent α-adrenoceptor blocking therapy.

**Diabetics:** the symptoms of hypoglycaemia may be masked by atenolol, in particular tachycardia. Diabetic patients should be warned that this 'warning sign' may not occur.
Insulin sensitivity may be reduced in patients treated with atenolol.

**Thyrotoxicosis:** atenolol as with other beta-blockers may mask the signs of thyrotoxicosis.

**Allergies:** beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat allergic reactions.

**Hypersensitivity:** atenolol may cause a hypersensitivity reaction including angio-oedema and urticaria.

**Psoriasis:** patients with anamnestically known psoriasis should take beta-blockers only after careful consideration.

**Elderly:** these patients should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly.

**Anaesthesia:** in patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthesist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradycardia, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it
is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

4.5 Interaction with other medicinal products and other forms of interaction

- Alcohol – concomitant use with alcohol may lead to an enhanced hypotensive effect.
- Alpha blockers – some patients experience acute postural hypotension, tachycardia and palpitations when they start to take certain alpha blockers (e.g. prazosin, alfuzosin, and terazosin), this can be exacerbated if they are already taking a beta-blocker. It is recommended that they should start with a low dose of these alpha blockers, and the first dose should be taken just before they go to bed. Patients should be warned about the possibility of postural hypotension and how to manage it (lay down, raise legs and get up slowly). When adding a beta-blocker to an alpha blocker it may be advisable to decrease the dose of the alpha blocker and re-titrate as necessary.
- Anaesthetics – caution must be exercised when using anaesthetic agents with atenolol (see section 4.4). The anaesthetist 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 the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.
- Anti-arrhythmics - caution should be exercised when prescribing a beta-adrenoceptor blocking drug with Class I antiarrhythmic agents such as disopyramide, quinidine and amiodarone.
- Antidiabetics - concomitant use with insulin and oral antidiabetic drugs may intensify the blood sugar lowering effect. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia). (See section 4.4).
- Calcium channel blockers – concomitant administration of dihydropyridine derivatives (e.g. nifedipine), may increase the risk of hypotension, and in patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure. Beta-adrenoceptor blocking drugs should be used with caution in combination with verapamil and to a lesser extent diltiazem in patients with impaired ventricular function, and not at all in patients with conduction abnormalities due to the negative influence on contractility and auriculo-ventricular conduction. May result in severe hypotension, bradycardia and cardiac failure.
- Cardiac glycosides - digitalis glycosides in association with beta-blockers may increase auriculo-ventricular conduction time.
- Clonidine - care should be taken when transferring patients from clonidine to beta-adrenoceptor blocking agents; and if they are given concurrently, clonidine should not be discontinued until several days after the withdrawal of the beta-adrenoceptor.
- Non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. indometacin) may reduce the hypotensive effect of beta-blockers.
• Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine) – combination with atenolol may reduce effects of both agents.
• Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline (norepinephrine), adrenaline (epinephrine)) – combination with atenolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with non selective beta-blockers.
• Concomitant use with antihypertensive agents as well as other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

4.6 Fertility, pregnancy and lactation

Pregnancy
Atenolol has been used under close supervision for the treatment of pregnancy-associated 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. No studies have been performed on the use of atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol crosses the placental barrier and appears in cord blood.

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.

Lactation
There is significant accumulation of atenolol in breast milk. Breast feeding is therefore not recommended during administration of these compounds. The possibility of foetal injury cannot be excluded and the use of atenolol in women who are, or may become pregnant, or who are breast feeding, requires that anticipated benefits be weighed against possible risks, particularly in the first and second trimester.

4.7 Effects on ability to drive and use machines
There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.
4.8 Undesirable effects

The following undesirable effects have been observed during treatment with atenolol and other beta blockers with the following frequencies: Common (>1/100), uncommon (>1/1,000, <1/100), rare (>1/10000, <1/1000) very rare (<1/10000), including isolated reports.

- Blood and Lymphatic System Disorders
  - Rare: Thrombocytopenia.

- Endocrine Disorders
  - Beta-blockers may mask the symptoms of thyrotoxicosis.

- Metabolic and Nutrition Disorders
  - Beta-blockers may mask the symptoms of hypoglycaemia.

- Psychiatric Disorders
  - Uncommon: Sleep disturbances.
  - Rare: Hallucinations, psychoses, confusion, mood changes and nightmares have been reported. Rarely cases of insomnia have been reported.
  - Unknown: Depression

- Nervous System Disorders
  - Rare: Dizziness, headaches, paraesthesia.

- Eye Disorders
  - Rare: Dry eyes, impaired vision.

- Cardiac Disorders
  - Common: Bradycardia.
  - Rare: A slowed AV-conduction or increase of an existing AV-block, postural hypotension which may be associated with syncope, heart failure deterioration
  - Unknown: cardiac arrest and circulatory collapse.

- Vascular Disorders
  - Common: Cold extremities.
  - Rare: increase of an existing intermittent claudication, Raynauds phenomenon
  - Unknown: Cyanotic extremities.

- Respiratory Disorders
  - Rare: Bronchospasm in patients with bronchial asthma or a history of asthmatic complaints.

- Gastrointestinal Disorders
  - Common: Nausea, diarrhoea, gastrointestinal disturbances.
  - Rare: Dry mouth.
  - Unknown: Vomiting.

- Hepatobiliary Disorders
  - Uncommon: Elevations of transaminase levels
  - Rare: cases of hepatic toxicity, including intrahepatic cholestasis have been reported.

- Skin and Subcutaneous Tissue Disorders
  - Rare: Skin rash, purpura, exacerbation of psoriasis, alopecia, psoriasiform skin reactions.
  - Unknown: Hypersensitivity reactions, including angio-oedema, urticaria.

- Musculoskeletal and Connective Tissue Disorders:
  - Common: Muscle fatigue.
  - 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 Anti Nuclear Antibodies has been reported. 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. In all cases cessation of therapy should be gradual.

Report 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 www.mhra.gov.uk/yellowcard.

4.9 Overdose
The most important effects are on the heart. Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. First or second degree AV block may occur and rarely arrhythmias.

After investigation of an overdose or in the case of hypersensitivity the patient should be kept under close supervision and be treated in an intensive care ward.

Activated charcoal and a laxative should be used to prevent absorption of any drug still present in the gastrointestinal tract, plasma or plasma substitutes can be used to treat hypotension or shock. The use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be treated with atropine 1-2 mg intravenously and or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously and 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. 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-blocker 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.
5.1 Pharmacodynamic properties

ATC CODE CO7A B03

Atenolol is a beta-adrenoceptor blocking agent which is cardioselective, its principal action being on beta-adrenergic receptors in the heart. 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). 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.

Atenolol is effective and well-tolerated in most ethnic populations. However 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 (but 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.

Human studies have shown that a negligible amount of atenolol crosses the blood brain barrier.

Early intervention in acute myocardial infarction reduces infarct size and may decrease 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: following oral dosing of atenolol absorption is consistent but incomplete (approximately 40 – 50 %) with peak plasma concentrations occurring 2 – 4 hours after dosing.

Distribution: only small amounts are reported to cross the blood-brain barrier and plasma-protein binding is minimal (approximately 3%). The plasma half-life is about 6-7 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

(Women - it crosses the placenta and is distributed into breast milk where concentrations higher than those in maternal plasma have been achieved).

Metabolism: atenolol undergoes little or no hepatic metabolism and more than 90% of that absorbed reaches systemic circulation unaltered.

Elimination: mainly in the urine.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablets contain:
- Gelatin
- Heavy Magnesium Carbonate
- Magnesium Stearate
- Microcrystalline Cellulose
- Maize Starch
- Sodium Laurilsulfate
- Purified Talc
- Purified Water

6.2 Incompatibilities
None known.

6.3 Shelf life
5 years.
6.4 Special precautions for storage
Do not store above 25°C.
For blisters: ‘Store in the original packaging’
For bottles/containers: ‘Keep the container tightly closed’

6.5 Nature and contents of container
1. Amber glass bottles with closures of LD-polyethylene
2. PP container with desiccant
3. PVDC- PVC blister pack

6.6 Special precautions for disposal
No special instructions.

7 MARKETING AUTHORISATION HOLDER
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