SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Atenolol 25mg Tablets

2. Qualitative and Quantitative Composition
Each tablet contains 25 mg of Atenolol.

Excipients with known effect:

Each Atenolol 25mg tablet contains 35mg of lactose

For the full list of excipients, see section 6.1

3. Pharmaceutical
Form Film-coated
tablet (tablet).

White round bi-convex film coated, unscored tablet, marked “A25”, approximate size 6.4mm X 3.2mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
1) For the management of hypertension, angina pectoris and cardiac dysrhythmias.
2) For early intervention in the acute phase of myocardial infarction.

4.2 Posology and method of administration

Posology

Adults and children over 12 years
Hypertension: Most patients respond to 100 mg daily given 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 antihypertensive agents.
Angina: Most patients respond to 100 mg once daily or 50 mg twice daily. It is unlikely that a higher daily dose would be additionally beneficial.

Dysrhythmias: Initially controlled intravenously. A suitable oral maintenance dosage is 50-100 mg daily, given as a single dose.

Myocardial infarction: In suitable patients, initially controlled intravenously, followed by 50mg orally about 15 minutes after the intravenous dose provided no adverse effects occur. This should be followed by a further 50mg orally 12 hours later and then 12 hours later by 100mg orally to be given once daily.

If bradycardia and/or hypertension requiring treatment, or any other side effects occur, atenolol therapy should be discontinued.

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

Paediatric population
Children under 12 years: Atenolol is not recommended for use in children under 12 years of age.

Renal failure
Atenolol is excreted via the kidneys, therefore the dosage will need to be adjusted in severe renal conditions. No significant accumulation of atenolol occurs at a GFR greater than 35 ml/min/1.73m² (normal range is 100-150 ml/min/1.73m²). For patients with a creatinine clearance of 15-35 ml/min/1.73m², the oral dose should be 50 mg daily or 100 mg once every two days, and for those with a creatinine clearance of less than 15 ml/min/1.73m², the oral dose should be 50 mg once every two days or 100 mg once every four days.

Patients on haemodialysis should be given 50 mg orally after each dialysis, when careful observations for a fall in blood pressure should be exercised.

Method of Administration
For oral administration.

4.3 Contraindications

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

- Hypersensitivity to atenolol or any of the excipients listed in section 6.1
- Second or third degree heart block
- Cardiogenic shock
- Uncontrolled cardiac failure
• Sick sinus syndrome (including sino-atrial block)
• Untreated phaeochromocytoma
• Metabolic acidosis
• Bradycardia (heart rate less than 45-50 beats per minute)
• Hypotension
• Severe peripheral arterial 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, caution must be exercised if atenolol is given 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 dose should be reduced.

*Prinzmetal's Angina:* beta-blockers may increase the number and duration of angina 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, atenolol is a beta1-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.

*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 or isoprenaline.

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 reaction. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.

Hypersensitivity: atenolol may cause a hypersensitivity reaction including angioedema 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 anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw betablocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

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-titrated 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 anti-arrhythmic drugs (e.g. disopyramide, quinidine and amiodarone).

**Antidiabetics** - concomitant use with insulin and oral antidiabetic drugs may intensify the blood sugar lowering effects. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia). (See section 4.4).

**Calcium channel blockers** - concomitant administration of dihydropyridines derivatives (e.g. nifedipine), may increase the risk of hypotension with latent cardiac insufficiency, treatment with betablocking 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 auriculoventricular 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. ibuprofen and indomethacin) may reduce the hypotensive effects 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 the 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.

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 the anticipated benefits be weighed against the possible risks, particularly in the first and second trimester.

Breast-feeding

There is significant accumulation of atenolol in breast milk. Breast feeding is therefore not recommended during administration of these compounds.

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 undesired 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, unknown (cannot be estimated from the available data).

**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, headache, 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, Raynaud's 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 Antinuclear 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.

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 at: www.mhra.gov.uk/yellowcard.

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

After ingestion of an overdose or in the case of hypersensitivity, the patient should be kept under close supervision and 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 and 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 10 mg intravenously and 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 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Selective Beta blocking agents.
ATC code: C07AB

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 betablockers, has negative inotrope 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 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 to standard 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 (approx. 40-50%) with peak plasma concentrations occur 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
Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, microcrystalline cellulose, talc, maize starch, povidone, lactose (tablettose), sodium starch glycollate, sodium lauryl sulfate, colloidal silicon dioxide, stearic acid, magnesium stearate, titanium dioxide (E171), methylcellulose and PEG 6000.

6.2 Incompatibilities
None known.

6.3 Shelf life
4 years.
6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Blister packaging (14 tablets/strip) in aluminium foil, subsequently packed in printed cardboard carton containing 28 tablets in each.

Polypropylene securitainer with a polythene (LDPE) cap with a tamper evident tear-strip closure containing 100 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
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8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0019

9. Date of Authorisation/Renewal of Authorisation

Date of first authorisation: 09th February 1994
Date of latest renewal: 23rd September 2010

10 DATE OF REVISION OF THE TEXT