SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atenolol 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg of Atenolol.

Excipients with known effect:

Each Atenolol 100mg tablet contains 140mg of lactose and 0.742mg sunset yellow (E110)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange, bi-convex, film-coated, unscored tablet, marked “A100”, approximate size 10.4 mm X 4.9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
The dosage should be determined on an individual basis. It is recommended to start with the lowest possible dosage so that heart failure, bradycardia and bronchial symptoms are noticed timely. This is especially important in elderly. Further adaptation should be done gradually (e.g., once a week) under controlled conditions or based on the clinical effect.

Adults and children over 12 years:

Hypertension: A starting dose of 25mg is recommended. The usual maintenance dosage in hypertension is one tablet (50-100mg) daily. The maximum effect will be reached after 1-2 weeks. If further improvement of the blood pressure is desired, atenolol may be combined with another anti-hypertensive e.g.: a diuretic.

Angina pectoris: 50-100mg daily, depending on the clinical effect, in order to obtain a heartbeat in rest of 55-60 beats per minute. Increasing the dose above 100mg daily does not generally lead to an increased antianginous effect. If desired the dosage of 100mg daily can be divided in two dosages.

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

Secondary prevention after myocardial infarction: Initially controlled intravenously, followed by 50mg orally about 10 minutes after the intravenous dose provided no adverse effects occur. This should be followed by a further 50mg orally 12 hours later. Maintenance dose is 100mg daily in 1-2 dosages for 6 days or until discharge from hospital.

The Elderly: Dosage requirements may be reduced, especially in patients with impaired renal function. Dosage should be titrated according to clinical effect.

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

Impaired renal function: Atenolol is excreted via the kidneys, therefore the dosage will need to be adjusted in severe renal conditions.

GFR (mL/min/1,73 m^2 BSA)	Recommended daily dose atenolol (mg/day)
>35	No dose adjustment necessary
15-35	25-50 (or 50-100 every second day)
<15	25-50 every second day

In haemodialysis a 50mg tablet is administered after each dialysis. The administration should be done in hospital since sudden decrease of the arterial pressure may occur.

Decreased hepatic function: No dose adjustment is necessary.

Method of Administration
For oral administration.

4.3 Contraindications

This medicine, 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
- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome
- Second-or third-degree heart block

- Untreated phaeochromocytoma
- Metabolic acidosis
- Bradycardia (heart rate less than 45 beats per minute)
- Hypotension
- Severe peripheral arterial circulatory disturbances

4.4 Special warnings and precautions for use

This medicine, as with other beta-blockers:

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 foreach 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 contraindicated in uncontrolled heart failure (see section 4.3), may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

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 maybe considered although utmost caution must be exercised.

Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), may also aggravate less severe peripheral arterial circulatory disturbances.

Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first-degree heart block.

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).

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 should be reduced.

May cause a more severe reaction to a variety of 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 (epinephrine) used to treat the allergic reactions.

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 35ml/min/1.73 m^2.

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, 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.

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

Patient information leaflets and labels will carry the following warnings:

Patient Information Leaflet: If you have ever had asthma or wheezing, do not take this medicine without first checking with your doctor.

Labels: Do not take this medicine if you have a history of wheezing or asthma.

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

4.5 Interaction with other medicinal products and other forms of interaction

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.

Digitalis glycosides, in association with beta-blockers, may increase atrio-ventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several

days after clonidine administration has stopped (see also prescribing information for clonidine).

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

Concomitant use of sympathomimetic agents e.g. adrenaline (epinephrine), may counteract the effect of beta-blockers.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. 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).

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

Caution must be exercised when using anaesthetic agents with atenolol. 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.

4.6 Pregnancy and lactation

Caution should be exercised when atenolol is administered during pregnancy or to a woman who is breast-feeding.

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

Breast-feeding
There is significant accumulation of atenolol in breast milk.
A risk in the breastfed child cannot be excluded, therefore, breastfeeding should be discontinued during treatment with atenolol.

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 has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Atenolol is well tolerated. In clinical studies, the undesired events 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 (≥1/1,000 to < 1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000) including isolated reports, not known (cannot be estimated from the available data).

Blood and Lymphatic System Disorders
Rare: Thrombocytopenia, purpura

Psychiatric Disorders
Uncommon: Sleep disturbances of the type noted with other beta-blockers
Rare: Hallucinations, psychoses, confusion, mood changes and nightmares

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, increase of an existing intermittent claudication, 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

Hepatobiliary Disorders
Uncommon: Elevations of transaminase levels
Rare: Hepatic toxicity including intrahepatic cholestasis

Skin and Subcutaneous Tissue Disorders
Rare: Skin rashes, exacerbation of psoriasis, alopecia, psoriasiform skin reactions
Unknown: Hypersensitivity reactions, including angioedema and urticaria

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 Antinuclear Antibodies (ANA) 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.

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 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, bronchospasm and acute cardiac insufficiency.

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 can be used to treat hypotension and shock. The possible uses of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can 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. 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-blocking agents, plain.
ATC code: C07AB03

Mechanism of action
Atenolol is a beta-blocker which is $beta_1$-selective, (i.e. acts preferentially on $beta_1$-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

Atenolol 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).

As with other beta-blockers, the mode of action of atenolol 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.

Clinical efficacy and safety
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 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 (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.

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 (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. 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 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

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, sunset yellow (E110) 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 polythylene (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

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Limited
220 Butterfield
Great Marlings
Luton
LU2 8DL
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0015

9. Date of Authorisation/Renewal of Authorisation

Date of first authorisation: 08th February 1999
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