Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nortenolol 25mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains atenolol 25 mg

Excipients with known effect: Each tablet contains 47.5 mg of lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets
White, biconvex, film-coated unscored tablet, marked ‘A25’.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of hypertension.
Management of angina pectoris.
Management of cardiac dysrhythmias.
Myocardial infarction - early intervention in the acute phase.

4.2 Posology and method of administration

Posology

Hypertension:
The usual dose is one 100 mg tablet daily. Some patients may respond to a dose of one 50 mg tablet daily. The therapeutic effect is fully established after administration for one to two weeks. Further reduction in blood pressure, if desired, can be achieved by combining Atenolol with other antihypertensive agents.

Angina pectoris:
One 100 mg tablet once daily or one 50 mg tablet twice daily are taken. Additional benefit is unlikely to be gained by increasing the dose.

Cardiac dysrhythmias:
Having controlled the dysrhythmia with intravenous Atenolol the maintenance oral dose is one 50mg tablet to one 100 mg tablet daily as a single dose.

Myocardial infarction:
Patients presenting within 12 hours of the onset of chest pains and suitable for beta blockade therapy:
5 to 10 mg of Atenolol is administered by slow intravenous injection (1 mg/minute). If no adverse effects occur following the intravenous dose, then 15 minutes later one 50 mg tablet is administered orally followed by a further 50 mg tablet, 12 hours after the intravenous dose. Then 12 hours later one 100 mg tablet is given orally, once daily. If bradycardia and/or hypertension requiring treatment, or any other side effects, occur Atenolol therapy should be discontinued.

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

Children:
Atenolol is not recommended for use in children as there is no paediatric experience with atenolol.

Renal failure:
Since Atenolol is excreted via the kidneys dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of Atenolol occurs at a glomerular filtration rate (GFR) greater than 35 m//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 one 50 mg tablet daily or one 100 mg tablet once every two days; 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 one 25 mg tablet daily, one 50 mg tablet on alternate days or one 100 mg tablet once every four days; 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

Hypersensitivity to the active substsance or to any of the excipients listed in section 6.1.

Nortenolol as with other beta-blockers should not be used in patiens with any of the following: in the presence of second or third degree heart block, cardiogenic shock, uncontrolled heart failure, sick sinus syndrome (including sino-atrial block), untreated phaeochromocytoma, metabolic acidosis, bradycardia (< 45–50 bpm), hypotension, severe peripheral arterial circulatory disturbances.

4.4 Special warnings and precautions for use

- Nortenolol should not be taken if there is a history of wheezing or asthma, until a doctor or pharmacist has been consulted. (Note: The labelling of packs will carry a statement to this effect).

- Special care should be taken with patients whose cardiac reserve is poor. Beta-adrenoceptor blockers should be avoided in overt heart failure (see section 4.3). However, they may be used in patients whose signs of failure have been controlled.

- Nortenolol 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.

- One of the pharmacological actions of atenolol is to reduce heart rate. In the rare instances when symptoms may be attributable to the slow heart rate, the dose may be reduced. 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.

Atenolol modifies the tachycardia of hypoglycaemia. Atenolol should be used with caution in diabetics subject to frequent episodes of hypoglycaemia. Symptoms of hypoglycaemia and of hyperthyroidism may be masked.

- Although cardioselective beta-adrenoceptor blocking drugs may have less effect on lung function than non-selective beta-adrenoceptor blocking drugs, as with all beta-adrenoceptor 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, in such instances atenolol should be discontinued and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.

- In patients with chronic obstructive pulmonary disorders, airway obstructions may be aggravated. Therefore, non-selective beta-blockers should not be used for these patients, and beta-$_1$ selective blockers only with the utmost care.

- Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

- Patients with liver or kidney insufficiency may need a lower dosage, depending on the pharmacokinetic profile of the compound. The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly. 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.

- 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. Atenolol is a beta$_1$-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.

- Patients with anamnestically known psoriasis should take beta-blockers only after careful consideration as psoriasis may be aggravated.

- May mask the signs of thyrotoxicosis

- In addition, hypertension and arrhythmias may develop.

- When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for 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 contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), may also aggravate less severe peripheral arterial circulatory disturbances.

- 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.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Adrenergic neurone-blocking agents

Adrenergic neurone-blocking agents such as guanethidine, reserpine, diuretics and antihypertensive agents, including the vasodilator group, will have an additive effect on the hypotensive action of the drug.

Clonidine or other hypotension producing medications

Beta-adrenoceptor blocking drugs may exacerbate the rebound hypertension which can follow the withdrawal of clonidine, calcium channel blocking agents, diayoxide, reserpine or other hypotension producing medications. If clonidine and beta-adrenoceptors 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 (see also prescribing information on clonidine).

Antiarrhythmic agents (Class 1)

Care should be taken in prescribing a beta-adrenoceptor blocking drug with Class I anti-dysrhythmic agents (such as disopyramide, quinidine) and amiodarone. This may have potentiating effects on atrial-conductuon time and induce negative inotropic effect. Concomitant use of other drugs affecting cardiac conduction with increased risk of bradycardia, hypotension, ventricular fibrillation, heart block or asystole - avoid concomitant use should be avoided.

Insulin and oral antidiabetic drugs

Precaution is also necessary in prescribing beta-blockers with insulin and oral antidiabetic drugs as this may intensify the blood sugar lowering effect (especially non-selective beta-blockers).) Symptoms of hypoglycaemia, particularly tachycardia, may be masked (See Section 4.4). Hypoglycaemia is more likely in Type I than in Type II diabetics and may be associated with delayed recovery.

Calcium channel blockers

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects, e.g. verapamil or 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.

Digitalis glycosides

Digitalis glycosides are also not recommended as their association with beta-blockers may increase auriculo-ventricular conduction time.

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. 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.

Myocardial depressants

The beta-blocker should only be used with caution in patients who are receiving concomitant myocardial depressants such as halogenated anaesthetics, lidocaine, procainamide and beta-adrenoceptor stimulants such as noradrenaline (norepinephrine).

Prostaglandin synthetase-inhibiting drugs/non-steroidal anti-inflammatory drugs

Prostaglandin synthetase inhibiting drugs, e.g. ibuprofen, indometacin, may decrease the hypotensive effects of beta-blockers.

Sympathomimetic agents

Sympathomimetic agents/sympathomimetic amines (adrenaline, noradrenaline and ephedrine) may counteract the effect of beta-adrenergic blocking agents.

The following should also be taken into account:

- Calcium antagonists: dihydropyridine derivates such as nifedipine: the risk of hypotension may be increased. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure.
- Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents may increase the blood pressure lowering effect.
- Monoamineoxidase inhibitors (exception MAO-B inhibitors) are also not recommended in association with beta-blockers.
- In general, beta-adrenoceptor blocking agents should not be given concomitantly with amphetamines.
- Reduced bioavailability may occur if calcium or aluminium hydroxide is administered concurrently.
- Concomitant use with cimetidine, hydralazine and alcohol may induce increased plasma levels of hepatically metabolised beta-blockers.

4.6 Fertility, pregnancy and lactation

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 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.

Breastfeeding

There is 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.

Caution should be exercised when Atenolol is administered during pregnancy or to a woman who is breast-feeding, infants should be monitored for bradycardia, respiratory depression, hypotension and hypoglycaemia.

4.7 Effects on ability to drive and use machines

The use of Atenolol is unlikely to result in any impairment on the ability to drive, operate machinery or undertake tasks which require a high degree of concentration. 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 (≥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).

System Organ Class	Frequency	Undesirable Effect
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
	Not Known	peripheral vasoconstriction
Nervous System Disorders	Rare	Dizziness, headache, paraesthesia
	Not Known	Peripheral neuritis
Psychiatric disorders	Uncommon	Sleep disturbances of the type noted with other beta-blockers
	Rare	Mood changes, nightmares, confusion, psychoses and hallucinations
	Not Known	Anxiety and nervousness
Gastrointestinal disorders	Common	Gastrointestinal disturbances
	Rare	Dry mouth
	Not Known	constipation and abdominal cramps, sclerosing peritonitis and retroperitoneal fibrosis
Hepato-biliary disorders	Rare	Hepatic toxicity including intrahepatic cholestasis
Blood and lymphatic system disorders	Rare	Purpura, thrombocytopenia
	Not Known	Eosinophilia and leucopenia including agranulocytosis
Skin and subcutaneous tissue disorders	Rare	Alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
	Not Known	Hypersensitivity reactions, including angioedema and urticarial, pruritis
Eye disorders	Rare	Dry eyes, visual disturbances including blurred vision, sore eyes, conjunctivitis
Reproductive system and breast disorders	Rare	Impotence
	Not Known	Peyronie's disease

Respiratory, thoracic and mediastinal disorders	Rare Not Known	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints pneumonitis, pulmonary fibrosis and pleurisy
Musculoskeletal and connective tissue disorder	Not Known	Lupus-like syndrome
General disorders and administration site conditions	Common	Fatigue
Investigations	Uncommon Very rare Not Known	Elevations of transaminase levels An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear Elevated liver enzymes and/or bilirubin

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdosage are bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.
After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Absorption of any drug material still present in the gastro-intestinal tract can be prevented by gastric lavage, administration of activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract.
Artificial respiration may be required. Maintenance of a clear airway and adequate ventilation is mandatory.
Bronchospasm can usually be reversed by bronchodilators.

Excessive bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine 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 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 should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.
Administration of calcium ions, or the use of a cardiac pacemaker may also be considered. In patients intoxicated with hydrophylic beta-blocking agents hemodialysis or hemoperfusion may be considered.
Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective.
ATC Code: C07AB03.

Mechanism of action
Atenolol is a beta-adrenoceptor blocking drug which is Beta, selective (i.e. acts preferentially on Beta-adrenergic receptors in the heart). It is without intrinsic sympathomimetic and membrane stabilising activities. 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.

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

Distribution
Atenolol diffuses across the placenta and is excreted in breast milk. Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (about 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.

5.3 Preclinical safety data

Atenolol is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

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

Coating Constituents:
Titanium dioxide (E171)
Dibutyl phthalate
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Blister packs: Store in the original package in order to protect from light and moisture.
Securitainers: Store in the original container 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.

Blister packaging (15 tablets/strip) in aluminium foil, subsequently packed in printed cardboard carton containing 30 tablets in each.

Polypropylene securitainer with a polyethylene (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. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
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Great Marlings
Luton
LU2 8DL
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8 MARKETING AUTHORISATION NUMBER

PA0644/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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