Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trantalol Atenolol 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg of atenolol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, biconvex, film-coated tablet, approximately 8mm in diameter, marked ‘2U1’ on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Control of hypertension
- Management of angina pectoris
- Control of cardiac arrhythmias

Early intervention in the acute phase of myocardial infarction and long-term prophylaxis after recovery from myocardial infarction.

4.2 Posology and method of administration

Posology

Adults
Control of hypertension:
Most patients respond to 50 mg daily given orally as a single dose. If necessary the dose may be increased to 100 mg daily. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining Trantalol Atenolol tablets with other anti-hypertensive agents.

Management of angina Pectoris:
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.

Control of cardiac arrhythmias:
An oral maintenance dose of Trantalol Atenolol is 50 – 100 mg, given once daily.

Early and late intervention after myocardial infarction:
Oral treatment with Trantalol Atenolol can be initiated in haemodynamically stable patients with 50 mg twice daily, and then 100 mg once daily. During the early phase of acute myocardial infarction, treatment with Trantalol Atenolol should be initiated in hospital under close monitoring. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, Trantalol Atenolol should be discontinued.

Trantalol Atenolol 100 mg daily is recommended for long-term prophylaxis of myocardial infarction.

Renal impairment:
Atenolol is excreted via the kidneys, dosage adjustment should therefore be considered in patients with severe impairment of renal function.
No significant accumulation of Trantalol Atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m2 (normal range is 100-150 ml/min/1.73 m2).
For patients with a creatinine clearance of 15-35 ml/min/1.73 m2 (equivalent to serum creatinine of 300-600 micromol/litre), the dose should be 50 mg daily.

For patients with a creatinine clearance of less than 15 ml/min/1.73 m2 (equivalent to serum creatinine of greater than 600 micromol/litre), the dose should be 25 mg daily or 50 mg on alternate 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.

Children:
There is no paediatric experience with atenolol and for this reason it is not recommended for use in children.

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

Method of administration
For administration by the oral route.

4.3 Contraindications

Trantalol Atenolol should not be used in patients with any of the following:
- known hypersensitivity to atenolol or any of the ingredients listed in 6.1
- bradycardia
- cardiogenic shock
- hypotension
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- second or third degree atrioventricular block
- sick sinus syndrome
- untreated phaeochromocytoma
- uncontrolled or digitalis/diuretic-refractory heart failure

4.4 Special warnings and precautions for use

Trantalol Atenolol 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 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 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. Trantalol 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), 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.
- 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 may 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.
- May cause an increase in airways resistance in asthmatic patients. If increased airways resistance does occur, Trantalol Atenolol should be discontinued and bronchodilator therapy (e.g. salbutamol) administered if necessary.
- Should only be given to patients with psoriasis after careful consideration, as psoriasis may be aggravated.
- Since Trantalol 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.
- 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.

Anaesthetic agents
Caution must be exercised when using anaesthetic agents with Trantalol 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.

Antiarrhythmic agents (Class 1)
Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effect.

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.

Clonidine
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).

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

Dihydropyridines
Concomitant therapy with dihydropyridines, e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Insulin and oral antidiabetic drugs
Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (See Section 4.4).

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

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

4.6 Fertility, 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 the 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.

Breast-feeding
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 for hypoglycemia.

4.7 Effects on ability to drive and use machines

Use is unlikely to result in any 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

Atenolol is well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of atenolol.

Tabulated list of adverse reactions
The following undesirable effects listed by body system classification 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 (≥1/10,000 to <1/1,000), very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).

System Organ Class	***Frequency***	***Undesirable Effect***
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
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, intermittent claudication may be increased if already present, 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	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 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	Uncommon	Elevations of transaminase levels
	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.

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

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 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-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: Beta-blocking agents, plain, selective, ATC code: CO7A BO3

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 stabilizing 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.

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.

Atenolol is compatible with diuretics, other antihypertensive agents and antianginal agents (see Section 4.5).

5.2 Pharmacokinetic properties

Following intravenous administration, the blood levels of atenolol decay tri-exponentially with an elimination half-life of about 6 hours. Throughout the intravenous dose range of 5-10 mg the blood level profile obeys linear pharmacokinetics and beta-blockade is still measurable 24 hours after a 10 mg intravenous dose.

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

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 monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica

Coating:
Carnauba Wax
Opadry OY-S 58905 (containing Hypromellose, Titanium Dioxide (E171), Macrogol and Talc)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years – Blister packs
2 years – HDPE / polypropylene containers

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in original package.

6.5 Nature and contents of container

HDPE or polypropylene containers with LDPE caps.
Blister Strips: PVC/PVDC with hard temper aluminium foil strip.
Pack Sizes: 28, 30, 100, 250, 500 and 1000.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
(Trading as Pinewood Healthcare)
Ballymacarbry
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0281/083/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 January 1996

Date of last renewal: 03 January 2006

10 DATE OF REVISION OF THE TEXT

March 2017