Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atenolol 5mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 5mg Atenolol.

Excipients with known effect:
Each ml of oral solution contains 280mg sorbitol (E420), 1.8mg methyl parahydroxybenzoate (E218), 0.2mg propyl parahydroxybenzoate (E216), 3.03mg propylene glycol (E1520) and 2.79mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution
Clear colourless oral solution with orange flavour

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

i. Management of hypertension
ii. Management of angina
iii. Management of cardiac arrhythmias
iv. Myocardial infarction. Early intervention in the acute phase

4.2 Posology and method of administration

Posology

Oral administration

As food impairs the bioavailability of atenolol, it should not be taken with the food.

The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage. The following are guidelines:

Adults

Hypertension
A starting dose of 25 mg is recommended. The usual maintenance dosage in hypertension is one tablet (50-100 mg) 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
50-100 mg daily, depending on the clinical effect, in order to obtain a heartbeat in rest of 55-60 beats per minute. Increasing the dose above 100 mg daily does not generally lead to an increased antianginous effect. If desired the dosage of 100 mg daily can be divided in two dosages.

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

Myocardial infarction

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

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.

Renal failure
Since Atenolol is excreted via the kidneys, the dosage should be adjusted in cases of severe impairment of renal function.

No significant accumulation of Atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m^2 (normal range is 100–150 ml/min/1.73 m^2).

For patients with a creatinine clearance of 15–35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300–600 micromol/litre), the oral dose should be 50 mg (two 5ml spoonfuls) daily and the intravenous dose should be 10 mg once every two days.

For patients with a creatinine clearance of less than 15 ml/min/1.73 m^2 (equivalent to serum creatinine of greater than 600 micromol/litre), the oral dose should be 25 mg (one 5ml spoonfuls) daily or 50 mg (two 5ml spoonfuls) on alternate days and the intravenous dose should be 10 mg once every four days.

Patients on haemodialysis should be given 50 mg (two 5ml spoonfuls) orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

4.3 Contraindications

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

- known hypersensitivity to the active substance, or 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 (<45 bpm)
- hypotension
- severe peripheral arterial circulatory disturbances

4.4 Special warnings and precautions for use

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. Atenolol is a β_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 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 35 ml/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. The label and patient information leaflet for this product state the following warning: "If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor".

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

Excipient warning:

Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216): May cause allergic reactions (possibly delayed).

Sorbitol (E420): This medicinal product contains 280mg sorbitol in each ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sodium: This medicinal product contains 2.79mg sodium per ml, equivalent to 0.14% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Propylene glycol (E1520): This medicinal product contains 3.03mg propylene glycol in each ml.

4.5 Interaction with other medicinal products and other forms of interactions

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 atrioventricular 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. 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 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 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.

Neonates born to mothers who are receiving Atenolol at parturition or breast-feeding may be at risk of hypoglycaemia and bradycardia.

Fertility
No human data on the effect of atenolol on fertility are available. In rats, there was no effect on mating or fertility with atenolol treatment.

4.7 Effects on ability to drive and use machines

The use of Atenolol is unlikely to result in the impairment of the ability of patients to drive or operate 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.

Tabulated list of adverse reactions
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).

Organ Systems	Frequency	Adverse events
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
Hepato-biliary disorders	Uncommon	Elevations of transaminase levels
	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
Reproductive system and breast disorders	Rare	Impotence
General disorders and administration site conditions	Common	Fatigue
Investigations	Very rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear
Musculoskeletal and connective tissue disorders	Not known	Lupus-like syndrome

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 viaHPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms:

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

Management:

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 1–2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed 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-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: Beta-blocking agents, plain, selective,
ATC code: C07A B03.

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.

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 once daily dosing with 10 ml or 20 ml Atenolol 5 mg/ml Oral Solution. 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 (see section 4.5). Since it acts preferentially on beta- adrenergic 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.

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%).

Biotransformation
There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

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

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Citric acid monohydrate (E330)
Sodium citrate (E331)
Sorbitol liquid (non-crystallising) (E420)
Saccharin sodium (E954)
Orange flavour [containing propylene glycol (E1520)]
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months
For 100ml and 150ml: Discard 30 days after first opening.
For 300ml: Discard 60 days after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bottle: Amber coloured PET bottles
Closure: Tamper evident, child resistant, polypropylene/polyethyleneplastic cap with a LDPE liner
Dosing Device: a double ended polypropylene plastic spoon having smaller end measuring 2.5ml and larger end measuring 5ml
Pack size: 100 ml, 150 ml and 300 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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