ATENOLOL 25 MG / 5 ML ORAL SOLUTION.

(Atenolol)

PL 13931/0060

UKPAR

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LAY SUMMARY

The MHRA granted Chanelle Medical a Marketing Authorisation (licence) for the medicinal product Atenolol 25 mg / 5 ml Oral Solution on 08 December 2011. This product is a prescription-only medicine (POM).

Atenolol 25 mg / 5 ml Oral Solution contains the active ingredient atenolol which belongs to a group of medicines called beta-blockers. Atenolol is used to:

- treat high blood pressure (hypertension) and some arrhythmias (irregular heart beats)
- help treat angina (chest pain)
- protect the heart after a heart attack

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Atenolol 25 mg / 5 ml Oral Solution outweigh the risks and a Marketing Authorisation was granted.
ATENOLOL 25 MG / 5 ML ORAL SOLUTION.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Chanelle Medical, a Marketing Authorisation for the medicinal product Atenolol 25 mg / 5 ml Oral Solution (PL 13931/0060) on 08 December 2011. This product is a prescription-only medicine (POM).

Atenolol 25 mg / 5 ml Oral Solution is used for the following indications:
- management of hypertension
- management of angina
- management of cardiac arrhythmias
- myocardial infarction. Early intervention in the acute phase.

This is an abridged application submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Tenormin 25 mg/5 ml Syrup (PL 17901/0051, AstraZeneca Limited, UK) which was originally licensed as PL 00029/0195 (Imperial Chemical Industries Plc, UK), prior to 01 October 1993.

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.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns were raised during the assessment of this application and it was therefore judged that the benefits of taking Atenolol 25 mg / 5 ml Oral Solution outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Atenolol.
Chemical name: 2-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl)acetamide
Structure:

Molecular formula: C_{14}H_{22}N_{2}O_{3}
Molecular weight: 266.3
Appearance: Atenolol is a white or almost white powder, sparingly soluble in water, soluble in ethanol, slightly soluble in methylene chloride and practically insoluble in ether.

Atenolol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance atenolol are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients, citric acid monohydrate, Lemon and lime flavour (containing ethanol), methyl hydroxybenzoate, propyl hydroxybenzoate, purified water, saccharin sodium, sodium citrate, sorbitol solution and mono propylene glycol.

Appropriate justification for the inclusion of each excipient has been provided.

All of the excipients comply with their respective European Pharmacopoeia monograph with the exception of Lemon and lime flavour which is controlled to suitable in-house specifications and is in compliance with current EEC directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical development
The aim of the development programme was to formulate a safe, efficacious, stable oral solution that could be considered a generic medicinal product of Tenormin 25 mg/5 ml Syrup (AstraZeneca Limited, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparable impurity profiles have been provided for the proposed and originator products.
Manufacture
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. In addition, the manufacturing authorisation holder has also committed to perform process validation on the first three commercial scale batches.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is packaged in amber polyethylene terephthalate (PET) bottles with tamper evident high density polyethylene (HDPE) cap with low density polyethylene (LDPE) plug containing 300 ml of oral solution.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened bottle which decreases to 3 months once opened with the storage conditions ‘Store below 25°C. Keep the bottle upright. Store in the original container.’

Bioequivalence/Bioavailability
A bioequivalence study is not required to support an application of this type as per European guidance.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
MAA (Marketing Authorisation Application) Form
The MAA form is satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a marketing authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that the proposed product is a generic medicinal product of an originator product that has been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for the non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
Pharmacokinetics
In accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), a bioequivalence study is not required if the product is to be administered as an aqueous oral solution at time of administration and contains the same active substance in the same concentration as the currently licensed product.

EFFICACY
No new efficacy data have been submitted and none are required for an application of this type.

SAFETY
No new safety data have been submitted and none are required for this application.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the respective originator product. The PIL is consistent with the SmPC and is in line with current guidance. The labelling is in line with current guidance.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

CONCLUSION
There are no objections to the approval of this product from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Atenolol 25 mg / 5 ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data have been submitted and none are required for an application of this type.

EFFICACY
No new data have been submitted and none are required for an application of this type.

SAFETY
No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with atenolol is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is therefore considered to be positive.
ATENOLOL 25 MG / 5 ML ORAL SOLUTION

PL 13931/0060

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 05 January 2009.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 14 January 2009.

3 Following assessment of the application the MHRA requested further information on 03 July 2009, 30 June 2010, 30 November 2010 and 03 October 2011.

4 The applicant responded to the MHRA’s requests, providing further information on 26 February 2010, 02 November 2010, 08 September 2011 and 07 November 2011.

5 The application was determined on 08 December 2011.
ATENOLOL 25 MG / 5 ML ORAL SOLUTION.

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STEPS TAKEN AFTER ASSESSMENT

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|  | QUALITATIVE AND QUANTITATIVE COMPOSITION  |
|  | Atenolol 25 mg / 5 ml  |

For the full list of excipients, see section 6.1.

|  | PHARMACEUTICAL FORM  |
|  | Oral solution  |

The solution is a clear, colourless and viscous liquid.

|  | CLINICAL PARTICULARS  |

### 4.1 Therapeutic Indications

- i. Management of hypertension.
- ii. Management of angina.
- iii. Management of cardiac arrhythmias.

|  | Posology and method of administration  |
|  | Oral administration.  |

Atenolol Solution is intended for patients unable to swallow Atenolol tablets. The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage. The following are guidelines:

**Adults**

**Hypertension**

Two or four 5 ml spoonfuls daily i.e. 50 mg or 100 mg in patients unable to take 50 mg or 100 mg tablets.

Most patients respond to 100 mg once daily. 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 with angina pectoris will respond to 100 mg (four 5 ml spoonfuls) given orally once a day, or 50 mg (two 5 ml spoonfuls) given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

**Cardiac arrhythmias**

A suitable initial dose of Atenolol injection is 2.5 mg (5 ml) injected intravenously over a 2.5 minute period (i.e. 1 mg/minute). (See also prescribing information for Atenolol Injection.) This may be repeated at 5 minute intervals, until a response is observed up to a maximum dosage of 10 mg. If Atenolol is given by infusion, 0.15 mg/kg bodyweight may be administered over a 20 minute period. If required, the injection or infusion may be repeated every 12 hours. Having controlled the arrhythmias with intravenous Atenolol, a suitable oral maintenance dosage is 50–100 mg (two to four 5 ml spoonfuls of Atenolol Solution) daily, given as a single dose.

**Myocardial infarction**

For patients suitable for treatment with intravenous beta-blockade and presenting within 12 hours of the onset of chest pain, Atenolol 5–10 mg should be given by slow intravenous injection (1 mg/minute) followed by Atenolol 50 mg orally about 15 minutes later, provided no untoward effects have occurred from the intravenous dose. This should be followed by a further 50 mg orally 12 hours after the intravenous dose, and then 12 hours later by 100 mg orally, once daily. If bradycardia
and/or hypotension requiring treatment, or any other untoward effects occur, Atenolol should be discontinued.

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

Children
There is no pediatric 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 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 oral dose should be 50 mg 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 m² (equivalent to serum creatinine of greater than 600 micromol/litre), the oral dose should be 25 mg daily or 50 mg on alternate days and 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.

4.3 Contraindications
Atenolol, as with other beta-blockers, should not be used in patients with any of the following:
- cardiogenic shock
- uncontrolled heart failure
- sick sinus syndrome
- second-or third-degree heart block
- untreated phaeochromocytoma
- metabolic acidosis
- bradycardia (<45 bpm)
- hypotension
- known hypersensitivity to the active substance, or any of the excipients
- 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 beta₁-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 m².

Although cardioselective (beta₁) 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.

### 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 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 Pregnancy and lactation
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.

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.

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.

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).

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.

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.

### 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 1–2 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

Beta-blocking agents, plain, selective.
CO7AB03.

Atenolol is a beta-blocker which is beta₁-selective, (i.e. acts preferentially on beta₁-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 Solution. Atenolol Solution facilitates compliance by its acceptability to patients and the once daily dosing regimen. 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 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. 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. 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%).

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

Citric acid monohydrate
Lemon and lime flavour (containing ethanol)
Methyl hydroxybenzoate
Propyl hydroxybenzoate
Purified water
Saccharin sodium
Sodium citrate
Sorbitol solution
Mono Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Unopened: 3 years
Opened: 3 months

6.4 Special precautions for storage
Store below 25°C. Keep the bottle upright.
Store in the original container.

6.5 Nature and contents of container
Amber Polyethylene Terephthalate (PET) bottle with tamper evident High Density Polyethylene (HDPE) cap with Low Density Polyethylene (LDPE) plug, containing 300 ml.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
Chanelle Medical, Loughrea, Galway Co. Ireland.

8 MARKETING AUTHORISATION NUMBER(S)
PL 13931/0060

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
08/12/2011

10 DATE OF REVISION OF THE TEXT
08/12/2011
Module 3

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Atenolol 25 mg / 5 ml Oral Solution

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:
1. What Atenolol Solution is and what it is used for.
2. Before you take Atenolol Solution.
3. How to take Atenolol Solution.
4. Possible side effects.
5. How to store Atenolol Solution.
6. Further information.

1. What Atenolol Solution is and what it is used for

The name of your medicine is Atenolol Solution. Atenolol belongs to a group of drugs called beta blockers.

Atenolol is used to:
- treat high blood pressure (high blood pressure) and some arrhythmias (irregular heart rate).
- help prevent angina (chest pain).
- protect the heart in the early treatment after an myocardial infarction (heart attack).

2. Before you take Atenolol Solution

Do not take Atenolol Solution:
- If you have ever had an allergic reaction to Atenolol or to any of the other ingredients in this medicine. (See section 6 for a list of the ingredients.)
- If you have or have ever had any heart conditions including heart failure which is not under control, second- or third-degree heart block, or very slow or very irregular heartbeats.
- If you have suffered from very low blood pressure, or very poor circulation.
- If you have been told that you have a condition called propranolol (a high blood pressure medicine) caused by a tumour which usually affects the thyroid, which is not being treated. If you are being treated for this condition, your doctor will give you another medicine, called an alpha blocker, to take as well as your Atenolol.
- If you have been told you have metabolic acidosis (abnormal levels of acid in your blood).

Do not give Atenolol to children.

If you are not sure whether you are taking Atenolol, talk to your doctor.

Tell your doctor before taking Atenolol Solution if you have or have had any medical condition, especially the following:
- You have asthma or you get allergic reactions, for example to insect bite. If you have ever had asthma or allergic reactions, you should not take this medicine unless you have discussed these symptoms with the doctor who first gave you the medicine.
- If you suffer from allergy reactions while taking this medicine, which may include raised lumps (wells), swelling of the skin and swelling around the mouth, you may need urgent medical attention.
- You have a type of chest pain called angina.
- You have poor blood circulation, which may be due to chest problems or drug therapy.
- You have diabetes. Atenolol may change your normal response to low blood sugar, which usually involves an increase in heart rate, especially with physical activity.
- You have thyrotoxicosis (condition caused by an overactive thyroid gland). Atenolol may hide the symptoms of thyrotoxicosis.
- You have kidney problems. You may need to have some check-ups during your treatment if you have problems with your kidneys.
- You are an elderly person, especially if you have problems with your kidneys.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines. Atenolol can affect the way some other medicines work and some medicines can have an effect on Atenolol.

The following medicines can cause some problems if you take them with Atenolol:
- Tell your doctor if you are taking any of these:
  - Candesartan (a high blood pressure medicine); you are taking candesartan and Atenolol together, you must not stop taking candesartan. If you have to stop taking candesartan, your doctor will give you written instructions on how to do it.
  - Etorphine, Dopamine and other drugs (which are used to treat high blood pressure or angina).
  - Dopamine receptor blockers (which are used to treat heart failure and angina).
  - Adenosine, also known as epinephrine, is a heart stimulant.
  - Insulin and oral antidiabetic drugs (for diabetes).
  - Naloxone and other cough medicines (including the ones you can buy in the pharmacy).

You may notice that your pulse rate becomes slower while you are taking the medicine. This is normal, but if you are concerned, please tell your doctor.

Operations

If you go into hospital to have an operation, tell the anaesthetist and the medical staff that you are taking Atenolol.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

There is little information regarding the safety of Atenolol during pregnancy. Atenolol should therefore not be used during pregnancy. If you are pregnant, do not become pregnant while taking Atenolol, and you should not drive a car or operate machinery if you are affected.

Driving and using machines

Your medicine is unlikely to have any effect on your ability to drive a car or to operate machinery. However, some patients may occasionally experience dizziness and fatigue when taking Atenolol, and you should not drive a car or operate machinery if you are affected.

Important information about some of the ingredients of Atenolol

Atenolol Solution contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking the medicinal product. Atenolol solution also contains methyldibromoglutethimide (MDI) which is a preservative (possibly delayed). The lemon taste (flavour) contains small amounts of ethanol (alcohol) (less than 100 mg per 5ml). Atenolol may cause other side effects (including a change in your sense of taste). These side effects may be temporary, and may possibly be delayed.

3. How to take Atenolol Solution

Always take Atenolol exactly as your doctor has told you. Also read the label on the container. You should check with your doctor or pharmacist if you are not sure.

The usual doses are given below. Your doctor may gradually increase or decrease your dose depending on how you respond to the treatment.

Atenolol Solution should be swallowed. Try to take your medicine at the same time each day.
Adults
(Treatment of hypertension (high blood pressure)).
50 mg to 100 mg (two to four 5 ml spoonfuls) a day.

(Treatment of angina (chest pain)).
100 mg (four 5 ml spoonfuls) once a day or 50 mg (two 5 ml spoonfuls) twice a day.

(Treatment of arrhythmias (irregular heartbeat)).
20 mg to 100 mg (two to four 5 ml spoonfuls) once a day.

Early treatment of myocardial infarction (heart attack).
50 mg to 100 mg (two to four 5 ml spoonfuls) once a day.

Patients with kidney problems.
Patients with severe kidney problems may receive a lower dose.

Elderly
Elderly patients may get a lower dose, especially in patients with kidney problems.

Children
The medicine must not be given to children.

If you take more medicine than you should
If you have taken more medicine than you have been told to take, contact your doctor immediately or go to your nearest hospital casualty department. A number of symptoms may occur which include slow heartbeat, low blood pressure or difficulty breathing. Take along any left over solution, as well as the container and label, so that the solution can be identified.

If you forget to take a dose
If you forget to take a dose, take it as soon as you remember. However, if it is the almost time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose. If you are worried, ask your doctor or pharmacist.

If you stop taking your medicine
Do not stop taking your medicine without talking to your doctor first. It is necessary to stop taking the medicine gradually. Your doctor will reduce your dose over a 7 – 14 day period.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Atenolol Solution can have side effects. Do not be alarmed by this list of possible effects. You may not have any of them. Most patients do not notice any side effects. However if you do and they bother you, talk to your doctor.

Allergic reactions
If you have any allergic reaction, see your doctor straight away. The signs may include hypersensitivity (allergic) reactions causing bumps on your skin (rash) or swelling of your face, mouth, lips, tongue or throat.

Common side effects (These may affect between 1 in 10 and 1 in 100 patients):
- the heart beats more slowly
- dizziness
- tiredness

Uncommon side effects (These may affect between 1 in 100 and 1 in 1,000 patients):
- disturbed sleep

Rare side effects (These may affect between 1 in 1,000 and 1 in 10,000 patients):
- heart block which may cause an abnormal heartbeat, dizziness, weakness or fainting
- worsening of breathing difficulties, if you have or have had asthma, breathlessness and/or swollen ankles, if you also have heart failure
- worsening of your blood circulation if you already suffer from poor circulation, numbness and aching in the fingers which is followed by warmth and pain (Raynaud’s phenomenon)
- indigestion
- nightmares
- confusion
- palpitations or hallucinations (disturbances of the mind)
- headache
- dizziness, particularly when standing up
- trouble with the hands
- impotence
- dry mouth
- blurry vision
- disturbance of vision
- hair loss
- skin rash, including worsening of psoriasis
- thrombocytopenia (bruising more easily)
- purpura (purple spots on the skin)
- jaundice (which you may notice as yellow colouring of your skin and eyes)

Very rare side effects (These may affect less than 1 in 10,000 patients):
- very rarely, there may be changes to some of the cells or other parts of your blood. It is possible that your doctor may occasionally take blood samples to check whether Atenolol Solution has had any effect on your blood.

Conditions that may get worse
If you have any of the following conditions, they may get worse when you start to take your medicine:
- prostate or skin conditions
- being short of breath or having swollen ankles (if you have heart failure)
- asthma or breathing problems
- poor circulation

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Atenolol Solution

Store below 25°C. Keep the bottle upright.
Store in the original container.
Keep out of the reach and sight of children.

Do not use Atenolol Solution after the expiry date which is stated on the carton and the label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Atenolol Solution contains
The active substance is atenolol. Atenolol Solution contains 25 mg of atenolol per 5 millilitre (5 ml).

The other ingredients are: citric acid, lemon–lime flavour, methyl hydroxybenzoate, propyl hydroxybenzoate, purified water, ascorbic acid, sodium citrate, sorbitol solution, and mono propylene glycol.

What Atenolol Solution looks like and contents of the pack
Atenolol Solution is a clear, colourless viscous liquid. It is available in plastic bottles containing 300 ml.

Marketing authorisation Holder and Manufacturer
The marketing authorisation holder and the manufacturer is Channelle Medical, Loughrea, Co. Galway, Ireland.
The distributor is Channelle Medical U.K. Ltd.

This leaflet was last revised in 12/2011.
CARTON:

Solution for oral use.
Each 5 ml contains Atenolol 25 mg.

Read the package leaflet before use.
For full details of the package leaflet, see end of this leaflet.

Please read the leaflet for further information.

BOTTLE LABEL:

Solution for oral use.
Each 5 ml contains Atenolol 25 mg.

BN:

EXP:

MHRA PAR – Atenolol 25 mg / 5 ml oral Solution (PL 13931/0060)