Public Assessment Report

Atenolol 25mg/5ml Oral Solution

Atenolol

PL 20249/0003

Kappin Limited

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Lay Summary

The MHRA has granted Marketing Authorisations (licences) for the medicinal product Atenolol 25mg/5ml Oral Solution (PL 20249/0003) on 30th March 2007.

Atenolol Oral Solution is a prescription only medicine and is used in the treatment of high blood pressure, chest pain due to inadequate supply of oxygen to the heart and heart attack

Atenolol Oral Solution is intended for use in patients unable to swallow atenolol tablets. The active ingredient is atenolol, a $beta_1$- selective blocker (ie acts preferentially on $beta_1$-adrenergic receptors in the heart).

Atenolol Oral Solution was demonstrated to be a generic medical product of the reference product (PL 17901/0051, Tenormin Syrup 0.5%w/v) held by ASTRAZENECA, UK, Limited and granted on 1st June 2000.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Pliva Pharma Ltd a marketing authorisation for the medicinal product Atenolol 25mg/5ml Oral Solution (PL 20249/0003) on 30th March 2007 . The product is a prescription only medicine.

The reference product is PL 17901/0051, Tenormin Syrup 0.5%w/v, held by ASTRAZENECA, UK, Limited and granted on 1st June 2000. As the product is in solution form, the bioequivalence performance of the product has not been tested.

Atenolol Oral Solution is indicated for:
i) Management of hypertension
ii) Management of angina
iii) Management of cardiac arrhythmias
iv) Myocardial infarction. Early intervention in the acute phase

Atenolol Oral Solution is intended for use in patients unable to swallow atenolol tablets. The acitive ingredient is atenolol, a $beta_1$- selective blocker, (ie acts preferentially on $beta_1$-adrenergic receptors in the heart).

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

An appropriate specification based on the European Pharmacopoeia has been provided, in addition to in-house tests for residual solvents, bulk density and particle size.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active atenolol is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months, with no specific storage instructions.

DRUG PRODUCT

Other Ingredients

The other ingredients of Atenolol 25mg/5ml Oral Solution are listed below.

Maltitol liquid (E965)
Saccharin sodium (E954)
Citric acid monohydrate
Sodium citrate
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)
Orange flavour and
Purified water

All the excipients except the orange flavour comply with their respective current Ph Eur monograph requirements. Each ingredient is supplied with a C of A from suppliers. Orange flavour supplied by Givaudan is food grade and complies with the in-house specifications. All suppliers of the excipients have supplied certificates stating that the materials are not from animal sources.

Dissolution and impurity profiles

No dissolution tests were performed as the product is an aqueous solution. Impurity profiles were similar to those of the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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

Atenolol oral solution is filled in 150ml or 300ml size standard type III amber glass bottles, and capped with tamper evident child resistant 28mm cap made from high density polyethylene material. Compliance to EC requirements of directives 94/62, 2002/172, 2004/I, 97/48 and 93/42 are stated.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is

satisfactory. Storage conditions are “Do not store above 25 degrees” and “Store in original container”.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRECLINICAL ASSESSMENT

No new pre-clinical data were submitted for this application and none were required.

MEDICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

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 Oral Solution. Atenolol Oral 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.

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%).

Bioequivalence Study

According to EU guidelines (CPMP/EWP/QWP/1401/98) no bioequivalence study is required provided that, the product is an aqueous solution that contains an active substance in the same concentration as an oral solution currently approved, and that the excipients do not affect gastrointestinal transit, absorption or in vivo stability of the active substance. As the product is an oral solution and excipients are not considered to significantly effect GI transit/atenolol absorption, a bioequivalence study was not performed.

Efficacy

A satisfactory review of efficacy is contained in the Clinical Expert Report. The reference product is established.

Safety

A satisfactory review of efficacy is contained in the Clinical Expert Report. The reference product is established.

Conclusion

A Marketing Authorisation may be granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Atenolol 25mg/5ml 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.

Pre-Clinical

No new preclinical data were submitted and none are required for applications of this type.

Clinical

No new or unexpected safety concerns arise from these applications. A bioequivalence study was not required for this product.

The SPC, PIL and labelling are satisfactory and consistent with that for Tenormin Syrup 0.5%w/v.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 29/03/2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 07/04/2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 09/09/2005, 23/11/2005, 06/02/2007 and on the medical assessment on 28/11/2005
4	The applicant provided further information in regard to the quality assessment on 23/11/2005, 27/02/2006, 05/02/2007 and 07/02/2007 and on the medical assessment on 26/06/2006
5	The application was determined on 30/03/2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atenolol 25mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains Atenolol 25mg.
Also contains Maltitol, parahydroxybenzoate and flavouring which contains ethanol. For further information see section 4.4.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Solution
Clear solution with an aroma of oranges

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atenolol Oral Solution is indicated for:
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

Atenolol oral 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.

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

Myocardial Infarction: For patients suitable for treatment with intravenous beta-adrenoceptor blockade and presenting within 12 hours of the onset of the chest pain, Atenolol Injection 5 - 10 mg should be given by slow intravenous administration (1 mg/minute) followed by Atenolol Oral Solution 50 mg (two 5 ml spoonfuls) orally about 15 minutes later, provided no untoward effects occur 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 (four 5 ml spoonfuls) orally, to be given once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, Atenolol should be discontinued.

Elderly Patients: 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, 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 daily and the intravenous dose should be 10 mg once every two days. For patients with a creatinine clearance of <15 ml/min/1.73 m^2 (equivalent to serum creatinine of>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-adrenoceptor blocking drugs, 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 (<45bpm)
- 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 $beta_1$ -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 50-55bpm 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 used to treat the allergic reactions.
• may cause a hypersensitivity reaction including angioedema and urticaria
• should be used with caution in the elderly, starting with a lesser dose (See Section 4.2).

Since Atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35ml/min/1.7m^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.
Atenolol Oral Solution contains sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate (E217). These may cause allergic reactions (possibly delayed).
It also contains Orange Flavouring which contains small amount of ethanol less than 100mg per 10ml.
This product also contains Maltitol Liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects e.g. verapamil and diltiazem can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

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

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

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped. (See also prescribing information for clonidine).

Caution must be exercised when prescribing a beta-blocker with Class I antiarrhythmic agents such as disopyramide and quinidine.

Concomitant use of sympathomimetic agents, e.g. adrenaline, 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 indomethacin), 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:

Cardiovascular: bradycardia; heart failure deterioration; postural hypotension which may be associated with syncope; cold extremities. In susceptible patients: precipitation of heart block; intermittent claudication; Raynaud's phenomenon.

CNS: confusion; dizziness; headache; mood changes; nightmares; psychoses and hallucinations; sleep disturbances of the type noted with other beta-blockers.

Gastrointestinal: dry mouth; gastrointestinal disturbances. Elevations of transaminase levels have been seen infrequently; rare cases of hepatic toxicity, including intrahepatic cholestasis have been reported.

Haematological: purpura; thrombocytopenia.

Integumentary: alopecia; dry eyes; psoriasiform skin reactions; exacerbation of psoriasis; skin rashes.

Neurological: paraesthesia.

Reproductive: impotence

Respiratory: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Special senses: visual disturbances.

Others: hypersensitivity reactions, including angioedema and urticaria; fatigue; 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 use 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
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 Oral Solution. Atenolol Oral 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

Maltitol liquid (E965)
Saccharin sodium (E954)
Citric acid monohydrate
Sodium citrate
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)

Orange flavour and
Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in the original container.
Discard after 3 months of first opening.

6.5 Nature and contents of container
Amber Type III Glass
Child Resistant Tamper Evident Cap- High density polypropylene cap with a polyethylene lining
5 ml polypropylene Spoon

Pack sizes available: 300ml

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER

Kappin Limited
Cunard Road
Park Royal
London
NW10 6PN

8 MARKETING AUTHORISATION NUMBER(S)

PL 20249/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/03/2007

10 DATE OF REVISION OF THE TEXT

29/03/2007

Labels and Leaflet

Atenolol 25mg/5ml Oral Solution

3060/1

This leaflet contains important information about Atenolol 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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should 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 gets serious, or if you have any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

Atenolol Oral Solution contains an active substance called Atenolol.

Atenolol is one of a group of drugs called beta blockers. It has effects on the heart and circulation. It is used to treat hypertension (high blood pressure) and some arrhythmias (disorders of heart rhythm). Atenolol can help prevent angina (chest pain). Atenolol can also be used to protect the heart in the early treatment of myocardial infarction (heart attack).

Atenolol solution is intended for patients unable to swallow atenolol tablets.

2. Before you take Atenolol Oral Solution

Do not take Atenolol Oral Solution:

- if you have previously had an allergic reaction to atenolol or any of the other ingredients in this medicine.
- if you have heart failure which is not under control or
- If you have certain other conditions such as heart block, very slow or very irregular heart beats, very low blood pressure or very poor circulation.
- If you have phaeochromocytoma (a tumour which causes increased blood pressure, palpitations, increased heart rate and headaches) which is not being treated.
- If you are being treated for phaeochromocytoma your doctor will give you another medicine, called an alpha blocker, to take as well as your Atenolol.
- If you have metabolic acidosis (imbalance of chemicals in the blood). Your doctor will know about these conditions.

Take special care with Atenolol Oral Solution:

- If you have asthma or you get allergic reactions, for example, to insect stings. If you have ever had asthma or wheezing, 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 allergic reactions while taking your medicine, which may include raised lumps (weals), swelling of the skin and swelling around the mouth, you may need urgent medical attention.
- If you have a type of chest pain called Prinzmetal's angina.
- If you have poor blood circulation, controlled heart failure or first-degree heartblock.
- If you have diabetes. Atenolol may change your normal response to low blood sugar, which usually involves an increase in heart rate.
- If you have thyrotoxicosis (a condition caused by an overactive thyroid gland). Atenolol may hide the symptoms of thyrotoxicosis.
- If you have kidney problems. You may need to have some check-ups during your treatment if you have problems with your kidneys.
- If you are an elderly person, especially if you have problems with your kidneys.

Pregnancy and Breast-feeding

- Are you pregnant or are you breast feeding a baby? If so, tell your doctor.

Driving and using machines

- Your medicine is unlikely to affect your ability to drive or to operate machinery. However, some people may occasionally feel dizzy or tired when taking Atenolol. If this happens to you, ask your doctor for advice.

Important information about some of the ingredients of Atenolol Oral Solution

- Maltitol liquid: If you have been told by your doctor that you have intolerance to some sugars,contact your doctor before taking this medicinal product.
- Sodium methylhydroxybenzoate (E219) and sodium propylhydroxbenzoate (E217): May cause allergic reactions (possibly delayed).
- This medicinal product contains 2.7mmol (or 63.1mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.
- This medicinal product contains small amounts of ethanol (alcohol) from the flavouring, less than 100mg per 10ml.

Taking other medicines

- Are you taking any other medicines? If so, tell your doctor.

Atenolol can interfere with the action of some other drugs and some drugs can have an effect on Atenolol. The following drugs can cause some problems when taken together with Atenolol:

- Clonidine (for hypertension or migraine). If you are taking Clonidine and Atenolol together, you must NOT stop taking Clonidine unless your doctor tells you to do so. If it becomes necessary for you to stop taking the Clonidine, your doctor will give you careful instructions on how to do it.
- Verapamil, diltiazem, nifedipine (which are used to treat hypertension or angina)
- Disopyramide or quinidine (for irregular heart beats)
- Digoxin (for heart failure)
- Adrenaline (a heart stimulant)
- Ibuprofen and indomethacin (for pain and inflammation)
- Insulin and oral anti diabetic drugs (for diabetes)
- Nasal decongestants or other cold remedies (including theones you can buy in the pharmacy).

If you are taking any other medicines, including any you have bought from the pharmacy, you should tell your doctor.

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

3. How to take Atenolol Oral Solution

Atenolol Oral Solution should be swallowed. Follow your doctor's instructions about when and how to take your medicine. Also read the label. Your pharmacist can also help if you are not sure.

Your doctor will have decided what dose you should take each day depending on your condition. The usual daily dosages for an adult are:

- Hypertension (high blood pressure) 50 mg to 100 mg (two to four 5 ml spoonfuls) daily
- Angina (chest pains) 100 mg (four 5 ml spoonfuls) daily or50 mg (two 5 ml spoonfuls) twice a day
- Arrhythmias (irregular heart beats) 50 mg to 100 mg (two to four 5 ml spoonfuls) daily.
- In the early treatment of myocardial infarction (heart attack) 50 mg to 100 mg (two to four 5 ml spoonfuls) a day.

If you take more Atenolol Oral Solution than you should

- If you accidentally take an overdose of your medicine, either call your doctor straight away, or go to your nearest hospital casualty department. Always take any remaining medicine, the container and the label with you, so that the medicine can be identified.

If you forget to take Atenolol Oral Solution

- If you forget to take your medicine, take your dose when you remember and then take your next dose at the usual time. Don't take two doses at the same time. If you are worried, ask your doctor or pharmacist for advice.

Do not stop taking your medicine without talking to your doctor first. In some cases, it may be necessary to stop taking the medicine gradually.

4. Possible side effects

Like all medicines, Atenolol Oral Solution can have side effects.

If any of the following happen, stop taking Atenolol Oral Solution and tell your doctor immediately or go to the casualty department at your nearest hospital

- Swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing
- Hives
- Fainting
- Yellowing of the skin and eyes also called jaundice

These are all very serious side effects. If you have them, you may have a serious allergic reaction to Atenolol Oral Solution. You may need urgent medical attention or hospitalisation. All of these very serious side effects are very rare.

Tell your doctor if you notice any of the following:

Cold hands and feet, tiredness, slow heart beat, headache, dry mouth, nausea, diarrhoea, disturbed sleep, thinning of the hair, mood changes, confusion, psychoses or hallucinations, bruising more easily or purplish marks on the skin, tingling of the hands, dry eyes, disturbances of vision, skin rashes, dizziness, particularly when standing up or very rarely, jaundice (yellowing of the skin or the whites of your eyes).

Other possible events which may occur in susceptible people are numbness and spasm in the fingers (Raynaud's phenomenon), heart block (which can cause dizziness or fainting).

If you suffer from any of the following conditions, they may get worse when you start to take Atenolol:

- Psoriasis.
- Breathlessness or swollen ankles, if you have heart failure
- Asthma or breathing problems
- Poor circulation.

Do not be alarmed by this list of possible events. You may not have any of them.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing Atenolol Oral Solution

- As with all medicines, it is important to keep Atenolol Oral Solution out of the reach and sight of children.
- Do not store above 25^{o}C. Store in the original container.
- Do not use Atenolol Oral Solution after 3 months of first opening the bottle or after the expiry date printed on the carton or the bottle.
- Do not keep outdated medicine or medicine that is no longer wanted. Take it to your pharmacist for safe disposal.
- Always keep the medicine in the bottle in which it was originally given to you.
- You may wish to read the leaflet again. Do not throw it away until you have finished your medicine.

6.Further Information

Atenolol 25mg/5ml Oral Solution is a clear colourless solution with a smell of oranges.

Each 5 ml of Atenolol Oral Solution contains Atenolol 25mg as active ingredient.

It also contains the following inactive ingredients: maltitol liquid (E965), saccharin sodium (E954), citric acid monohydrate, sodium citrate, sodium methyl parahydroxybenzoate(E219), sodium propyl parahydroxybenzoate(E217),orange flavour (containing ethanol) and purified water

Each bottle contains 300ml of oral solution. A double ended 5ml and 2.5ml polypropylene spoon is also included to help measure the dose.

The Marketing Authorisation for Atenolol Oral Solution is held by Kappin Ltd., Northfield Industrial Estate, Middlesex HA0 1NW.

Atenolol Oral Solution is manufactured by Orbis Consumer Products Ltd Northfield Industrial Estate, Middlesex HA0 1NW

REMEMBER

This medicine is for you. Only a doctor can prescribe it for you. Never give it to anybody else, even if their symptoms are the same as yours.

This leaflet does not tell you all about your medicine. If you have any questions or are not sure about anything then ask your doctor or pharmacist.

The information in this leaflet only applies to Atenolol 25mg/5ml Oral Solution.

This leaflet was prepared in January 2006

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Braille reads:
Atenolol
#25 mg/#5 ml
Oral Solution
Atenolol
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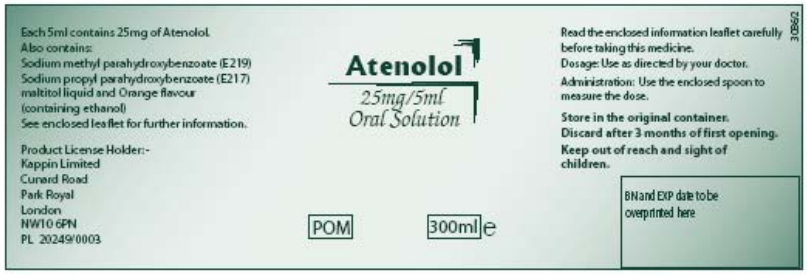
Oral Solution
Atenolol
25mg/5ml
Oral Solution
Atenolol
25mg/5ml
Oral Solution
Atenolol
25mg/5ml
Oral Solution
Each 5ml contains 25mg of Atenolol.
Also contains:
maltitol liquid (E965)
sodium methyl parahydroxybenzoate (E219)
sodium propyl parahydroxybenzoate (E217)
orange flavour (containing ethanol)
See enclosed leaflet for further information.
Dosage: Use as directed by the doctor.
Administration: Use the enclosed spoon to measure the dose.
Store in the original container.
Discard after 3 months of first opening.
Keep out of reach and sight of children.
Barcode to be printed here
300ml
POM
affix dispensing label here
Product License Holder: -
Kappin Limited
Cunard Road
Park Royal
London
NW10 6PN
PL 20249/0003
300ml
POM
3085/2
BN and EXP date to be overprinted here


Each 5ml contains 25mg of Atenolol.
Also contains:
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)
maltitol liquid and Orange flavour
(containing ethanol)
See enclosed leaflet for further information.
Product License Holder:-
Kappin Limited
Cunard Road
Park Royal
London
NW10 6PN
PL 20249/0003
Atenolol
25mg/5ml
Oral Solution
POM
300ml
Read the enclosed information leaflet carefully before taking this medicine.
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Administration: Use the enclosed spoon to measure the dose.
Store in the original container.
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Keep out of reach and sight of children.
BN and EXP date to be overprinted here
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