SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atenolol 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains atenolol 100 mg

Excipients with known effect:
Sodium Laurilsulfate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Plain, white to off white, round, flat tablets 12 mm in diameter, scored on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. The management of hypertension
2. The management of angina pectoris
3. The management of cardiac dysrhythmias
4. The management of myocardial infarction: early intervention in the acute phase and long- term prophylaxis after recovery from myocardial infarction.

4.2 Posology and method of administration

<u>Posology</u>

The dosage should be determined on an individual basis. It is recommended to start with the lowest possible dosage.

Adults:

Hypertension:

A starting dose of 25 mg is recommended. The usual maintenance dosage in hypertension is 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 antihypertensive e.g. a diuretic.

Angina pectoris:

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:

Having controlled the dysrhythmias with intravenous atenolol a suitable maintenance dosage is 50 mg – 100 mg daily, given as a single dose.

Myocardial infarction:

Initially controlled intravenously, followed by 50 mg orally about 15 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 is 100 mg daily in 1-2 dosages for 6 days or until discharge from hospital. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, atenolol should be discontinued.

Impaired renal function:

Atenolol is excreted via the kidneys, therefore the dosage will need to be adjusted in severe renal conditions.

GFR (mL/min/1.73 m^2 BSA)	**Recommended daily dose atenolol (mg/day)**
>35	No dose adjustment necessary
15-35 (equivalent to serum creatinine of 300–600 micromol/litre)	50
<15 (equivalent to serum creatinine of greater than 600 micromol/litre)	25 (or 50 every second day)

Patients on haemodialysis should be given 50 mg atenolol orally following each dialysis. Because of the possibility of marked falls in blood pressure, this should be carried out under hospital supervision.

Elderly:

Dosage requirements may be reduced, especially in patients with impaired renal function. Dosage should be titrated according to clinical effect.

Paediatric population:

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

Decreased hepatic function:

No dose adjustment is necessary.

Method of administration

For oral administration.

4.3 Contraindications

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

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Second or third-degree heart block.
- Cardiogenic shock.
- Uncontrolled heart failure.
- Sick sinus syndrome (including sino-atrial block).
- Untreated phaeochromocytoma.
- Metabolic acidosis
- Bradycardia (less than 45-50 beats per minute)
- Hypotension
- Severe peripheral circulatory disturbances
- Concomitant intravenous use of verapamil or diltiazem
- Severe asthma and severe chronic obstructive pulmonary disease such as airway obstructions.

4.4 Special warnings and precautions for use

Heart Failure: Although contraindicated in uncontrolled heart failure (see section 4.3), may be used in patients whose signs of heart failure have been controlled. Similarly, care must be taken with patients with poor cardiac reserve.

Ischaemic Heart disease: especially in patients with ischaemic heart disease, treatment should not be discontinued suddenly. The dosage should be gradually reduced, i.e. over 1-2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop. Furthermore, there is a risk of myocardial infarction and sudden death. Patients should be followed during withdrawal, especially those with ischaemic heart disease.

Untreated Congestive Heart disease: beta-blockers should not be used in such patients. The condition should be stabilised first.

First Degree Heart Block: due to its negative effect on conduction time, beta-blockers should only be given with caution to such patients.

Heart rate disorders: beta-blockers may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

Prinzmetal's angina: Atenolol may increase the number and duration of anginal 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.

Peripheral Arterial CirculatoryDisturbances: Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), may also aggravate less severe peripheral arterial circulatory disturbances

Respiratory Disorders: In patients with chronic obstructive pulmonary disorders, airway obstructions may be aggravated. Therefore, atenolol should only be used for these patients with the utmost care.

Patient information leaflets and labels will carry the following warnings:

Patient Information Leaflet: Do not take this medicine if you have a history of wheezing or asthma. Consult your doctor or pharmacist first.

Labels: Do not take this medicine if you have a history of wheezing or asthma.

Renal impairment: In patients with impaired renal function, the dose should be adjusted to reduce glomerular filtration rate (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.

Treated phaeochromocytoma: atenolol should be used with blood pressure monitoring in patients with treated phaeochromocytoma.

Hypoglycaemia: the symptoms of hypoglycaemia may be masked by atenolol, in particular tachycardia. Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels. (see Section 4.5)

Thyrotoxicosis: Beta-blockade may mask cardiovascular signs of thyrotoxicosis.

Allergies: Atenolol may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Atenolol may reduce the efficacy of the usual dose of adrenaline (epinephrine) used to treat allergic reactions.

Hypersensitivity: atenolol may cause a hypersensitivity reaction including angio-oedema and urticaria. (see section 4.8)

Psoriasis: patients with anamnestically known psoriasis should take beta-blockers only after careful consideration.

Elderly: these patients should be treated with caution, starting with a lower dosage

Surgery: When a patient has been scheduled for surgery, and it has been decided to interupt beta-blockade, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypotension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine.

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.

This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

- Alcohol: concomitant use with alcohol may lead to an enhanced hypotensive effect.
- Alpha blockers – some patients experience acute postural hypotension, tachycardia and palpitations when they start to take certain alpha blockers (e.g. prazosin, alfuzosin, and terazosin), this can be exacerbated if they are already taking a beta-blocker. It is recommended that they should start with a low dose of these alpha blockers, and the first dose should be taken just before they go to bed. Patients should be warned about the possibility of postural hypotension and how to manage it (lay down, raise legs and get up slowly). When adding a beta-blocker to an alpha blocker it may be advisable to decrease the dose of the alpha blocker and re-titrate as necessary.
- Anaesthetic drugs: Attenuation of the reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockades reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, lidocaine, procainamide and beta-adrenoceptor stimulants such as noradrenaline (norepinephrine) are best avoided.
- *Class I anti-arrhythmic drugs (e.g. disopyramide, quinidine) and amiodarone*: May have potentiating effect on atrial-conduction time and induce a negative inotropic effect.
- *Insulin and oral antidiabetic drugs:* May intensify the blood sugar lowering effects of these drugs (especially nonselective beta-blockers). The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia. Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).
- *Baclofen:* Causes an increased antihypertensive activity.
- *Contrast media, iodinated:* Atenolol may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodinated contrast products.
- Calcium channel blockers: concomitant administration of dihydropyridine derivatives (e.g. nifedipine), may increase the risk of hypotension, and in patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure. Beta-adrenoceptor blocking drugs should be used with caution in combination with verapamil and to a lesser extent diltiazem in patients with impaired ventricular function, and not at all in patients with conduction abnormalities due to the negative influence on contractility and auriculo-ventricular conduction. May result in severe hypotension, bradycardia and cardiac failure.
- *Cardiac glycosides*: digitalis glycosides in association with beta-blockers may increase auriculo-ventricular conduction time.
- *Clonidine:* Beta-blockers increase the risk of rebound hypertension. 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.

- *Non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. indometacin):* -may reduce the hypotensive effect of beta-blockers.
- Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine) – combination with atenolol may reduce effects of both agents.
- Sympathomimetic agents (e.g. adrenaline (epinephrine): may counteract the effect of atenolol.
- *Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents*: May increase the blood pressure lowering effect and/or risk of bradycardia.
- *Ampicillin:* May reduce the bioavailability of atenolol. Therefore the physician should watch for evidence of altered atenolol response especially when large doses of ampicillin are administered concomitantly.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from the use of atenolol in pregnant women to determine its potential harmfulness. 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

Administration of atenolol in pregnancy has been associated with reduced foetal growth. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester.

On the basis of its pharmacological properties, adverse effects may occur in the foetus and newborn infant, if used in the first and second trimesters (especially hypoglycaemia, hypotension and bradycardia). Beta-blockers reduce placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Breast-feeding

Atenolol is excreted into breast milk reaching higher concentration than in plasma. A risk in the breastfed child cannot be excluded (beta-blockade). Neonates born to mothers who are receiving atenolol at parturition or breastfeeding may be at risk of hypoglycaemia and bradycardia.

4.7 Effects on ability to drive and use machines

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with atenolol and other beta blockers with the following frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to < 1/1000), very rare (<1/10,000), Not known (cannot be estimated from the available data).

• Blood and Lymphatic System Disorders

Rare: Thrombocytopenia, purpura

• Endocrine Disorders

Beta-blockers may mask the symptoms of thyrotoxicosis.

• Metabolic and Nutrition Disorders

Beta-blockers may mask the symptoms of hypoglycaemia.

• Psychiatric Disorders

Uncommon: Sleep disturbances of the type noted with other beta-blockers

Rare: Hallucinations, psychoses, confusion, depression, mood changes and nightmares

• Nervous System Disorders

Rare: Dizziness, headaches, paraesthesia.

• Eye Disorders

Rare: Dry eyes, impaired vision.

• Cardiac Disorders

Common: Bradycardia,

Rare: Precipitation of heart block, heart failure deterioration

• Vascular Disorders

Common: Cold extremities.

Rare: increase of an existing intermittent claudication may be increased if already present in susceptible patients Raynaud's phenomenon, postural hypotension which may be associated with syncope

• Respiratory, Thoracic and Mediastinal Disorders

Rare: Bronchospasm in patients with bronchial asthma or a history of asthmatic complaints.

• Gastrointestinal Disorders

Common: Gastrointestinal disturbances.

Rare: Dry mouth.

• Hepatobiliary Disorders

Rare: Cases of hepatic toxicity, including intrahepatic cholestasis have been reported.

Uncommon: Elevations of transaminase levels

• Skin and Subcutaneous Tissue Disorders

Rare: Skin rash, purpura, exacerbation of psoriasis, alopecia, psoriasiform skin reactions.

Not known: Hypersensitivity reactions, including angioedema, urticaria.

• Musculoskeletal and Connective Tissue Disorders:

Not known: Lupus-like syndrome

• Reproductive System and Breast Disorders:

Rare: Impotence

• General Disorders and Administration Site Conditions:

Common: Fatigue.

• Investigations:

Very rare: An increase in ANA (Antinuclear Antibodies) has been reported, however the clinical relevance of this is not clear.

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The most important effects are on the heart. Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. First or second degree AV block may occur and rarely arrhythmias.

After ingestion of an overdose or in the case of hypersensitivity the patient should be kept under close supervision and be treated in an intensive care ward.

Activated charcoal and a laxative should be used to prevent absorption of any drug still present in the gastrointestinal tract, plasma or plasma substitutes can be used to treat hypotension or shock. The use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be treated with atropine 1-2 mg intravenously and or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously and if required, this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-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, selective.

ATC code: CO7A B03.

Atenolol is a beta-adrenoceptor blocking agent which is cardioselective, its principal action being on beta-adrenergic receptors in the heart. It 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). Its mode of action in the treatment of hypertension is unclear.

It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

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. However, the response may be less in black patients.

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. 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 (but see section 4.5). Since it acts preferentially on beta-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.

Human studies have shown that a negligible amount of atenolol crosses the blood brain barrier.

Early intervention in acute myocardial infarction reduces infarct size and may decrease 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: The oral bioavailability is consistent but incomplete (about 40 to 50 %). Peak plasma concentrations are found 2-4 hours after repeated oral administration. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90 % of that absorbed reaches the systemic circulation unaltered.

Distribution: Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3 %).

Elimination: The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

5.3 Preclinical safety data

Atenolol is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Prescribing Information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets contain:

Gelatin

Heavy Magnesium Carbonate

Magnesium Stearate

Microcrystalline Cellulose

Maize Starch

Sodium Laurilsulfate

Purified Talc

Purified Water

6.2 Incompatibilities

None known

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original packaging.

6.5 Nature and contents of container

Clear, transparent PVC/PVdC /aluminium blisters.

Pack sizes 28, 100, 250 tablets.

6.6 Special precautions for disposal

No special precautions.

7 MARKETING AUTHORISATION HOLDER

Medley Pharma Limited
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Liverpool
L30 1RD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 43870/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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