SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Atenomel-100 film coated tablets

2. Qualitative and quantitative composition

Each tablet contains 100mg of Atenolol

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Tablets

Off White, circular, biconvex, film coated tablets with a break score on one side and engraved with“Atenol 100" on the other side

4. Clinical particulars

4.1 Therapeutic indications

a. Management of hypertension.

b. Management of angina pectoris.

c. Management of cardiac dysrhythmias.

d. 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

Oral administration.

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

Adults

Hypertension

One tablet daily. Most patients respond to 100 mg daily given orally as a single dose. 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 tablets with other antihypertensive agents. For example, co-administration of Atenolol tablets with a diuretic provides a highly effective and convenient antihypertensive therapy.

Angina

Most patients with angina pectoris will respond to 100 mg given orally once daily or 50 mg given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

Cardiac arrhythmias

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

Older population

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

Paediatric population

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

Renal failure

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

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

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

For patients with a creatinine clearance of less than 15 ml/min/1.73 m^2 (equivalent to serum creatinine of greater than 600 micromol/litre), the oral dose should be 25 mg 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.

Method of administration

For administration by the oral route.

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 (including sino-atrial block)

- Second-or third-degree heart block

- Untreated phaeochromocytoma

- Metabolic acidosis

- Bradycardia (< 50 bpm before treatment initiation)

- Hypotension

- Known hypersensitivity to the active substance, or any of the excipients

- Severe peripheral arterial circulatory disturbances

- Severe asthma and severe chronic obstructive pulmonary disorders, such as airway obstructions

- The intravenous application of calcium channel blockers (verapamil / diltiazem type) is contraindicated in patients who use atenolol (except in intensive care unit).

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. Furthermore there is a risk on myocardial infarction and sudden death.

• 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. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation, however the risk of hypotension may be increased as well. 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 (Raynaud's disease or syndrome, intermittent claudication).

• 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. Insulin sensitivity may be reduced in patients treated with atenolol.

• 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

Since Atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73 m^2.

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, Atenolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline. The label and patient information leaflet for this product state the following warning: "If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor".

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

Patients with anamnestically known psoriasis should take atenolol only after careful consideration.

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.)

Caution must be exercised when prescribing a beta-blocker with Class I antiarrhythmic agents such as disopyramide, and quinidine which may have potentiating effect on atrial-conduction time and induce a negative inotropic effect.

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

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 such as cyclopropane and trichlorethylene, lidocaine, procainamide and beta-adrenoceptor stimulants such as noradrenaline (norepinephrine) are best avoided.

Not recommended association with monoamineoxidase inhibitors (except MAO-B inhibitors)

Not recommended association with Baclofen: Causes an increased antihypertensive activity.

Not recommended association with contrast media, iodinated: Atenolol may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodinated contrast products.

Amiodarone: Combination with atenolol may result in additive depressant effects on conduction and negative inotropic effects, especially in patients with underlying sinus node dysfunction or atrioventricular node dysfunction.

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

Peripheral muscle relaxants (e.g. Suxamethonium halogenide, Tubocurarine): concomitant use of atenolol could increase and extent the relaxative effect of muscle relaxants.

4.6 Fertility, pregnancy and lactation

Caution should be exercised when Atenolol tablets is administered during pregnancy or to a woman who is breast-feeding.

Pregnancy

Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of Atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of Atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

The use of Atenolol in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Breast-feeding

There is significant accumulation of Atenolol in breast milk.

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

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).*Blood and lymphatic system disorders:*

Rare: Purpura, thrombocytopenia, leucopenia.

Psychiatric disorders:

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

Rare: Mood changes, depression, anxiety, nightmares, confusion, psychoses and hallucinations.

Nervous system disorders:

Rare: Dizziness, headache, paraesthesia of extremities.

Eye disorders:

Rare: Dry eyes, impaired vision, 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, constipation.

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.

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, sweating.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medical products 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 TMDA ADR reporting tool; website: *https://imis.tmda.go.tz/arrt* or search for TMDA adverse reactions reporting tool in the google play store.

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

Pharmacotherapeutic group: Beta-blocking agents, plain, selective.

ATC code: CO7A B03.

Mechanism of action

Atenolol is a beta-blocker, which is $beta_1$-selective, (i.e. acts preferentially on $beta_1$-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

Atenolol is without intrinsic sympathomimetic and membrane-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.

Clinical efficacy and safety

Atenolol is effective and well tolerated in most ethnic populations although the response may be less in black patients.

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. 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-receptors in the heart, Atenolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

Early intervention with Atenolol in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to frank infarction; the incidence of ventricular arrhythmias is decreased and marked pain relief

may result in reduced need of opiate analgesics. Early mortality is decreased. Atenolol is an additional treatment to standard coronary care.

5.2 Pharmacokinetic properties

Absorption

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. The bioavailability is decreased by 20% when taken with food. There is a linear relationship between dosage and plasma concentration. The inter-subject variability in AUC and Cmax is about 30-40%. 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. The volume of distribution is 50 to 75 L. The protein binding is low (approximately 3%). Most of an absorbed dose (85-100%) is excreted unchanged via the urine.

Elimination

The clearance is about 6 l/h and the half-life is about 6 to 9 hours. In elderly patients, clearance is decreased and elimination half-life increased. The clearance is correlated to renal function and the elimination is prolonged in patients with renal impairment. Impaired liver function does not influence the pharmacokinetics of atenolol.

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

Maize starch
Microcrystalline Cellulose
Lactose Monohydrate
Colloidal anhydrous Silica
Croscarmellose sodium
Purified talc
Magnesium stearate

Coating agent (Tabcoat orange TC-2113, polymer, plasticizer, additives and Titanium dioxide, lake sunset yellow CI 15985)

6.2 Incompatibilities

None

6.3 Shelf life

24 months (2 years)

6.4 Special precautions for storage

Do not store above 30°C, protect from light

6.5 Nature and contents of container

Blisters made of PVC and Aluminium foil

Pack size: 2 x 14 tablets

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorization holder and manufacturing site

7.1 Marketing authorization holder

Mankind Life Sciences Limited
No 2 Aggrey Road, Fegge Onitsha Anambra State Nigeria

8. Registration number(s)

TZ 17 H 0290

9. Date of first registration

8/11/2017

10. Date of revision of the text

June 2020