1. NAME OF THE MEDICINAL PRODUCT

Tenolol-50

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Atenolol BP ….. 50mg

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Hypertension: Atenolol is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents.

Angina pectoris due to coronary atherosclerosis: Atenolol is indicated for the long-term management of patients with angina pectoris.

Acute myocardial infarction: Atenolol is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows.

4.2 Posology and Method of Administration

Hypertension: The initial dose of atenolol is 50 mg given as one tablet a day either alone or when added to other antihypertensive agents. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to atenolol 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

Atenolol may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. **Angina pectoris**: The initial dose of atenolol is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to atenolol 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Acute myocardial infarction: Treatment should begin with the intravenous

administration of 5 mg atenolol over 5 minutes followed by another 5 mg intravenous injection 10 minutes later.

In patients who tolerate the full intravenous dose (10 mg), atenolol tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, atenolol can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, atenolol should be discontinued.

If there is any question concerning the use of IV beta-blocker or clinical estimate that there is a contraindication, the IV beta-blocker may be eliminated and patients fulfilling the safety criteria may be given atenolol Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Treatment with beta-blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

Elderly patients or patients with renal impairment: Atenolol is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of atenolol occurs until creatinine clearance falls below 35 mL/min/1.73m^2.

The following maximum oral dosages are recommended for elderly, renal-impaired patients and for patients with renal impairment due to other causes:

Creatinine clearance (mL/min/1.73m^2)	**Atenolol elimination half-life (h)**	**Maximum dosag**
15-35	16-27	50 mg daily
<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of atenolol: 25 mg given as one tablet a day.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

4.2. Contra-indications

Atenolol is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, severe peripheral arterial circulatory disturbances, metabolic acidosis, sick sinus syndrome, hypotension and overt cardiac failure.

Atenolol is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components.

4.3. Special Warnings and Precautions for Use

i. Cardiac failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, atenolol should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment. In addition, good clinical judgment suggests that patients whose cardiac output and/or blood pressure depends on sympathetic stimulation are not good candidates for beta adrenergic blocker therapy for acute myocardial infarction and such use is not recommended for patients whose systolic blood pressure or heart rate persistently is less than 100mm Hg or 50 beats/minute respectively.

ii. In patients without a history of cardiac failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, atenolol should be withdrawn.

iii. Cessation of therapy with atenolol: Patients with coronary artery disease, who are being treated with atenolol, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta-blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. When discontinuation of atenolol is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency

develops, it is recommended that atenolol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly even in patients treated only for hypertension.

iv. Concomitant use of calcium channel blockers: Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible. Bronchospastic diseases: Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of its relative beta1 selectivity, however, atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta1 selectivity is not absolute, the lowest possible dose of atenolol should be used with therapy initiated at 50 mg and a beta2- stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

v. Anesthesia and major surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Atenolol, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution.

vi. Diabetes and hypoglycemia: Atenolol should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta-blockers, does not delay recovery of blood glucose to normal levels.

vii. Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom atenolol therapy is to be withdrawn should be monitored closely.

viii. Untreated pheochromocytoma: Atenolol should not be given to patients with untreated pheochromocytoma.

PRECAUTIONS

General: Patients already on a beta-blocker must be evaluated carefully before Atenolol is administered. Initial and subsequent atenolol dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. Atenolol may aggravate peripheral arterial circulatory disorders.

Impaired renal function: The drug should be used with caution in patients with impaired renal function.

Usage in paediatrics

Safety and effectiveness in pediatric patients have not been established.

Usage in geriatrics

In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

Hence dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

i. Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with atenolol plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

ii. Calcium channel blockers may also have an additive effect when given with the drug. Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible. Concomitant therapy with dihydropyridines e.g. nifedipine may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

iii. Beta-blockers may exacerbate the rebound hypertension which can follow the

withdrawal of clonidine. If the two drugs are coadministered, the beta-blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

iv. Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, currently do not suggest any clinical interaction between aspirin and beta-blockers in the acute myocardial infarction setting.

v. While taking beta-blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

vi. Concomitant use of prostaglandin synthase inhibiting drugs e.g. indomethacin, may decrease the hypotensive effects of beta blockers.

vii. Digitalis glycosides, in association with beta adrenoceptor blocking drugs, may increase atrio-ventricular conduction time.

viii. Caution must be exercised when prescribing a beta-adrenoceptor blocking drug with Class I antiarrhythmic agents such as disopyramide.

ix. Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effect of beta-adrenoceptor blocking drugs.

x. Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs.

4.6. Pregnancy and Lactation

Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester, and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol is excreted in human breast milk. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

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. Most adverse effects have been mild and transient.

The following adverse events 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 judgment, the well-being of the patient is adversely affected by any of the above reactions.

4.9. Overdose

Overdosage with atenolol has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in atenolol overdose are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

Bradycardia: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

Heart block (Second or third degree): Isoproterenol or transvenous cardiac pacemaker.

Cardiac failure: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

Hypotension: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

Bronchospasm: A beta$_2$ stimulant such as isoproterenol or terbutaline and/or aminophylline.

Hypoglycemia: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Atenolol is a beta1-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

A significant beta-blocking effect of atenolol is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours.Consistent with its negative chronotropic effect due to beta blockade of the SA node, Atenolol increases sinus cycle length and sinus node

recovery time. Conduction in the AV node is also prolonged.

Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta-blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

5.2. Pharmacokinetic Properties

Absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between two and four hours after ingestion. Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Approximately 50% of an oral dose is excreted in urine within 24 hours. Only a small amount (6% -16%) is bound to proteins in the plasma.

Atenolol is hydrophilic and in contrast to the lipophilic beta blockers, relatively low concentrations are found in brain tissue. This may possibly be responsible for the very low incidence of CNS-related side effects in patients on atenolol as compared with those treated with lipophilic beta blockers.

The elimination half-life of oral atenolol is approximately 6 to 7 hours.

Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m^2.

6. PHARMACEUTICAL PARTICULARS

6.1. Incompatibilities

Not applicable

6.2. Shelf Life

Three years

6.3. Special Precautions for Storage

Store below 30°C, in a dry place

Keep out of reach of children

6.4. Nature and Contents of Container

Tenolol (Atenolol Tablets 50mg and 100mg) are packaged in Blister Strip of 14 tablets. 2 such Blister in a printed showbox, along with a leaflet.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Ipca Pharma Nig Ltd.

No, 3, llupeju Bye Pass,

(Olajire House) llupeju Lagos,
ipcaharma@yahoo.com

8. DRUG PRODUCT MANUFACTURER

Ipca Laboratories Limited,

Plot No. 255/1, Village-Athal,

Silvassa 396230, Union Territory of Dadra & Nagar Haveli

and Daman & Diu, India

9. NAFDAC REGISTRATION NUMBER (S)

04-3378