ATENOLOL TABLETS I.P.

ATPARK® Tablets

1. GENERIC NAME

Atenolol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Atenolol I.P. 25 mg

Each uncoated tablet contains:
Atenolol I.P. 50 mg

List of excipients: Starch I.P., Methyl paraben I.P., Propyl paraben I.P., Sodium starch glycollate I.P., Talc I.P., Colloidal silicon dioxide I.P., Magnesium stearate I.P.

All strengths/presentation mentioned in this document may not be marketed.

3. DOSAGE FORM AND STRENGTH

25 mg and 50 mg uncoated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Atenolol is indicated in hypertension, angina pectoris, myocardial infarction.

4.2 Posology and Method of Administration

Adults: 50-100 mg in single daily doses as directed by Physician.

Children: Not recommended for children.

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

Renal Failure: Since atenolol is excreted *via* the kidneys, dosage should be adjusted in cases of severe impairment of renal function.

4.3 Contraindications

Atenolol is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, 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.

4.4 Special Warnings and Precautions for Use

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.

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 atrioventricular (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 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.

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. As with other beta blockers, 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.

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 $beta_1$ 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 $beta_1$ selectivity is not absolute, the lowest possible dose of atenolol should be used with therapy initiated at 50 mg and a $beta_2$-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.

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 intravenous).

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, *e.g.*, dobutamine or isoproterenol with caution.

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.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (*e.g.,* 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.

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

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

4.5 Drugs Interactions

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.

Calcium channel blockers may also have an additive effect when given with atenolol.

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 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.

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

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, *i.e.*, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

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.

4.6 Use in Special Populations

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 has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose*. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above

25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose*.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Usage in Pregnancy: Pregnancy Category D. 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 fetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol for longer periods 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. In general, beta blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labor.

Use in Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. 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.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

Most adverse effects have been mild and transient.

Clinical Studies

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient or elicited, *e.g.*, by checklist. The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of atenolol and placebo is similar, causal relationship to atenolol is uncertain.

	Volunteered		Total--Volunteered and Elicited	
	Atenolol (n=164) %	Placebo (n=206) %	Atenolol (n=399) %	Placebo (n=407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used.

Postmarketing Experience

During postmarketing experience with atenolol, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome, dry mouth and depression. Atenolol, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

Potential Adverse Effects

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of atenolol.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

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 Mechanism of Action

Atenolol is a beta-adrenoreceptor blocking agent which is $beta_1$ selective (*i.e.,* acts preferentially on $beta_1$-adrenergic receptors in the heart). It is without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential

effect is not absolute, however, and at higher doses, atenolol inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

5.2 Pharmacodynamic Properties

In animal & human pharmacological studies, beta-adrenoreceptor blocking activity has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, 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.

As with other beta-adrenergic blocking drugs, its mode of action in hypertension is not clear. In patients with angina pectoris probably its action in reducing cardiac rate and contractibility makes it effective in eliminating or reducing the symptoms.

Early intervention with atenolol in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infraction 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.

Following oral doses of 50 to 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hrs. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma levels.

5.3 Pharmacokinetic Properties

In man, 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. Unlike propranolol or metoprolol, but like nadolol, atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. Atenolol also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a four-fold interpatient variation.

The elimination half-life of oral atenolol is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes.

Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. 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/1.73 m^2.

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose, did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), *in vivo* cytogenetics test (Chinese hamster) or Ames test (*S. typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

7. DESCRIPTION

Atenolol 25 mg

White biconvex tablets with marking ‘25’ on one side and a break line on other side.

Atenolol 50 mg

White biconvex tablets with marking ‘50’ on one side and a break line on other side.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None specific.

8.2 Shelf-life

24 months

8.3 Packaging Information

Blister strip pack. 14 tablets/blister

8.4 Storage and Handling Instructions

Store below 30^{o}C.
As directed by physician.
Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Cessation of Therapy with Atenolol

Advise patients against abrupt discontinuation of atenolol because it may cause exacerbation of angina, and occurrence of myocardial infarction and ventricular arrhythmias. Advise patients to limit physical activity to a minimum when discontinuation of atenolol is planned. See section 4.4 Special Warnings and Precautions for Use.

10. DETAILS OF MANUFACTURER

Pfizer Limited
Plot No. L-137, Phase III A,
Verna Industrial Estate,
Verna, Salcete-Goa,
India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing licence number 544 dated 19 Feb 2018

12. DATE OF REVISION

April 2022