APO-ATENOL
Atenolol Tablets 50mg and 100mg
Antihypertensive and Anti-anginal Agent

Actions: Apo-Atenol (atenolol) is a beta-adrenergic receptor blocking agent with predominant effect on $beta_1$ receptors. It does not possess membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. The mechanism of the antihypertensive effect has not been established. Among the factors that may be involved are a) competitive ability to antagonize catecholamine-induced tachycardia at the beta-receptor sites in the heart thus decreasing cardiac output; b) inhibition of renin release by the kidneys; c) inhibition of the vasomotor centres. The mechanism of the anti-anginal effect is also uncertain. An important factor may be the reduction of myocardial oxygen requirements by blocking catecholamine-induced increases in heart rate, systolic blood pressure and the velocity and extent of myocardial contraction.

Pharmacokinetics: Approximately 50% of an oral dose of atenolol is absorbed from the gastrointestinal tract and the remainder being excreted unchanged in the feces. 6% to 16% of atenolol is bound to plasma protein. Maximum plasma concentrations are reached within 2-4 hours. The mean peak plasma concentrations of atenolol were approximately 300 and 700 nanogram/mL following administration of 50 and 100mg respectively. The plasma half-life is approximately 6-7 hours. Atenolol is extensively distributed to extravascular tissues but only a small amount is found in the central nervous system. Approximately 10% of atenolol is metabolized in man. About 3% of the material recovered in the urine was the hydroxylated metabolite which has been shown in animal studies to have 10% of the pharmacological activity of atenolol. Approximately 47 and 53% of the oral dose is eliminated in the urine and feces respectively. Recovery is complete after 72 hours. A comparative bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single oral 100mg dose of Tenormin 100mg or Apo-Atenol 100mg was measured and compared. The results can be summarized as follows:-

	Tenormin 100mg	Apo-Atenol 100mg	% Diff
AUC 0-48 (ng-hr/mL)	6202.1	5781.8	-6.8
Cmax (ng/mL)	697.3	660.4	-5.3
Tmax (hr)	2.5	3.3	+32
t 1/2 (hr)	7.1	7.0	-1.4

Indications: Hypertension: Apo-Atenol (atenolol) is indicated in patients with mild or moderate hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. However, it may be tried alone as an initial agent in those patients in whom, in the judgement of the physician treatment should be started with a beta blocker rather than a diuretic. Atenolol may be used in combination with diuretics and/or vasodilators to treat severe hypertension. The combination of atenolol with a diuretic or peripheral vasodilator has been found to be compatible. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with atenolol. Atenolol is not recommended for the emergency treatment of hypertensive crises. Angina Pectoris: Atenolol is indicated in the long term management of patients with angina pectoris due to ischemic heart disease.

Contraindications: Apo-Atenol (atenolol) should not be used in the presence of 1) sinus bradycardia 2) second and third degree AV block 3) right ventricular failure secondary to pulmonary hypertension 4) congestive heart failure 5) cardiogenic shock 6) anesthesia with agents that produce myocardial depression e.g. ether 7) hypersensitivity to atenolol.

Warnings: a) Cardiac Failure: Special caution should be exercised when administering Apo-Atenol (atenolol) to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Atenolol acts selectively without abolishing the inotropic action of digitalis on heart muscle. However, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of atenolol when the two drugs are used concomitantly. The effects of beta blocker and digitalis are additive in depressing AV conduction in patients without a history of cardiac failure, continued depression of the myocardium over a period of time can in some cases lead to cardiac failure. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalised and/or given diuretic and the response observed closely. If cardiac failure continues despite adequate digitalisation and diuretic therapy, atenolol therapy should be immediately withdrawn. b) Abrupt Cessation of

Therapy with Apo-Atenol: Patients with angina should be warned against abrupt discontinuation of atenolol. There have been reports of severe exacerbation of angina and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris following abrupt discontinuation of beta blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of atenolol is planned in patients with angina pectoris the dosage should be gradually reduced over a period of about 2 weeks and the patient should be carefully observed and advised to limit physical activity to a minimum. The same frequency of administration should be maintained. In situations of greater urgency, atenolol should be discontinued stepwise over a shorter time and under closer observation. If angina markedly worsens or acute coronary insufficiency develops. It is recommended that treatment with atenolol be reinstituted promptly at least temporarily c) Oculomucocutaneous Syndrome: Various skin rashes and conjunctival xerosis have been reported with beta blockers including atenolol. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis and sclerosing serositis has occurred with the chronic use of one beta adrenergic blocking agent (practolol). This syndrome has not been observed with atenolol or any other such agent. However physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur. d) Sinus Bradycardia: Severe sinus bradycardia may occur with the use of atenolol from unopposed vagal activity remaining after blockade of beta adrenergic receptors; in such cases dosage should be reduced. e) In Patients with Thyrotoxicosis: In patients with thyrotoxicosis, possible deleterious effects from long term use of atenolol have not been adequately appraised. Beta blockade may mask the clinical signs of continuing hyperthyroidism or its complications and give a false impression of improvement. Therefore abrupt withdrawal of atenolol may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Precautions: a) Because of its predominantly $beta_1$-blocking effect, Apo-Atenol (atenolol) may be tried in patients with diseases associated with bronchospasm who require beta blocker therapy. However careful monitoring of such patients is mandatory and a bronchodilator must be administered concomitantly. If initial bronchodilator therapy is being contemplated, a sympathomimetic bronchodilator might be considered. In patients already on bronchodilator therapy, the dose may have to be increased if necessary. Despite these precautions, the respiratory status of some patients may worsen, and, in such cases atenolol should be withdrawn. b) There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension. c) Atenolol should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia. d) Animal Studies: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15mg/kg/day or 7.5 times the maximum recommended human dose) and an increased incidence of atrial degeneration of hearts of male rats at 300 but not 150mg atenolol/kg/day (150 and 75 times the maximum recommended human dose respectively). e) Appropriate laboratory tests for monitoring renal, hepatic and hematopoietic function should be performed at regular intervals during long term treatment. f) Atenolol should be used with caution in patients with impaired renal function (see Dosage and Administration). When renal function is impaired clearance of atenolol is closely related to the glomerular filtration rate; however, significant accumulation does not occur until the creatinine clearance falls below $35mL/min/1.73m^2$. g) The management of patients being treated with beta-blockers and undergoing elective or emergency surgery is controversial. Although beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta adrenergically mediated reflex stimuli, abrupt discontinuation of therapy with atenolol may be followed by severe complications (see Warnings). Some patients receiving beta-adrenergic blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients with angina undergoing elective surgery, atenolol should be withdrawn cautiously following the recommendation given under Abrupt Cessation of Therapy (See Warnings). According to available evidence, all clinical and physiologic effects of beta blockade are no longer present 72 hours after cessation of medication. In emergency surgery, since atenolol is a competitive inhibitor of beta-adrenergic receptor agonists, its effects may be reversed if necessary, by sufficient doses of such agonists as isoproterenol or levarterenol. h) Usage in

Pregnancy: Atenolol has been shown to produce a dose related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50mg/kg or 25 or more times the maximum recommended human dose. There are no adequate and well controlled studies in pregnant women. Studies in humans have shown that transplacental passage of atenolol does occur in pregnant women with fetal drug serum level equal to those of the mother. Accumulation is unlikely to occur in the fetus. Information on the use of atenol in pregnancy women is limited to a few patients who were given the drug during the last trimester. Atenolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. i) Usage in Lactating Women: In humans, atenolol has been found in the breast milk of lactating women. If use of atenolol is considered essential, then mothers should stop nursing. j) Usage in Children: There is no experience with atenolol in the treatment of pediatric age groups.

Drug interactions: Should it be decided to discontinue therapy in patients receiving beta-blockers and clonidine concurrently, the beta-blocker should be discontinued several days before the gradual withdrawal of clonidine. It has been suggested that withdrawal of clonidine in the presence of beta-blockade may exaggerate the clonidine withdrawal syndrome (see also prescribing information for clonidine). Patients receiving catecholamine depleting drugs, such as reserpine or guanethidine should be closely monitored because the added beta-adrenergic blocking action of atenolol may produce an excessive reduction of sympathetic activity. Atenolol should not be combined with other beta-blockers.

Adverse Reactions: The most serious adverse reactions encountered are congestive heart failure, AV block and bronchospasm. The most common adverse reactions reported in clinical trials with atenolol were bradycardia (3%), dizziness (3%), vertigo (2%), fatigue (3%), diarrhea (2%) and nausea (3%). Adverse reactions, grouped by system are as follows: Cardiovascular: Congestive heart failure (see Warnings). severe bradycardia, AV Block, palpitations, lengthening of P.R interval, chest pain, lightheadedness and postural hypotension, raynaud's phenomenon, claudication, leg pain and cold extremities, edema. Respiratory: Dyspnea, wheeziness, cough bronchospasm. Central Nervous System: Dizziness, vertigo, faintness, ataxia, tiredness, fatigue, lethargy, nervousness, depression, drowsiness, vivid dreams, insomnia, paresthesia, headache, tinnitus. Gastrointestinal: Abdominal discomfort, indigestion, diarrhea, nausea, anorexia. Miscellaneous: Skin rash, itchy and/or dry eyes, decreased exercise tolerance, epistaxis, flushes, impotence, decreased libido, sweating. General body aches. The following adverse reactions have occurred with other beta-blockers but have not been reported with atenolol. Cardiovascular: pulmonary edema, cardiac enlargement, hot flushes, syncope and sinus arrest. Central Nervous System: aggressiveness, confusion, anxiety and hallucinations. Respiratory: laryngospasm and status asthmaticus. Dermatological: exfoliative dermatitis. Ophthalmological: blurred vision, burning, grittiness and visual disturbances. Hematological: thrombocytopenic purpura.

Symptoms and Treatment of Overdosage: The most common signs to be expected with overdosage of beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia. If overdosage occurs, in all cases therapy with atenolol should be discontinued and the patient observed closely. In addition, if required the following therapeutic measures are suggested: 1) Bradycardia. Atropine or another anticholinergic drug. 2) Heart block (second or third degree) isoproterenol or transvenous cardiac pacemaker. 3) Congestive heart failure: Conventional therapy. 4) Hypotension (depending on associated factors). Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis. (See Precaution concerning the use of epinephrine in beta blocked patients). 5) Bronchospasm: aminophyline or isoproterenol. 6) Hypoglycemia: intravenous glucose.
It should be remembered that atenolol is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of atenolol. However the complications of excess isoproterenol should not be overlooked.

Dosage and Administration: Hypertension: Apo-Atenol (atenolol) is usually used in conjunction with other antihypertensive agents particularly a thiazide diuretic but may be used alone (See Indications). The dose of Apo-Atenol should be administered in accordance with individual patients needs. The following guidelines are recommended. The initial dose of Apo-Atenol is 50mg administered as one tablet a day either added to diuretic therapy or alone. The full effect of this dose will usually be seen within 1 to 2 weeks. If an adequate response is not achieved, the dose should be increased to 100mg once daily. Increasing the dose beyond 100mg a day is unlikely to produce any further benefit. If further lowering of the blood pressure is required, another antihypertensive agent should be added to the regimen. Angina Pectoris: The initial dose of Apo-Atenol is 50mg given as one tablet a day. The full effect of this dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved within 1 week, the dosage should be increased to 100mg given as 1 tablet a day. Some patients may require a dosage of 200mg a day for optimal effect. Patients with Renal Impairment:

Since atenolol is eliminated predominantly via the kidneys, dosage should be adjusted in patients with severe renal impairment. Significantly accumulation of atenolol occurs when creatinine clearance falls below 35mL/min/1.73m^2 (normal range is 100-150mL/min/1.73m^2). The following maximum dosages are recommended for patients with renal impairment:-

Creatinine Clearance (mL/min/1.73m^2)	Atenolol Elimination Half-Life (hr)	Maximum Dosage
15-35	16-27	50mg daily
<15	>27	50mg every other day

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

Availability of dosage forms:

Apo-Atenolol 50mg:

Each white, round, flat-faced, bevelled-edge tablet, engraved "APO" on one side, “ATE” over score "50" on the other side contains atenolol 50mg. Available in PVC blisters of 30’s and 500’s tablets.

Apo-Atenolol 100mg:

Each white, round, flat-faced, bevelled-edge tablet, engraved "APO" on one side, “ATE” over score "100" on the other side contains atenolol 100mg. Available in PVC blisters of 30’s and 500’s tablets.

Storage conditions:

Protect from light and moisture. Store below 30ºC.

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