PRODUCT MONOGRAPH

Pr APO-ATENOL

Atenolol Tablets

Apotex Standard

50 mg and 100 mg

Beta-adrenergic receptor blocking agent

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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PRODUCT MONOGRAPH

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Apotex Standard

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THERAPEUTIC CLASSIFICATION

Beta-adrenergic receptor blocking agent

ACTIONS AND CLINICAL PHARMACOLOGY

Atenolol is a $beta_1$-selective, beta adrenergic blocking agent, devoid of membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. It is a racemic mixture and the $beta_1$-properties reside in the S (-) enantiomer. $Beta_1$-selectivity decreases with increasing dose.

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 centers

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.

In man atenolol reduces both isoproterenol- and exercise-induced increases in heart rate over the dose range of 50 to 200 mg. At an oral dose of 100 mg the $beta_1$ blocking effects persist for at least 24 hours; the reduction in exercise-induced heart rate increase being about 32% and 13%, 2 and 24 hours after dosing, respectively. The logarithm of the plasma atenolol level correlates with the degree of $beta_1$ blockade but not with the antihypertensive effect.

Pharmacokinetics

Approximately 40 to 50% of an oral dose of atenolol is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak plasma concentrations occur 2 to 4 hours after dosing and are subject to a 4-fold variability. The plasma levels are proportional to dose over the range 50 to 400 mg and 6 to 16% of atenolol is bound to plasma proteins. The mean peak plasma concentrations of atenolol were approximately 300 and 700 nanogram/mL following 50 and 100 mg, respectively. The plasma half-life is approximately 6 to 7 hours. Atenolol is extensively distributed to extravascular tissues, but only a small amount is found in the central nervous system.

There is no significant hepatic metabolism of atenolol in man and more than 90% of the absorbed dose reaches the systemic circulation unaltered. Small quantities of a hydroxy metabolite and a glucuronide are produced but neither has major pharmacological activity. As a consequence no accumulation occurs in patients with liver disease and no dosage adjustment is required. Approximately 47 and 53% of the oral dose is eliminated in the urine and feces, respectively. Recovery is complete after 72 hours.

Atenolol is primarily eliminated by the kidney, predominantly by glomerular filtration. The normal elimination half-life may increase in severe renal impairment but no significant accumulation occurs in patients who have creatinine clearance greater than 35 mL/min. The oral dose should be reduced in patients with a creatinine clearance less than 35 mL/min (see DOSAGE and ADMINISTRATION).

Following intravenous administration, peak plasma levels were reached within 5 minutes. Declines from peak plasma 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. Over 85% of an intravenous dose is excreted in urine within 24 hours.

Atenolol is excreted in human breast milk and crosses the placental barrier -the maternal to cord blood ratio being about unity.

COMPARATIVE BIOAVAILABILITY

A comparative bioavailability study was performed on healthy male volunteers under fasting conditions. The study was performed as a randomized single dose, crossover study of Apo-Atenol 100 mg and Tenormin 100 mg tablets (AstraZeneca, Canada). The results from measured data for the 24 subjects who completed the study are summarized in the following table.

Summary Table of the Comparative Bioavailability Data
Atenolol
(A single 100 mg dose: 1 x 100 mg)
From Measured Data/Fasting Conditions
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Apo-Atenol Tablets	Tenormin®† Tablets	Ratio of Geometric Means (%)##	90% Confidence Interval (%)##
AUCt (ng•h/mL)	5369.20 5639.9 (30)	5106.88 5361.7 (31)	105.4	96.3 – 115.4
AUCinf (ng•h/mL)	5682.41 5932.7 (28)	5411.24 5650.3 (30)	105.3	96.9 – 114.4
Cmax (ng/mL)	617.45 660.6 (34)	569.52 605.6 (36)	108.6	96.7 – 121.9
Tmax# (h)	3.40 (35)	3.32 (37)		
Thalf# (h)	7.62 (25)	7.65 (21)		

Arithmetic means (CV%).

Based on the least squares estimate.
† Tenormin® is manufactured by AstraZeneca Canada Inc. and was purchased in Canada.

INDICATIONS AND CLINICAL USE

Hypertension

APO-ATENOL (atenolol) tablets are 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

APO-ATENOL tablets are 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, or bradycardia of other origin
2. second and third degree A-V block
3. sick sinus syndrome
4. right ventricular failure secondary to pulmonary hypertension
5. uncontrolled heart failure
6. cardiogenic shock
7. hypotension
8. severe peripheral arterial disorders
9. anesthesia with agents that produce myocardial depression
10. pheochromocytoma, in the absence of alpha-blockade
11. metabolic acidosis

12. known hypersensitivity to the product

WARNINGS

a) Cardiac Failure

Special caution should be exercised when administering 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 the 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-blockers and digitalis are additive in depressing A-V 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 a 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 two 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) Prinzmetal's Angina

Atenolol 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, therefore, should only be used in these patients with the utmost care.

e) Sinus Bradycardia

Severe sinus bradycardia may occur with the use of atenolol from unopposed vagal activity remaining after blockade of $beta_1$-adrenergic receptors; in such cases, dosage should be reduced.

f) 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.

g) Pregnancy

Atenolol can cause fetal harm when administered to a pregnant woman. 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. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age.

Studies in humans have shown that transplacental passage of atenolol does occur in pregnant women, with fetal drug serum levels equal to those of the mother. In a limited number of patients who were given the drug during the last trimester of pregnancy, low birth weight, neonatal hypoglycemia, bradycardia in the fetus/newborn, and placental insufficiency were observed.

Neonates born to mothers who are receiving APO-ATENOL at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia. Caution should be exercised when APO-ATENOL is administered during pregnancy or to a woman who is breast-feeding. (See PRECAUTIONS, Use in Lactating Women.)

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 dose.

PRECAUTIONS

a) Bronchospastic Disorders

Patients with bronchospastic diseases should, in general, not receive beta-blockers. Due to the relative $beta_1$-selectivity of atenolol, 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, a $beta_2$-stimulating agent should be administered concomitantly, the lowest possible dose of atenolol should be used. Despite these precautions, the respiratory status of some patients may worsen, and, in such cases, atenolol should be withdrawn.

b) First Degree Heart Block

Due to its negative effect on A-V conduction time, atenolol should be used with caution in patients with first degree block.

c) Peripheral Arterial Circulatory Disorders

Atenolol may aggravate less severe peripheral arterial circulatory disorders (see CONTRAINDICATIONS).

d) Anaphylaxis-Epinephrine and Beta-Blockers

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 included 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.

e) Diabetes and Patients Subject to Hypoglycemia

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 (e.g. tachycardia) and symptoms of acute hypoglycemia.

f) Impaired Renal Function

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 35 mL/min/1.73 m^2.

g) Elective or Emergency Surgery

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

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.

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 norepinephrine.

h) Ethnic Populations

Atenolol appears to be effective and well-tolerated in most ethnic populations, although the responses may be less in black patients than in Caucasians.

i) Use in Lactating Women

In humans, there is a significant accumulation of atenolol in the breast milk of lactating women. Neonates born to mothers who are breastfeeding may be at risk for hypoglycemia and bradycardia. If the use of atenolol is considered essential, then mothers should stop nursing.

j) Use in Children

There is no experience with atenolol in the treatment of pediatric age groups.

k) Activities Requiring Mental Alertness

Use of atenolol 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 dizziness or fatigue may occur.

l) Geriatric Use

Clinical studies of atenolol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, 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 concomitant diseases or other drug therapy.

m) Drug Interactions

Clonidine

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. (Also see prescribing information for clonidine).

Reserpine or Guanethidine

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.

Antiarrhythmic Agents

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Calcium Channel Blockers

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects can lead to prolongation of S-A and A-V conduction, particularly in patients with impaired ventricular function, conduction abnormalities, or diminished cardiac output. This may result in severe

hypotension, bradycardia and cardiac failure. 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

Digitalis glycosides may potentiate the bradycardia of $beta_1$-blockade.

Non-Steroidal Anti-Inflammatory Agents

The concomitant use of non-steroidal anti-inflammatory agents may blunt the antihypertensive effects of beta-blockers.

Anaesthetic Agents

Anaesthetics can produce a hypotensive state with associated reflex tachycardia. Since beta-blockade will inhibit reflex tachycardia, the hypotensive potential of anaesthetic agents is increased with concomitant use of atenolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible (see CONTRAINDICATIONS and PRECAUTIONS, Elective or Emergency Surgery).

Fingolimod

Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such co-administration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

ADVERSE REACTIONS

The most serious adverse reactions encountered are congestive heart failure, A-V block and bronchospasm. Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

The most common adverse reactions reported in clinical trials with oral atenolol in 2500 patients are bradycardia (3%), dizziness (3%), vertigo (2%), fatigue (3%), diarrhea (2%) and nausea (3%). Adverse reactions occuring with an incidence of less than 1%, grouped by system, are as follows:

Cardiovascular

- Heart failure deterioration (see WARNINGS)
- Heart block
- Palpitations
- Lengthening of P-R interval
- Chest pain
- Lightheadedness
- Postural hypotension which may be associated with syncope
- Raynaud's phenomenon
- Intermittent claudication, or worsening of pre-existing intermittent claudication

Leg pain and cold extremities

Edema

Respiratory

Dyspnea, Wheeziness

Cough

Bronchospasm

Central Nervous System

Faintness

Ataxia

Tiredness

Lethargy

Nervousness

Depression

Drowsiness

Vivid dreams

Insomnia

Paresthesia

Headache

Tinnitus

Mood Changes

Visual disturbances

Psychoses and hallucinations

Gastrointestinal

Constipation

Anorexia

Abdominal discomfort, indigestion

Miscellaneous

Skin rash

Itchy and/or dry eyes

Psoriasiform skin reactions

Exacerbation of psoriasis

Decreased exercise tolerance

Alopecia

Epistaxis

Flushes

Impotence, decreased libido

Sweating

General body aches

Thrombocytopenia and purpura

POST MARKETING EXPERIENCE

During the post-marketing experience with atenolol, cold extremities, gastrointestinal disturbances and fatigue were commonly reported. The following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, headache, confusion, nightmares, impotence, Peyronie's disease, psoriasiform rash or exacerbation of psoriasis, purpura, reversible alopecia and thrombocytopenia. Rare cases of hepatic toxicity including intrahepatic cholestasis have been reported. Atenolol, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

In a long-term, well-controlled trial of 1,627 elderly patients with systolic hypertension, the incidence of dry mouth was significantly higher in patients taking atenolol (12.2%).

Potential Adverse Reactions

The following adverse reactions have occurred with other beta-blockers but have not been reported with atenolol:

Cardiovascular:	pulmonary edema, cardiac enlargement, hot flushes and sinus arrest
Central Nervous System:	aggressiveness, anxiety, short term memory loss, and emotional lability with slightly clouded sensorium
Allergic:	laryngospasm, status asthmaticus and fever combined with aching and sore throat
Dermatological:	exfoliative dermatitis
Ophthalmological:	blurred vision, burning, and grittiness
Hematological:	agranulocytosis
Gastrointestinal:	mesenteric arterial thrombosis and ischemic colitis

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited information is available with regard to overdosage with atenolol in humans. 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 overdosage are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment should be symptomatic and supportive and directed to the removal of any unabsorbed drug by induced emesis, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.

Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA:	Atropine 1 to 2 mg intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated. Glucagon in a 10 mg intravenous bolus has been reported to be useful. If required, this may be repeated or followed by an intravenous infusion of glucagon 1 to 10 mg/h 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 or isoproterenol 10 to 25 micrograms given as an infusion at a rate not exceeding 5 micrograms/minute may be given, although larger doses may be required.
HEART BLOCK: (second or third degree)	Isoproterenol or transvenous pacemaker.
CONGESTIVE HEART FAILURE:	Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.
HYPOTENSION:	Vasopressors such as dopamine or norepinephrine. Monitor blood pressure continuously.
BRONCHOSPASM:	A $beta_2$-stimulant such as isoproterenol or terbutaline and/or intravenous aminophylline.
HYPOGLYCEMIA:	Intravenous glucose.

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

DOSAGE AND ADMINISTRATION

Hypertension

Atenolol is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic, but may be used alone (see INDICATIONS).

The dose of atenolol should be administered in accordance with individual patient's needs.

The following guidelines are recommended:

The initial dose of APO-ATENOL is 50 mg administered as one tablet a day either added to diuretic therapy or alone. The full effect of this dose will usually be seen within one to two weeks. If an adequate response is not achieved, the dose should be increased to APO-ATENOL 100 mg once daily. Increasing the dose beyond 100 mg 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

Initial dose of APO-ATENOL is 50 mg given as one tablet a day. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved within one week, the dosage should be increased to APO-ATENOL 100 mg given as one tablet a day or 50 mg twice daily. Some patients may require a dosage of 200 mg 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. Significant accumulation of atenolol occurs when creatinine clearance falls below 35 mL/min/1.73 m^2 (normal range is 100 to 150 mL/min/1.73 m^2).

The following maximum dosages are recommended for patients with renal impairment:

Dosage in Renal Impairment

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

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

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

PHARMACEUTICAL INFORMATION

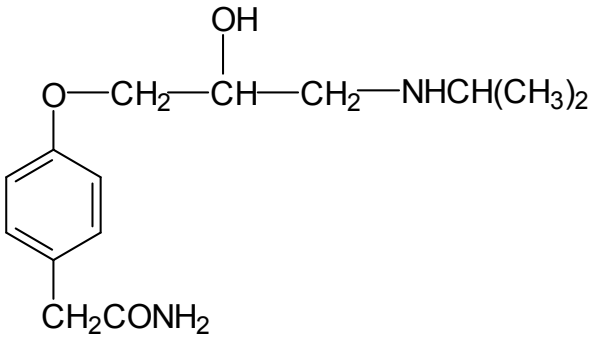
Drug Substance

Proper name: Atenolol

Chemical Name: 4-[2'-hydroxy-3'[1-methyletyl)amino] propoxy]-benzeneacetamide

Molecular Formula: $C_{14}H_{22}N_2O_3$

Structural Formula



Molecular Weight (free base): 266.34 g/mol

Description: Atenolol is a white or almost white crystalline powder. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. Atenolol is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C). The melting point for atenolol is 152.0°C to 155.0°C.

Composition

In addition to atenolol, each tablet contains the non-medicinal ingredients colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose.

Stability and Storage Recommendations

Store at room temperature (15°C to 30°C).
Protect from light and moisture.

AVAILABILITY OF DOSAGE FORMS

APO-ATENOL 50 mg: Each white, round, flat-faced, bevelled-edge tablet scored and engraved "ATE" over "50" on one side and "APO" on the other side contains atenolol 50 mg. Available in bottles of 100 and 500, unit-dose packages of 30 and 100, and in Apotex Long-Term care Packages (Apo-LTC Paks) of 620 and 700 tablets.

APO-ATENOL 100 mg: Each white, round, flat-faced, bevelled-edge tablet scored and engraved "ATE" over "100" on one side and "APO" on the other side contains atenolol 100 mg. Available in bottles of 100 and 500, and in unit dose packages of 30 and 100 tablets.

PHARMACOLOGY

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 15 mg/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 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

Effect on the Cardiovascular System

In anesthetized cats, atenolol infusion reduces the chronotropic response to isoproterenol and right cardiac sympathetic nerve stimulation.

In anesthetized dogs, atenolol 0.03 mg/kg i.v. depresses the heart rate by 22%, cardiac contractile force by 16% and diastolic blood pressure by 11%.

Studies in rats showed that atenolol was devoid of intrinsic sympathomimetic activity.

Atenolol in concentrations up to 10 mg/mL had no local anesthetic effect on the isolated sciatic nerve of the frog.

Atenolol (5-20 mg/kg i.v.) was without effect on the ventricular tachycardia produced by toxic levels of ouabain in anesthetized dogs. Atenolol (0.2 mg/kg i.v.) protected coronary ligated dogs from the arrhythmogenic activity of adrenaline on the fourth day after ligation (when the cardiac rhythm was predominantly sinus).

Single oral doses of 100 mg atenolol given to volunteers reduced exercise-induced tachycardia by 31% at 4 hours and by 15% at 24 hours after administration. The maximal suppression of the systolic blood pressure response to exercise was 21% at 4 hours.

Effects on Plasma Renin Activity

Studies in hypertensive patients have shown that the antihypertensive effect of atenolol is associated with a decrease in plasma renin activity.

Effects on Pulmonary Function

The effects of a single 100 mg dose of atenolol on forced expiratory volume (FEV_1) and airways resistance (AWR) were assessed in ten patients with labile asthma. The cardioselective agents tested in this comparative trial, including atenolol, usually had a lesser dose-related effect on airway function than non-selective beta-blockers. Atenolol produced a smaller decrease in FEV_1 than did the non-selective agents and did not inhibit the bronchodilator response to isoprenaline. The decrease in FEV_1 was 8 to 9%.

Other studies in asthmatic patients have reported similar decreases in FEV_1 with atenolol. Dose-effect comparisons with cardioselective agents have shown a fall in FEV_1 values at the higher doses, indicating some $beta_2$-blocking effect.

Metabolic Effects

Atenolol did not potentiate the hypoglycemic effects of insulin in 12 patients with diabetes.

TOXICOLOGY

Acute Toxicity

Species	Sex	Concentration	Route	LD_{50} (mg/kg)
Mouse	M/F	20% (1)	Oral	>2000
Mouse	M/F	0.8–1.2% (2)	i.v.	100
Rat	M/F	30% (1)	Oral	>3000
Rat	Male	21.3% (3)	Oral	4960
Rat	Female	21.3% (3)	Oral	6600
Rat	M/F	1.0– 4.0% (2)	i.v.	50 – 60
Rat	Male	0.5% (2)	i.v.	129 (±25)
Rat	Female	0.5% (2)	i.v.	114 (±30)
Rhesus Monkey	M/F	Variable (1)	Oral	>6000

(1) Suspension (2) Solution (3) Formulated Tablet

Toxic signs in rats were: depression, ataxia, labored respiration, cyanosis, tremors and convulsions. Effects occurred within 5 minutes following intravenous administration and surviving rats appeared normal after 2 hours. Effects following oral administration occurred within 1 hour and some persisted through 48 hours. Surviving rats appeared normal within 72 hours. Following intravenous administration, all mice convulsed immediately and those animals dying did so within 5 minutes.

Toxic signs in monkeys following oral administration were emesis, lethargy, slight mydriasis, occasional ptosis, salivation and decreased respiration. Surviving monkeys appeared normal within 24 hours.

Subacute Toxicity

Species	Sex Strain	Dose M	Dose F	mg/kg/day	Route	Duration Route(mo)	Effect
Rat	Alderly PK. Strain 1	40	40	0, 5, 50, 200	oral	3	High and intermediate groups showed increased heart and spleen weights. High dose males (3/10) showed focal myocarditis. (1 male control showed focal myocardial necrosis.)
Dog	Beagle	16	16	0, 5, 50, 100	oral	3	High and intermediate dose females showed increased liver weights. Mean heart rate and blood pressure decreased in high and inter-mediate dose animals.

Chronic Toxicity

Species	Sex / Strain	Dose M	Dose F	mg/kg/day	Route	Duration Route (mo)	Effect
Rat	Alderly PK. Strain 1	80	80	0, 75, 150, 300	oral	6	Reduction in heart rate. High and intermediate dose showed decreased blood pressure. Spleen and heart weights increased. Chronic myocarditis was seen in all groups including controls. Three high dose and 2 mid-dose animals were killed in moribund state.
Dogs	Beagle	20	20	0, 50, 100, 200	oral	12	Decreased heart rate. Prolongation of PR interval on ECG. Vacuolation of epithelial cells of duodenal Brunner's glands: 5/10 low dose, 2/10 mid-dose, 7/10 high dose. One high dose female died.
Dog	Beagle	15	15	0, 15, 200	oral	12	Vacuolation of epithelium of Brunner's glands 9/10 high dose; 1/10 low dose.

Teratology and Reproduction Studies

Atenolol associated malformations were not observed when atenolol was administered at oral doses of up to 200 mg/kg/day, days 6 to 15 of gestation in rats or at doses of up to 25 mg/kg/day, days 6-18 of gestation in rabbits.

Dose levels of 50 or more mg/kg/day were, however, associated with an increased incidence of resorptions in rats. Although a similar effect was not seen in rabbits, it should be noted that the compound was not evaluated in rabbits at doses above 25 mg/kg/day.
Atenolol, administered at doses of up to 200 mg/kg/day, for 11 weeks prior to mating in males or 2 weeks prior to mating in females, did not adversely affect fertility of male or female rats. Growth or survival of offspring were not affected when pregnant females were exposed at 200 mg/kg/day from day 15 of gestation to day 21 post partum.

Mutagenic Potential

Atenolol was negative in the mouse dominant lethal test, the Chinese hamster *in vivo* cytogenetic test and the *Salmonella typhimurium* back mutation test (Ames test), with or without metabolic activation.

Carcinogenicity Studies

Atenolol was administered to 3 groups of 65 male and 65 female CR7B1/10J mice at dietary levels of 0, 150 and 300 mg/kg/day for 18 months followed by the control diet for an additional three months. A fourth group received 2-AAF (positive control) and a fifth was the negative control group. Retardation in weight gain was observed. There was no statistically significant difference in mortality, number of tumor bearers, number of tumors in each animal or the total number of tumors in treated and negative control animals.

Two studies were conducted in Alderley Park Strain I rats. One study employed doses of 150 and 300 mg/kg/day for 18 months followed by the control diet for an additional six months, while the second study used doses of 75, 150 and 300 mg/kg/day for 24 months. Results from the two studies showed no significant difference in mortality for treated and control groups. No apparent carcinogenic potential was observed.