

PRODUCT MONOGRAPH

^{Pf} MYLAN-ATENOLOL

(Atenolol Tablets, BP)

25 mg, 50 mg and 100 mg

Beta-adrenergic receptor blocking agent

Mylan Pharmaceuticals ULC
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PRODUCT MONOGRAPH

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(Atenolol Tablets, BP)

25 mg, 50 mg and 100 mg

THERAPEUTIC CLASSIFICATION

Beta-adrenergic receptor blocking agent

ACTIONS AND CLINICAL PHARMACOLOGY

MYLAN-ATENOLOL (atenolol) is a beta₁-selective, beta adrenergic blocking agent, devoid of membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. It is a racemic mixture and the beta₁ properties reside in the S(-) enantiomer. Beta₁-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 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.

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 beta₁ 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 beta₁ 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 2-4 hours after dosing and are subject to a 4-fold variability. The plasma levels are proportional to dose over the range 50-400 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 6-7 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.

Clinical Pharmacology:
Comparative Bioavailability

A comparative two-way, single-dose bioavailability study on MYLAN-ATENOLOL 100 mg tablets against the Canadian Reference Product Tenormin[®] (manufactured by I.C.I. Pharma) was conducted in 24 healthy male subjects. The results can be summarized as follows:

Atenolol (1 x 100 mg) From Measured Data Geometric Mean Arithmetic Mean (CV %)
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Parameter	Test Mylan-Atenolol	Reference[†] Tenormin[®]	%Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng.h/mL)	6995 7256 (23.0)	7052 7377 (29.0)	0.99	0.90 - 1.09
AUC _I (ng.h/mL)	7465 7697 (24.1)	7503 7812 (27.6)	0.99	0.91 - 1.08
C _{MAX} (ng/mL)	792 818 (25.0)	784 818 (28.5)	1.01	0.91 - 1.12
T _{MAX} [§] (h)	3.56 (28.3)	3.06 (37.6)	---	---
T _{1/2} [§] (h)	6.92 (20.4)	6.73 (20.2)	---	---

[†] Tenormin 100 mg tablets (Manufactured by ICI Pharma, Canada) were purchased in Canada.

[§] Expressed as arithmetic mean (CV%)

INDICATIONS AND CLINICAL USE

Hypertension

MYLAN-ATENOLOL (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

MYLAN-ATENOLOL tablets are indicated in the long-term management of patients with angina pectoris due to ischemic heart disease.

CONTRAINDICATIONS

MYLAN-ATENOLOL (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 MYLAN-ATENOLOL (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 MYLAN-ATENOLOL

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 reinstated 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 beta₁-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 atenolol at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia. Caution should be exercised when atenolol 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 beta₁-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 beta₁-selectivity is not absolute, a beta₂-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 m².

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 (1-2 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 beta₁-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 occurring 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:

<u>Cardiovascular:</u>	pulmonary edema, cardiac enlargement, hot flushes and sinus arrest
<u>Central Nervous System:</u>	aggressiveness, anxiety, short term memory loss, and emotional lability with slightly clouded sensorium
<u>Allergic:</u>	laryngospasm, status asthmaticus and fever combined with aching and sore throat
<u>Dermatological:</u>	exfoliative dermatitis
<u>Ophthalmological:</u>	blurred vision, burning, and grittiness
<u>Hematological:</u>	agranulocytosis
<u>Gastrointestinal:</u>	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 1-2 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
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useful. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 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: Isoproterenol or transvenous pacemaker.
(second or third degree)

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 beta₂-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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 MYLAN-ATENOLOL (atenolol) should be administered in accordance with individual patient's needs.

The following guidelines are recommended:

The initial dose of MYLAN-ATENOLOL 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 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

The initial dose of MYLAN-ATENOLOL 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 MYLAN-ATENOLOL 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 m² (normal range is 100-150 mL/min/1.73 m²).

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	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 MYLAN-ATENOLOL: 25 mg given as one tablet as day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose (“trough” blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

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.

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

PHARMACEUTICAL INFORMATION

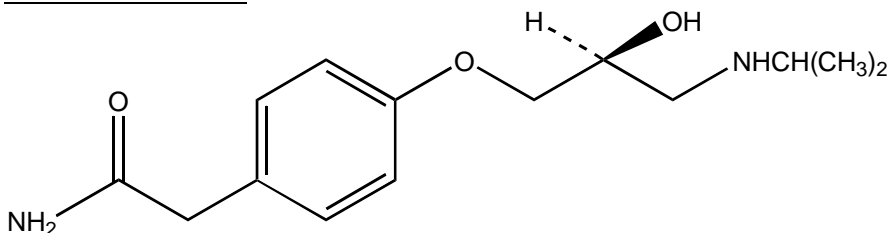
Drug Substance

Proper Name: Atenolol, BP

Chemical Name: (*RS*)-4-(2-hydroxy-3-isopropyl-aminopropoxy)-phenylacetamide

Molecular Formula: C₁₄H₂₂N₂O₃

Structural Formula:



Molecular Weight: 266.34 g/mol
(free base)

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 the active ingredient atenolol, each tablet contains the following inactive ingredients: Microcrystalline cellulose, povidone, sodium starch glycolate and magnesium stearate.

Storage Recommendations

Protect from light and moisture. Store between 15° and 30°C.

AVAILABILITY OF DOSAGE FORMS

MYLAN-ATENOLOL 25 mg tablets: white, round, biconvex tablets with "G" on one side and "AT" over "25" on the other side. Available in bottles of 100, 500 and blister packs of 30 (3 strips of 10 tablets).

MYLAN-ATENOLOL 50 mg tablets: white, round, biconvex tablets with "G" scoreline "G" on one side and "AT" scoreline "50" on the other side. Available in bottles of 100 and 500 and blister packs of 30 (3 strips of 10 tablets).

MYLAN-ATENOLOL 100 mg tablets: white, round, biconvex tablets with "G" on one side and "AT" scoreline "100" on the other side. Available in bottles of 100 and 500 and blister packs of 30 (3 strips of 10 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 (FEV₁) 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 FEV₁ than did the non-selective agents and did not inhibit the bronchodilator response to isoprenaline. The decrease in FEV₁ was 8-9%. Other studies in asthmatic patients have reported similar decreases in FEV₁ with atenolol. Dose-effect comparisons with cardioselective agents have shown a fall in FEV₁ values at the higher doses, indicating some beta₂-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		Mg/kg/day	Route	Duration Route (mo)	Effect
		M	F				
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 intermediate dose animals.

Chronic Toxicity

Species	Sex Strain	Dose		Mg/kg/day	Route	Duration Route (mo)	Effect
		M	F				
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.
Dog	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 6-15 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.

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TENORMIN® (atenolol), AstraZeneca Canada Inc. Mississauga, Ontario. Date of revision: July 12, 2016, Control Number: 190682

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr MYLAN-ATENOLOL Atenolol Tablets

Read this carefully before you start taking Mylan-Atenolol and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Mylan-Atenolol.

What is Mylan-Atenolol used for?

Mylan-Atenolol is used to treat high blood pressure (also known as hypertension) in adults. It can be used alone or with other medicines.

Mylan-Atenolol is also used to prevent chest pain (also known as angina) in adults.

How does Mylan-Atenolol work?

Mylan-Atenolol belongs to a group of drugs called “beta blockers”. It makes your heart beat more slowly and less forcefully. This medicine does not cure your disease but helps to control it.

What are the ingredients in Mylan-Atenolol?

Medicinal ingredients: atenolol

Non-medicinal ingredients: Microcrystalline cellulose, povidone, sodium starch glycolate and magnesium stearate.

Mylan-Atenolol comes in the following dosage forms:

Tablets: 25 mg, 50 mg and 100 mg

Do not use Mylan-Atenolol if you:

- are allergic to atenolol or any of the ingredients in Mylan-Atenolol.
- have slow or irregular heartbeats or if you have been told that you have heart block.
- have severe heart damage and your heart is not able to pump enough blood to meet your body’s needs.
- have heart failure and you notice that your symptoms are getting worse. For example you feel more tired, are out of breath more often, or have swelling of the ankles.
- have a problem with your heart’s electrical conduction (that causes you to have chest pain, difficulty breathing, nausea, fatigue and fainting).
- have low blood pressure.
- have serious problems with blood flow in your feet and legs (peripheral artery disease).
- have loss of sensation with agents that cause heart failure.

- have a condition called pheochromocytoma (a tumour of the adrenal gland).
- have a condition called metabolic acidosis (abnormal levels of acids in your blood).
- are 18 years or younger.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Mylan-Atenolol. Talk about any health conditions or problems you may have, including if you:

- have a history of heart problems.
- have a history of fainting.
- have asthma or other lung problems (like bronchitis or emphysema).
- have thyroid problems.
- have kidney problems.
- have circulation problems.
- have diabetes and take medicine to control your blood sugar or have low blood sugar (hypoglycemia).
- have ever been told that you suffer from a particular type of chest pain (angina), called Prinzmetal's angina.
- have had allergic reactions or have allergies.
- develop a skin rash while taking Mylan-Atenolol.
- are pregnant, are trying or planning on becoming pregnant. Mylan-Atenolol is not usually recommended for use during pregnancy. Your healthcare professional will consider the benefit to you versus the risk to your unborn baby.
- are breastfeeding. You should not breastfeed while using Mylan-Atenolol.

Other warnings you should know about:

Do not stop taking Mylan-Atenolol suddenly. This could cause chest pain or a heart attack. If your doctor decides that you should stop taking Mylan-Atenolol, your dose may be reduced so that you need to use it less and less before you stop the medication completely.

Tell your doctor if you are going into the hospital for an operation. If you go into the hospital, let the medical staff know and in particular the anaesthetist (if you are having an operation) that you are taking Mylan-Atenolol.

Driving and using machines: Before doing tasks that require special attention, wait until you know how you respond to Mylan-Atenolol.

You may notice that your pulse rate becomes slower while taking Mylan-Atenolol. This is normal but if you are concerned, please talk to your doctor about it.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Mylan-Atenolol:

- drugs used for lowering blood pressure or treating angina:
 - beta-blockers (such as clonidine)
 - calcium channel blockers (such as verapamil, diltiazem or nifedipine)
 - catecholamine-depleting drugs (such as reserpine or guanethidine)
- drugs used to treat irregular heartbeats (such as disopyramid or amiodarone)
- drugs used to treat heart failure (such digoxin)
- non-steroidal anti-inflammatory agents (NSAIDs) (such as indomethacine or ibuprofen)
- anesthetic drugs used during surgery
- fingolimod, a drug used to treat multiple sclerosis

How to take Mylan-Atenolol:

Take Mylan-Atenolol:

- exactly as prescribed by your doctor.
- by swallowing the tablet whole with water.
- at the same time each day.

Your doctor:

- will decide how much Mylan-Atenolol you should take each day depending on your condition.
- may add another medicine like a diuretic (water pill) and/or a vasodilator for you to take along with Mylan-Atenolol to treat your high blood pressure.

If you have the impression that the effect of Mylan-Atenolol is too strong or too weak, talk to your doctor or pharmacist as soon as possible.

Do not stop taking Mylan-Atenolol or change your dose without consulting your doctor. This can be dangerous.

Usual adult dose:

High Blood Pressure:

The usual recommended dose is 50 mg to 100 mg taken once a day.

Chest Pain:

The usual recommended dose is 50 mg to 100 mg taken once a day. Up to 200 mg per day may be required in some patients.

Overdose:

If you think you have taken too much Mylan-Atenolol, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take the dose as soon as you remember. Do not take two doses at the same time.

What are possible side effects from using Mylan-Atenolol?

These are not all the possible side effects you may feel when taking Mylan-Atenolol. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- cough
- cold fingers and toes
- diarrhea
- dizziness
- dry mouth
- headache
- joint and back pain
- nausea
- tiredness
- trouble sleeping
- vertigo

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Bradycardia: decreased heart rate that causes you to be dizzy or faint		√	
Chest pain			√
UNCOMMON			
Allergic reactions: rash, swelling of the lips, face or neck, difficulty breathing or speaking			√
RARE			
Heart conduction disorders: feeling lightheaded, dizzy or passing out			√
Hypotension (low blood pressure): dizziness or lightheadedness leading to fainting can occur when		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
changing positions, for example from lying down to standing up			
Irregular heart beat or heart palpitations (skipped beats)		√	
Leg swelling from fluid retention		√	
Memory problems		√	
Shortness of breath		√	
Skin reactions: rash	√		
Vision problems	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15° and 30°C.

Protect from light and moisture.

Do not take your tablets after the expiry date on the container.

Keep out of reach and sight of children.

If you want more information about Mylan-Atenolol:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); or by calling 1-844-596-9526

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