PRODUCT MONOGRAPH

PrMINT-ATENOL

Atenolol Tablets, BP

50 mg and 100 mg

Beta-adrenergic receptor blocking agent

Mint Pharmaceuticals Inc.
6575 Davand Drive
Mississauga, Ontario
Canada L5T 2M3

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PRODUCT MONOGRAPH

NAME OF DRUG

PrMINT-ATENOL
Atenolol Tablets, BP

50 mg and 100 mg

THERAPEUTIC CLASSIFICATION

Beta-adrenergic receptor blocking agent

ACTION 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 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 $beta_1$ -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 administration of 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 randomized, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of MINT-ATENOL (atenolol) 100 mg tablets (Mint Pharmaceuticals Inc.) with Tenormin® (atenolol) 100 mg tablets (AstraZeneca Canada Inc.) was conducted under fasting conditions with 27 healthy adult male human subjects.

Atenolol (1 x 100 mg atenolol tablets) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng.h/ml)	6265.83 6495.06 (27.37)	5770.79 5937.46 (23.89)	108.57	97.92 – 120.38
AUC_I (ng.h/ml)	6516.17 6730.78 (26.58)	6083.19 6227.51 (21.57)	107.11	97.86 – 117.24
C_{max} (ng.h/ml)	714.50 750.61 (31.58)	667.67 688.70 (24.85)	107.01	95.94 – 119.36
T_{max}§ (h)	2.81 (33.10)	3.26 (24.51)		
$T_{½}$§ (h)	5.99 (13.24)	5.94 (13.69)		

* MINT-ATENOL 100mg tablets manufactured by Mint Pharmaceuticals Inc.
† Tenormin® tablets (AstraZeneca Canada Inc.) were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

INDICATIONS AND CLINICAL USE

Hypertension

MINT-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

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

CONTRAINDICATIONS

MINT-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 MINT-ATENOL 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 digitalized and/or given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, MINT-ATENOL therapy should be immediately withdrawn.

(b) Abrupt Cessation of Therapy with MINT-ATENOL

Patients with angina should be warned against abrupt discontinuation of MINT-ATENOL. 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 MINT-ATENOL 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, MINT-ATENOL 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 MINT-ATENOL 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

MINT-ATENOL may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. MINT-ATENOL, therefore, should only be used in these patients with the utmost care.

(e) Sinus Bradycardia

Severe sinus bradycardia may occur with the use of MINT-ATENOL 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 MINT-ATENOL 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 randomized controlled 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. In general, beta-blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour.

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 MINT-ATENOL at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia. MINT-ATENOL should not be given during pregnancy or to a woman who is breast-feeding unless its use is essential. (See PRECAUTIONS, Use in Lactating Women.). MINT-ATENOL should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human 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, MINT-ATENOL 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 MINT-ATENOL 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, MINT-ATENOL should be used with caution in patients with first degree block.

(c) Peripheral Arterial Circulatory Disorders

MINT-ATENOL 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

MINT-ATENOL 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

MINT-ATENOL 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 MINT-ATENOL 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 intravenous).

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 MINT-ATENOL 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 MINT-ATENOL 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. MINT-ATENOL 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 1627 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/hour 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.

For management of a suspected drug overdose, contact your regional poison control centre.

DOSAGE AND ADMINISTRATION

Hypertension:
MINT-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 MINT-ATENOL should be administered in accordance with individual patient's needs.

The following guidelines are recommended:

The initial dose of MINT-ATENOL is 50 mg administered as 1 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 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 MINT-ATENOL is 50 mg given as one tablet a day. The full effect of this dose will usually be seen within 1 or 2 weeks. If an optimal response is not achieved within 1 week, the dosage should be increased to 100 mg given as 1 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 100-150 mL/min/ 1.73 m^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	50 mg daily
<15	>27	50 mg every other day

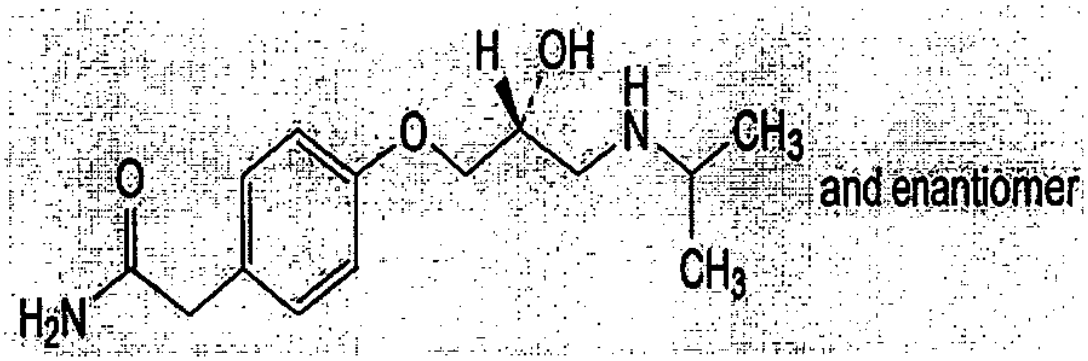
Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur. Dosage requirements may be reduced in the elderly, especially in patients with impaired renal function.

PHARMACEUTICAL INFORMATION

Drug substance

Proper name: Atenolol
Chemical name: 4-[2-hydroxy-3-[(1-methylethyl) amino] propoxy] benzeneacetamide

Structural formula: $C_{14}H_{22}N_2O_3$



Molecular weight: 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 26.5mg/mL at 37°C and a log partition coefficient (Octanol/water) of 0.23. Atenolol is freely soluble in 1N HCl(300mg/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: maize starch, heavy magnesium carbonate, sodium lauryl sulphate, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, colloidal silicon dioxide, polyethylene glycol 6000, purified talc and titanium dioxide.

Storage Recommendations

MINT-ATENOL tablets should be stored between 15° and 30°C, protected from light and moisture.

AVAILABILITY OF DOSAGE FORMS

MINT-ATENOL Tablets, 50 mg are white to off white, circular biconvex, film coated tablets with "50" debossed on one side and breakline on other side.

MINT-ATENOL Tablets, 100 mg are white to off white, circular biconvex, film coated tablets with "100" debossed on one side and breakline on other side.

Packaging:

MINT-ATENOL Tablets, 50 mg: Available in HPDE bottles of 100's and 500's.

MINT-ATENOL Tablets, 100 mg: Available in HPDE bottles of 100's and 500's.

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 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 intravenous 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 intravenous) was without effect on the ventricular tachycardia produced by toxic levels of ouabain in anesthetized dogs. Atenolol (0.2 mg/kg intravenous) 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.

Effect 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.

Effect 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 8-9%. 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)	intravenous	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)	intravenous	50-60
Rat	Male	0.5% (2)	intravenous	129(±25)
Rat	Female	0.5% (2)	intravenous	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	Strain	Sex M	Sex F	Dose Mg/kg/day	Route	Duration (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	Strain	Sex M	Sex F	Dose Mg/kg/day	Route	Duration (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.
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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Product Monograph: Tenormin® (atenolol) (Control #253818), Searchlight Pharma Inc., Date of Revision: July 23, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrMINT-ATENOL
Atenolol Tablets

Read this carefully before you start taking **MINT-ATENOL** 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 **MINT-ATENOL**.

What is MINT-ATENOL used for?

MINT-ATENOL is used to treat high blood pressure (also known as hypertension) in adults. It can be used alone or with other medicines.
MINT-ATENOL is also used to prevent chest pain (also known as angina) in adults.

How does MINT-ATENOL work?

MINT-ATENOL 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 MINT-ATENOL?

Medicinal ingredients: atenolol

Non-medicinal ingredients: maize starch, heavy magnesium carbonate, sodium lauryl sulphate, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, colloidal silicon dioxide, polyethylene glycol 6000, purified talc and titanium dioxide

MINT-ATENOL comes in the following dosage forms:

Tablets: 50 mg and 100 mg

Do not use MINT-ATENOL if you:

- are allergic to atenolol or any of the ingredients in MINT-ATENOL.
- 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 MINT-ATENOL. 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 MINT-ATENOL.
- are pregnant, are trying or planning on becoming pregnant. MINT-ATENOL 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 MINT-ATENOL.

Other warnings you should know about:

Do not stop taking MINT-ATENOL suddenly. This could cause chest pain or a heart attack. If your doctor decides that you should stop taking MINT-ATENOL, 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 MINT-ATENOL.

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

You may notice that your pulse rate becomes slower while taking MINT-ATENOL. 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 MINT-ATENOL:

- 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 as 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 MINT-ATENOL:
Take MINT-ATENOL:
- 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 MINT-ATENOL 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 MINT-ATENOL to treat your high blood pressure.

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

Do not stop taking MINT-ATENOL 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, or a person you are caring for, have taken too much MINT-ATENOL, contact a 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 MINT-ATENOL?
These are not all the possible side effects you may feel when taking MINT-ATENOL. 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 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		√	

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

Storage:
Store at room temperature (15º to 30ºC).

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 MINT-ATENOL:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.mintpharmaceuticals.com, or by calling 1-877-398-9696

NOTE: This PATIENT MEDICATION INFORMATION leaflet provides you with the most current information at the time of printing.

This leaflet was prepared by Mint Pharmaceuticals Inc., 6575 Davand Drive, Mississauga, L5T 2M3. Toll Free: +1- 877 398 9696.

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