PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrMINT-ATENOL

Atenolol Tablets, BP

25 mg

Beta-adrenergic receptor blocking agent ATC Code:
C07AB

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

Date of Initial Authorization:
May 6, 2011

Date of Revision:
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Control #:

RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, 7.1.1 Pregnant Women	11/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

MINT-ATENOL (atenolol tablets) is indicated in:

- patients with mild or moderate hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. However, it may be tried alone as an initial agent in those patients in whom, in the judgement of the physician, treatment should be started with a beta-blocker rather than a diuretic. Atenolol may be used in combination with diuretics and/or vasodilators to treat severe hypertension.

The combination of atenolol with a diuretic or peripheral vasodilator has been found to be compatible. Limited experience with other antihypertensive agents has not shown evidence of incompatibility with atenolol.

Atenolol is not recommended for the emergency treatment of hypertensive crises.

- the long-term management of patients with angina pectoris due to ischemic heart disease.

1.1 Pediatrics

Pediatrics (0-18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2. CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredients, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

MINT-ATENOL is contraindicated in patients with:

- sinus bradycardia or bradycardia of other origin
- second-and third-degree A-V block
- sick sinus syndrome
- right ventricular failure secondary to pulmonary hypertension
- uncontrolled heart failure
- cardiogenic shock
- hypotension
- severe peripheral arterial disorders
- anesthesia with agents that produce myocardial depression
- pheochromocytoma in the absence of alpha-blockade
- metabolic acidosis
- known hypersensitivity to the product.

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Abrupt Cessation of Therapy with atenolol

Patients with angina should be warned against abrupt discontinuation of atenolol. There have been reports of myocardial infarction, ventricular arrhythmias or severe exacerbation of angina 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.

4. DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Hypertension:

Atenolol is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic, but may be used alone, See 1 INDICATIONS.

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

The following guidelines are recommended:

The initial dose of atenolol is 50 mg a day, administered as two 25 mg tablets 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.

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

Angina Pectoris:

The initial dose of atenolol is 50 mg, given as two 25 mg tablets 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 optimal response is not achieved within one week, the dosage should be increased to 100 mg a day or 50 mg twice daily, given as two 25 mg tablets. Some patients may require a dosage of 200 mg daily 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 oral 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 MINT-ATENOL of 25 mg/day. If the 25 mg/day 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.

Patients on hemodialysis should be given 50 mg given as two 25 mg tablets 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.

4.5 Missed Dose

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

5. 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 atenolol 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.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets, 25 mg	colloidal silicon dioxide, heavy magnesium carbonate, hydroxypropyl methylcellulose, magnesium stearate, maize starch, sodium lauryl sulphate, polyethylene glycol 6000, purified talc, sodium starch glycolate, and titanium dioxide.

Atenolol Tablets, 25 mg, are white to off white, round biconvex, film coated tablets with "25" embossing on one side and plain on other side.

Available in HDPE bottles of 100 and 500.

7. WARNINGS AND PRECAUTIONS

Cardiovascular

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

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.

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.

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.

Peripheral Arterial Circulatory Disorders

Atenolol may aggravate less severe peripheral arterial circulatory disorders. See 2 CONTRAINDICATIONS.

Driving and Operating Machinery

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.

Endocrine and Metabolism

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 atenolol withdrawal may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

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.

Immune

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 pharmacologic effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha-adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta-agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Ophthalmologic

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.

Peri-Operative Considerations

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 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.

Renal

Impaired Renal Function

Atenolol should be used with caution in patients with impaired renal function (see 4 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.

Respiratory
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 $beta_1$-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.

7.1 Special Populations
7.1.1 Pregnant Women
Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in the cord blood. Atenolol should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

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.

7.1.2 Breast-feeding
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.

7.1.3 Pediatrics
Pediatrics (0-18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics
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.

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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%).

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions occurring with an incidence of less than 1%, grouped by system, are as follows:

Cardiovascular:
Heart failure deterioration See 7 WARNINGS AND PRECAUTIONS
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
Decreased exercise tolerance

Eye Disorders:
Itchy and/or dry eyes

Gastrointestinal:
Constipation

Anorexia
Abdominal discomfort,
Indigestion

Neurologic:
Faintness
Ataxia
Tiredness
Lethargy
Nervousness
Depression
Drowsiness
Vivid dreams
Insomnia
Paresthesia
Headache
Tinnitus
Mood changes
Visual disturbances
Psychoses and hallucinations
General body aches
Fatigue

Respiratory:
Dyspnea, wheeziness
Cough
Bronchospasm

Skin and Subcutaneous Disorders
Skin rash
Psoriasiform skin reactions
Exacerbation of psoriasis
Alopecia

Vascular Disorders
Epistaxis
Flushing

8.5 Post-Market Adverse Reactions

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:

Dermatologic: Psoriasiform rash or exacerbation of psoriasis, purpura, reversible alopecia

Hematologic: Thrombocytopenia

Liver and Biliary diseases: Elevated liver enzymes and/or bilirubin

Neurologic: Headache, confusion, nightmares

Reproductive system: Impotence, Peyronie's disease

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.

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.

9. DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Clonidine:
Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the 2 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 (see also 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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, PERIOPERATIVE CONSIDERATIONS).

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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 increase 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.

10.3 Pharmacokinetics

Absorption:
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.

Distribution:
Atenolol is extensively distributed to extravascular tissues, but only a small amount is found in the central nervous system.

Metabolism:
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.

Elimination:
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 4 DOSAGE AND ADMINISTRATION).

Duration of Effect
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.

11 STORAGE, STABILITY AND DISPOSAL

MINT-ATENOL tablets should be stored between 15 and 25°C, protected from light and moisture

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

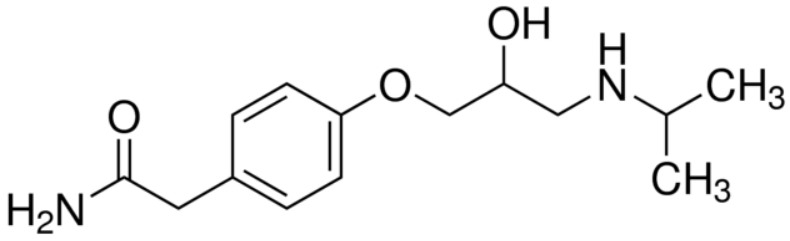
Proper name: Atenolol

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

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

Molecular mass: 266.34

Structural formula:



Physiocochemical properties: 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.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

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.

Table 1. SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

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

16 NON-CLINICAL TOXICOLOGY

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:
MINT-ATENOL did not potentiate the hypoglycemic effects of insulin in 12 patients with diabetes.

Carcinogenicity
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.

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.

Reproductive and Developmental Toxicology
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.

16.1.2 Comparative Toxicology
Acute toxicity

Table 2: A summary of acute toxicity of atenolol in mice, rats and Rhesus Monkey

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

Table 3: A summary of subacute toxicity of atenolol among rats and dogs

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

Table 4: A summary of chronic toxicity of atenolol among rats and dogs

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. TENORMIN (Atenolol tablets, 50 and 100 mg) 253818, Product Monograph JUL 23, 2021

2. TEVA-ATENOLOL (Atenolol tablets, 25 mg) 198565. Product Monograph OCT 11, 2016

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]MINT-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**.

Serious Warnings and Precautions

Stopping your treatment: You should follow your healthcare professional's instructions on how to reduce and stop your dose carefully and safely. If you have chest pain (angina) and then suddenly stop taking MINT-ATENOL, you can experience serious side effects. This can include heart attacks, irregular heartbeats, or worsening of your chest pain.

To reduce your chances of developing these effects:

- You should talk to your healthcare professional before stopping or lowering your dose of MINT-ATENOL.
- Your healthcare professional will monitor your health as you gradually reduce and/or stop your dose. However, if you notice any unusual symptoms tell your healthcare professional right away. They may temporarily prescribe another dose to prevent these symptoms.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

What is MINT-ATENOL used for?
MINT-ATENOL is used in adults:

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

How does MINT-ATENOL work?
MINT-ATENOL belongs to a group of medicines known as "beta blockers". It works by blocking the effects of certain hormones, such as adrenaline. This causes your heart to beat more slowly and with less force.

What are the ingredients in MINT-ATENOL?
Medicinal ingredient: atenolol.
Non-medicinal ingredients: colloidal silicon dioxide, heavy magnesium carbonate, hydroxypropyl methylcellulose, magnesium stearate, maize starch, polyethylene glycol 6000, purified talc, sodium lauryl sulphate, sodium starch glycolate, and titanium dioxide.

MINT-ATENOL comes in the following dosage forms:
Tablets: 25 mg of atenolol.

Do not use MINT-ATENOL if:

- you have the following heart or blood vessel problems:
  - bradycardia (abnormally slow heart beat).
  - second or third degree heart block (a type of irregular heart beat and rhythm).
  - sick sinus syndrome (heart's natural pacemaker is unable to create normal heartbeats at the normal rate).
  - heart failure (heart does not pump blood as well as it should).

    - cardiogenic shock (heart is unable to pump enough blood to the organs of the body).
    - severe peripheral arterial disorder (arteries are narrowed which reduces blood flow to your limbs).
    - right ventricular failure (right side of the heart is not pumping normal amounts of blood to the lungs).
- you have low blood pressure.
- you are receiving anesthesia and are taking medicines that can affect your heart.
- you have a condition known as pheochromocytoma (a tumour in the adrenal gland).
- you have a condition known as metabolic acidosis (abnormal levels of acid in the body).
- you are allergic to atenolol or to any other ingredients in MINT-ATENOL.

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 Prinzmetal's angina (a type of chest pain).
- have first degree heart block (a type of irregular heart beat and rhythm).
- have lung problems (e.g., bronchospastic disease).
- have blood vessels problems (e.g., peripheral arterial disorder).
- have kidney problems.
- have thyroid problems (e.g., thyrotoxicosis).
- are planning to get surgery or are taking medicines known as anaesthetics that are used to prevent pain during surgery. In this case, let that particular anaesthetist know that you are taking MINT-ATENOL before your surgery.
- have diabetes (body can't produce insulin or can't properly use insulin) and are taking medicine to control your blood sugar.
- have hypoglycemia (low blood sugar) and are taking medicines for hypoglycemia.
- have asthma or a history of problems related to asthma.
- are on hemodialysis (a treatment that filters wastes and extra fluid from your blood).
- have allergies or have had allergic reactions.
- are elderly.

Other warnings you should know about:

Taking MINT-ATENOL can cause the following side effects:

- **Heart failure** (heart does not pump blood as well as it should): Beta blockers, such as MINT-ATENOL, can slow your heart rate and cause heart failure. If you notice any signs or symptoms of a heart failure tell your healthcare professional right away. They may prescribe additional medication and will closely monitor your health.

- **Bradycardia** (abnormally slow heart beat): MINT-ATENOL can cause severe sinus bradycardia. Tell your healthcare professional if this occurs. They may reduce your dose of MINT-ATENOL. They will tell you how to safely stop your treatment with MINT-ATENOL.

- **Severe skin reactions:** MINT-ATENOL can cause a variety of skin reactions such as rashes and severe skin dryness. If you notice any signs and symptoms of a skin reaction, tell your healthcare professional. They will tell you how to safely stop your treatment with MINT-ATENOL.

- **Breathing problems:** Beta blockers, such as MINT-ATENOL, can affect your breathing. If this occurs, tell your healthcare professional. They will tell you how to safely stop your treatment with MINT-ATENOL.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Pregnancy and breastfeeding: Taking atenolol while pregnant or breastfeeding can cause your baby to develop unwanted effects (e.g., hypoglycemia and/or bradycardia). There are specific risks for you and your

unborn baby that you must discuss with your healthcare professional. Tell your healthcare professional if you are:

- pregnant,
- able to become pregnant,
- breastfeeding, or
- planning to breastfeed.

Driving and using machines: MINT-ATENOL can cause dizziness and fatigue. Before you drive or do tasks that require special attention, wait until you know how you respond to MINT-ATENOL.

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:

- medicines used to lower blood pressure:
  - other beta blockers (e.g., carvedilol and bisoprolol);
  - alpha-2 adrenergic agonist (e.g., clonidine);
  - catecholamine-depleting medicines (e.g., reserpine and guanethidine); or
  - calcium channel blockers (e.g., dihydropyridines such as nifedipine).
- medicines known as digitalis glycosides used to treat heart failure (e.g., digoxin).
- medicines known as non-steroidal anti-inflammatory agents (NSAIDS) used to reduce pain and swelling (e.g., aspirin, indomethacin, and ibuprofen).
- medicines known as anaesthetics used to prevent pain during surgery.
- fingolimod, a medicine used to treat multiple sclerosis (MS).
- medicines used to treat abnormal heart rhythms (e.g., disopyramide and amiodarone).

How to take MINT-ATENOL:

- Take MINT-ATENOL:
  - exactly as prescribed by your healthcare professional.
  - by swallowing the tablet whole with water.
  - at the same time each day.
- **Do not** stop or reduce your dose of MINT-ATENOL suddenly without first talking with your healthcare professional. This could cause chest pain or a heart attack. If your healthcare professional 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.
- If you think that the effect of MINT-ATENOL is too strong or too weak, talk to your healthcare professional as soon as possible.

Usual dose:
Your healthcare professional will decide how much MINT-ATENOL you should take each day depending on your condition. They may add another medicine such as a diuretic (water pill) and/or a vasodilator for you to take along with MINT-ATENOL to treat your high blood pressure.

The usual recommended adult doses are:

- **High blood pressure:** Two to four 25 mg tablets (50 mg to 100 mg) once a day.
- **Chest pain:** Two to four 25 mg tablets (50 mg to 100 mg) once a day. The dose may be increased up to eight 25 mg tablets (200 mg) once a day.

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:

Do not take a double dose to make up for a missed dose. If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, then do not take the missed dose at all. If you are unsure what to do, ask your healthcare professional.

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.

The side effects of MINT-ATENOL may include:

- **Very common (may affect more than 1 in 10 people)**
  - dry mouth.
- **Common (may affect up to 1 in 10 people)**
  - vertigo.
- **Uncommon (may affect up to 1 in 100 people)**
  - cold fingers and toes;
  - burning or prickling sensation in the hands, arms, legs, or feet;
  - drowsiness;
  - flushes;
  - hair loss or thinning (alopecia);
  - impotence;
  - insomnia;
  - lack of energy;
  - leg pain;
  - loss of coordination;
  - mood changes;
  - nervousness;
  - nosebleeds;
  - ringing in the ears;
  - sweating;
  - vivid dreams.

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 (abnormally slow heartbeat): decreased heart rate that causes you to be dizzy or faint.		**X**	
Gastrointestinal (GI) problems: constipation, anorexia, abdominal discomfort, indigestion, diarrhea, nausea, or vomiting.		**X**	
UNCOMMON			
Allergic reactions: rash, swelling of the lips, face or neck, shortness of breath, difficulty speaking, wheezing, drop in blood pressure, feeling sick to your stomach, vomiting, hives, or rash.			**X**
Heart block: feeling lightheaded, fainting, dizziness, shortness of breath,			**X**

nausea, or fatigue.			
Heart problems (including heart failure): irregular heartbeat**,** heart palpitations, shortness of breath, fatigue, weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, or reduced ability to exercise.		**X**	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		**X**	
Severe skin reactions: rash, dermatitis, itching, hives, red patches of skin, dry cracked skin that may bleed, itching, burning, or soreness.	**X**		
Vision changes: blurred vision, loss of vision, or increased sensitivity to light.	**X**		
Mental state changes: memory loss, psychoses, or seeing or hearing things that are not there (hallucinations).		**X**	
Breathing problems (including bronchospasm, when there is a sudden narrowing of the airway): difficulty breathing, wheezing, or coughing.		**X**	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue, or weakness.		**X**	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive), or thoughts of death or suicide.		**X**	
RARE			
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain, swelling, nausea, vomiting, unusual dark urine, or unusual tiredness.		**X**	
UNKNOWN FREQUENCY			
Congestive heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue, weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, or reduced ability to exercise.			**X**
Lupus (an autoimmune disease that occurs when your body's immune system attacks your own tissues and organs, including your joints, skin, kidneys, blood		**X**	

cells, heart and lungs): fatigue, fever, joint pain, stiffness and swelling, rash on the face that covers the cheeks and the bridge of the nose or rashes elsewhere on the body, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion, or memory loss.			
Peyronie's disease (a condition where scar tissue forms under the skin of the penis): penile pain, shortening of the penis, erection problems, or significant bend to the penis.		**X**	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 MINT-ATENOL at room temperature between 15ºC 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 Drug Product Database (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); Mint Pharmaceuticals Inc.'s website www.mintpharmaceuticals.com, or by calling 1-877-398-9696.

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