PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-ATENOLOL

Atenolol Tablets

Tablets, 25 mg, 50 mg and 100 mg, Oral

BP Standard

Beta-adrenergic Receptor Blocking Agent

ATC Code: C07AB03

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RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

1 INDICATIONS

pms-ATENOLOL (atenolol) is indicated for:

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

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. pms-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.

pms-ATENOLOL is not recommended for the emergency treatment of hypertensive crises.

1.1 Pediatrics

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

1.2 Geriatrics

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 (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

pms-ATENOLOL is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any nonmedicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- with sinus bradycardia, or bradycardia of other origin
- with second- and third-degree A-V block
- with sick sinus syndrome
- with right ventricular failure secondary to pulmonary hypertension
- with uncontrolled heart failure
- with cardiogenic shock
- with hypotension
- with severe peripheral arterial disorders
- under anesthesia with agents that produce myocardial depression

- with pheochromocytoma, in the absence of alpha-blockade
- with metabolic acidosis

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 pms-ATENOLOL. There have been reports of severe exacerbation of angina and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of pms-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 pms-ATENOLOL be reinstituted promptly, at least temporarily.

4 DOSAGE AND ADMINISTRATION

4.1. Dosing Considerations

Hypertension
pms-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 pms-ATENOLOL should be administered in accordance with individual patient's needs.

4.2 Recommended Dose and Dosage Adjustment

Hypertension
The initial dose of pms-ATENOLOL is 50 mg administered as one tablet a day either added to diuretic therapy or alone. The full effect of this dose will usually be seen within one to two weeks. If an adequate response is not achieved, the dose should be increased to pms-ATENOLOL 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 pms-ATENOLOL is 50 mg given as one tablet a day. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved within one

week, the dosage should be increased to pms-ATENOLOL 100 mg given as one tablet a day or 50 mg twice daily. Some patients may require a dosage of 200 mg a day for optimal effect.

Patients with Renal Impairment
Since atenolol is eliminated predominantly via the kidneys, dosage should be adjusted in patients with severe renal impairment. Significant accumulation of atenolol occurs when creatinine clearance falls below 35 mL/min/1.73 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/1.73 m^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 pms-ATENOLOL: 25 mg given as one tablet as day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

4.4 Administration

pms-ATENOLOL tablets should be swallowed whole with water.

4.5 Missed Dose

In case of missed dose, the next dose should be taken as scheduled. A double dose should not be taken.

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 drug by induced emesis, or administration of activated charcoal. Atenolol can be removed from the general circulation by hemodialysis. Further consideration should be given to dehydration, electrolyte imbalance and hypotension by established procedures.
Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA:	Atropine 1-2 mg intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated. Glucagon in a 10 mg intravenous bolus has been reported to be useful. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/h depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion or isoproterenol 10 to 25 micrograms given as an infusion at a rate not exceeding 5 micrograms/minute may be given, although larger doses may be required.
HEART BLOCK: (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

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets / 25 mg, 50 mg or 100 mg	Croscarmellose Sodium, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Magnesium Trisilicate, Microcrystalline Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide.

pms-ATENOLOL (atenolol) 25 mg tablets are white, round, biconvex, coated tablets, debossed with "A25" on one side and plain on the other side. Available in white HDPE bottles of 100 and 500 tablets

pms-ATENOLOL (atenolol) 50 mg tablets are round, biconvex, film-coated white tablets, debossed with deep score over "50" on one side and "ATENOLOL" on the other side. Available in bottles of 100 and 500 tablets, and blister pack of 30 tablets.

pms-ATENOLOL (atenolol) 100 mg tablets are round, biconvex, film-coated white tablets, debossed with *deep* score over "100" on one side and "ATENOLOL" on the other side. Available in bottles of 100 and 500 tablets, and blister pack of 30 tablets.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Cardiac Failure

Special caution should be exercised when administering pms-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.

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).

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. pms-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 treatment from unopposed vagal activity remaining after blockade of $beta_1$-adrenergic receptors; in such cases, dosage should be reduced.

Driving and Operating Machinery
Use of pms-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
In patients with thyrotoxicosis, possible deleterious effects from long-term use of atenolol have not been adequately appraised. Beta-blockade may mask the clinical signs of continuing hyperthyroidism or its complications and give a false impression of improvement. Therefore, abrupt withdrawal of atenolol may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Hepatic/Biliary/Pancreatic
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
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.

Peri-Operative Considerations
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 pms-ATENOLOL with anaesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

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
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/1.73m^2.

Respiratory
Patients with bronchospastic diseases should, in general, not receive beta-blockers. Due to the relative beta$_1$-selectivity of atenolol, pms-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 pms-ATENOLOL should be used. Despite these precautions, the respiratory status of some patients may worsen, and, in such cases, pms-ATENOLOL should be withdrawn.

Skin
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.

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.

No randomised 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, β-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 atenolol at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia. pms-ATENOLOL should not be given during pregnancy or to a woman who is breast-feeding unless its use is essential. (See 7 WARNINGS AND PRECAUTIONS, 7.1.2 Breastfeeding) pms-ATENOLOL 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.

7.1.2 Breastfeeling

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 pms-ATENOLOL is considered essential, then mothers should stop nursing.

7.1.3 Pediatrics

Pediatrics (< 18 years): There is no experience with atenolol in the treatment of pediatric age groups.

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.

7.1.5 Ethnic Origin

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

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 2,500 patients are bradycardia (3%), dizziness (3%), vertigo (2%), fatigue (3%), diarrhea (2%) and nausea (3%).

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 preexisting intermittent claudication, leg pain and cold extremities and edema.

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 and 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.

Respiratory: Dyspnea, wheeziness, cough, and bronchospasm.

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: elevated liver enzymes and/or bilirubin, headache, confusion, nightmares, impotence, Peyronie's disease, psoriasiform rash or exacerbation of psoriasis, purpura, reversible alopecia and thrombocytopenia. Rare cases of hepatic toxicity including intrahepatic cholestasis have been reported. Atenolol, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

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

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

Allergic: Laryngospasm, status asthmaticus and fever combined with aching and sore throat

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

Dermatological: Exfoliative dermatitis

Gastrointestinal: Mesenteric arterial thrombosis and ischemic colitis

Hematological: Agranulocytosis

Ophthalmological: Blurred vision, burning, and grittiness

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Clonidine	T	Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.	If the two drugs are coadministered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by betablocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped. (See prescribing information for clonidine)
Reserpine or Guanethdine	T	The added beta-adrenergic blocking action of atenolol may produce an excessive reduction of sympathetic activity.	Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored. pms-ATENOLOL should not be combined with other betablockers.
Antiarrhythmic Agents	T	Class I anti-arrhythmic drugs (e.g., disopyramide) and amiodarone may have potentiating effect on atrial conduction time and induce negative inotropic effect.	Caution is warranted.
Calcium Channel Blockers	T	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.	Caution is warranted.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		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	T	Digitalis glycosides may potentiate the bradycardia of beta$_1$-blockade.	Caution is warranted.
Non-Steroidal Anti-Inflammatory Agents	T	The concomitant use of nonsteroidal anti-inflammatory agents may blunt the antihypertensive effects of beta-blockers.	Caution is warranted.
Anaesthetic Agents	T	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 pms-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, Peri-Operative Considerations).
Fingolimod	T	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.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

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 beta1 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.

10.2 Pharmacodynamics

In man, atenolol reduces both isoproterenol- and exercise-induced increases in heart rate over the dose range of 50 to 200 mg. At an oral dose of 100 mg the beta1 blocking effects persist for at least 24 hours; the reduction in exercise-induced heart rate increase being about 32% and 13%, 2 and 24 hours after dosing, respectively. The logarithm of the plasma atenolol level correlates with the degree of beta1 blockade but not with the antihypertensive effect.

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.

Distribution:

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

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.

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

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.

Elimination:
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 4 DOSAGE AND ADMINISTRATION).

Over 85% of an intravenous dose is excreted in urine within 24 hours.

11 STORAGE, STABILITY AND DISPOSAL

Blisters: Store at room temperature 15°C – 25°C. Protect from light and moisture.
Bottles: Store at room temperature 15°C – 30°C. Protect from light and moisture.

12 SPECIAL HANDLING INSTRUCTIONS

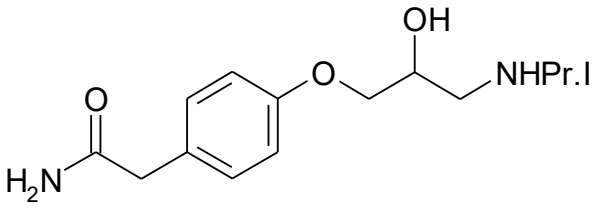
Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Atenolol
Chemical Name:	4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy] benzeneacetamide
Structural Formula:	$C_{14}H_{22}N_2O_3$ C 63.13%, H 8.33%, N 10.52% O18.02%
Molecular Mass:	266.34 g/mol



Physicochemical properties:

Physical form:	White or almost white hydrophilic compound.
Solubility:	Water solubility of 26.5 mg/mL at 37°C. Freely soluble in HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C)
pKa:	~9
Partition co-efficient:	n-octanol/buffer of 0.015 at pH 7.4 and 37°C Lipid water = 10g P = 0.23
Melting point:	146°C-148°C

14 CLINICAL TRIALS

14.2 Study Results

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

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

Effects on Pulmonary Function
The effects of a single 100 mg dose of atenolol on forced expiratory volume (FEV_1) and airways resistance (AWR) were assessed in ten patients with labile asthma. The cardioselective agents tested in this comparative trial, including atenolol, usually had a lesser dose-related effect on airway function than non-selective beta-blockers. Atenolol produced a smaller decrease in FEV1 than did the non-selective agents and did not inhibit the bronchodilator response to isoprenaline. The decrease in FEV1 was 8-9%. Other studies in asthmatic patients have reported similar decreases in FEV1 with atenolol.

Dose-effect comparisons with cardioselective agents have shown a fall in FEV1 values at the higher doses, indicating some $beta_2$-blocking effect.

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

14.3 Comparative Bioavailability Studies

The relative bioavailability of pms-ATENOLOL (Atenolol) 100 mg tablets versus TENORMIN® (Atenolol) 100 mg tablets from ICI Pharma was compared. The study was a single dose, randomized, open-label, 2-way crossover design, with 100 mg tablets administered orally to each of 26 healthy male subjects under fasting conditions. Blood samples were collected pre-dose and at the following times after drug administration: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24 and 30 hours. Whole blood atenolol was analysed by HPLC with fluorescence detection.

Atenolol (1 x 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**(95%) Confidence Interval**
$AUC_{(0-30)}$ (ng ·h/mL)	5174.63 5515.00 (32.03)	5339.01 5485.23 (21.51)	96.92	83.1 to 105.8
AUC_{inf} (ng ·h/mL)	5587.10 5867.85 (28.75)	5666.17 5805.08 (20.40)		
C_{max} (ng/mL)	613.86 675.73 (39.09)	623.26 642.62 (23.89)	98.49	84.2 to 111.7
T_{max}[3] (h)	2.85 (30.94)	2.88 (24.66)		
$T_{1/2}$[4] (h)	8.04 (27.81)	7.04 (19.47)		

[1] pms-ATENOLOL (atenolol), tablets, 100 mg, Pharmascience Inc.
[2] TENORMIN® (atenolol), tablets, 100 mg, ICI Pharma Canada Inc.
[3] Expressed as the arithmetic mean (CV %) only
[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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)	IV	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)	IV	50-60
Rat	Male	0.5% (2)	IV	129(±25)
Rat	Female	0.5% (2)	IV	114(±30)
Rhesus Monkey	M/F	Variable (1)	Oral	>6000

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

Toxic signs in rats were: depression, ataxia, labored respiration, cyanosis, tremors and convulsions. Effects occurred within 5 minutes following intravenous administration and surviving rats appeared normal after 2 hours. Effects following oral administration occurred within 1 hour and some persisted through 48 hours. Surviving rats appeared normal within 72 hours.

Following intravenous administration, all mice convulsed immediately and those animals dying did so within 5 minutes.

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

Subacute Toxicity

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

Chronic Toxicity

Species	Sex Strain	Dose M	Dose F	mg/kg/day	Route	Duration Route (mo.)	Effect
Rat	Alderly PK. Strain 1	80	80	0, 75, 150, 300	oral	6	Reduction in heart rate. High and intermediate dose showed decreased blood pressure. Spleen and heart weights increased. Chronic myocarditis was seen in all groups including controls. Three high dose and 2 mid-dose animals were killed in moribund state.
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.

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 Amery* 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.

Special Toxicology:
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).

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

In anesthetized dogs, atenolol 0.03 mg/kg IV 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 IV) was without effect on the ventricular tachycardia produced by toxic levels of ouabain in anesthetized dogs. Atenolol (0.2 mg/kg IV) protected coronary ligated dogs from the arrhythmogenic activity of adrenaline on the fourth day after ligation (when the cardiac rhythm was predominantly sinus).

17 SUPPORTING PRODUCT MONOGRAPH

1. TENORMIN® (tablets, 50 mg and 100 mg), submission control 270737, Product Monograph, Searchlight Pharma Inc., May 31, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-ATENOLOL
Atenolol Tablets

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

Serious Warnings and Precautions

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 pms-ATENOLOL, you can experience serious side effects, including:

- worsening of chest pain (angina);
- reduction of blood flow to the heart;
- heart attack; and/or
- irregular heartbeats and rhythms.

You should talk to your healthcare professional before stopping or lowering your dose of pms-ATENOLOL. You may be requested to limit your physical activity and/or to temporarily re-establish your previous dosing.

What is pms-ATENOLOL used for?
pms-ATENOLOL is used in adults (18 years of age or older) to:
- treat high blood pressure (also known as hypertension) with or without other medicines; and
- manage long-term chest pain (also known as angina).

How does pms-ATENOLOL work?
pms-ATENOLOL belongs to a group of drugs called "beta blockers". It makes your heart beat more slowly and less forcefully. This medicine does not cure your disease but helps to control it.

What are the ingredients in pms-ATENOLOL?
Medicinal ingredients: atenolol.

Non-medicinal ingredients: Croscarmellose Sodium, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Magnesium Trisilicate, Microcrystalline Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide.

pms-ATENOLOL comes in the following dosage forms:
Tablets: 25mg, 50 mg and 100 mg

Do not use pms-ATENOLOL if:

- you are allergic to atenolol or any of the other ingredients in pms-ATENOLOL.
- you have slow heartbeats.
- you have been told that you have second- or third-degree heart block (a type of irregular heartbeat and rhythm.
- you have severe heart damage and your heart is not able to pump enough blood to meet your body's needs.
- you 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.
- you have a problem with your heart's electrical conduction (that causes you to have chest pain, difficulty breathing, nausea, fatigue and fainting).
- you have low blood pressure.
- you have serious problems with blood flow in your feet and legs (peripheral artery disease).
- you have loss of sensation with agents that cause heart failure.
- you have a condition called pheochromocytoma (a tumour of the adrenal gland).
- you have a condition called metabolic acidosis (abnormal levels of acids in your blood).

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

- have a history of heart problems.
- 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.
- are pregnant, are trying or planning on becoming pregnant. pms-ATENOLOL is not usually recommended for use during pregnancy. Your healthcare professional will consider the.
- benefit to you versus the risk to your unborn baby.
- are breastfeeding or planning to breastfeed. You should not breastfeed while using pms-ATENOLOL.
- **are going to have an operation or surgery.** In addition, let the medical staff of the operation or surgery know and in particular, the anaesthetist that you are taking pms-ATENOLOL.

Other warnings you should know about:

Driving and using machines: pms-ATENOLOL can cause dizziness or fatigue. Before doing tasks that require special attention, wait until you know how you respond to pms-ATENOLOL.

Heart rate: You may notice that your heart rate becomes slower while taking pms-ATENOLOL. This is normal but if you are concerned, please talk to your healthcare professional 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 pms-ATENOLOL:

- drugs used for lowering blood pressure or treating angina:
    - beta-blockers (such as clonidine);
    - calcium channel blockers (such as verapamil, diltiazem or nifedipine);
    - catecholamine-depleting drugs (such as reserpine or guanethidine).
- drugs used to treat irregular heartbeats (such as disopyramid or amiodarone).
- drugs used to treat heart failure (such 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 pms-ATENOLOL:
Take pms-ATENOLOL:

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

Your healthcare professional may add another medicine like a diuretic (water pill) and/or a vasodilator for you to take along with pms-ATENOLOL to treat your high blood pressure.

If you have the impression that the effect of pms-ATENOLOL is too strong or too weak, talk to your healthcare professional as soon as possible.

Do not stop taking pms-ATENOLOL or change your dose without consulting your healthcare professional. This can be dangerous. If you suddenly stop taking pms-ATENOLOL, this could cause chest pain or a heart attack. If your healthcare professional decides that you should stop taking pms-ATENOLOL, your dose may be reduced so that you need to use it less and less before you stop the medication completely.

Usual dose:
Your healthcare professional will decide how much pms-ATENOLOL you should take each day depending on your condition. The usual dose is as follows:

- **High Blood Pressure:** 50 mg to 100 mg taken once a day.

- **Chest Pain:** 50 mg to 100 mg taken once a day. Up to 200 mg per day may be required in some adults.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-ATENOLOL, contact your healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take the dose as soon as you remember. Do not take two doses at the same time to make up for the missed dose.

What are possible side effects from using pms-ATENOLOL?
These are not all the possible side effects you may have when taking pms-ATENOLOL. If you experience any side effects not listed here, tell 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 (abnormally slow heartbeat): decreased heart rate that causes you to be dizzy or faint		✓	
Chest pain			✓
UNCOMMON			
Allergic reactions: rash, hives, swelling of the lips, face, tongue, throat or neck, difficulty breathing, difficulty speaking,			✓

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	
difficulty swallowing, wheezing, drop in blood pressure, feeling sick to your stomach, or vomiting.			
RARE			
Bronchospasm (when there is a sudden narrowing of the airway): difficulty breathing with wheezing or coughing.		✓	
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.		✓	
Depression (sad mood that won't go away)**:** difficulty sleeping, 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.		✓	
Edema: unusual swelling of the arms, hands, legs, feet and ankles, face, or airway passages.		✓	
Heart conduction disorders: feeling lightheaded, dizzy or passing out, fainting, feeling that your heart skips beats, chest pain, nausea, difficulty breathing, shortness of breath, or fatigue.			✓
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision,		✓	

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	
nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).			
Irregular heartbeat (such as skipped beats) or heart palpitations		✓	
Memory problems		✓	
Shortness of breath		✓	
Skin reactions: rash, itchiness, flushing, red patches of skin covered with thick, silvery scales, dry cracked skin that may bleed, burning, or soreness.	✓		
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, 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 health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Blisters: Store at room temperature 15°C – 25°C.
- Bottles: Store at room temperature 15°C – 30°C.
- Protect from light and moisture.
- Do not take your tablets after the expiry date on the container.
- Keep out of reach and sight of children.

If you want more information about pms-ATENOLOL:

- Talk to your healthcare professional
- Find the full Product Monograph, that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

This leaflet was prepared by Pharmascience Inc.

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