

**PRODUCT MONOGRAPH**

**PrMINT-NADOLOL**

**Nadolol Tablets, USP  
40 mg and 80 mg**

**Anti-anginal and Antihypertensive Agent**

**Mint Pharmaceuticals Inc.  
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Control No: 219225**

**Date of Preparation:** February 18, 2020

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### THERAPEUTIC CLASSIFICATION

Anti-anginal and Antihypertensive Agent

### ACTIONS

MINT-NADOLOL (nadolol) is a non-cardioselective beta-adrenergic blocking agent.

The exact mechanism by which nadolol exercises its anti-anginal effect is not certain, but it may reduce the oxygen requirements of the heart by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. However, oxygen requirements may be increased by such actions as increases in left ventricular fibre length, end diastolic pressure and the systolic ejection period. When the net physiological effect is advantageous in angina patients, it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks. Nadolol can therefore increase the capacity for work and exercise in such patients.

The mechanism of the antihypertensive effect of nadolol has not yet 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 vasomotor centers.

### Pharmacokinetics:

In humans, approximately 34% of orally-administered nadolol is slowly absorbed. Approximately 30% of the nadolol present in serum is reversibly bound to plasma proteins and the drug is extensively distributed to extravascular tissues. Maximum serum concentrations are reached 2-4 hours after oral administration, while steady state serum concentrations are reached after 6-9 days. The serum half-life is 20-24 hours at therapeutic dose levels.

Nadolol is not detectably metabolized by man. Urinary and fecal excretion of nadolol after oral administration to humans averaged approximately 20% and 70% respectively. The latter fraction would include both unabsorbed drug and that fraction of the absorbed drug which is excreted by the liver.

Nadolol elimination was found to be proportional to creatinine clearance in patients with renal impairment. In the presence of severe renal impairment (creatinine clearance less than 5 mL/min), the average serum half-life of nadolol was 45 hours and most of the drug was excreted by non-renal routes.

Nadolol can be removed from the circulation by hemodialysis.

### CLINICAL TRIALS

A double-blinded, randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study of MINT-NADOLOL 80 mg tablets (Mint Pharmaceuticals Inc.) and NADOLOL 80 mg tablets (AA Pharma Inc.) was performed in 47 healthy, adult, Asian male human subjects under fasting conditions. The pharmacokinetic data from the 40 subjects who completed the study are summarized in the following table.

#### **SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

Nadolol (1 x 80 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>T</sub> (ng·hr/mL)	3321.44 3530.82 (33.67)	3153.70 3297.58 (29.40)	105.3	96.0 – 115.5
AUC <sub>I</sub> (ng·hr/mL)	3414.81 3626.07 (33.29)	3236.55 3381.90 (29.23)	105.5	96.3 – 115.6
C <sub>max</sub> (ng/mL)	258.60 291.24 (51.90)	246.86 275.73 (52.35)	104.8	90.5 – 121.2
T <sub>max</sub> <sup>§</sup> (hr)	3.00 (1.50 – 8.00)	3.17 (0.50 – 6.00)		
T <sub>½</sub> <sup>€</sup> (hr)	13.68 (12.16)	13.69 (13.10)		

\*MINT-NADOLOL (nadolol) 80 mg tablets (Mint Pharmaceuticals Inc.)

†NADOLOL (nadolol) 80 mg tablets (AA PHARMA INC.) were purchased in Canada.

§Expressed as the median (range) only.

€Expressed as the arithmetic mean (CV%) only.

## INDICATIONS

### Angina:

MINT-NADOLOL (nadolol) is indicated for prophylaxis of angina pectoris.

### Hypertension:

MINT-NADOLOL is indicated in patients with mild or moderate hypertension. MINT-NADOLOL 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 judgment of the physician, treatment should be started with a beta-blocker rather than a diuretic.

The combination of nadolol with a diuretic has been found to be compatible and generally more effective than nadolol alone. In a few cases where peripheral vasodilators were used with nadolol, no evidence of incompatibility was seen.

MINT-NADOLOL is not recommended for the emergency treatment of hypertensive crises.

## CONTRAINDICATIONS

Allergic rhinitis, bronchospasm (including bronchial asthma), or severe chronic obstructive pulmonary disease (see PRECAUTIONS).

Sinus bradycardia.

Second and third degree A-V block.

Right ventricular failure secondary to pulmonary hypertension.

Congestive heart failure (see WARNINGS).

Cardiogenic shock.

Anesthesia with agents that produce myocardial depression, e.g. ether.

Hypersensitivity to nadolol.

## WARNINGS

### Cardiac Failure:

Special cautions should be exercised when administering MINT-NADOLOL (nadolol) 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 a potential hazard of further depressing myocardial contractility and precipitating cardiac failure. 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 during MINT-NADOLOL therapy, patients should be fully digitalized, and/or given a diuretic, and the response observed closely.

Nadolol acts selectively without blocking 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 nadolol when the two drugs are used concomitantly. The effects of nadolol and digitalis are additive in depressing A-V conduction. If cardiac failure continues despite adequate digitalization and diuretic therapy MINT-NADOLOL therapy should be discontinued (see WARNING below).

#### Abrupt Cessation of Therapy with MINT-NADOLOL:

Patients with angina should be warned against abrupt discontinuation of MINT-NADOLOL. There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation of beta-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of MINT-NADOLOL is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about 2 weeks and the patient should be carefully observed. The same frequency of administration should be maintained.

In situations of greater urgency, MINT-NADOLOL therapy should be discontinued stepwise and under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with MINT-NADOLOL be reinstated promptly, at least temporarily.

Various skin rashes and conjunctival xerosis have been reported with beta-blockers including nadolol. A severe syndrome (oculo-muco-cutaneous 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 nadolol 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.

Severe sinus bradycardia due to unopposed vagal activity occurs in approximately 3% of patients following administration of nadolol. In such cases, dosage should be reduced or the use of intravenous atropine could be considered; if no improvement is seen, intravenous isoproterenol should be considered

In patients with thyrotoxicosis, nadolol may give a false impression of improvement by diminishing peripheral manifestations of hyperthyroidism without improving thyroid function; therefore, abrupt withdrawal may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

### PRECAUTIONS

MINT-NADOLOL (nadolol) should be administered with caution to patients prone to non-allergic bronchospasm (e.g., chronic bronchitis, emphysema) since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

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 the 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 those 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.

MINT-NADOLOL 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 and symptoms of acute hypoglycemia. As beta-blockade also reduces the release of insulin in response to hyperglycemia, it may be necessary to adjust the dosage of anti-diabetic drugs.

MINT-NADOLOL dosage should be individually adjusted when used concomitantly with other antihypertensive agents (see DOSAGE AND ADMINISTRATION).

Patients receiving catecholamine-depleting drugs, such as reserpine and guanethidine, should be closely monitored if MINT-NADOLOL is administered concomitantly. The added catecholamine blocking action of nadolol may produce an excessive reduction of the resting sympathetic nervous activity.

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

Suitable laboratory tests should be carried out at appropriate intervals and caution should be observed in patients with impaired renal or hepatic function. Since nadolol is excreted mainly by the kidneys, dosage reduction may be necessary when renal insufficiency is present.

#### In Patients Undergoing Elective or Emergency Surgery:

The management of patients being treated with beta-blockers and undergoing elective or emergency surgery is controversial. Although beta-adrenergic-receptor blockade impairs the ability of the heart to respond to beta-adrenergically-mediated reflex stimuli, abrupt discontinuation of therapy with MINT-NADOLOL may be followed by severe complications (see WARNINGS). Some patients receiving beta-adrenergic-blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heart beat has also been reported.

For these reasons, in patients with angina undergoing elective surgery, MINT-NADOLOL should be withdrawn gradually following the recommendation given under Abrupt Cessation of Therapy (see WARNINGS). The available evidence suggests that the clinical and physiologic effects of beta-blockade induced by nadolol are essentially absent 5 days after cessation of therapy.

In emergency surgery, since nadolol 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 levarterenol.

#### Usage in Pregnancy and Nursing Mothers:

Since nadolol has not been studied in human pregnancy, the drug should not be given to pregnant women. The use of any drug in patients of child-bearing potential requires that the anticipated benefit be weighed against possible hazards.

When given to pregnant rats, nadolol readily crossed the placental barrier. Nadolol was found to be concentrated in the milk of lactating rats. Information in humans is lacking. Therefore, the use of this drug in lactating women is not recommended.

#### Usage in Children:

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

### ADVERSE REACTIONS

The most serious adverse reactions encountered are congestive heart failure, A-V block and bronchospasm.

The most common adverse reactions reported are severe bradycardia (3%), dizziness (3%), fatigue (2%), hypotension (1%), congestive heart failure (1%), and cold sensations (1%).

Adverse reactions, grouped by system are as follows:

#### Cardiovascular:

- Congestive heart failure, pulmonary edema, cardiac enlargement. Rhythm or conduction disturbances including A-V block, bigeminy and Adams-Stokes syndrome.
- Chest pain
- Severe bradycardia
- Hypotension, orthostatic hypotension, and syncope.
- Peripheral vascular insufficiency including intermittent claudication and cold extremities
- Edema

Respiratory:

- Bronchospasm
- Dyspnea
- Cough

Central Nervous System:

- Dizziness
- Depression, anxiety, nervousness, irritability, and hallucinations
- Lethargy, fatigue
- Sleep disturbances including insomnia and nightmares
- Paresthesia
- Headache
- Tinnitus Slurred speech

Gastrointestinal:

- Abdominal pain or pressure
- Nausea, vomiting, diarrhea, constipation, and flatulence
- Gastritis
- Anorexia

Dermatological (See WARNINGS):

- Rash
- Pruritus
- Dry skin

Ophthalmologic:

- Conjunctivitis
- Blurred vision
- Dry eyes

Miscellaneous:

- Impotence, decreased libido
- Enlarged thyroid
- Nasal stuffiness, dry mouth, sweating



- Weight gain

#### Clinical Laboratory:

The following parameters have most frequently been found to be outside the normal range: serum triglycerides, blood glucose, serum potassium, SGOT, SGPT, LDH, BUN.

### SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

The most common signs to be expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

If overdosage occurs, in all cases therapy with MINT-NADOLOL (nadolol) should be discontinued and the patient observed closely. In addition, if required, the following therapeutic measures are suggested:

1. Bradycardia: Atropine or another anticholinergic drug.
2. Heart Block:(second or third degree): Isoproterenol or transvenous cardiac pacemaker.
3. Congestive Heart Failure:  
Conventional therapy.
4. Hypotension (depending on associated factors):  
Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis (see precautions concerning the use of epinephrine in beta-blocked patients).
5. Bronchospasm: Aminophylline or isoproterenol.
6. Hypoglycemia:  
Intravenous glucose.

It should be remembered that nadolol is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of nadolol. However, the complications of excess isoproterenol should not be overlooked.

### DOSAGE AND ADMINISTRATION

It is recommended that MINT-NADOLOL (nadolol) be administered as a single daily dose. MINT-NADOLOL may be administered without regard to meals since the presence of food

in the gastrointestinal tract does not affect the rate or extent of nadolol absorption.

MINT-NADOLOL dosage must always be adjusted to the individual needs of the patient, in accordance with the following guidelines:

Angina Pectoris:

MINT-NADOLOL treatment should be initiated with doses of 80 mg daily. If an adequate response is not observed after one week, dosage may be increased by 80 mg increments at weekly intervals, until a satisfactory response is achieved. The maximum recommended daily dose is 240 mg. Patients stabilized on 80 mg daily might be tried on 40 mg daily as this dose has been found to be effective in some cases.

The value and safety of doses above 240 mg daily in angina pectoris have not been established.

Hypertension:

MINT-NADOLOL treatment should be initiated with doses of 80 mg daily. If an adequate response is not observed after one week, dosage may be increased by 80 mg increments at weekly intervals, until a satisfactory response is achieved. The maximum recommended daily dose is 320 mg, although most patients respond to 240 mg or less. The value and safety of doses above 320 mg daily have not been established.

AVAILABILITY

40 mg tablets: Round, white to off white, biconvex tablets, debossed MN above the break line, 40 below the break line on one side and pain on the other side. Available in bottles of 100 tablets.

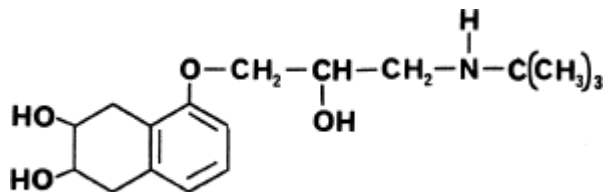
80 mg tablets: Round, white to off white, biconvex tablets, debossed MN above the break line, 80 below the break line on one side and pain on the other side. Available in bottles of 100 tablets.

Storage:

Store tightly closed, at 15°C – 30°C. Keep out of reach and sight of children.

## PHARMACOLOGY

### Chemistry:



Molecular Formula: C<sub>17</sub>H<sub>27</sub>NO<sub>4</sub>

Molecular Weight: 309.41g/mol

Chemical Name: 2,3-cis-1,2,3,4-tetrahydro-5-(2-hydroxy-3-(tert-butylamino)propoxy)-2,3-naphthalenediol.

### Description:

Nadolol is a white to off-white crystalline powder, freely soluble in 95% ethanol and dilute acids (pH 2.0); slightly soluble in chloroform and insoluble in acetone, benzene, ethyl ether, hexane, propylene glycol and aqueous buffers (pH 7.0-9.0).

### Pharmacokinetics:

The principle details of the human pharmacokinetics of nadolol may be found under ACTIONS. Mean minimum serum concentrations at steady state were approximately 28, 70, and 131 ng/mL at doses of 80, 160 and 240 mg daily, respectively.

After intravenous administration 73% of the dose was excreted via the kidneys and about 23% via the gastrointestinal tract, the latter of biliary origin.

In dog studies, the highest concentrations of nadolol were present in the kidneys, lungs and heart.

### Effects on the Cardiovascular System:

Animal studies in vitro and in vivo showed nadolol to be an antagonist of the beta-stimulatory effects of catecholamines and to consistently block isoproterenol-induced tachycardia and vasodepression in anesthetized dogs and cats, as well as in unanesthetized monkeys and spontaneously hypertensive rats.

Nadolol possesses no significant intrinsic sympathomimetic or membrane-stabilizing (quinidine-like) activities.

In human studies, nadolol has been shown to inhibit the effects of both isoproterenol- and exercise- induced tachycardia at doses as low as 10 mg. Maximum inhibition was seen at 60-90 minutes and 3-8 hours respectively. Significant inhibition of exercise induced increases in double product (heart rate x blood pressure) persisted for at least 26 hours following single oral doses of 40-160 mg.

The iv administration of 0.3-10 ug/kg of nadolol to normotensive male volunteers produced reductions in peripheral plasma renin activity. A similar effect was also seen in hypertensive patients.

A study of the effects of nadolol on human cardiac electrophysiology and hemodynamics showed that nadolol reduces cardiac output without affecting stroke volume.

Studies involving guinea pig atria, papillary muscle of cats, anesthetized dogs, and unanesthetized atherosclerotic rabbits indicated that nadolol produces little direct myocardial depression in doses much greater than those required to produce complete beta-blockade. However, in other studies involving anesthetized dogs and cats, intravenous infusions of 0.05-1 mg/kg (dogs) and 0.1 to 10 mg/kg (cats) produced decreases in heart rate from 15 to 30% and 23 to 45% respectively.

In studies to determine the effect of intravenous nadolol on excitability, refractoriness, and conduction velocity of both atrial and ventricular tissue in anesthetized dogs, nadolol produced prolongation of ventricular refractoriness and depression of conduction through the A-V node.

In anesthetized dogs, intravenous doses of 0.03-1.0 mg/kg nadolol prevented ECG changes caused by coronary artery occlusion. Exacerbation of these changes by isoproterenol were similarly prevented.

Results from human studies have shown that nadolol possesses some anti-arrhythmic activity.

In a limited trial involving 11 hypertensive patients uncontrolled by diuretic alone, addition of nadolol to the regimen caused a significant increase (9.5%) in mean PAH clearance (effective renal plasma flow) and a 21% decrease in mean renovascular resistance after 16 weeks of combination therapy. Significant reduction in blood pressure and heart rate occurred. No significant changes were observed in plasma volume, serum creatinine or creatinine clearance.

Similar findings were reported following intravenous doses of nadolol to both hypertensive and normal subjects fed a low sodium diet.

#### Effects of Respiratory Function:

Studies of the effects of intravenous doses of nadolol on bronchial-airway resistance and on histamine-induced bronchial constriction in anesthetized cats indicated that nadolol increased bronchial-airway resistance. Histamine-induced increases of bronchial-airway resistance were dose dependent and potentiated slightly by nadolol.

In normal male volunteers, both forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1.0</sub>) decreased after ingestion of 80 mg of nadolol and to a lesser extent after a 120 mg dose.

Other Effects:

A 60 mg daily dose of nadolol for 7 days produced a slightly faster initial rate of disappearance of glucose from the serum following glucose loading in six patients with moderate hypertension or cardiac arrhythmia. Mean insulin responses at 1 and 2 hours after ingestion of the glucose load were decreased approximately 30-35% by nadolol. Nadolol had no significant effect on fasting serum glucose or insulin levels.

## TOXICOLOGY

### Acute Toxicity:

Species	Sex	Oral LD <sub>50</sub> (mg/kg)	Animal
			Albino
Mice*	F	3213	
	M	3774	
	M/F	3530	
Albino Rats**	M/ F	>5000	

\*6 groups, each with 5 animals/sex were treated with nadolol at logarithmically spaced doses.

\*\*Single group of 5 animals/sex were treated with the test article at a maximum single dose of 5000 mg/kg.

Mortality generally occurred over a 4-hour period post dosing in mice and one male rat died during the first four-hour period post dosing.

Toxicity was generally characterized by weakness, slight tremors, labored breathing, piloerection, and reduced motor activity in mice. In rats, toxicity was characterized by ptosis, hunched back, piloerection, ataxia, ocular discharge, and reduced motor activity.

Necropsy of animals succumbing during the study generally demonstrated reddening of the lungs

and stomach mucosa. Animals sacrificed after completion of the study generally demonstrated no meaningful tissue abnormality.

### Acute Oral Interaction Study:

Nadolol was administered orally to mice in combination with: hydralazine hydrochloride, hydrochlorothiazide, digoxin, furosemide, norethindrone/mestranol, quinidine sulfate, nitroglycerin, lithium carbonate or methyldopa.

Under the conditions of the study, there was no evidence of toxicity potentiation of nadolol with any of the nine marketed compounds. Signs of toxicity observed with nadolol alone or in combination with quinidine sulfate, hydralazine hydrochloride, furosemide, methyldopa, or lithium carbonate were ataxia and convulsion.

Subacute Toxicity:

Species	Strain	Sex	No. of animals per group	No. of groups	Dose (mg/kg/day)	Route	Duration of Study	Toxic Effects
Rats	Charles River COBS	M	15	4	0,100,300 or	p.o.	12 wks	None
		F	15	4	1000-6 days a week.			
Rats	Sprague-Dawley	M	5	4	0,2.5,7.5 or 25 (in saline)	i.p.	4 wks	None
		F	5	4				
Dogs	Beagle	M	1	4	0,25,75 or 250	p.o.	3.5 wks	Slight loss of body weight; emesis
		F	1	4				
Dogs	Beagle	M	2	4	0,1.25,3.75, or 12.5	i.v.	4 wks	Bradycardia
		F	2	4				
Monkeys	Rhesus	M	2	4	0,25,75,250	p.o.	12 wks	Bradycardia
		F	1	4				

Chronic Toxicity:

Species	Strain	Sex	No. of animals per group	No. of groups	Dose (mg/kg/day)	Route	Duration of Study	Toxic Effects
Mice	Charles-River CD-1	Male	60	4	0, 80, 200 or 500	p.o.	18 mos.	Slightly lower mean body weight in all test animals; higher (statistically non-significant) incidence of eye lesions such as synechia, retinal detachment/degeneration, chronic iritis at 500 mg/kg.
		Female	60	4				
Rats	Sprague-Dawley	Male	60	4	0, 160, 400 or 1000	p.o.	18 mos.	Slightly lower mean body weight; higher (statistically non-significant) incidence of cataracts at 400 and 1000 mg/kg.
		Female	60	4				
Dogs	Beagle	Male	4	4	0, 24, 60, 150	p.o.	1 yr	Moderate weight loss; decreased mean heart rate; decrease in glucose tolerance; decreased food consumption; dose-related increases in blood triglyceride levels (33-61%), within the normal range.
		Female	4	4				



### Carcinogenicity Studies:

Nadolol was administered to 3 groups of 60 male and 60 female Charles River CD Sprague-Dawley rats at dietary levels of 160, 400 and 1000 mg/kg/day, for 18 months. A similar study was conducted in 3 groups of 60 male and 60 female Charles River CD-1 mice. Doses of 80, 200 or 500 mg/kg/day were given in the diet for 18 months.

Under the conditions of testing, nadolol did not influence the development of tumors.

### Teratology Studies:

Rats: Doses of 100 or 300 mg/kg/day were administered orally to male rats for 10 weeks, and to female rats for 2 weeks before mating. Half of the females were dosed until day 13 or 14 of gestation; the remaining females were dosed through gestation and 21 days of lactation. Nadolol had no effect on gestation or on viability of the newborn at birth and at 4 days.

Rats, Hamsters: When administered orally to pregnant rats and hamsters, doses of 100 or 300 mg/kg did not affect fetal development or induce teratogenic changes in the offspring.

Rabbits: When daily doses of 100 or 300 mg/kg were administered orally to Small Russian rabbits from day 6 through day 18 of gestation, nadolol was found to be embryo and fetotoxic, although no teratogenic changes were seen in any of the viable offspring.

Similar effects were noted when pregnant New Zealand and White rabbits were administered daily doses of 100 mg/kg on days 7 through 18 of gestation. These effects were not, however, seen in Small Russian rabbits at dose levels of 25 or 50 mg/kg.

Rats: Total daily doses of 300, 900 or 1800 mg/kg of nadolol were given to rats from day 15 of gestation through to day 21 of lactation. At these dose levels, nadolol did not have any significant adverse effects on pregnant rats or their offspring.

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  20. <sup>P</sup>rNadolol (Nadolol) Tablets 40 mg, 80 mg, and 160 mg, Control no # 190672, Product Monograph, AA Pharma Inc. Canada, Inc. (June 24, 2016).

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION**

**PrMINT-NADOLOL**

**Nadolol Tablets, USP  
40 mg and 80 mg**

Read this carefully before you start taking MINT-NADOLOL 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-NADOLOL.

**What is MINT-NADOLOL used for?**

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

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

**How does MINT-NADOLOL work?**

MINT-NADOLOL belongs to a group of drugs called “beta blockers.”

- It makes your heart beat more slowly and less forcefully.
- It lowers your blood pressure by relaxing your blood vessels so that your blood flows more easily.

This medicine does not cure your disease but helps to control it.

**What are the ingredients in MINT-NADOLOL?**

Medicinal ingredients: nadolol.

Non-medicinal ingredients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, croscarmellose sodium, colloidal silicon dioxide

**MINT-NADOLOL comes in the following dosage forms:**

Tablets: 40 mg (white to off-white) and 80 mg (white to off-white)

**Do not use MINT-NADOLOL if you:**

- Are allergic to nadolol or any of the other ingredients in MINT-NADOLOL.
- Have heart failure and you notice that your symptoms are getting worse. For example you feel more tired, are out of breath more often, or have swelling of the ankles.
- Have severe heart damage and your heart is not able to pump enough blood to meet your body’s needs.
- Have a slow or irregular heart beat.
- Have an abnormal heart rate or rhythm.
- Have a problem with your heart’s electrical conduction (that causes you to have chest pain, difficulty breathing, nausea, fatigue and fainting).

- Have severe liver disease.
- Have serious problems with blood flow in your feet and legs (peripheral artery disease).
- Have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption
- Are 18 years and younger.

**To make sure you take the drug properly and don't have side effects, talk to your healthcare professional before you take MINT-NADOLOL. Talk about any health conditions or problems you may have, including if you:**

- Have asthma or other lung problems (like bronchitis or emphysema).
- Have a history of heart problems.
- Have a history of fainting.
- Have diabetes and take medicine to control your blood sugar or have low blood sugar (hypoglycemia).
- Have a condition called pheochromocytoma (a tumour of the adrenal gland).
- Have thyroid problems.
- Have liver or kidney problems.
- Have had allergic reactions or have allergies.
- Are pregnant or trying to become pregnant. MINT-NADOLOL is not usually recommended for use during pregnancy. Your doctor will consider the benefit to you versus the risk to your unborn baby.
- Are breastfeeding. You should not breastfeed while using MINT-NADOLOL.
- Are scheduled for surgery and will be given an anesthetic.
- Develop a skin rash while taking MINT-NADOLOL.

**Other warnings you should know about:**

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

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

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

**The following drugs may interact with MINT-NADOLOL:**

- Drugs used for lowering blood pressure:
  - ACE inhibitors (such as lisinopril)
  - Calcium channel blockers (such as verapamil and diltiazem)
  - Clonidine
- Drugs used to treat depression and mood disorders (such as fluoxetine, paroxetine, and

venlafaxine)

- Anesthetic drugs used during surgery (such as ether and cyclopropane)
- Drugs used to treat diabetes such as insulin and oral medicines. You could become less aware of the symptoms of low blood sugar.
- Drugs used to treat heartburn and ulcers (such as cimetidine)
- Antidiuretic drugs used to reduce the fluid build-up in your body (such as hydrochlorothiazide, furosemide and spironolactone)
- Sildenafil, a drug used to treat erectile dysfunction
- Drugs used to treat HIV/AIDS
- Drugs used to treat heart rhythm disorders (such as amiodarone, disopyramide, flecainide digoxin)
- Fingolimod, a medicine used to treat multiple sclerosis
- Dexamethasone, a steroid drug used to treat inflammation
- Rifampin used to treat tuberculosis

### **How to take MINT-NADOLOL:**

Take MINT-NADOLOL:

- Exactly as prescribed
- Everyday
- Once a day, at about the same time each day
- With or without food

### **Usual Adult Dose:**

#### **High Blood Pressure:**

Usual starting daily dose: 80 mg once a day.

Maximum daily dose: 320 mg once a day.

#### **Chest Pain:**

Usual starting daily dose: 80 mg once a day.

Maximum daily dose: 240 mg once a day.

Do **NOT** stop taking MINT-NADOLOL or change your dose without consulting with your doctor. This can be dangerous.

### **Overdose:**

If you think you have taken too much MINT-NADOLOL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.
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### **Missed Dose:**

If you have forgotten to take your dose, carry on and take your next dose at the usual time. **Do NOT** double the dose.

### **What are the possible side effects from taking MINT-NADOLOL?**

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

Side effects may include:

- Cough
- Diarrhea
- Dizziness
- Dry mouth
- Headache
- Joint and back pain
- Nausea
- Stuffy nose and colds
- Tiredness
- Trouble sleeping

<b>Serious side effects and what to do about them</b>			
<b>Symptom / effect</b>	<b>Talk to your healthcare professional</b>		<b>Stop taking drug and get immediate medical help</b>
	<b>Only if severe</b>	<b>In all cases</b>	
<b>COMMON</b>			
• <b>Bradycardia:</b> decreased heart rate that causes you to be dizzy or faint		✓	
→ <b>Chest pain</b>			✓
<b>UNCOMMON</b>			
• <b>Allergic reactions:</b> rash, swelling of the lips, face or neck, difficulty breathing or speaking			✓
• <b>Heart attack:</b> chest pain, squeezing or pressure, fast or irregular heartbeat, nausea, trouble breathing, sweating			✓
• <b>Heart conduction disorders:</b> feeling lightheaded, dizzy, or passing out			✓
• <b>Hypotension (low blood pressure):</b> dizziness or lightheadedness leading to fainting can occur when changing positions, for example from lying down to standing up		✓	
• <b>Irregular heart beat or heart palpitations (skipped beats)</b>		✓	
• <b>Leg swelling from fluid retention</b>		✓	

• <b>Memory problems</b>		✓	
• <b>Shortness of breath</b>		✓	
• <b>Skin reactions:</b> rash	✓		
• <b>Vision problems</b>	✓		

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

#### **REPORTING SIDE EFFECTS**

##### **Reporting Side Effects**

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

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

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

#### **Storage:**

Store tightly closed, at 15°C – 30°C. Keep out of reach and sight of children

#### **If you want more information about MINT-NADOLOL:**

Talk to your healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be found by visiting the Health Canada website ([www.healthcanada.gc.ca](http://www.healthcanada.gc.ca)) or by contacting the sponsor, Mint Pharmaceuticals Inc. at:

1-877-398-9696

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