NADOLOL - nadolol tablet
Physicians Total Care, Inc.

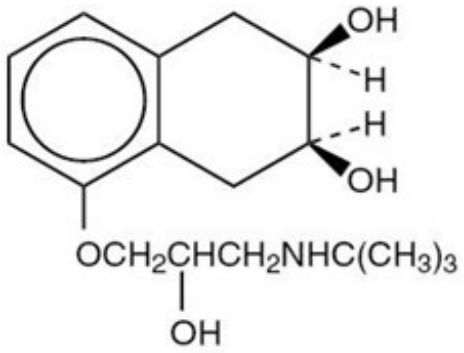
Rx only

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

DESCRIPTION

Nadolol is a synthetic nonselective beta-adrenergic receptor blocking agent designated chemically as 1-(*tert*-butylamino)-3-[(5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol. Its structural formula is:



$C_{17}H_{27}NO_4$
M.W. 309.41

Nadolol is a white crystalline powder. It is freely soluble in ethanol, soluble in hydrochloric acid, slightly soluble in water and in chloroform, and very slightly soluble in sodium hydroxide.

Each tablet for oral administration contains 20 mg, 40 mg or 80 mg of nadolol, USP and the following inactive ingredients: croscarmellose sodium, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, and D&C Yellow No. 10 aluminum lake.

CLINICAL PHARMACOLOGY

Nadolol is a nonselective beta-adrenergic receptor blocking agent. Clinical pharmacology studies have

demonstrated beta-blocking activity by showing (1) reduction in heart rate and cardiac output at rest and on exercise, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Nadolol specifically competes with beta-adrenergic receptor agonists for available beta receptor sites; it inhibits both the $beta_1$ receptors located chiefly in cardiac muscle and the $beta_2$ receptors located chiefly in the bronchial and vascular musculature, inhibiting the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation proportionately. Nadolol has no intrinsic sympathomimetic activity and, unlike some other beta-adrenergic blocking agents, nadolol has little direct myocardial depressant activity and does not have an anesthetic-like membrane stabilizing action. Animal and human studies show that nadolol slows the sinus rate and depresses AV conduction. In dogs, only minimal amounts of nadolol were detected in the brain relative to amounts in blood and other organs and tissues. Nadolol has low lipophilicity as determined by octanol/water partition coefficient, a characteristic of certain beta-blocking agents that has been correlated with the limited extent to which these agents cross the blood-brain barrier, their low concentration in the brain, and low incidence of CNS-related side effects.

In controlled clinical studies, nadolol at doses of 40 to 320 mg/day has been shown to decrease both standing and supine blood pressure, the effect persisting for approximately 24 hours after dosing.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents has not been established; however, factors that may be involved include (1) competitive antagonism of catecholamines at peripheral (non-CNS) adrenergic neuron sites (especially cardiac) leading to decreased cardiac output, (2) a central effect leading to reduced tonic-sympathetic nerve outflow to the periphery, and (3) suppression of renin secretion by blockade of the beta-adrenergic receptors responsible for renin release from the kidneys.

While cardiac output and arterial pressure are reduced by nadolol therapy, renal hemodynamics are stable, with preservation of renal blood flow and glomerular filtration rate.

By blocking catecholamine-induced increases in heart rate, velocity and extent of myocardial contraction, and blood pressure, nadolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, nadolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

Although beta-adrenergic receptor blockade is useful in treatment of angina and hypertension, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. Beta-adrenergic blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Absorption of nadolol after oral dosing is variable, averaging about 30%. Peak serum concentrations of nadolol usually occur in 3 to 4 hours after oral administration and the presence of food in the gastrointestinal tract does not affect the rate or extent of nadolol absorption. Approximately 30% of the nadolol present in serum is reversibly bound to plasma protein.

Unlike many other beta-adrenergic blocking agents, nadolol is not metabolized by the liver and is excreted unchanged, principally by the kidneys.

The half-life of therapeutic doses of nadolol is about 20 to 24 hours, permitting once daily dosage. Because nadolol is excreted predominantly in the urine, its half-life increases in renal failure (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Steady-state serum concentrations of nadolol are attained in 6 to 9 days with once daily dosage in persons with normal renal function. Because of variable absorption and different individual responsiveness, the proper dosage must be determined by titration.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmias have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

INDICATIONS AND USAGE

Angina Pectoris

Nadolol tablets are indicated for the long-term management of patients with angina pectoris.

Hypertension

Nadolol tablets are indicated in the management of hypertension; it may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

CONTRAINDICATIONS

Nadolol tablets are contraindicated in bronchial asthma, sinus bradycardia and greater than first-degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

Cardiac Failure

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or nadolol should be discontinued (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Nadolol should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery

Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase the

risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of nadolol can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia

Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm.

PRECAUTIONS

Impaired Renal Function

Nadolol should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

Information for Patients

Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of nadolol therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure. The patient should also be advised of a proper course in the event of an inadvertently missed dose.

Drug Interactions

When administered concurrently, the following drugs may interact with beta-adrenergic receptor blocking agents:

Anesthetics, general: Exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery).

Antidiabetic drugs (oral agents and insulin): Hypoglycemia or hyperglycemia; adjust dosage of antidiabetic drug accordingly (see WARNINGS, Diabetes and Hypoglycemia).

Catecholamine-depleting drugs (e.g.,reserpine): Additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia (e.g., vertigo, syncope, postural hypotension).

Response to Treatment for Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In chronic oral toxicologic studies (1 to 2 years) in mice, rats, and dogs, nadolol did not produce any significant toxic effects. In 2 year oral carcinogenic studies in rats and mice, nadolol did not produce any neoplastic, preneoplastic, or nonneoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, nadolol caused no adverse effects.

Pregnancy Category C

In animal reproduction studies with nadolol, evidence of embryotoxicity and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses five to ten times greater (on a mg/kg basis) than the maximum indicated human dose. No teratogenic potential was observed in any of these species.

There are no adequate and well controlled studies in pregnant women. Nadolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonates whose mothers are receiving nadolol at parturition have exhibited bradycardia, hypoglycemia, and associated symptoms.

Nursing Mothers

Nadolol is excreted in human milk. Because of the potential for adverse effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of nadolol to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required withdrawal of therapy.

Cardiovascular: Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first-degree and third-degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Central Nervous System: Dizziness or fatigue has been reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior have each been reported in approximately 6 of 1,000 patients.

Respiratory: Bronchospasm has been reported in approximately 1 of 1,000 patients (see CONTRAINDICATIONS and WARNINGS).

Gastrointestinal: Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence have been reported in 1 to 5 of 1,000 patients.

Miscellaneous: Each of the following has been reported in 1 to 5 of 1,000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Reversible alopecia has been reported infrequently.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Miscellaneous: Pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with nadolol.

OVERDOSAGE

Nadolol can be removed from the general circulation by hemodialysis.

In addition to gastric lavage, the following measures should be employed, as appropriate. In determining the duration of corrective therapy, note must be taken of the long duration of the effect of nadolol.
Excessive Bradycardia

Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
Cardiac Failure

Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.
Hypotension

Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)
Bronchospasm

Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. NADOLOL MAY BE ADMINISTERED WITHOUT REGARD TO MEALS.
Angina Pectoris

The usual initial dose is 40 mg nadolol once daily. Dosage may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response is obtained or there is pronounced slowing of the heart rate. The usual maintenance dose is 40 or 80 mg administered once daily. Doses up to 160 or 240 mg administered once daily may be needed.

The usefulness and safety in angina pectoris of dosages exceeding 240 mg per day have not been established. If treatment is to be discontinued, reduce the dosage gradually over a period of 1 to 2 weeks (see WARNINGS).
Hypertension

The usual initial dose is 40 mg nadolol once daily, whether it is used alone or in addition to diuretic therapy. Dosage may be gradually increased in 40 to 80 mg increments until optimum blood pressure reduction is achieved. The usual maintenance dose is 40 or 80 mg administered once daily. Doses up to 240 or 320 mg administered once daily may be needed.
Dosage Adjustment in Renal Failure

Absorbed nadolol is excreted principally by the kidneys and, although nonrenal elimination does occur, dosage adjustments are necessary in patients with renal impairment. The following dose intervals are recommended:

Creatinine Clearance ($mL/min/1.73^2$)	**Dosage Interval (hours)**
Greater Than 50	24
31 to 50	24 to 36
10 to 30	24 to 48

Less Than 10	40 to 60

HOW SUPPLIED

Nadolol Tablets, USP are available containing 20 mg, 40 mg or 80 mg of nadolol, USP.

The 20 mg tablets are yellow, round, scored tablets debossed with **M** above the score and **28** below the score on one side of the tablet and blank on the other side. They are available as follows:

Bottles of 30	NDC 54868-5295-1
Bottles of 90	NDC 54868-5295-0

The 40 mg tablets are yellow, round, scored tablets debossed with **M** above the score and **171** below the score on one side of the tablet and blank on the other side. They are available as follows:

Bottles of 10	NDC 54868-3257-4
Bottles of 30	NDC 54868-3257-2
Bottles of 90	NDC 54868-3257-6
Bottles of 100	NDC 54868-3257-1

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Protect from light.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REV OCTOBER 2006
NAD:R9

Distributed and Repackaged by:
Physicians Total Care, Inc.
Tulsa, Oklahoma 74146

PRINCIPAL DISPLAY PANEL

Nadolol Tablets, USP 20 mg

Nadolol Tablets, USP 40 mg

NADOLOL

nadolol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:54868-5295(NDC:0378-0028)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NADOLOL (NADOLOL)	NADOLOL	20 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
ANHYDROUS LACTOSE	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
SODIUM LAURYL SULFATE	
D&C YELLOW NO. 10	

Product Characteristics

Color	yellow	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	M;28
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-5295-0	90 in 1 BOTTLE		
2	NDC:54868-5295-1	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074172	05/16/2005	

NADOLOL

nadolol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:54868-3257(NDC:0378-1171)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NADOLOL (NADOLOL)	NADOLOL	40 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
ANHYDROUS LACTOSE	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
SODIUM LAURYL SULFATE	
D&C YELLOW NO. 10	

Product Characteristics

Color	yellow	**Score**	2 pieces
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	M;171
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-3257-1	100 in 1 BOTTLE		

2	NDC:54868-3257-2	30 in 1 BOTTLE		
3	NDC:54868-3257-4	10 in 1 BOTTLE		
4	NDC:54868-3257-6	90 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074172	01/14/2010	

NADOLOL

nadolol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:54868-3721(NDC:0378-1132)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NADOLOL (NADOLOL)	NADOLOL	80 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
ANHYDROUS LACTOSE	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
SODIUM LAURYL SULFATE	
D&C YELLOW NO. 10	

Product Characteristics

Color	yellow	**Score**	2 pieces
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	M;132
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-3721-1	30 in 1 BOTTLE		
2	NDC:54868-3721-2	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074172	08/13/2004	06/30/2010

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel(54868-3721, 54868-5295, 54868-3257), repack(54868-3721, 54868-5295, 54868-3257)

Revised: 10/2012 Physicians Total Care, Inc.