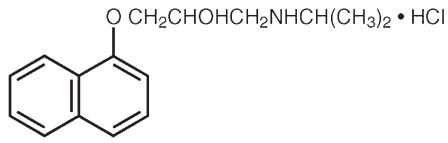
## DESCRIPTION

**Rx Only**

Propranolol hydrochloride is a synthetic beta-adrenergic receptor-blocking agent chemically described as (±)-1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride. Its structural formula is:




Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80.

Propranolol hydrochloride extended release is formulated to provide a sustained release of propranolol hydrochloride. Propranolol hydrochloride extended release is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

Propranolol hydrochloride extended release capsules contain the following inactive ingredients: microcrystalline cellulose, methylcellulose, ethylcellulose. The capsules contain gelatin and titanium dioxide. In addition, propranolol hydrochloride extended release 60 mg and 80 mg contain FD&C Blue No. 1. Propranolol hydrochloride extended release 120 mg and 160 mg contain FD&C Blue No.1 and FD&C Red No.40.

These capsules comply with USP Drug Release Test 1.



## CLINICAL PHARMACOLOGY

Propranolol hydrochloride is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol hydrochloride, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol hydrochloride extended release capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with propranolol hydrochloride extended release occur at about 6 hours, and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of propranolol hydrochloride tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours, then decline exponentially.

Propranolol hydrochloride extended release should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to propranolol hydrochloride extended release from conventional propranolol, a possible need for retitration upwards should be considered, especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, propranolol hydrochloride extended release has been therapeutically equivalent to the same mg dose of conventional propranolol hydrochloride as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Propranolol hydrochloride extended release can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of propranolol hydrochloride has not been established. Among the factors that may be involved in contributing to the antihypertensive action are: (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. Propranolol hydrochloride has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, propranolol hydrochloride also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta-receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive, which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity, which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

## INDICATIONS AND USAGE

**Hypertension**
Propranolol hydrochloride extended release is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Propranolol hydrochloride is not indicated in the management of hypertensive emergencies.

**Angina Pectoris Due to Coronary Atherosclerosis**
Propranolol hydrochloride extended release is indicated for the long-term management of patients with angina pectoris.

**Migraine**
Propranolol hydrochloride extended release is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established, and propranolol is not indicated for such use.

**Hypertrophic Subaortic Stenosis**
Propranolol hydrochloride extended release is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Propranolol hydrochloride extended release also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient, which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

## CONTRAINDICATIONS

Propranolol hydrochloride is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see **WARNINGS**), unless the failure is secondary to a tachyarrhythmia treatable with propranolol hydrochloride.

## WARNINGS

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of propranolol (see **ADVERSE REACTIONS**).

**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 close follow-up in patients with a history of failure who are well compensated and are receiving 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 propranolol hydrochloride should be discontinued (gradually, if possible).

**In Patients with Angina Pectoris**, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of propranolol hydrochloride therapy. Therefore, when discontinuance of propranolol hydrochloride is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol hydrochloride therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol hydrochloride therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

**Nonallergic Bronchospasm (e.g., Chronic Bronchitis, Emphysema)**—-PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Propranolol hydrochloride should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

**Major Surgery:** The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Propranolol hydrochloride, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

**Diabetes and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure in patients on propranolol.

Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting as in preparation for surgery. Hypoglycemia also has been found after this type of drug therapy and prolonged physical exertion and has occurred in renal sufficiency, both during dialysis and sporadically, in patients on propranolol.

Acute increases in blood pressure have occurred after insulin-induced hypoglycemia in patients on propranolol.

**Thyrotoxicosis:** Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing $T_4$ and reverse $T_3$, and decreasing $T_3$.

**In Patients with Wolff-Parkinson-White Syndrome**, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

**Skin Reactions:** Cutaneous reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol (see **ADVERSE REACTIONS**).

## PRECAUTIONS

**General**
Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol hydrochloride is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that propranolol hydrochloride may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

*Risk of 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.

**Clinical Laboratory Tests**
Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

**Drug Interactions**
Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol hydrochloride is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported.

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

*Aluminum hydroxide gel* greatly reduces intestinal absorption of propranolol.

*Ethanol* slows the rate of absorption of propranolol.

*Phenytoin, phenobarbitone*, and *rifampin* accelerate propranolol clearance.

*Chlorpromazine*, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

*Antipyrine* and *lidocaine* have reduced clearance when used concomitantly with propranolol.

*Thyroxine* may result in a lower than expected $T_3$ concentration when used concomitantly with propranolol.

*Cimetidine* decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

*Theophylline* clearance is reduced when used concomitantly with propranolol.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
In dietary administration studies in which mice and rats were treated with propranolol for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. In a study in which both male and female rats were exposed to propranolol in their diets at concentrations of up to 0.05%, from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol in bacteria (*S. typhimurium* strain TA 1538).

**Pregnancy: Pregnancy Category C**
In a series of reproductive and developmental toxicology studies, propranolol was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day (> 10 times the maximum recommended human daily dose of propranolol on a body weight basis), but not at doses of 80 mg/kg/day, treatment was associated with embryotoxicity (reduced litter size and increased resorption sites) as well as neonatal toxicity (deaths). Propranolol also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (> 15 times the maximum recommended daily human dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation, small placentas, and congenital abnormalities have been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers are receiving propranolol at parturition have exhibited bradycardia, hypoglycemia and/or respiratory depression. Adequate facilities for monitoring these infants at birth should be available. Propranolol hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**
Propranolol hydrochloride is excreted in human milk. Caution should be exercised when propranolol hydrochloride is administered to a nursing woman.

**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**
Clinical studies of propranolol 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 the 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 the decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

## ADVERSE REACTIONS

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

**Cardiovascular**: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

**Central Nervous System:** Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

**Gastrointestinal:** Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, and ischemic colitis.

**Allergic:** Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

**Respiratory:** Bronchospasm.

**Hematologic:** Agranulocytosis, nonthrombocytopenic purpura, and thrombocytopenic purpura.

**Autoimmune:** In extremely rare instances, systemic lupus erythematosus has been reported.

**Miscellaneous:** Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

**Skin:** Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticia.

## OVERDOSAGE

Propranolol hydrochloride is not significantly dialyzable. In the event of overdosage or exaggerated response, the following measures should be employed:

**General**
If ingestion is, or may have been, recent, evacuate gastric contents, taking care to prevent pulmonary aspiration.

**Bradycardia**
ADMINISTER ATROPINE (0.25 TO 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

**Cardiac Failure**
DIGITALIZATION AND DIURECTICS.

**Hypotension**
VASOPRESSORS, e.g., NOREPINEPHRINE OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE).

**Bronchospasm**
ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

## DOSAGE AND ADMINISTRATION

Propranolol hydrochloride extended release provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from propranolol hydrochloride tablets to propranolol hydrochloride extended-release capsules, care should be taken to assure that the desired therapeutic effect is maintained. Propranolol hydrochloride extended release should not be considered a simple mg-for-mg substitute for propranolol hydrochloride. Propranolol hydrochloride extended release has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

**Hypertension**
*Dosage must be individualized.* The usual initial dosage is 80 mg propranolol hydrochloride extended release once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

**Angina Pectoris**
*Dosage must be individualized.* Starting with 80 mg propranolol hydrochloride extended release once daily, dosage should be gradually increased at three-to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see **WARNINGS**).

**Migraine**
*Dosage must be individualized.* The initial oral dose is 80 mg propranolol hydrochloride extended release once daily. The usual effective dose range is 160 to 240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, propranolol hydrochloride extended release therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

**Hypertrophic Subaortic Stenosis**
80 to 160 mg propranolol hydrochloride extended release once daily.

**Pediatric Dosage**
At this time the data on the use of the drug in this age group are too limited to permit adequate direction for use.

## HOW SUPPLIED

The 60 mg capsules are aqua blue printed "par 282" in gray ink and the cap is white opaque printed "par 282" in blue ink.

NDC 49984-282-01 Bottle of 100
NDC 49884-282-10 Bottle of 1000

The 80 mg capsules are aqua blue opaque printed "par 328" in gray ink and the cap is aqua blue opaque printed "par 328" in gray ink.

NDC 49884-328-01 Bottle of 100
NDC 49884-328-10 Bottle of 1000

The 120 mg capsules are aqua blue opaque printed "par 329" in gray ink and the cap is dark blue opaque printed "par 329" in gray ink.

NDC 49884-329-01 Bottle of 100
NDC 49884-329-10 Bottle of 1000

The 160 mg capsules are dark blue opaque printed "par 330" in white ink and the cap is dark blue opaque printed "par 330" in white ink.

NDC 49884-330-01 Bottle of 100
NDC 49884-330-10 Bottle of 1000

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]

Protect from light, moisture, freezing, and excessive heat.

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

Manufactured by:
**PAR PHARMACEUTICAL COMPANIES, INC.**
Spring Valley, NY 10977

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