CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75203

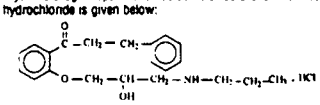
DRAFT FINAL PRINTED LABELING

PROPAFENONE HYDROCHLORIDE TABLETS

Rx only

DESCRIPTION

Propafenone hydrochloride is an antiarrhythmic drug. Propafenone has some structural similarities to beta-blocking agents. The structural formula of propafenone hydrochloride is given below:



$C_{21}H_{27}NO_3 \cdot HCl$ M.W.=377.91

2'-[2-Hydroxy-3-(propylamino) -propoxy]-3-phenylpropiophenone hydrochloride

Propafenone hydrochloride occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. Each tablet, for oral administration, contains 150 mg or 225 mg of propafenone hydrochloride. The following inactive ingredients are contained in the tablet: colloidal silicon dioxide, croscarmellose sodium, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, sodium lauryl sulfate, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action: Propafenone hydrochloride is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone hydrochloride manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone hydrochloride reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

Studies in anesthetized dogs and isolated organ preparations show that propafenone has beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations *in vitro*, propafenone can inhibit the slow inward current carried by calcium but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Propafenone has local anesthetic activity approximately equal to procaine.

Electrophysiology: Electrophysiology studies in patients with ventricular tachycardia have shown that propafenone prolongs atrioventricular conduction while having little or no effect on sinus node function. Both AV nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged. In patients with WPW, propafenone reduces conduction and increases the effective refractory period of the accessory pathway in both directions. Propafenone slows conduction and consequently produces dose-related changes in the PR interval and QRS duration. QTc interval does not change.

Mean Changes in ECG Intervals*

Total Daily Dose (mg)

	337.5 mg		450 mg		675 mg		900 mg	
Interval	msec	%	msec	%	msec	%	msec	%
RR	-14.5	-1.8	30.6	3.8	31.5	3.9	41.7	5.1
PR	3.6	2.1	19.1	11.6	28.9	17.8	35.6	21.9
QRS	5.6	6.4	5.5	6.1	7.7	8.4	15.6	17.3
QTc	2.7	0.7	-7.5	-1.8	5.0	1.2	14.7	3.7

*Change and percent change based on mean baseline values for each treatment group.

In any individual patient, the above ECG changes cannot be readily used to predict either efficacy or plasma concentration.

Propafenone hydrochloride causes a dose-related and concentration-related decrease in the rate of single and multiple PVCs and can suppress recurrence of ventricular tachycardia. Based on the percent of patients attaining substantial (80 to 90%) suppression of ventricular ectopic activity, it appears that trough plasma levels of 0.2 to 1.5 mcg/mL can provide good suppression, with higher concentrations giving a greater rate of good response.

Hemodynamics: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by the beta blockade produced by propafenone may in itself aggravate congestive heart failure.

Additionally, like other Class 1C antiarrhythmic drugs, studies in humans have shown that propafenone exerts a negative inotropic effect on the myocardium. Cardiac catheterization studies in patients with moderately impaired ventricular function (mean C.I.=2.61 L/min/m^2) utilizing intravenous propafenone infusions (2 mg/kg over 10 min +2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 mcg/mL, (well above the therapeutic range of 0.2 to 1.5 mcg/mL) showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

Pharmacokinetics and Metabolism: Propafenone hydrochloride is nearly completely absorbed after oral administration with peak plasma levels occurring approximately 3.5 hours after administration in most individuals. Propafenone exhibits extensive saturable presystemic biotransformation (first pass effect) resulting in a dose dependent and dosage form dependent absolute bioavailability; e.g., a 150 mg tablet had absolute bioavailability of 3.4%, while a 300 mg tablet had absolute bioavailability of 10.6%. A 300 mg solution which was rapidly absorbed, had absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability increases still further. Decreased liver function also increases bioavailability; bioavailability is inversely related to indocyanine green clearance reaching 60 to 70% at clearances of 7 mL/min and below. The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (**see PRECAUTIONS**).

Propafenone follows a nonlinear pharmacokinetic disposition presumably due to saturation of first pass hepatic metabolism as the liver is exposed to higher concentrations of propafenone and shows a very high degree of interindividual variability. For example, for a three-fold increase in daily dose from 300 to 900 mg/day there is a ten-fold increase in steady-state plasma concentration. The top 25% of patients given 375 mg/day, however, had a mean concentration of propafenone larger than the bottom 25%, and about equal to the second 25% of patients given a dose of 900 mg. Although food increased peak blood level and bioavailability in a single dose study, during multiple dose administration of propafenone to healthy volunteers food did not change bioavailability significantly.

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination *half-life* from 2 to 10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone and N-depropylpropafenone. *In vitro* preparations have shown these two metabolites to have antiarrhythmic activity comparable to propafenone but in man they both are usually present in concentrations less than 20% of propafenone. Nine additional metabolites have been identified, most in only trace amounts. It is the saturable hydroxylation pathway that is responsible for the nonlinear pharmacokinetic disposition.

In less than 10% of patients (and in any patient also receiving quinidine, **see PRECAUTIONS**), metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. The estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs (encainide, metoprolol, dextromethorphan). In these patients, the N-depropylpropafenone occurs in quantities comparable to the levels occurring in extensive metabolizers. In slow metabolizers propafenone pharmacokinetics are linear.

There are significant differences in plasma concentrations of propafenone in slow and extensive metabolizers, the former achieving concentrations 1.5 to 2.0 times those of the extensive metabolizers at daily doses of 675 to 900 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations more than five times that of extensive metabolizers. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen is the same for all patients. The greater variability in blood levels require that the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (**See DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE

Propafenone hydrochloride tablets are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of propafenone, its use with lesser ventricular arrhythmias is not recommended, even if patients are symptomatic, and any use of the drug should be reserved for patients in whom, in the opinion of the physician, the potential benefits outweigh the risks.

Initiation of propafenone treatment, as with other antiarrhythmics used to treat life-threatening ventricular arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Propafenone hydrochloride tablets are contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

WARNINGS

Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an increased rate of death or reversed cardiac arrest (7.7%; 56/730) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared with that seen in patients assigned to a placebo (3.0%; 22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) or other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with non-life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Proarrhythmic Effects: Propafenone hydrochloride, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes; i.e., tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given propafenone be evaluated electrocardiographically and clinically, prior to and during therapy, to determine whether the response to propafenone supports continued treatment.

Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that an increased risk is present throughout treatment.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema): PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE PROPAFENONE or other agents with beta-adrenergic-blocking activity.

Congestive Heart Failure: During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients with ventricular arrhythmia; of those, 0.9% were considered probably or definitely related to propafenone. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to propafenone developed rarely (<0.2%) in patients who had no previous history of CHF.

As propafenone exerts both beta blockade and a (dose-related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving propafenone. If congestive heart failure worsens, propafenone should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Conduction Disturbances: Propafenone slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2,127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of propafenone. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

Effects on Pacemaker Thresholds: Propafenone hydrochloride may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances: Agranulocytosis (fever, chills, weakness, and neutropenia) has been reported in patients receiving propafenone. Generally, the agranulocytosis occurred within the first two months of propafenone therapy and upon discontinuation of therapy, the white count usually normalized by 14 days. Unexplained fever and/or decrease in white cell count, particularly during the initial three months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

Hepatic Dysfunction: Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction increases the bioavailability of propafenone to approximately 70% compared to 3 to 40% for patients with normal liver function. In eight patients with moderate to severe liver disease, the mean half-life was approximately 9 hours. As a result, the dose of propafenone given to patients with impaired hepatic function should be approximately 20 to 30% of the dose given to patients with normal hepatic function (**see DOSAGE AND ADMINISTRATION**). Careful monitoring for excessive pharmacological effects (**see OVERDOSAGE**) should be carried out.

Renal Dysfunction: A considerable percentage of propafenone metabolites (18.5% to 38% of the dose/48 hours) are excreted in the urine.

Until further data are available, propafenone hydrochloride should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (**see OVERDOSAGE**).

Elevated ANA Titers: Positive ANA titers have been reported in patients receiving propafenone. They have been reversible upon cessation of treatment and may disappear even in the face of continued propafenone therapy. These laboratory findings were usually not associated with clinical symptoms, but there is one published case of drug-induced lupus erythematosis (positive rechallenge); it resolved completely upon discontinuation of therapy. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

Impaired Spermatogenesis: Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration. Evaluation of the effects of short-term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short-term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

Neuromuscular Dysfunction: Exacerbation of myasthenia gravis has been reported during propafenone therapy.

Drug Interactions: ***Quinidine:*** Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (**see CLINICAL PHARMACOLOGY**). There is, as yet, too little information to recommend concomitant use of propafenone and quinidine.

Local Anesthetics: Concomitant use of local anesthetics (i.e., during pacemaker implantations, surgery, or dental use) may increase the risks of central nervous system side effects.

Digitalis: Propafenone hydrochloride produces dose-related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day of propafenone without affecting digoxin renal clearance. These elevations of dioxin levels were maintained for up to 16 months during concomitant administration. Plasma digoxin levels of patients on concomitant therapy should be measured, and digoxin

dosage should ordinarily be reduced when propafenone is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.

Beta-antagonists: In a study involving healthy subjects, concomitant administration of propafenone and propranolol has resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. Similar observations have been reported with metoprolol. Propafenone appears to inhibit the hydroxylation pathway for the two beta-antagonists (just as quinidine inhibits propafenone metabolism). Increased plasma concentrations of metoprolol could overcome its relative cardioselectivity. In propafenone clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects. While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.

Warfarin: In a study of eight healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary.

Cimetidine: Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.

Desipramine: Concomitant administration of propafenone and desipramine may result in elevated serum desipramine levels. Both desipramine, a tricyclic antidepressant, and propafenone are cleared by oxidative pathways of damthylation and hydroxylation carried out by the hepatic-P-450 cytochrome.

Cyclosporin: Propafenone therapy may increase levels of cyclosporin.

Theophylline: Propafenone may increase theophylline concentration during concomitant therapy with the development of theophylline toxicity.

Rifampin: Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.

Other: Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone.

Propafenone was not mutagenic when assayed for genotoxicity in 1) mouse Dominant Lethal test, 2) rat bone marrow Chromosome Analysis, 3) Chinese hamster bone marrow and spermatogonia chromosome analysis, 4) Chinese hamster micronucleus test, and 5) Ames bacterial test.

Propafenone administered intravenously to rabbits, dogs, and monkeys has been shown to decrease spermatogenesis. These effects were reversible, were not found following oral dosing of propafenone, were seen only at lethal or sublethal dose levels and were not seen in rats treated either orally or intravenously (see **PRECAUTIONS, Impaired Spermatogenesis**). Propafenone did not affect fertility rates when administered orally to male and female rats at doses up to 270 mg/kg/day or when administered orally or intravenously to male rabbits at doses of 120 mg/kg/day or 3.5 mg/kg/day, respectively. On a body weight basis, the above noted oral doses in rat and rabbit are 18 times and 8 times, respectively, the maximum recommended daily human dose of 900 mg (based on 60 kg human body weight).

Pregnancy: ***Teratogenic Effects*** *Pregnancy Category C.* Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well-controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

Labor and Delivery: It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from propafenone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of propafenone in pediatric patients have not been established.

Geriatric Use: There do not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, propafenone should be used with caution. The effective dose may be lower in these patients.

Animal Toxicology: Renal changes have been observed in the rat following 6 months of oral administration of propafenone at doses of 180 and 360 mg/kg/day (12 to 24 times the maximum recommended human dose) but not 90 mg/kg/day. Both inflammatory and non-inflammatory changes in the renal tubules with accompanying interstitial nephritis were observed. These lesions were reversible in that they were not found in rats treated at these dosage levels and allowed to recover for 6 weeks. Fatty degenerative changes of the liver were found in rats following chronic administration of propafenone at dose levels 19 times the maximum recommended human dose.

ADVERSE REACTIONS

Adverse reactions associated with propafenone hydrochloride occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients treated with propafenone hydrochloride have discontinued treatment because of adverse reactions.

Results of controlled trials in ventricular arrhythmia patients comparing adverse reaction rates on propafenone and placebo, and on propafenone and quinidine are shown in the following table. Adverse reactions reported in ≥ 1% of the patients receiving propafenone are shown, unless they were more frequent on placebo than propafenone. The most common events were unusual taste, dizziness, first degree AV block, intraventricular conduction delay, nausea and/or vomiting, and constipation. Headache was relatively common also, but was not increased compared to placebo.

Adverse Reactions Reported for ≥ 1% of Ventricular Arrhythmia Patients

	Prop./Placebo Trials		Prop./Quinidine Trial	
	Prop. (N=247)	Placebo (N=111)	Prop. (N=53)	Quinidine (N=52)
Unusual Taste	7%	1%	23%	0%
Dizziness	7%	5%	15%	10%
First Degree AV Block	5%	1%	2%	0%
Headache(s)	5%	5%	2%	8%
Constipation	4%	0%	6%	2%
Intraventricular Conduction Delay	4%	0%	—	—
Nausea and/or Vomiting	3%	1%	6%	15%
Fatigue	—	—	4%	2%
Palpitations	2%	1%	—	—
Blurred Vision	2%	1%	6%	2%
Dry Mouth	2%	1%	6%	6%
Dyspnea	2%	3%	4%	0%
Abdominal Pain/Cramps	—	—	2%	8%
Dyspepsia	—	—	2%	8%
Congestive Heart Failure	—	—	2%	0%
Fever	—	—	2%	10%
Tinnitus	—	—	2%	2%
Vision Abnormal	—	—	2%	2%
Esophagitis	—	—	2%	0%
Gastroenteritis	—	—	2%	0%
Anxiety	2%	2%	—	—
Anorexia	2%	1%	—	2%
Proarrhythmia	1%	0%	2%	0%
Flatulence	1%	0%	2%	0%
Angina	1%	0%	2%	4%
Second Degree AV Block	1%	0%	—	—
Bundle Branch Block	1%	0%	2%	2%
Loss of Balance	1%	0%	—	—
Diarrhea	1%	1%	6%	39%

Adverse reactions reported for ≥ 1% of 2,127 ventricular arrhythmia patients who received propafenone in U.S. clinical trials are presented in the following table by propafenone daily dose. The most common adverse reactions in controlled clinical trials appeared dose related (but note that most patients spent more time at the larger doses), especially dizziness, nausea and/or vomiting, unusual taste, constipation, and blurred vision. Some less common reactions may also have been dose related such as first degree AV block, congestive heart failure, dyspepsia, and weakness. The principal causes of discontinuation were the most common events and are shown in the table.

Adverse Reactions Reported For ≥ 1% of Ventricular Arrhythmia Patients
N = 2127

	Incidence by Total Daily Dose			Total Incidence	% of Pts. Who Discont.
	450 mg (N=1430)	600 mg (N=1337)	≥ 900 mg (N=1333)	(N=2127)	
Dizziness	4%	7%	11%	13%	2.4%
Nausea and/or Vomiting	2%	6%	9%	11%	3.4%
Unusual Taste	3%	5%	6%	9%	0.7%
Constipation	2%	4%	5%	7%	0.5%
Fatigue	2%	3%	4%	6%	1.0%
Dyspnea	2%	2%	4%	5%	1.6%
Proarrhythmia	2%	2%	3%	5%	4.7%
Angina	2%	2%	3%	5%	0.5%
Headache(s)	2%	3%	3%	5%	1.0%
Blurred Vision	1%	2%	3%	4%	0.8%
CHF	1%	2%	3%	4%	1.4%
Ventricular Tachycardia	1%	2%	3%	3%	1.2%
Dyspepsia	1%	2%	3%	3%	0.9%
Palpitations	1%	2%	3%	3%	0.5%
Rash	1%	1%	2%	3%	0.8%
AV Block First Degree	1%	1%	2%	3%	0.3%
Diarrhea	1%	2%	2%	3%	0.6%
Weakness	1%	2%	2%	2%	0.7%
Dry Mouth	1%	1%	1%	2%	0.2%
Syncope/Near Syncope	1%	1%	1%	2%	0.7%
QRS Duration, Increased	1%	1%	2%	2%	0.5%
Chest Pain	1%	1%	1%	2%	0.2%
Anorexia	1%	1%	2%	2%	0.4%
Abdominal Pain/ Cramps	1%	1%	1%	2%	0.4%
Ataxia	0%	1%	2%	2%	0.2%
Insomnia	0%	1%	1%	2%	0.3%
Premature Ventricular Contraction(s)	1%	1%	1%	2%	0.1%
Bradycardia	1%	1%	1%	2%	0.5%
Anxiety	1%	1%	1%	2%	0.6%
Edema	1%	0%	1%	1%	0.2%
Tremor(s)	0%	1%	1%	1%	0.3%
Diaphoresis	1%	0%	1%	1%	0.3%
Bundle Branch Block	0%	1%	1%	1%	0.5%
Drowsiness	1%	1%	1%	1%	0.2%
Atrial Fibrillation	1%	1%	1%	1%	0.4%
Flatulence	0%	1%	1%	1%	0.1%
Hypotension	0%	1%	1%	1%	0.4%
Intraventricular Conduction Delay	0%	1%	1%	1%	0.1%
Pain, Joints	0%	0%	1%	1%	0.1%

In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience (*adverse events for marketing experience are given in italics*). Causality and relationship to propafenone therapy cannot necessarily be judged from these events.

Cardiovascular System: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia.

Nervous System: Abnormal dreams, abnormal speech, abnormal vision, *ageusia, coma,* confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo.

Gastrointestinal: A number of patients with liver abnormalities associated with propafenone therapy have been reported in postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms including fulminant hepatitis and death. One case was rechallenged with a positive outcome.

Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%).

Hematologic: Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time,* leukopenia, purpura, thrombocytopenia.

Other: Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion,* impotence, increased glucose, *kidney failure,* positive ANA (0.7%), *lupus erythematosis,* muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

OVERDOSAGE

The symptoms of overdosage, which are usually most severe within 3 hours of ingestion, may include hypotension, somnolence, bradycardia, intra-atrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

DOSAGE AND ADMINISTRATION

The dose of propafenone hydrochloride tablets must be individually titrated on the basis of response and tolerance. It is recommended that therapy be initiated with 150 mg propafenone given every eight hours (450 mg/day). Dosage may be increased at a minimum of 3 to 4 day intervals to 225 mg every 8 hours (675 mg/day) and, if necessary, to 300 mg every 8 hours (900 mg/day). The usefulness and safety of dosages exceeding 900 mg per day have not been established. In those patients in whom significant widening of the QRS complex or second or third degree AV block occurs, dose reduction should be considered.

As with other antiarrhythmic agents, in the elderly or in patients with marked previous myocardial damage, the dose of propafenone hydrochloride tablets should be increased more gradually during the initial phase of treatment.

HOW SUPPLIED

Propafenone hydrochloride tablets, 150 mg are available as round, white, film-coated tablets debossed with Watson **582** on one side and bisected on the other side. They are supplied as follows:

Bottles of 100 NDC-52544-582-01
Bottles of 500 NDC-52544-582-05

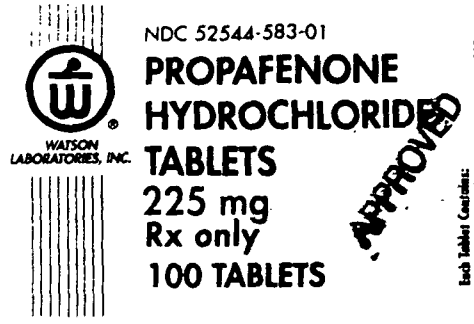
Propafenone hydrochloride tablets, 225 mg are available as round, white, film-coated tablets debossed with Watson **583** on one side and bisected on the other side. They are supplied as follows:

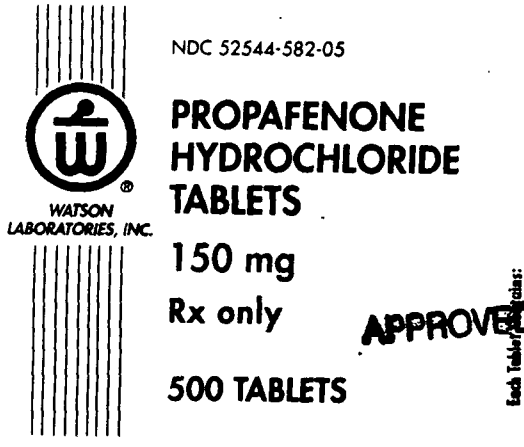
Bottles of 100 NDC-52544-583-01
Bottles of 500 NDC-52544-583-05

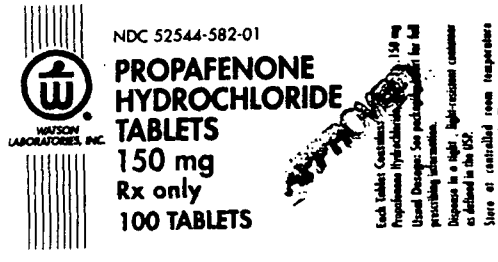
Store at controlled room temperature, 15°C to 30°C (59°F to 86°F). Dispense in a tight, light-resistant container as defined in the U.S.P.

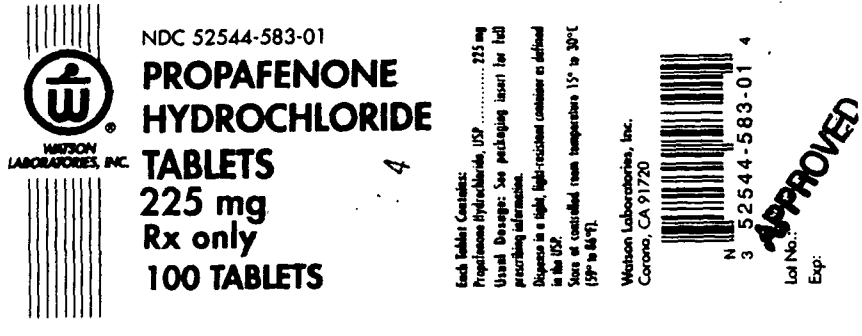
Watson Laboratories, Inc.
Corona, CA 92880

Date: June, 2000


NDC 52544-583-01
PROPAFENONE HYDROCHLORIDE TABLETS
225 mg
Rx only
100 TABLETS
APPROVED
WATSON LABORATORIES, INC.
Each Tablet Contains:
Propafenone Hydrochloride, USP ..... 225 mg
Usual Dosage: See packaging insert for full prescribing information.
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Watson Laboratories, Inc.
Corona, CA 91720
N 3 52544-583-01 4
Lot No.:
Exp:


NDC 52544-582-05
PROPAFENONE HYDROCHLORIDE TABLETS
150 mg
Rx only
500 TABLETS
APPROVED
WATSON LABORATORIES, INC.
Each Tablet Contains:
Propafenone Hydrochloride, USP ..... 150 mg
Usual Dosage: See packaging insert for full prescribing information.
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Watson Laboratories, Inc.
Corona, CA 91720
N 3 52544-582-05 5
Lot No.:
Exp:


NDC 52544-582-01
PROPAFENONE HYDROCHLORIDE TABLETS
150 mg
Rx only
100 TABLETS
WATSON LABORATORIES, INC.
Watson Laboratories, Inc.
Corona, CA 91720
N 3 52544-582-01 7
Lot No.:
Exp:


NDC 52544-583-01
PROPAFENONE HYDROCHLORIDE TABLETS
225 mg
Rx only
100 TABLETS
WATSON LABORATORIES, INC.
Each Tablet Contains:
Propafenone Hydrochloride, USP ..... 225 mg
Usual Dosage: See packaging insert for full prescribing information.
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Watson Laboratories, Inc.
Corona, CA 91720
N 3 52544-583-01 4
APPROVED
Lot No.:
Exp: