

- **Very low white blood cell levels in your blood (agranulocytosis).** Your bone marrow may not produce enough of a certain type of white blood cells called neutrophils. If this happens, you are more likely to get infections. Tell your doctor right away if you have any of these symptoms, especially during the first 3 months of treatment:
 - fever
 - sore throat
 - chills
- **Worsening of myasthenia gravis in people who already have this condition.** Tell your doctor about any change in your symptoms.
- **Propafenone hydrochloride tablets may cause lower sperm counts in men.** This could affect the ability to father a child. Talk to your doctor if this is a concern for you.

Common side effects of propafenone hydrochloride tablets include:

- unusual taste
- nausea
- vomiting
- dizziness
- constipation
- headache
- tiredness
- irregular heartbeats

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of propafenone hydrochloride tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store propafenone hydrochloride tablets?

- Store propafenone hydrochloride tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the bottle tightly closed.

Keep propafenone hydrochloride tablets and all medicines out of the reach of children.

General information about propafenone hydrochloride tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use propafenone hydrochloride tablets for a condition for which it was not prescribed. Do not give propafenone hydrochloride tablets to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about propafenone hydrochloride tablets that is written for health professionals. For more information about propafenone hydrochloride tablets, call 1-877-244-9825.

What are the ingredients in propafenone hydrochloride tablets?

Active ingredient: propafenone hydrochloride

Inactive ingredients: hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized corn starch, sodium starch glycolate, macrogol, talc, titanium dioxide, glycerol monocaprylocaprate and polyvinyl alcohol.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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7.5 Beta-Antagonists

Concomitant use of propafenone and propranolol in healthy subjects increased propranolol plasma concentrations at steady state by 113%. In 4 patients, administration of metoprolol with propafenone increased the metoprolol plasma concentrations at steady state by 100% to 400%. The pharmacokinetics of propafenone was not affected by the coadministration of either propranolol or metoprolol. In clinical trials using propafenone immediate release tablets, subjects who were receiving beta-blockers concurrently did not experience an increased incidence of side effects.

7.6 Lidocaine

No significant effects on the pharmacokinetics of propafenone or lidocaine have been seen following their concomitant use in patients. However, concomitant use of propafenone and lidocaine has been reported to increase the risks of central nervous system side effects of lidocaine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies of propafenone hydrochloride in pregnant women. Available data from published case reports and several decades of postmarketing experience with use of propafenone hydrochloride in pregnancy have not identified any drug-associated risks of miscarriage, birth defects, or adverse maternal or fetal outcomes. Untreated arrhythmias during pregnancy may pose a risk to the pregnant woman and fetus (see *Clinical Considerations*). Propafenone and its metabolite, 5-OH-propafenone, cross the placenta in humans. In animal studies, propafenone was not teratogenic. At maternally toxic doses (ranging from 2 to 6 times the maximum recommended human dose [MRHD]), there was evidence of adverse developmental outcomes when administered to pregnant rabbits and rats during organogenesis or when administered to pregnant rats during mid-gestation through weaning of their offspring (see *Data*).

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk: The incidence of VT is increased and may be more symptomatic during pregnancy. Ventricular arrhythmias most often occur in pregnant women with underlying cardiomyopathy, congenital heart disease, valvular heart disease, or mitral valve prolapse. Breakthrough arrhythmias may also occur during pregnancy, as therapeutic treatment levels may be difficult to maintain due to the increased volume of distribution and increased drug metabolism inherent in the pregnant state.

Fetal/Neonatal Adverse Reactions: Propafenone and its metabolite have been shown to cross the placenta. Adverse reactions such as fetal/neonatal arrhythmias have been associated with the use of other antiarrhythmic agents by pregnant women. Fetal/neonatal monitoring for signs and symptoms of arrhythmia is recommended during and after treatment of pregnant women with propafenone. *Labor or Delivery:* Risk of arrhythmias may increase during labor and delivery. Patients treated with propafenone hydrochloride should be monitored continuously for arrhythmias during labor and delivery (see *Warnings and Precautions (5.1)*).

Data

Propafenone has been shown to cause embryo-fetal mortality in rabbits and rats when given orally during organogenesis at maternally toxic doses of 150 mg/kg/day (rabbit; maternal mortality, decreased body weight gain and food consumption at approximately 3 times the MRHD on a mg/m² basis) and 600 mg/kg/day (rat; maternal decreased body weight gain and food consumption at approximately 6 times the MRHD on a mg/m² basis). In addition, a maternally toxic dose of 600 mg/kg/day (approximately 6 times the MRHD on a mg/m² basis) also caused decreased fetal weights in rats. Increased placental weights and delayed ossification occurred in rabbits at a dose of 30 mg/kg/day (less than the MRHD on a mg/m² basis) in the absence of maternal toxicity. No adverse developmental outcomes in the absence of maternal toxicity were seen following oral doses of 15 mg/kg/day to rabbits or up to 270 mg/kg/day to rats administered during organogenesis (equivalent to 0.3 times or approximately 3 times the MRHD on a mg/m² basis, respectively). In an oral study, female rats received propafenone up to 500 mg/kg/day from mid-gestation through weaning. At 90 mg/kg/day (equivalent to the MRHD on a mg/m² basis), there were no adverse developmental outcomes in the absence of maternal toxicity. However, doses ≥180 mg/kg/day (2 or more times the MRHD on a mg/m² basis) produced increases in maternal deaths and resulted in reductions in neonatal survival, body weight gain, and delayed development in the presence of maternal toxicity.

8.2 Lactation

Risk Summary

Propafenone and its active metabolite, 5-OH-propafenone, are present in human milk, but the levels are likely to be low. There are no data on the effects of propafenone on the breastfed infant or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for propafenone and any potential adverse effects on the breastfed infant from propafenone or the effects on milk production.

8.3 Females and Males of Reproductive Potential

Infertility

Males: Based on human and animal studies, propafenone hydrochloride may transiently impair spermatogenesis in males. Evaluation of the effects on spermatogenesis was performed in 11 healthy males given oral propafenone 300 mg b.i.d. for 4 days, which was then increased to 300 mg 1 i.d. for an additional 4 days. Study findings included a 28% reduction in semen sample volume on Treatment Day 8 and a 27% reduction in sperm count 64 days after treatment (both values remained within the laboratories normal reference range). These effects were not seen in followup visits up to 120 days after treatment. Reversible decreases in spermatogenesis have been demonstrated in monkeys, dogs, and rabbits after lethal or near-lethal intravenous doses of propafenone (see *Nonclinical Toxicology (13.1)*).

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical trials of propafenone hydrochloride did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

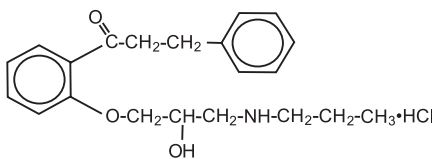
10 OVERDOSAGE

The symptoms of overdose 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, has been effective in controlling abnormal 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. The hemodynamics of propafenone in patients with an overdose is expected to be of limited value in the removal of propafenone as a result of both its high protein binding (greater than 95%) and large volume of distribution.

11 DESCRIPTION

Propafenone hydrochloride tablets, USP are an antiarrhythmic drug supplied in scored, film-coated tablets of 150, 225 and 300 mg for oral administration. Propafenone has some structural similarities to beta-blocking agents.

Chemically, propafenone hydrochloride (HCl) is 2'-[2-Hydroxy-3-(propylamino)- propoxy]-3-phenylpropiofenone hydrochloride, with a molecular weight of 377.92. The molecular formula is C₁₈H₁₉NO₃·HCl. The structural formula of propafenone HCl is given below:



Propafenone HCl occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. The following inactive ingredients are contained in the tablet: hypromellose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized corn starch, sodium starch glycolate, macrogol, talc, titanium dioxide, glycerol monocaprylocaprate and polyvinyl alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Propafenone is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone 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 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. Moreover, propafenone inhibits a variety of cardiac potassium currents in *in vitro* studies (i.e., the transient outward, the delayed rectifier, and the inward rectifier current). Propafenone has local anesthetic activity approximately equal to procaine. Compared with procaine, the main metabolite, 5-hydroxypropafenone, has similar sodium and calcium channel activity, but about 10 times less beta-blocking activity. (N-depropylpropafenone has weaker sodium channel activity but equivalent affinity for beta-receptors.)

12.2 Pharmacodynamics

Cardiac Electrophysiology: Electrophysiology trials in subjects with ventricular tachycardia have shown that propafenone prolongs atrioventricular conduction while having little or no effect on sinus node function. Both atrioventricular 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 Wolff-Parkinson-White syndrome, propafenone hydrochloride reduces conduction and increases the effective refractory period of the accessory pathway in both directions.

Electrocardiograms: Propafenone prolongs the PR and QRS intervals. Prolongation of the QRS interval makes it difficult to interpret the effect of propafenone on the QT interval.

Table 2: Mean Changes in Electrocardiogram Intervals^a

Interval	Total Daily Dose (mg)							
	337.5 mg		450 mg		675 mg		900 mg	
	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

^aChange 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.

When 600 mg/day propafenone was administered to subjects with paroxysmal atrial tachyarrhythmias, mean heart rate during arrhythmia decreased 14 beats/min and 37 beats/min for subjects with PAF and subjects with PSVT, respectively.

Hemodynamics: Trials in humans have shown that propafenone HCl exerts a negative inotropic effect on the myocardium. Cardiac catheterization trials in subjects with moderately impaired ventricular function (mean CI = 2.61 L/min/m²) utilizing intravenous propafenone infusions (loading dose of 2 mg/kg over 10 min followed by 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 mcg/mL (a dose that produces plasma levels of propafenone greater than recommended oral dosing) showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

12.3 Pharmacokinetics

Absorption/Bioavailability: Propafenone HCl 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.

Propafenone HCl follows a nonlinear pharmacokinetic disposition presumably because of saturation of first-pass hepatic metabolism as the liver is exposed to higher concentrations of propafenone and shows a very high degree of inter-individual variability. For example, for an increase in daily dose from 300 to 900 mg/day there is a 10-fold increase in steady-state plasma concentration. The top 25% of subjects given 337.5 mg/day, however, had a mean concentration of propafenone larger than the bottom 25%, and about equal to the second 25%, of subjects given a dose of 900 mg. Although food increased peak blood level and bioavailability in a single-dose trial, during multiple-dose administration of propafenone to healthy volunteers, food did not change bioavailability significantly.

Distribution: Following intravenous administration of propafenone, plasma levels decline in a bi-phasic manner consistent with a 2 compartment pharmacokinetic model. The average distribution half-life corresponding to the first phase was about 5 minutes. The volume of the central compartment was about 88 liters (1.1 L/kg) and the total volume of distribution about 252 liters.

In serum, propafenone is greater than 95% bound to proteins within the concentration range of 0.5 to 2 mcg/mL.

Metabolism: 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 10 to 10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2.

In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, 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, such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.

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 requires that the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see *Dosage and Administration (2)*).

Stereochemistry: Propafenone hydrochloride is a racemic mixture. The R- and S-enantiomers of propafenone display stereoselective disposition characteristics. *In vitro* and *in vivo* studies have shown that the R-isomer of propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-propafenone at steady state. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent beta-antagonist than the R-enantiomer. Following administration of propafenone hydrochloride immediate-release tablets, the S/R ratio for the area under the plasma concentration-time curve was about 1.7. In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time.

Specific Populations: Patients with Hepatic Impairment: Decreased liver function increases the bioavailability of propafenone. Absolute bioavailability of propafenone hydrochloride immediate-release tablets is inversely related to indocyanine green clearance, reaching 60 to 70% at clearances of 7 mL/min and below. Protein binding decreases to about 88% in patients with severe hepatic dysfunction. The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (see *Warnings and Precautions (5.9)*).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day, approximately twice the MRHD on a mg/m² basis) and rats (up to 270 mg/kg/day, approximately 3 times the MRHD on a mg/m² basis) provided no evidence of a carcinogenic potential for propafenone.

Propafenone was not mutagenic in the Ames (salmonella) test and the *in vivo* mouse dominant lethal test. Propafenone was not clastogenic in the human lymphocyte chromosome aberration assay *in vitro*, the rat and Chinese hamster micronucleus tests, and other *in vivo* tests for chromosomal aberrations in rat bone marrow and Chinese hamster bone marrow and spermatogonia.

Propafenone, administered intravenously, has been shown to decrease spermatogenesis at lethal doses in rabbits (≥3.5 mg/kg/day) or at near-lethal dose levels in monkeys and dogs (≤5 mg/kg/day); doses were less than the MRHD on a mg/m² basis. These effects were reversible and did not impair fertility in rabbits at an intravenous dose of 3.5 mg/kg/day (a spermatogenesis-imparing dose). Effects on spermatogenesis were not found when propafenone was administered to rats either orally or intravenously up to 360 mg/kg/day or 6 mg/kg/day, respectively, or in dogs at oral doses up to 240 mg/kg/day (up to approximately 4 or 9 times the MRHD on a mg/m² basis in rats and dogs, respectively). Treatment of male rabbits for 10 weeks prior to mating at an oral dose of 120 mg/kg/day (approximately 2 times the MRHD on a mg/m² basis) did not result in evidence of impaired fertility. Nor was there evidence of impaired fertility when propafenone was administered orally to male and female rats at dose levels up to 270 mg/kg/day (approximately 3 times the MRHD on a mg/m² basis) for 10 weeks (males) or 2 weeks (females) prior to mating through mating.

13.2 Animal Toxicology and/or Pharmacology

Renal changes have been observed in the rat following 6 months of oral administration of propafenone HCl at doses of 180 and 360 mg/kg/day (about 2 and 4 times, respectively, the MRHD on a mg/m² basis). Both inflammatory and non-inflammatory changes in the renal tubules, with accompanying interstitial nephritis, were observed. These changes were reversible, as they were not found in rats allowed to recover for 6 weeks. Fatty degenerative changes of the liver were found in rats following longer durations of administration of propafenone HCl at a dose of 270 mg/kg/day (about 3 times the MRHD on a mg/m² basis). There were no renal or hepatic changes at 90 mg/kg/day (equivalent to the MRHD on a mg/m² basis).

14 CLINICAL STUDIES

In two randomized, crossover, placebo-controlled, double-blind trials of 60 to 90 days duration in subjects with PAF or PSVT, propafenone reduced the rate of both arrhythmias, as shown in **Table 3**.

Table 3: Reduction of Arrhythmias in Subjects with Paroxysmal Atrial Fibrillation/Flutter or Paroxysmal Supraventricular Tachycardia

	Trial 1		Trial 2	
	Propafenone	Placebo	Propafenone	Placebo
PAF	n = 30	n = 30	n = 9	n = 9
Percent attack free	53%	13%	67%	22%
Median time to first recurrence	> 98 days	8 days	62 days	5 days

MFG. LOCATION: KRSG

ARTWORK DETAIL LABEL

NON PRINTING COLOUR

Product	Propafenone Hydrochloride Tablets, USP		
Buyer/Country	STRIDES PHARMA INC - US	Component	Outsert with Patient Information Leaflet
Dimension	500 x 350 mm	Pack	--
New Item Code	1052691	Old Item Code	1051625
Colour Shades	 BLACK		

Change Control No.	PC-ODF/2025/408 - Record Number: 460262 & PC-TSG/2025/052 - Record Number: 463027	Artwork Version	2.0
Design/Style	Front & Back Printing. To be supplied in FOLDED BOOKLET form with pasting & folded size: 34 x 34 mm.		
Substrate	40 GSM Bible Paper.		
Special Instructions	PRINTING CLARITY TO BE CLEAR AND SHARP.		
Autocartanator Requirements	NA		
Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.			

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