PRODUCT MONOGRAPH

[Pr]PROPAFENONE – 150
[Pr]PROPAFENONE – 300

Propafenone Hydrochloride Tablets

Film Coated

150 mg and 300 mg

Antiarrhythmic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablets, 150 mg and 300 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PROPAFENONE (propafenone hydrochloride) is indicated for:

- the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia and prevention.

PROPAFENONE may also be used for the treatment of patients with documented symptomatic ventricular arrhythmias when the symptoms are of sufficient severity to require treatment. Because of the proarrhythmic effects of PROPAFENONE, its use should be reserved for patients in whom, in the opinion of the physician, the benefit of treatment clearly outweighs the risks.

For patients with sustained ventricular tachycardia, PROPAFENONE therapy should be initiated in the hospital. Initiation in hospital may also be required for certain other patients depending on their cardiac status and underlying cardiac disease.
The effects of PROPAFENONE in patients with recent myocardial infarction have not been adequately studied and, therefore, its use in this condition cannot be recommended.

There is no evidence from controlled clinical trials that the use of PROPAFENONE favourably affects survival or the incidence of sudden death.

Geriatrics (≥ 65 years of age):

Evidence from clinical trials and experience showed that use in elderly patients is associated with differences in safety. See (**WARNINGS AND PRECAUTIONS**).

Pediatrics (< 18 years of age):

PROPAFENONE has not been studied in children in controlled clinical trials and therefore use in this age group is not recommended.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Severe or uncontrolled congestive heart failure. See (**WARNINGS AND PRECAUTIONS**).
- Cardiogenic shock.
- Sinoatrial, atrioventricular and intraventricular disorders of impulse conduction and sinus node dysfunction (e.g. sick sinus syndrome) in the absence of an artificial pacemaker.
- Severe bradycardia (less than 50 beats/min).
- Marked hypotension.
- Bronchospastic disorders.
- Severe disorders of electrolyte balance.
- Severe hepatic failure. See (**WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

Carcinogenesis and Mutagenesis

See (**TOXICOLOGY**, **Carcinogenicity and Mutagenicity**).

Cardiovascular

Mortality

The results of the Cardiac Arrhythmia Suppression Trials (CAST) in post-myocardial infarction patients with asymptomatic ventricular arrhythmias showed a significant increase in mortality and in the non-fatal cardiac arrest rate in patients treated with flecainide or encainide compared with a matched placebo-treated group. CAST was continued using a revised protocol with the moricizine and placebo arms only. The trial was prematurely terminated because of a trend towards an increase in mortality in the moricizine treated group.

The applicability of these results to other populations or other antiarrhythmic agents is uncertain, but at present it is prudent to consider these results when using any antiarrhythmic agent in patients with structural heart disease

Proarrhythmic Effects

PROPAFENONE (propafenone hydrochloride) may cause new or worsen existing arrhythmias. Such proarrhythmic effects range from an increase in frequency of premature ventricular contractions (PVCs) to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes. It is therefore essential that each patient administered propafenone hydrochloride be evaluated clinically and electrocardiographically prior to, and during therapy to determine whether the response to propafenone supports continued treatment.

Overall in clinical trials with propafenone hydrochloride, 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 ventricular tachycardia (VT) or ventricular fibrillation (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 suggests that a risk is present throughout treatment. See (**WARNINGS AND PRECAUTIONS**, **Cardiovascular**, **Mortality**).

Congestive Heart Failure

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

Propafenone hydrochloride exerts both beta blockade and a dose related direct negative inotropic effect on myocardium. Therefore, PROPAFENONE (propafenone hydrochloride) should not be prescribed in patients with uncontrolled congestive heart failure where left ventricular output is less than 35%.

Caution should be exercised when using PROPAFENONE in patients with minimal cardiac reserve or in those who are receiving other drugs with negative inotropic potential.

Effects on Cardiac Conduction

Propafenone hydrochloride slows cardiac conduction which may result in a dose-related prolongation of PR interval and QRS complex, development of first or higher degree AV block, bundle branch block and intraventricular conduction delay. See (**ADVERSE REACTIONS**).
Therefore, development of signs of increasing depression of cardiac conductivity during PROPAFENONE (propafenone hydrochloride) therapy requires a reduction in dosage or a discontinuation of PROPAFENONE unless the ventricular rate is adequately controlled by a pacemaker.

Effects on Pacemaker Threshold

Patients with permanent pacemakers should have their existing thresholds re-evaluated after initiation of or change in PROPAFENONE therapy because of a possible increase in endocardial stimulation threshold.

Hematologic

Hematologic Disturbances

Agranulocytosis has been reported infrequently in patients taking propafenone hydrochloride. The onset is generally within four to six weeks and presenting symptoms have included fever, fatigue, and malaise. Agranulocytosis occurs in less than 0.1% of patients taking propafenone hydrochloride. Patients should be instructed to immediately report fever, fatigue, malaise or any signs of infection, especially in the first three months of therapy. Prompt discontinuation of PROPAFENONE therapy is recommended when a decreased white blood cell count or other signs and symptoms warrant consideration of agranulocytosis/granulocytopenia. Cessation of propafenone hydrochloride therapy is usually followed by recovery of blood counts within two weeks.

Hepatic/Biliary/Pancreatic

Use in Patients with Impaired Hepatic Function

Since propafenone hydrochloride is highly metabolized by the liver it should be administered cautiously to patients with impaired hepatic function. See (**CONTRAINDICATIONS**).
Administration of propafenone hydrochloride to these patients results in an increase in bioavailability to approximately 70% compared to 3 to 40% for patients with normal liver function, prolongation of the half-life, a decrease in the systemic clearance, and a reduction in the serum protein binding of the drug. As a result, the dose of PROPAFENONE given to patients with impaired hepatic function should be reduced. See (**DOSAGE AND ADMINISTRATION**). It is important to monitor electrocardiographic intervals for signs of excessive pharmacological effects. See (**OVERDOSAGE**) and/or adverse reactions, until an individualized dosage regimen has been determined.

A number of patients with liver abnormalities associated with propafenone hydrochloride therapy have been reported in foreign post-marketing experience. Some appeared due to be 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. One case was rechallenged with a positive outcome.

Increased hepatic enzymes (alkaline phosphatase, serum transaminases) (0.2%), hepatitis (0.03%) and cholestasis (0.1%) have also been observed. See (**ADVERSE REACTIONS, Less Common Clinical Trial Adverse Drug Reactions (<1%).**

Immune

Elevated ANA Titres

In long-term studies, positive antinuclear antibody (ANA) titres have been reported in 21% of patients receiving propafenone hydrochloride. However, it is impossible to determine what exact percentage of patients had a new positive ANA titre as a result of propafenone hydrochloride therapy. This laboratory finding has not been associated with clinical symptoms. One case of Lupus-like syndrome has been reported which resolved upon discontinuation of therapy. Laboratory evaluation for antinuclear antibodies should be performed initially and at regular intervals. It is recommended that patients in whom an abnormal ANA test has occurred be evaluated regularly. If worsening elevation of ANA titres or clinical symptoms are detected, PROPAFENONE should be discontinued.

Neurologic

Exacerbation of myasthenia gravis has been reported during propafenone hydrochloride therapy.

Renal

There is limited experience with use of oral propafenone hydrochloride in patients with impaired renal function. In patients whose kidney function is impaired, there may be drug accumulation after standard therapeutic doses. Since a considerable percentage of propafenone metabolites are excreted in the urine (18.5 to 38% of the dose/48 hours), PROPAFENONE should be used cautiously in patients with renal impairment and only after consideration of the benefit/risk ratio. These patients should be carefully monitored for signs of toxicity. See (**OVERDOSAGE**). The dose in these patients has not been determined.

Respiratory

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

Patients with bronchospastic disease should, in general, not receive PROPAFENONE (propafenone hydrochloride) or other agents with beta-adrenergic blocking activity. See (**CONTRAINDICATIONS**).

Sexual Function/Reproduction

Impaired Spermatogenesis

Clinical evaluation of spermatogenesis was undertaken in 11 normal subjects, given oral propafenone hydrochloride 300 mg twice daily for four days which was then increased to 300 mg three times daily for an additional four days. Patients were followed for 128 days post-treatment and demonstrated a 28% reduction in semen sample volume following the last dose (Day 8) and a 27% reduction in sperm count, on Day 72. Follicle-stimulating hormone (FSH) and testosterone levels were also slightly decreased. Neither the decrease in sperm count nor the

decrease in sample volume were sustained beyond the single visit in which they occurred, and both values remained within the laboratories normal reference range. Reduced spermatogenesis was also observed in animal experiments. The significance of these findings is uncertain.

Special Populations

Pregnant Women

Propafenone hydrochloride has been shown to be embryotoxic in the rat when given in doses of 600 mg/kg (about six times the maximum recommended human dose on a mg/m^2 basis) and in the rabbit when given in doses of 150 mg/kg (about three times the maximum recommended human dose on a mg/m^2 basis). In a perinatal and postnatal study in rats, propafenone hydrochloride produced dose-dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

There are no adequate and well controlled studies in pregnant women. PROPAFENONE should be used during pregnancy only when the potential benefit outweighs the risk to the fetus. Propafenone hydrochloride is known to pass the placental barrier in humans. The concentration of propafenone hydrochloride in the umbilical cord has been reported to be about 30% of that in the maternal blood.

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

Nursing Women

Propafenone and 5-hydroxypropafenone are excreted in human milk. Because of possible serious adverse reactions in nursing infants, an alternative method of infant feeding should be considered when the use of PROPAFENONE (propafenone hydrochloride) is considered essential.

Pediatrics (< 18 years of age)

The use of PROPAFENONE (propafenone hydrochloride) in children is not recommended, since safety and efficacy have not been established.

Geriatrics (> 65 years of age)

A slight increase in the incidence of dizziness was observed in elderly patients. 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.

Gender

The effect of gender on propafenone hydrochloride, when administered as PROPAFENONE (propafenone hydrochloride) has not been investigated.

Race

The effect of different races on propafenone hydrochloride, when administered as PROPAFENONE (propafenone hydrochloride), has not been investigated.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In 2127 patients treated with propafenone hydrochloride in North American controlled and open clinical trials, the most common adverse reactions reported were dizziness (12.5%), nausea and/or vomiting (10.7%), unusual taste (8.8%) and constipation (7.2%). The adverse effects judged to be most severe were aggravation or induction of arrhythmia (4.7%), congestive heart failure (3.7%) and ventricular tachycardia (3.4%). The incidences for these three adverse reactions in patients with a previous history of myocardial infarction (MI) were 6.9, 5.3 and 5.5%, respectively, while in patients without a history of MI the incidences were 3.0, 2.4 and 1.8%, respectively. Approximately 20% of patients had propafenone hydrochloride discontinued due to adverse reactions.

Adverse reactions were dose related and occurred most frequently during the first month of therapy.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The adverse events listed in **Table 1** were observed in greater than one percent of patients.

Table 1. Adverse Events Observed in Greater than 1% of Patients Treated with propafenone hydrochloride tablets

	Incidence By Total Daily Dose (%)			Overall Incidence At Any Dose (%)	% Patients who Discontinued
	450 mg	600 mg	900 mg	(N=2127)	
Cardiovascular System					
Dyspnea	2.2	2.3	3.6	5.3	1.6
Proarrhythmia	2.0	2.1	2.9	4.7	4.7
Angina	1.7	2.1	3.2	4.6	0.5
Congestive Heart Failure	0.8	2.2	2.6	3.7	1.4
Ventricular Tachycardia	1.4	1.6	2.9	3.4	1.2
Palpitations	0.6	1.6	2.6	3.4	0.5
First Degree AV Block	0.8	1.2	2.1	2.5	0.3
Syncope	0.8	1.3	1.4	2.2	0.7
QRS Duration, Increased	0.5	0.9	1.7	1.9	0.5
Bradycardia	0.5	0.8	1.1	1.5	0.5
PVC's	0.6	0.6	1.1	1.5	0.1
Edema	0.6	0.4	1.0	1.4	0.2
Bundle Branch Block	0.3	0.7	1.0	1.2	0.5
Atrial Fibrillation	0.7	0.7	0.5	1.2	0.4
Intraventricular Conduction Delay	0.2	0.7	0.9	1.1	0.1
Hypotension	0.1	0.5	1.0	1.1	0.4
Central Nervous System					
Dizziness	3.6	6.6	11.0	12.5	2.4
Headaches	1.5	2.5	2.8	4.5	1.0
Blurred Vision	0.6	2.4	3.1	3.8	0.8
Ataxia	0.3	0.6	1.5	1.6	0.2
Insomnia	0.3	1.3	0.7	1.5	0.3
Tremor(s)	0.3	0.8	1.1	1.44	0.3
Drowsiness	0.6	0.5	0.7	1.2	0.2
Gastrointestinal System					
Nausea and/or Vomiting	2.4	6.1	8.9	10.7	3.4
Unusual Taste	2.5	4.9	6.3	8.8	0.7
Constipation	2.0	4.1	5.3	7.2	0.5
Dyspepsia	1.3	1.7	2.5	3.4	0.9
Diarrhea	0.5	1.6	1.7	2.5	0.6
Dry Mouth	0.9	1.0	1.4	2.4	0.2
Anorexia	0.5	0.7	1.6	1.7	0.4
Abdominal Pain/Cramping	0.8	0.9	1.1	1.7	0.4
Flatulence	0.3	0.7	0.9	1.2	0.1
Other					
Fatigue	1.8	2.8	4.1	6.0	1.0
Rash	0.6	1.4	1.9	2.6	0.8
Weakness	0.6	1.6	1.7	2.4	0.7
Atypical Chest Pain	0.5	0.7	1.4	1.8	0.2
Anxiety	0.7	0.5	0.9	1.5	0.6
Diaphoresis	0.6	0.4	1.1	1.4	0.3
Pain, Joints	0.2	0.4	0.9	1.0	0.1

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse reactions were reported less frequently than 1% in clinical trials. Causality and relationship to propafenone hydrochloride therapy cannot necessarily be judged from these events.

Cardiovascular:	atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia, Torsades de Pointes, ventricular fibrillation
Gastrointestinal:	gastroenteritis
Hepatic:	A number of patients with liver abnormalities associated with propafenone hydrochloride therapy have been reported in foreign 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. One case was rechallenged with a positive outcome. cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), hepatitis (0.03%)
Immune System:	allergic reactions
Nervous System:	abnormal dreams, abnormal speech, abnormal vision, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo
Other:	alopecia, eye irritation, impotence, increased glucose, positive ANA (0.7%), muscle cramps, muscle weakness, nephritic syndrome, pain, pruritus, reddening of the skin

Abnormal Hematologic and Clinical Chemistry Findings

Hematologic:	agranulocytosis See (**WARNINGS AND PRECAUTIONS**), anemia,bruising, granulocytopenia, leukopenia, purpura, thrombocytopenia

Post-Market Adverse Drug Reactions

Cardiovascular:	ventricular fibrillation
Gastrointestinal:	jaundice
Hematologic:	increased bleeding time
Nervous System:	apnea, coma

Other: hyponatremia/inappropriate ADH secretion, lupus erythematosis, chest pain, urticaria, kidney failure

There have been post-marketing reports of patients experiencing conversion of paroxysmal atrial fibrillation to atrial flutter with accompanying 2:1 or 1:1 conduction block. However, the clinical significance has not been established.

DRUG INTERACTIONS

Overview

Drugs that inhibit CYP2D6 (e.g. quinidine), CYP1A2 (e.g. cimetidine) and CYP3A4 (e.g. ketoconazole, cimetidine, erythromycin and grapefruit juice) might lead to increased plasma levels of propafenone. When PROPAFENONE (propafenone hydrochloride) is administered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

Coadministration of PROPAFENONE with drugs metabolized by CYP2D6 (e.g. venlafaxine) might lead to increased levels of these drugs and/or of propafenone.

Drug-Drug Interactions

Table 2. Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Digitalis	CT, T	Propafenone hydrochloride has been shown to produce doserelated increases in serum digoxin levels ranging from approximately 35% at 450 mg/day to 85% at 900 mg/day of propafenone hydrochloride without affecting digoxin renal clearance. Elevations of digoxin 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 hydrochloride is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.
Beta-agonists	CT, T	In a study involving healthy subjects, concomitant administration of propafenone hydrochloride and propranolol resulted in substantial increases in propranolol plasma concentration and elimination t½ 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	While the therapeutic range for betablockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone hydrochloride.

		cardioselectivity. In propafenone hydrochloride clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects.	
Anticoagulants	CT	In a study of eight healthy subjects receiving propafenone hydrochloride and concomitant warfarin, mean steady-state warfarin plasma concentrations increased 39% with a corresponding prolongation in prothrombin times of approximately 25%.	It is therefore recommended that in patients treated with propafenone hydrochloride and anticoagulants (e.g. warfarin, acenocoumarol) concomitantly, prothrombin time should be carefully monitored and the dose of anticoagulant adjusted as necessary.
Cimetidine	CT	Concomitant administration of propafenone hydrochloride tablets and cimetidine resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone hydrochloride alone.	Therefore, patients should be carefully monitored and the dose of propafenone hydrochloride adjusted when appropriate.
Lidocaine	T	No clinically significant effects on the pharmacokinetics of propafenone or lidocaine have been seen following their concomitant use in healthy volunteers. However, the concomitant use of propafenone hydrochloride and intravenous lidocaine has been reported to increase the frequency and severity of central nervous system side effects of lidocaine.	Therefore, the combination of propafenone hydrochloride and lidocaine should be used with caution.
Desipramine	C, T	Concomitant administration of propafenone hydrochloride and desipramine may result in elevated serum desipramine levels.	Both desipramine, a tricyclic antidepressant, and propafenone are cleared by oxidative pathways of demethylation and hydroxylation carried out by the hepatic P-450 cytochrome.
Cyclosporin	C, T	Propafenone hydrochloride therapy may increase levels of cyclosporin.	
Theophylline	C, T	Propafenone hydrochloride may increase theophylline concentration during concomitant therapy with the development of theophylline toxicity.	
Rifampin	T	Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.	

Ritonavir, Lopinavir/ritonavir	T		Due to the potential for increased plasma concentrations, coadministration of 800-1200 mg/day doses of ritonavir and propafenone hydrochloride is contraindicated. Furthermore, based on results of a desipramine interaction study, lopinavir/ritonavir does not inhibit CYP2D6-mediated metabolism at clinically relevant concentrations. However, caution should be used when co-administering propafenone with any ritonavir-boosted protease inhibitors.
Amiodarone	T	Combination therapy of amiodarone and propafenone hydrochloride can affect conduction and repolarization and lead to abnormalities that have the potential to be proarrhythmic.	Dose adjustments of both compounds based on therapeutic response may be required.
Phenobarbital	T	Phenobarbital is a known inducer of CYP3A4	Response to propafenone hydrochloride therapy should be monitored during concomitant chronic phenobarbital use.
Fluoxetine, Paroxetine and Fluvoxamine	C, T	Concomitant administration of propafenone hydrochloride and fluoxetine in extensive metabolizers increased the S propafenone C_{max} and AUC by 39 and 50% and the R propafenone C_{max} and AUC by 71 and 50%. Elevated levels of plasma propafenone may occur when propafenone hydrochloride is used concomitantly with paroxetine.	Lower doses of propafenone may be sufficient to achieve the desired therapeutic response. In poor metabolizers, concomitant administration of propafenone hydrochloride and fluvoxamine may require a dose reduction of propafenone.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Co-administration of PROPAFENONE (propafenone hydrochloride) with grapefruit juice might lead to increased plasma levels of propafenone. Bioavailability is enhanced by administration of the drug with food.

Drug-Herb Interactions

Caution should be exercised when administering PROPAFENONE (propafenone hydrochloride) with cytochrome P450 modulating herbal products such as St. John's wort.

Drug-Lifestyle Interactions

Driving and Using Machines

Blurred vision, dizziness, fatigue and postural hypotension may affect the patient's speed of reaction and impair the individual's ability to operate machinery and motor vehicles.

DOSAGE AND ADMINISTRATION

Dosing Considerations

1. The dose of PROPAFENONE (propafenone hydrochloride) must be individually determined on the basis of patient's response and tolerance. The usefulness of monitoring plasma levels for optimization of therapy has not been established. The recommended dose titration regimen can be used for both fast and slow metabolizers. See (**ACTION AND CLINICAL PHARMACOLOGY**)

Recommended Dose and Dosage Adjustment

The initial dose of PROPAFENONE is 150 mg given every 8 hours (450 mg/day). Dosage may be increased at three to four day intervals to 300 mg every 12 hours (600 mg/day). Should a further increase in dosage be necessary a maximum dose of 300 mg every 8 hours (900 mg/day) may be given.

In those patients in whom widening of the QRS complex (>0.12 seconds) or prolongation of PR interval (>0.24 seconds) occurs, the dosage of PROPAFENONE should be reduced.

In patients with mild to moderate hepatic insufficiency PROPAFENONE therapy should be initiated with 150 mg given once daily (150 mg/day). See (**WARNINGS AND PRECAUTIONS**). The dosage may be increased at a minimum of 4 day intervals to 150 mg twice daily (300 mg/day)then to 150 mg every 8 hours (450 mg/day) and, if necessary, to 300 mg every 12 hours (600 mg/day).

There is no information on dosing with PROPAFENONE in patients with renal impairment. PROPAFENONE should be used cautiously in these patients and only after consideration of the benefit/risk ratio. These patients should be carefully monitored for signs of toxicity. Lower doses may be required. See (**WARNINGS AND PRECAUTIONS**).

In elderly patients, the effective dose of PROPAFENONE may be lower. See (**WARNINGS AND PRECAUTIONS**).

There is no information on the appropriate regimen for the transfer from lidocaine to PROPAFENONE.

Missed Dose

If you forget to take one tablet, take another as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all. Never double-up on a missed dose.

Administration

Administration of PROPAFENONE with food is recommended.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The symptoms of overdose may include hypotension, somnolence, convulsions, bradycardia, conduction disturbances, ventricular tachycardia and/or ventricular fibrillation. Death may occur.

If ingestion is recent, perform gastric lavage or induce emesis. Supportive measures such as mechanical respiratory assistance and cardiac massage may be necessary.

Defibrillation and the use of a temporary pacemaker, as well as infusion of isoproterenol and dopamine have been effective in controlling cardiac rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam.

Detoxification measures such as forced diuresis, hemoperfusion and hemodialysis have not proven useful.

Treatment

Owing to high protein binding (> 95%) and the large volume of distribution, hemodialysis is ineffective and attempts to achieve elimination via hemoperfusion are of limited efficacy.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PROPAFENONE (propafenone hydrochloride) is an antiarrhythmic agent which possesses class 1C properties in the modified electrophysiological classification of Vaughan-Williams. Propafenone hydrochloride has a direct stabilizing action on myocardial cell membranes. The electrophysiological effect of propafenone hydrochloride manifests itself as a reduction of the upstroke velocity (Phase 0) of the monophasic action potential, while Phase 4 spontaneous automaticity is depressed. Diastolic excitability threshold is increased and effective refractory period prolonged. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone hydrochloride reduces the fast inward sodium current.

In addition to a local anesthetic effect, approximately equal to procaine, propafenone hydrochloride has weak beta-blocking activity. Clinical trials employing isoproterenol challenge and exercise testing suggest that the affinity of propafenone hydrochloride for beta-adrenergic receptors, as calculated from dose ratios and drug concentrations, is about 1/40 that of propranolol. Propafenone hydrochloride also inhibits the slow calcium influx at high concentrations, however, this action is weak (approximately 1/100 of verapamil) and does not contribute to its antiarrhythmic effect.

Pharmacodynamics

Electrophysiology

Electrophysiology studies have shown that propafenone hydrochloride prolongs atrioventricular conduction and in some instances significantly lengthens sinus nodal recovery times with a nonsignificant effect on sinus cycle length. Both atrioventricular (AV) nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone hydrochloride increases atrial, AV nodal and ventricular effective refractory periods. Propafenone hydrochloride causes a dose-dependent increase in the PR interval and QRS complex duration. Non-significant increases in the QT_c interval and occasional slowing of the heart rate have also been observed.

Hemodynamics

Propafenone hydrochloride can exert a negative inotropic effect on the myocardium. Increases in pulmonary capillary wedge pressure and systemic and pulmonary vascular resistance, with a concurrent mild depression of cardiac output and cardiac index, have occurred following PROPAFENONE (propafenone hydrochloride) administration. Decreases in left ventricular function have been recorded in patients with depressed baseline function.

Pharmacokinetics

Absorption

Due to a genetically determined presence or deficiency of one metabolizing pathway (CYP2D6), patients may be categorized into fast (over 90% of all patients) or slow metabolizers of propafenone hydrochloride, resulting in low or high plasma concentrations respectively. Following oral administration in fast metabolizers, propafenone hydrochloride is nearly completely absorbed and undergoes extensive first-pass hepatic metabolism resulting in a dose-dependent absolute bioavailability ranging from 3 to 40%. Peak plasma concentrations occur within three hours. For fast metabolizers of propafenone hydrochloride, the elimination $t_{1/2}$ is 5.5 ± 2.1 hours; for slow metabolizers, the elimination $t_{1/2}$ is 17.2 ± 8.0 hours. In fast metabolizers, there is a non-linear increase in drug plasma concentration and bioavailability with increase in dosage, presumably due to saturation of first pass hepatic metabolism. This departure from dose linearity occurs when single doses above 150 mg are given. A 300 mg dose gives

plasma levels six times that of a 150 mg dose. Similarly, for a 3-fold increase in daily dose from 300 to 900 mg/day there is a 10-fold increase in steady-state plasma concentration. In slow metabolizers, as opposed to fast metabolizers, a linear relationship between propafenone hydrochloride dose and plasma concentration was observed.

Slow metabolizers had higher propafenone plasma concentrations which they required for suppression of arrhythmia since they did not produce the active metabolite 5-hydroxypropafenone (5-OHP). These higher propafenone plasma concentrations may lead to clinically evident beta-blockade.

Despite these differences in pharmacokinetics, steady-state conditions are achieved after three to four days in all patients. Therapeutic plasma levels of propafenone appear to be in the range of 0.5 to 2.0 mcg/mL.

Metabolism

In fast metabolizers, propafenone undergoes extensive hepatic metabolism with less than 1% excreted as unchanged drug. The major active metabolites are 5-hydroxypropafenone (5-OHP) which is formed by CYP2D6 and N-depropylpropafenone (NDPP) which is formed by CYP3A4 and CYP1A2; both metabolites occurring in concentrations less than 20% of the parent compound. In vitro preparations and animal studies have shown that the 5-OHP metabolite possesses antiarrhythmic and beta-adrenoreceptor blocking activity comparable to propafenone.

Propafenone is 97% bound to plasma proteins.

Influence of Food

Bioavailability is enhanced by administration of the drug with food.

Special Populations and Conditions

Pediatrics

Propafenone hydrochloride pharmacokinetics have not been evaluated in patients less than 18 years of age.

Geriatrics

Propafenone hydrochloride pharmacokinetics have not been evaluated in elderly patients greater than 65 years of age. However, a slight increase in the incidence of dizziness was observed in elderly patients. Because of the possible increased risk of impaired hepatic or renal function in this age group, propafenone hydrochloride should be used with caution. The effective dose may be lower in these patients.

STORAGE AND STABILITY

Store PROPAFENONE (propafenone hydrochloride) at room temperature 15 to 30°C (59 to 86°F). Do not use beyond the expiry date indicated on the label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PROPAFENONE 150 mg: Each round, white, film-coated, biconvex, tablet engraved 'P150' on one side contains 150 mg propafenone hydrochloride. Available in bottles of 100 and 500, and unit dose packages of 100.

PROPAFENONE 300 mg: Each round, white, film-coated, biconvex, tablet scored and engraved 'P300' on one side contains 300 mg propafenone hydrochloride. Available in bottles of 100 and 500, and unit dose packages of 100.

In addition to the active ingredient, propafenone hydrochloride, each film-coated tablet also contains the non-medicinal ingredients: croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, polyethylene glycol and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

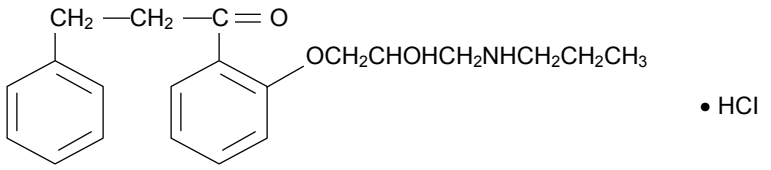
Drug Substance

Proper Name: propafenone hydrochloride

Chemical Name: 2'-(2-hydroxy-3-propylamino-propoxy)-3-phenylpropiophenone hydrochloride

Molecular formula and molecular mass: $C_{21}H_{27}NO_3 \cdot HCl$ 377.92

Structural Formula:



Physicochemical properties: Propafenone hydrochloride occurs as colourless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol.

CLINICAL TRIALS

Comparative Bioavailability Studies

Two comparative bioavailability studies were performed using healthy human volunteers - one under fasting conditions and one under fed conditions. The rate and extent of absorption of propafenone following administration of a single 300 mg (one 300 mg tablet) dose of PROPAFENONE and RYTHMOL were measured and compared. The results are summarized as follows:

Table 3: Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data
Propafenone
(A single 300 mg dose: 1 x 300 mg)
From Measured Data/Fasting Conditions
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test*	Reference†	Ratio of Geometric Means (%)#	95% Confidence Interval (%)#
AUCt (ng•h/mL)	1325 2679 (155)	1255 2641 (165)	103.5	91.2 – 117.3
AUCinf (ng•h/mL)	1372 2871 (165)	1301 2838 (176)	103.5	91.7 – 116.8
Cmax (ng/mL)	269 371 (86)	252 352 (88)	104.9	91.2 – 120.6
Tmax§ (h)	3.31 (30)	3.20 (27)		
Thalf§ (h)	3.09 (89)	3.09 (89)		

*Propafenone (propafenone hydrochloride) 300 mg tablets (Pro Doc Ltée)

† Rythmol® (propafenone hydrochloride) 300 mg tablets (Knoll Pharma Inc.) was purchased in Canada.

Based on Least Squares Estimates.

§ Expressed as arithmetic means (CV%) only.

Table 4: Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Propafenone (A single 300 mg dose: 1 x 300 mg) From Measured Data/Fed Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)#	95% Confidence Interval (%)#
AUCt (ng•h/mL)	1494 2204 (106)	1394 2112 (109)	108.1	94.7 – 123.4
AUCinf (ng•h/mL)	1539 2274 (111)	1437 2193 (118)	108.0	95.4 – 122.2
Cmax (ng/mL)	340 419 (57)	321 408 (65)	106.6	91.6 – 124.1
Tmax§ (h)	3.12 (36)	3.23 (34)		
Thalf§ (h)	2.72 (54)	2.70 (60)		

*Propafenone (propafenone hydrochloride) 300 mg tablets (Pro Doc Ltée)

† Rythmol® (propafenone hydrochloride) 300 mg tablets (Knoll Pharma Inc.) was purchased in Canada.

Based on Least Squares Estimates.

§ Expressed as arithmetic means (CV%) only.

Study Demographics and Trial Design

Table 5. Summary of Patient Demographics for Clinical Trials in Patients with severe ventricular arrhythmias

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n = number)
I	Double-blind, crossover, placebo controlled evaluation in patients with severe ventricular arrhythmias	150 mg b.i.d. 150 mg t.i.d. 300 mg b.i.d. 300 mg t.i.d. Oral dose. 4 weeks.	64 treated
II	Double-blind, randomized, placebo-controlled, crossover, In-hospital evaluation in patients with severe ventricular arrhythmias.	150 mg b.i.d. 150 mg t.i.d. 300 mg b.i.d. 300 mg t.i.d. Oral dose. 6 days	37 treated
Definitions:	b.i.d = twice daily; t.i.d. = three times daily		

Study Results

Study I was designed to evaluate the safety and efficacy of chronic PROPAFENONE (propafenone hydrochloride) administration in patients with severe ventricular arrhythmias. The study consisted of a one-week placebo run-in phase to establish eligibility followed by a four-week dose-ranging phase (300, 450, 600 and 900 mg/day) to establish each patient's optimal therapeutic dose of propafenone hydrochloride. A double-blind, randomized, crossover phase consisting of two two-week periods comparing propafenone hydrochloride to placebo followed. Each two-week period was proceeded by a one-week placebo washout period. Holter recordings were made at weekly intervals throughout the study and analyzed to determine efficacy. Results of this study are summarized in **Table 4**.

Table 6. Efficacy Results of Study I in Patients with severe ventricular arrhythmias

Efficacy Parameters	Treatment	Combined Double-Blind Period							
		N	Pretreatment						
			Mean ± S.D.	p-value[a]	Mean ± S.D.	Mean (Median) Change	p-value[b]	p-value[a]	p-value[c]
Average # of VPB's per hour	Propafenone	43	469.3 ± 510.8	N.S.	74.5 ± 177.2	-394.7 (-217.3)	<0.01	<0.01	<0.01
	Placebo	42	428.6 ± 402.0		503.5 ± 460.0	74.9 (52.8)	N.S.		
Average # of single VPB's per hour	Propafenone	43	425.5 ± 451.0	N.S.	71.6 ± 173.4	-354.0 (-210.6)	<0.01	<0.01	<0.01
	Placebo	42	498.8 ± 377.7		451.8 ± 395.3	53.0 (44.6)	N.S.		
Average # of paired VPB's per hour	Propafenone	43	40.6 ± 85.2	N.S.	1.6 ± 4.7	-39.0 (-3.8)	<0.01	<0.01	<0.01
	Placebo	42	26.8 ± 54.7		45.9 ± 106.6	19.1 (0.0)	N.S.		
Average # of VT beats per 24 hours	Propafenone	43	75.3 ± 221.7	N.S.	33.7 ± 216.3	-41.7 (-9.7)	<0.01	<0.01	<0.01
	Placebo	42	71.6 ± 204.7		139.5 ± 371.2	67.9 (0.0)	N.S.		
Average # of VT events per 24 hours	Propafenone	43	22.3 ± 64.7	N.S.	1.1 ± 5.6	-21.2 (-2.9)	<0.01	<0.01	<0.01
	Placebo	42	22.5 ± 64.3		40.7 ± 115.4	18.2 (0.0)	N.S.		

VPB's = Ventricular Premature Beats
Paired VPB's = The number of VPB's occurring in pairs or couplets (not the number of pairs).
VT beats or Ventricular Tachycardia beats = Ventricular Premature Beats occurring in events of 3 or more.
VT events = 3 or more VPB's.
N.S. = Not statistically significant at the 0.05 significance level.

[a]Between treatment p-value for current period values.
[b]Within treatment p-value for change from baseline.
[c]Between treatment p-value for change from baseline.

Propafenone hydrochloride was clinically and statistically ($p < 0.01$) superior to placebo in reducing the number of ventricular premature beats (total ventricular premature beats [VPB's], single VPB's, paired VPB's), ventricular tachycardia beats, and ventricular tachycardia events. In addition to the above combined period analysis, the first period was analyzed alone (results not shown) and propafenone hydrochloride was significantly superior to placebo for all efficacy parameters.

Study II was also designed to evaluate the safety and efficacy of chronic propafenone hydrochloride administration in patients with severe ventricular arrhythmias. The study began with a two-day placebo run-in phase during which patients must have 60 VPB's/hour or sustained VT or "R on T" etc. Patients fulfilling the entrance criteria were entered into an eight-day dose-ranging phase. A double-blind, randomized, crossover phase consisting of two three-day periods comparing propafenone hydrochloride to placebo followed. Each three-day period was preceded by a two- to three-day placebo washout period. Nine, 24-hour Holter recordings were obtained throughout the study for each completed patient.

Propafenone hydrochloride was shown clinically and statistically ($p < 0.0l$) superior to placebo in reducing all ventricular ectopy parameters as shown in the following **Table 5.**

Table 7 Efficacy Results of Study II in Patients with severe ventricular arrhythmias

Efficacy Parameters	Treatment	Combined Double-Blind Period							
		N	Pretreatment						
			Mean ± S.D.	p-value[a]	Mean ± S.D.	Mean (Median) Change	p-value[b]	p-value[a]	p-value[c]
Average # of VPB's per hour	Propafenone	19	633.2 ± 635.6	0.02[d,e]	66.9 ± 81.9	-566.3 (-452.1)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	542.7 ± 581.1		682.0 ± 789.7	139.3 (-2.4)	N.S.[d]		
Average # of single VPB's per hour	Propafenone	19	499.5 ± 433.8	<0.01[d,e]	62.5 ± 77.2	-437.0 (-438.9)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	399.2 ± 428.4		483.9 ± 475.5	84.7 (-10.4)	N.S.[d]		
Average # of paired VPB's per hour	Propafenone	19	77.9 ± 152.0	N.S.[d]	4.1 ± 13.5	-73.8 (-8.0)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	93.3 ± 184.8		121.4 ± 250.9	28.1 (0.0)	N.S.d		
Average # of VT beats per 24 hours	Propafenone	19	1340.3 ± 3851.4	N.S.[d]	7.0 ± 21.2	-1333.3 (-32.5)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	1204.7 ± 2550.2		1839.3 ± 5257.5	634.7 (0.0)	N.S.[d]		
Average # of VT events per 24 hours	Propafenone	19	317.0 ± 780.9	N.S.[d]	2.3 ± 7.0	-314.7 (-10.5)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	343.7 ± 708.0		476.3 ± 1301.1	132.6 (0.0)	N.S.[d]		

VPB's = Ventricular Premature Beats
Paired VPB's = The number of VPB's occurring in pairs or couplets (not the number of pairs).
VT beats or Ventricular Tachycardia beats = Ventricular Premature Beats occurring in events of 3 or more.
VT events = 3 or more VPB's.
N.S. = Not statistically significant at the 0.05 significance level.

[a]Between treatment p-value for current period values.
[b]Within treatment p-value for change from baseline.
[c]Between treatment p-value for change from baseline.
[d]This test was performed on transformed data.
[e]Indicates a difference in the behaviour of the two treatment sequences, possibly due to the inconsistent results during the placebo periods.

DETAILED PHARMACOLOGY

Electrophysiology

The antiarrhythmic effect of PROPAFENONE (propafenone hydrochloride) has been demonstrated in a number of different animal models. Electrically-induced ventricular fibrillation was controlled by propafenone hydrochloride (2 mg/kg intravenous) in the guinea pig and rabbit. Chloroform- and adrenaline-induced arrhythmias were reduced or abolished by propafenone hydrochloride in the cat (1 mg/kg intravenous, 2 to 10 mg/kg intravenous) and dog (1 mg/kg intravenous, 10 mg/kg oral) as were arrhythmias induced by calcium chloride, glycoside and coronary ligature in the dog (1 to 4 mg/kg intravenous). Aconitine-induced arrhythmias were also controlled by propafenone hydrochloride in the rabbit (3 mg/kg intravenous).

Propafenone can be classified as an antiarrhythmic drug with a membrane stabilizing effect.

Hemodynamics

In the dog, the force of ventricular contraction and blood pressure were not affected by doses of 3 mg/kg intravenous. However, after higher doses of 12 mg/kg intravenous or in hearts

predamaged by coronary ligature, or when administering beta-blockers concomitantly, a fall in blood pressure, a reduction in the heart rate and contractility, and an increase in ECG-intervals (PR and QRS) have been seen.

Other

Structural similarities between propafenone and propranolol prompted several animal investigations into the possible beta-blocking effects of propafenone. A $beta_1$-sympatholytic action on isolated heart preparations (guinea pigs) and a $beta_2$-sympatholytic action on the coronary arteries and tracheal muscles (bovine) have been demonstrated in vitro. In vivo studies in rats showed that the antiarrhythmic effect occurred with intravenous doses seven times lower than necessary for the beta-blocking effect (ED_{50} at 0.437 mg/kg and 3.25 mg/kg respectively). However, the in vitro beta-blocking effect of propafenone occurred in the same dose range as the antiarrhythmic effect.

In *in vitro* studies of bovine coronary arteries, propafenone (56.0 mg/L) yielded a relaxing effect weaker than that of etafenone, papaverine, hexobendine, fendiline and oxifedrine but stronger than that of theophylline, aminophylline and carbocromen. In bovine tracheal muscle, and guinea pig colon, the potency of propafenone was the same as that of papaverine. In vivo, canine duodenum tone decreased slightly after intravenous propafenone, 0.5 to 4.0 mg/kg, with a marked decrease of the amplitude of peristalsis following propafenone, 1.0 to 4.0 mg/kg.

The local anesthetic activity of propafenone was demonstrated in the cornea of conscious guinea pigs with a 0.5% solution of propafenone.

TOXICOLOGY

Acute Toxicity

Table 8 LD_{50} Values Observed in the Acute Toxicity Studies

Species	Route	Sex	LD_{50}	(95% Confidence Interval)
Mouse	oral	male	650	(445-888) mg/kg
		female	605	(434-840) mg/kg
	i.v.	male	29.3	(26.6-32.7) mg/kg
		female	31.1	(28.3-35.7) mg/kg
Rat (Adult)	oral	male	1,316	(978-1,729) mg/kg
		female	1,250	(263-5,934) mg/kg*
	i.v.	male	18.6	(16.8-22.0) mg/kg
		female	16.8	(14.4-19.4) mg/kg
Rat (Juvenile)	oral	male	3,556	(2731-4885) mg/kg
		female	2,902	(2090-4484) mg/kg
	i.v.	male	23.0	(16.0-32.0) mg/kg
		female	23.1	(16.1-31.8) mg/kg

*90% confidence interval

In an acute oral dose tolerance study in dogs with two animals per dose level, no dogs died at 350 mg/kg, one dog died at 500 mg/kg and both dogs died at 650 mg/kg. In a similar study in cats, no animals died at 60 mg/kg and both cats died at the 100 mg/kg dose level.

Primary symptoms of toxicity were ataxia, attenuated reflexes and tonic-clonic convulsions.

Subacute and Chronic Toxicity

The studies are summarized in **Table 9**. For all studies, animals in each group were equally divided by sex.

Table 9 Summary of Subacute and Chronic Toxicity Studies

Species	Route Of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. Animals Per Dose Group	No. of Deaths per Dose Group	Toxic Effects
Rabbit	i.v.	3 weeks	0	4	0	Dose related reduction in body weight increases and elevated SGPT values were observed in the high dose group. High dose group had significantly increased heart weights with focal muscle cell degeneration. Reduced spermatogenesis was found on histological examination in all groups.
			0.3	4	0	
			0.5	4	0	
			1.0	4	0	
Rat (Wistar)	i.v.	4 weeks	0	30	0	Changes were observed in the 3.5 mg/kg group. Sedation, tremor and reduced alertness were noted as well as reduction in body weight gain and food and water consumption. Clinical laboratory tests revealed decreases in erythrocyte count and serum urea, sodium and phosphorus values. Increases in serum chloride were also noted.
			0.35	30	0	
			1.75	30	0	
			3.5	30	0	
Rat (Wistar)	oral (gavage)	4 weeks	0	20	0	A decrease in serum sodium values was observed in rats receiving 300 mg/kg.
			30	20	0	
			150	20	0	
			300	20	0	
Rat (Wistar)	oral (gastric tube)	6 months	0	30	0	Due to high mortality, the intermediate and high doses were reduced after eight weeks. Death was preceded by weight loss or reduced weight gain. Intermediate doses produced sedation and reduced reflexes. Sedation, apathy, ataxia, impaired coordination, shaggy skin, loose stool and intermittent tonic-clonic convulsions occurred in the high dose group. Histopathology revealed a dose related increase in fatty liver cells and kidney protein cylinders in the tubuli. Nephritis was observed in the high dose group. Focal to complete degeneration of the tubular epithelial cells in the testes was observed equally in all dose groups.
			90	30	0	
			270 (180)	30	3	
			600 (360)	30	11	

Table 9 Summary of Subacute and Chronic Toxicity Studies

Species	Route Of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. Animals Per Dose Group	No. of Deaths per Dose Group	Toxic Effects
Rat (Sprague-Dawley)	oral (gavage)	26 weeks	0 90 180 500 (360)	52 52 52 52	0 0 14 27	Due to high mortality, the high dose was decreased after 6 weeks. Primarily in the high dose group, observations included unkempt coat, sedation, ataxia and apathy. Inhibition of body weight gain occurred in all groups. Inflammatory renal lesions (nephritis and nephrohydrosis) caused by precipitations of propafenone in the upper tubules was noted in several high dose and one intermediate dose animal.
Dog (Beagle)	i.v.	4 weeks	0 0.3 1.0 5.0	6 6 6 6	0 0 0 0	The 5 mg/kg animals showed a reduction in body weight and food consumption and increased restlessness, timidity, anxiety and shaggy coats. Tremor, reduced responses and spontaneous defecation were observed immediately post injection. ECG tracings taken at the end of the study revealed significant heart rate reduction. Laboratory evaluations revealed significantly lowered LDH, BUN, Na, CI and inorganic phosphorus. Complete cessation of spermatogenesis was observed on histopathology.
Dog (Beagle)	i.v.	4 weeks	0 1.0 2.2 5.0	6 6 6 6	0 0 0 0	The 5 mg/kg group showed a decrease in serum potassium.
Dog (Mongrel)	oral	4 weeks	0 20 50 100	2 2 2 2	0 0 0 0	Reduction in body weight and increased heart and liver weights were observed in the high dose group.

Table 9 Summary of Subacute and Chronic Toxicity Studies

Species	Route Of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. Animals Per Dose Group	No. of Deaths per Dose Group	Toxic Effects
Dog (Beagle)	oral	6 months	0 30 120 240 (180) (210) (240)	6 6 6 6	0 0 0 1	The following effects were observed in the 120 mg/kg group: sedation, intermittent tremor, reduced body weight gain and food consumption. Prothrombin time was also shortened. Due to one death and the marked deterioration of remaining animals in the 240 mg/kg group, the dose was reduced to 180 mg/kg at 9 weeks and gradually increased to 240 mg/kg at the thirtieth week. At this dose, animals exhibited apathy, sedation, ataxia, convulsions, vomiting, salivation, diarrhea, reduced body weight gain and food intake, reduced prothrombin time, decreased LDH values and increased uric acid.
Dog (Beagle)	oral	52 weeks	0 30 60 120	10 10 10 10	0 0 1 3	Vomiting was observed in the 60 mg/kg dosed dogs. The 120 mg/kg dogs exhibited vomiting, ataxia and tremor with tonic-clonic spasm. Biochemical analysis showed decreased total protein and globulins. One animal at 60 mg/kg and 3 animals at 120 mg/kg died. Probable cause of death: circulatory collapse.
Monkey (Rhesus)	i.v.	4 weeks	0 2.0 5.0	4 4 4	0 0 0	A dose related decrease in body weight gain was reported. All animals treated showed a decrease in the ejaculation volume and sperm count. Death of all spermatozoa was observed in the high dose group. The following was observed on histopathology: inhibition of spermatogenesis in the 2.0 mg/kg group and more severe disorders of spermatogenesis (including absence of spermatozoa maturation, severe degree of atypical nucleii with hyperchromasie and an increased number of nucleus pycnosis) in the 5.0 mg/kg dose group. Sperm counts returned to normal within 8 weeks post study.

Mutagenicity and Carcinogenicity

Mutagenicity Study

The mutagenic potential of propafenone was investigated in bacteria in vitro (Salmonella / microsome assay) as well as in Chinese hamsters, rats and mice in vivo. No indication of mutagenic activity was detected in any of these studies.

Carcinogenicity Studies

Propafenone hydrochloride was administered in doses of 60, 180 and 540 (360) mg/kg to NMR mice for 104 weeks. After 21 weeks, the maximum dose was reduced to 360 mg/kg for the remainder of the study. Sprague-Dawley rats were given doses of 30, 90 and 270 mg/kg in the food for 30 months. In these studies propafenone hydrochloride was not carcinogenic.

Reproduction and Teratology

Fertility and General Reproductive Performance

SPF albino rats (24/sex/dose) received 0, 30, 90and 270 mg/kg/day of propafenone hydrochloride (gavage). Males were treated for 70 days prior to mating and females began treatment 14 days prior to mating. Both continued treatment for a maximum of 14 days during the mating period. Propafenone hydrochloride did not produce any adverse effects on fertility but increased the time required for mating.

Male Wistar rats (20/group) and male albino rabbits (10/group) received oral propafenone hydrochloride at doses of 0 or 150 mg/kg (rats) and 0 or 120 mg/kg (rabbits) over 10 weeks (6 days/week). On the last day of treatment in the rat and after termination of treatment in the rabbit, each male was paired with two non-treated females. There was no effect in either species on fertility, mating behaviour, or litter size.

Teratology Studies

Female Wistar rats (20/group) received oral propafenone hydrochloride (gavage) at doses of 0, 90, 270 or 600 mg/kg from the 5th to the 15th day of pregnancy. There was no evidence of teratogenicity at any dose. An embryotoxic effect (i.e. increased resorption rates and decreased fetal weights) was detected at the highest dose level. This dose was already toxic to dams as evidenced by reduced weight gain.

White pregnant female New Zealand rabbits received oral (gavage) propafenone hydrochloride at doses of 0, 15, 30 or 150 mg/kg/day from the 6th to the 18th day of pregnancy. Fetuses of the intermediate and high dose group showed variations (retarded ossification of the skull, the coccygeal vertebra and end-phalanx). The number of resorption and dead fetuses was increased in the high dose group. This dose was toxic to the dam as evidenced by reduced weight gain and increased mortality.

Spermatogenesis

Intravenous administration of propafenone hydrochloride in doses of 0.3, 0.5 and 1.0 mg/kg forthree weeks to NZ-rabbits (two per dose) resulted in reduced spermatogenesis. The dose of 1.0 mg/kg produced degenerated spermatogenic epithelium in the testes of all animals.

Additional studies of spermatogenesis were performed in the monkey, dog and rabbit. After intravenous administration of 2 and 5 mg/kg propafenone hydrochloride per day to monkeys for four weeks, decreased spermatogenesis occurred, but was reversible eight weeks after discontinuation of propafenone hydrochloride. Minor alterations in the spermatogram (oligospermia) were observed in dogs administered 5 mg/kg intravenous for four weeks and rabbits administered 3.5 and 5 mg/kg intravenous for six days. The phenomenon was reversible four weeks after discontinuation of propafenone hydrochloride. No injury to the parenchyma of the testes occurred, nor did electron microscopy demonstrate any changes in the spermatogenic epithelium of rabbits.

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PART III: CONSUMER INFORMATION

[Pr]PROPAFENONE
Propafenone hydrochloride Tablets

This leaflet is part III of a three-part "Product Monograph" published when PROPAFENONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PROPAFENONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

PROPAFENONE is used to control certain types of irregular heartbeats (arrhythmias).

What it does:

PROPAFENONE is a heart rate regulating agent. It acts on the metabolism of the heart muscles to block some of the irregular heartbeats. It also acts as a local anaesthetic, blocks the sodium current and slows down the potential of heart muscles reacting fast.

When it should not be used:

PROPAFENONE should not be used if:

2. you are allergic to any component of PROPAFENONE, including active ingredients and non-active ingredients;
3. you have certain serious heart conditions;
4. you have serious liver failure;
5. you have certain respiratory conditions.

What the medicinal ingredient is:

Propafenone hydrochloride

What the important nonmedicinal ingredients are:

Each film-coated tablet also contains the non-medicinal ingredients: croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, polyethylene glycol and titanium dioxide.

What dosage forms it comes in:

PROPAFENONE is available as film-coated tablets in the following strengths: 150 mg and 300 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- PROPAFENONE is intended for use only in patients with lifethreatening irregular heartbeats (arrhythmias). Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increase of sudden death. Your doctor will tell you about the risk and benefits of anti-arrhythmic therapy.

BEFORE you use PROPAFENONE talk to your doctor or pharmacist if:

- you are pregnant or planning to become pregnant, or you are breast-feeding;
- you have any heart disease;
- you have abnormal blood cell counts;
- you have abnormal liver function;
- you have neuromuscular disease (e.g. myasthenia gravis);
- you have kidney disease;
- you have allergies to this drug or any of its ingredients.
- you perform tasks which require special attention (for example, driving automobile or operating dangerous machinery) because blurred vision, dizziness, fatigue and low blood pressure are common side effects associated with the administration of PROPAFENONE.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PROPAFENONE include:

- beta-blockers (e.g. propanolol, metoprolol);
- digoxin, venlafaxine, rifampin, cimetidine, quinidine, ketoconazole, erythromycin, amiodarone, phenobarbital;
- anticoagulants (e.g. warfarin);
- certain local anesthetics (e.g. lidocaine);
- certain antidepressants of the tricyclic group (e.g. desipramine), and other antidepressants (e.g. fluoxetine, paroxetine, fluvoxamine);
- some medication that can affect your immune system (e.g. cyclopsorine);

- some HIV-antiviral medication (e.g. ritonavir, lopinavir/ritonavir);
- grapefruit juice.

PROPER USE OF THIS MEDICATION

Usual dose:

Dosage must be individualized. The usual adult dose of PROPAFENONE is 150 mg which is to be taken every 8 hours, however your doctor may decide on different individual dosing.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take one tablet, take another as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all.

Never double-up on a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its needed effects, a medicine may cause some unwanted effects. These are referred to as "side effects". Although not all of these side effects may occur, if they do occur they may need medical attention.

The most common side effects with PROPAFENONE are dizziness, feeling sick (nausea), vomiting, unusual taste and constipation. Other less common side effects may include headaches, blurred vision, abnormal muscular control (ataxia), difficulty in sleeping, tremor, drowsiness, dyspepsia, dry mouth, loss of appetite, abdominal pain/cramping, flatulence, tiredness, skin rash, weakness, chest pain, anxiety, severe sweating and pain in the joints.

Check with your physician or pharmacist if you experience any unexpected effects, or are concerned by the above side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist as soon as possible
		Only if severe	In all cases	
Common	chest pain, irregular heart beats		√	√
	dizziness, lightheadedness, fainting		√	√
	liver problems (e.g., yellowing skin or eyes, prolonged vomiting and nausea or abdominal pain)		√	√
	bleeding problem (excessive bruising, easy bleeding)		√	√

This is not a complete list of side effects. For any unexpected effects while taking PROPAFENONE, contact your doctor or pharmacist.

Check with your pharmacist or doctor **immediately**, if you experience any of the above symptoms of the serious side effects.

HOW TO STORE IT

Keep PROPAFENONE and all other medicines out of reach of children.

PROPAFENONE tablets should be stored at room temperature 15 to 30°C (59 to 86°F).

Do not take your tablets after the expiry date shown on the label.

It is important to keep the PROPAFENONE tablets in the original package.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to : Canada Vigilance Program
    Health Canada
    Address Locator: 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcnada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting Pro Doc Ltée at 1-800-361-8559, http://www.prodoc.qc.ca or info@prodoc.qc.ca.

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