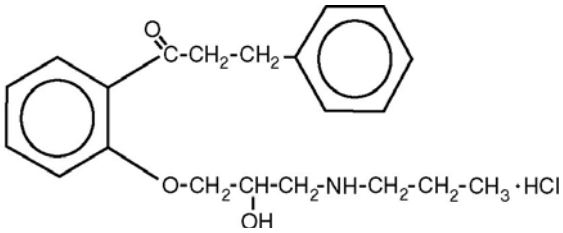
PRESCRIBING INFORMATION

RYTHMOL® SR
(propafenone hydrochloride)
Extended Release Capsules

DESCRIPTION

RYTHMOL SR (propafenone hydrochloride) is an antiarrhythmic drug supplied in extended-release capsules of 225, 325 and 425 mg for oral administration.

The structural formula of propafenone HCl is given below:



Chemically, propafenone hydrochloride is 2'-[2-Hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride, with a molecular weight of 377.92. The molecular formula is $C_{21}H_{27}NO_3$•HCl.Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone HCl occurs as colorless crystals or white crystalline power with a very bitter taste. It is slightly soluble in water (20°C), chloroform, and ethanol. RYTHMOL SR capsules are filled with cylindrical-shaped 2 x 2 mm microtablets containing propafenone and the following inactive ingredients: antifoam, gelatin, hypromellose, red iron oxide, magnesium stearate, shellac, sodium lauryl sulfate, sodium dodecyl sulfate, soy lecithin, and titanium dioxide.

CLINICAL PHARMACOLOGY

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 with the immediate-release formulation, 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 to propafenone, 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).

Electrophysiology: Electrophysiology studies in patients with ventricular tachycardia (VT) have shown that propafenone prolongs atrioventricular (AV) conduction while having little or no effect on sinus node function. Both atrioventricular (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 Wolff-Parkinson-White (WPW) syndrome, RYTHMOL immediate-release tablets reduce conduction and increase the effective refractory period of the accessory pathway in both directions (see ADVERSE REACTIONS, *Electrocardiograms*).

Hemodynamics: 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 (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 does recommended oral dosing), showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances, and depression of cardiac output and cardiac index.

Pharmacokinetics and Metabolism: *Absorption/Bioavailability:* Maximal plasma levels of propafenone are reached between 3 to 8 hours following the administration of RYTHMOL SR. Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose- and dosage form-dependent absolute bioavailability; e.g., a 150-mg immediate-release tablet had an absolute bioavailability of 3.4%, while a 300-mg immediate-release tablet had an absolute bioavailability of 10.6%. Absorption from a 300-mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate-release tablets increased still further.

Relative bioavailability assessments have been performed between RYTHMOL SR capsules and RYTHMOL immediate-release tablets. In extensive metabolizers, the bioavailability of propafenone from the SR formulation was less than that of the immediate-release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase of overall first-pass metabolism (see CLINICAL PHARMACOLOGY, *Metabolism*). As a result of the increased first-pass effect, higher daily doses of propafenone were required from

the SR formulation relative to the immediate-release formulation, to obtain similar exposure to propafenone. The relative bioavailability of propafenone from the 325 twice-daily regimen of RYTHMOL SR approximates that of RYTHMOL immediate-release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20 to 25% higher after SR capsule administration than after immediate-release tablet administration.

Food increased the exposure to propafenone 4-fold after single dose administration of 425 mg of RYTHMOL SR. However, in the multiple dose study (425 mg dose twice daily), the difference between the fed and fasted state was not significant.

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. Protein binding decreases to about 88% in patients with severe hepatic dysfunction.

Metabolism: There are 2 genetically determined patterns of propafenone metabolism. In more than 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 2 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.

As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics are linear. 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 of RYTHMOL SR is the same for all patients. The larger inter-subject variability in blood levels require that the dose of the drug be

titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see DOSAGE AND ADMINISTRATION).

The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiologic properties similar to propafenone in vitro. In man after administration of RYTHMOL SR, the 5-hydroxypropafenone metabolite is usually present in concentrations less than 40% of propafenone. The norpropafenone metabolite is usually present in concentrations less than 10% of propafenone.

Inter-Subject Variability: With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first-pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of RYTHMOL SR capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.

The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (see PRECAUTIONS). Decreased liver function also increases the bioavailability of propafenone. Absolute bioavailability assessments have not been determined for the RYTHMOL SR capsule formulation. Absolute bioavailability of RYTHMOL immediate-release tablets has been demonstrated to be inversely related to indocyanine green clearance, reaching 60 to 70% at clearances of 7 mL/min and below.

Stereochemistry: RYTHMOL 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 β-antagonist than the R-enantiomer. Following administration of RYTHMOL immediate-release tablets or RYTHMOL SR capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1.7. The S/R ratios of propafenone obtained after administration of 225, 325, and 425 mg RYTHMOL SR are independent of dose. In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time.

CLINICAL TRIALS

RYTHMOL SR has been evaluated in patients with a history of electrocardiographically documented recurrent episodes of symptomatic atrial fibrillation in 2 randomized, double-blind, placebo-controlled trials.

RAFT: In one US multicenter study (Rythmol SR Atrial Fibrillation Trial, RAFT), 3 doses of RYTHMOL SR (225 mg twice daily, 325 mg twice daily and 425 mg twice daily) and placebo were compared in 523 patients with symptomatic, episodic atrial fibrillation. The patient

population in this trial was 59% male with a mean age of 63 years, 91% white and 6% black. The patients had a median history of atrial fibrillation of 13 months, and documented symptomatic atrial fibrillation within 12 months of study entry. More than 90% were NYHA Class I, and 21% had a prior electrical cardioversion. At baseline, 24% were treated with calcium channel blockers, 37% with beta blockers, and 38% with digoxin. Symptomatic arrhythmias after randomization were documented by transtelephonic electrocardiogram and centrally read and adjudicated by a blinded adverse event committee. RYTHMOL SR administered for up to 39 weeks was shown to prolong significantly the time to the first recurrence of symptomatic atrial arrhythmia, predominantly atrial fibrillation, from Day 1 of randomization (primary efficacy variable) compared to placebo, as shown in Table 1.

Table 1. Analysis of Tachycardia-Free Period (Days) From Day 1 of Randomization

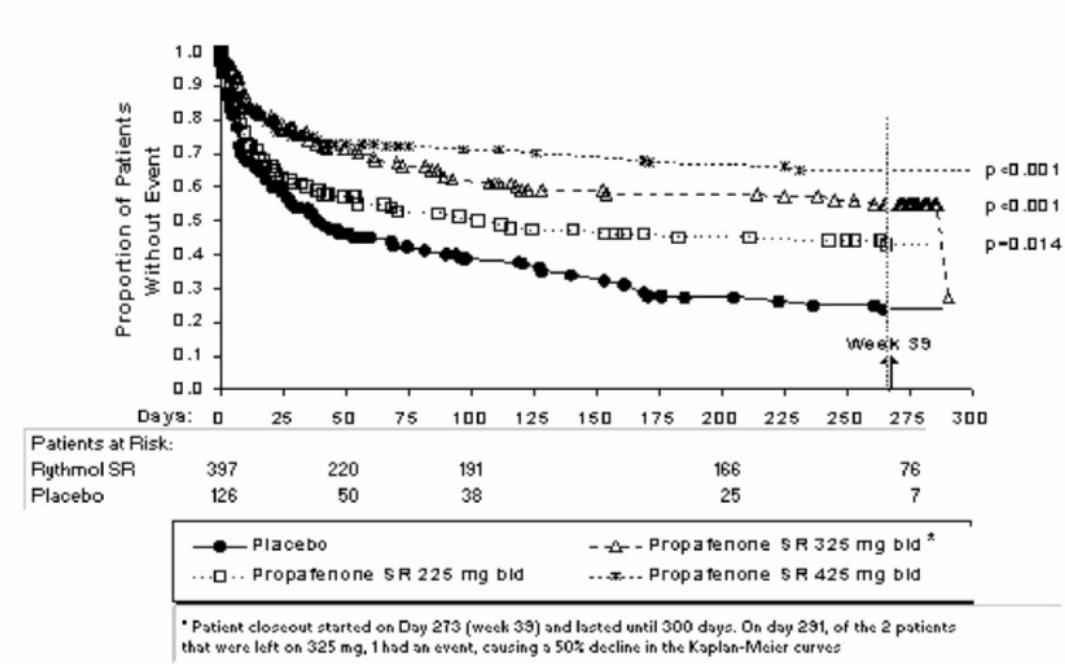
	RYTHMOL SR Dose			
Parameter	225 mg twice daily (N = 126) n (%)	325 mg twice daily (N = 135) n (%)	425 mg twice daily (N = 136) n (%)	Placebo (N = 126) n (%)
Patients completing with terminating event*	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier median	112	291	†	41
Range	0 - 285	0 - 293	0 - 300	0 – 289
p-Value (Log-rank test)	0.014	<0.0001	<0.0001	--
Hazard ratio compared to placebo	0.67	0.43	0.35	--
95% CI for hazard ratio	(0.49, 0.93)	(0.31, 0.61)	(0.24, 0.51)	--

*Fewer than 50% of the patients had events. The median time is not calculable.

†Terminating events comprised 91% atrial fibrillation, 5% atrial flutter, and 4% PSVT.

There was a dose response for RYTHMOL SR for the tachycardia-free period as shown in the proportional hazard analysis and the Kaplan-Meier curves presented in Figure 1.

Figure 1. RAFT Kaplan-Meier Analysis for the Tachycardia-Free Period From Day 1 of Randomization:



In additional analyses, RYTHMOL SR (225 mg twice daily, 325 mg twice daily, and 425 mg twice daily) was also shown to prolong time to the first recurrence of symptomatic atrial fibrillation from Day 5 (steady-state pharmacokinetics were attained). The antiarrhythmic effect of RYTHMOL SR was not influenced by age, gender, history of cardioversion, duration of atrial fibrillation, frequency of atrial fibrillation, or use of medication that lowers heart rate. Similarly, the antiarrhythmic effect of RYTHMOL SR was not influenced by the individual use of calcium channel blockers, beta-blockers, or digoxin. Too few non-white patients were enrolled to assess the influence of race on effects of RYTHMOL SR.

No difference in the average heart rate during the first recurrence of symptomatic arrhythmia between RYTHMOL SR and placebo was observed.

ERAFT: In a European multicenter trial [European Rythmonorm SR Atrial Fibrillation Trial (ERAFT)], 2 doses of RYTHMOL SR (325 mg twice daily and 425 mg twice daily) and placebo were compared in 293 patients. The patient population in this trial was 61% male, 100% white with a mean age of 61 years. Patients had a median duration of atrial fibrillation of 3.3 years, and 61% were taking medications that lowered heart rate. At baseline, 15% of the patients were treated with calcium channel blockers (verapamil and diltiazem), 42% with beta-blockers and 8% with digoxin. During a qualifying period of up to 28 days, patients had to have one ECG-documented incident of symptomatic atrial fibrillation. The double-blind treatment phase consisted of a 4-day loading period followed by a 91-day efficacy period. Symptomatic arrhythmias were documented by electrocardiogram monitoring.

In ERAFT, RYTHMOL SR was shown to prolong the time to the first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization (primary efficacy analysis). The proportional hazard analysis revealed that both RYTHMOL SR doses were superior to placebo. The antiarrhythmic effect of propafenone SR was not influenced by age, gender, duration of atrial fibrillation, frequency of atrial fibrillation, or use of medication that lowers heart rate. It was also not influenced by the individual use of calcium channel blockers, beta-blockers, or digoxin. Too few non-white patients were enrolled to assess the influence of race on the effects of RYTHMOL SR. There was a slight increase in the incidence of centrally diagnosed asymptomatic atrial fibrillation or atrial flutter in each of the 2 groups treated with RYTHMOL SR compared to placebo.

INDICATIONS AND USAGE

RYTHMOL SR is indicated to prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease.

The use of RYTHMOL SR in patients with permanent atrial fibrillation or in patients exclusively with atrial flutter or PSVT has not been evaluated. RYTHMOL SR should not be used to control ventricular rate during atrial fibrillation.

The effect of RYTHMOL SR on mortality has not been determined (see black box WARNINGS).

CONTRAINDICATIONS

RYTHMOL SR is contraindicated in the presence of congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular, and intraventricular disorders of impulse generation or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, electrolyte imbalance, or 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 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest rate (7.7%; 56/730) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared with that seen in patients assigned to placebo (3.0%; 22/725). The average duration of treatment with encainide or flecainide in this study was 10 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 has caused new or worsened arrhythmias. Such proarrhythmic effects include sudden death and life-threatening ventricular arrhythmias such as ventricular fibrillation, ventricular tachycardia, asystole and torsade de pointes. It may also worsen premature ventricular contractions or supraventricular arrhythmias, and it may prolong the QT interval. It is therefore essential that each patient given RYTHMOL SR be evaluated electrocardiographically prior to and during therapy, to determine whether the response to RYTHMOL SR supports continued treatment. Because propafenone prolongs the QRS interval in the electrocardiogram, changes in the QT interval are difficult to interpret.

In a 474 patient US uncontrolled, open-label multicenter trial using the immediate-release formulation in patients with symptomatic SVT, 1.9% (9/474) of these patients experienced ventricular tachycardia (VT) or ventricular fibrillation (VF) during the study. However, in 4 of the 9 patients, the ventricular tachycardia was of atrial origin. Six of the 9 patients that developed ventricular arrhythmias did so within 14 days of onset of therapy. About 2.3% (11/474) of all patients had recurrence of SVT during the study which could have been a change in the patients' arrhythmia behavior or could represent a proarrhythmic event. Case reports in patients treated with RYTHMOL for atrial fibrillation/flutter have included increased PVCs, VT, VF, torsade de pointes, asystole, and death.

In the RAFT study, there were 5 deaths, 3 in the pooled RYTHMOL SR group (0.8%) and 2 in the placebo group (1.6%). In the overall RYTHMOL SR and RYTHMOL immediate-release database of 8 studies, the mortality rate was 2.5% per year on RYTHMOL and 4.0% per year on placebo. Concurrent use of propafenone with other antiarrhythmic agents has not been well studied.

Use With Drugs That Prolong the QT Interval and Antiarrhythmic Agents: The use of RYTHMOL SR in conjunction with other drugs that prolong the QT interval has not been

extensively studied and is not recommended. Such drugs may include many antiarrhythmics, some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and oral macrolides. Class Ia and III antiarrhythmic agents should be withheld for at least 5 half-lives prior to dosing with RYTHMOL SR. The use of propafenone with Class Ia and III antiarrhythmic agents (including quinidine and amiodarone) is not recommended. There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics.

Nonallergic Bronchospasm (e.g., Chronic Bronchitis, Emphysema): Patients with bronchospastic disease should not, in general, receive propafenone or other agents with beta-adrenergic-blocking activity.

Congestive Heart Failure: Propafenone exerts a negative inotropic activity on the myocardium as well as beta-blockade effects and may provoke overt congestive heart failure. In the US trial (RAFT) in patients with symptomatic atrial fibrillation, congestive heart failure was reported in four (1.0%) patients receiving RYTHMOL SR (all doses), compared to one (0.8%) patient receiving placebo. Proarrhythmic effects are more likely to occur when propafenone is administered to patients with congestive heart failure (NYHA III and IV) or severe myocardial ischemia (see CONTRAINDICATIONS).

Conduction Disturbances: Propafenone causes dose-related first-degree AV block. Average PR interval prolongation and increases in QRS duration are also dose-related.

Propafenone should not be given to patients with atrioventricular and intraventricular conduction defects in the absence of a pacemaker (see CONTRAINDICATIONS).

In a US trial (RAFT) in 523 patients with a history of symptomatic atrial fibrillation treated with RYTHMOL SR, electrocardiograms obtained in response to symptoms were associated with no patients having sinus rhythm with Mobitz Type I (Wenckenbach) second degree AV block, sinus rhythm with Mobitz Type II second degree AV block, or third degree AV block. Sinus bradycardia (rate <50 beats/min) was reported with the same frequency with RYTHMOL SR and placebo.

Effects on Pacemaker Threshold: Propafenone 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 2 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 3 months of therapy, warrant consideration of possible agranulocytosis or granulocytopenia. Patients should be instructed to report promptly 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% in patients with normal liver function when given RYTHMOL immediate-release tablets. In 8 patients with moderate to severe liver disease administered RYTHMOL immediate-release tablets, the mean half-life was approximately 9 hours. No studies are currently available comparing bioavailability of propafenone from RYTHMOL SR in patients with normal and impaired hepatic function. Increased bioavailability of propafenone in these patients may result in excessive accumulation. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be performed for patients with impaired hepatic function.

Renal Dysfunction: Approximately 50% of propafenone metabolites are excreted in the urine following administration of RYTHMOL immediate-release tablets. No studies have been performed to assess the percentage of metabolites eliminated in the urine following the administration of RYTHMOL SR capsules.

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

Information for Patients: ***Medications and Supplements:*** Assessment of patients' medication history should include all over-the-counter, prescription, and herbal/natural preparations with emphasis on preparations that may affect the pharmacodynamics or kinetics of RYTHMOL SR (see WARNINGS, Use With Drugs That Prolong QT Interval and Antiarrhythmic Agents). Patients should be instructed to notify their healthcare providers of any change in over-the-counter, prescription, and supplement use. If a patient is hospitalized, or is prescribed new medication for any condition, the patient must inform the healthcare provider of ongoing therapy with RYTHMOL SR. Patients should also check with their healthcare providers prior to taking a new over-the-counter medicine.

Electrolyte Imbalance: If patients experience symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, vomiting, or loss of appetite or thirst, these conditions should be immediately reported to their healthcare provider.

Dosing Schedule: Patients should be instructed NOT to double the next dose if a dose is missed. The next dose should be taken at the usual time.

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 erythematosus (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 of propafenone. Evaluation of the effects of short-term administration of propafenone on spermatogenesis in 11 normal subjects suggested that propafenone produced a reversible, short-

term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving RYTHMOL chronically have found no effect of propafenone on sperm count.

Neuromuscular Dysfunction: Exacerbation of myasthenia gravis has been reported during therapy with RYTHMOL immediate-release tablets.

Drug Interactions: Propafenone is metabolized by CYP2D6 (major pathway) and CYP1A2 and CYP3A4. Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline), CYP1A2 (such as amiodarone), and CYP3A4 (such as ketaconazole, ritonavir, saquinavir, erythromycin, and grapefruit juice) can be expected to cause increased plasma levels of propafenone. Appropriate monitoring is recommended when RYTHMOL SR is used together with such drugs. In addition, propafenone is an inhibitor of CYP2D6. Coadministration of propafenone with drugs metabolized by CYP2D6 (such as desipramine, imipramine, haloperidol, venlafaxine) might lead to increased plasma concentrations of these drugs. The effect of propafenone on the P-Glycoprotein transporter has not been studied.

Quinidine: Small doses of quinidine completely inhibit the CYP2D6 hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (see CLINICAL PHARMACOLOGY). Concomitant administration of quinidine (50 mg three times daily) with 150 mg immediate-release propafenone three times daily decreased the clearance of propafenone by 60% in extensive metabolizers, making them poor metabolizers. Steady-state plasma concentrations increased by more than 2-fold for propafenone, and decreased 50% for 5-OH-propafenone. A 100-mg dose of quinidine increased steady state concentrations of propafenone 3-fold. Concomitant use of propafenone and quinidine is not recommended.

Digoxin: Concomitant use of propafenone and digoxin increased steady-state serum digoxin exposure (AUC) in patients by 60 to 270%, and decreased the clearance of digoxin by 31 to 67%. Plasma digoxin levels of patients receiving propafenone should be monitored and digoxin dosage adjusted as needed.

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.

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, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects.

Warfarin: The concomitant administration of propafenone and warfarin increased warfarin plasma concentrations at steady state by 39% in healthy volunteers and prolonged the prothrombin time in patients taking warfarin. Adjustment of the warfarin dose should be guided by monitoring of the prothrombin time.

Cimetidine: Concomitant administration of propafenone immediate-release tablets and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone.

Rifampin: Concomitant administration of rifampin and propafenone in extensive metabolizers decreased the plasma concentrations of propafenone by 67% with a corresponding decrease of 5OH-propafenone by 65%. The concentrations of norpropafenone increased by 30%. In poor metabolizers, there was a 50% decrease in propafenone plasma concentrations and an increase in AUC and C_{max} of norpropafenone by 74 and 20%, respectively. Urinary excretion of propafenone and its metabolites decreased significantly. Similar results were noted in elderly patients: Both the AUC and C_{max} of propafenone decreased by 84%, with a corresponding decrease in AUC and C_{max} of 5OH-propafenone by 69 and 57%.

Fluoxetine: Concomitant administration of propafenone 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%, respectively.

Amiodarone: Concomitant administration of propafenone and amiodarone can affect conduction and repolarization and is not recommended.

Postmarketing Reports: Orlistat may limit the fraction of propafenone available for absorption. In postmarketing reports, abrupt cessation of orlistat in patients stabilized on propafenone has resulted in severe adverse events including convulsions, atrioventricular block, and acute circulatory failure.

Renal and Hepatic Toxicity in Animals: 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 maximum recommended human daily dose [MRHD] on a mg/m^2 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/m^2 basis). There were no renal or hepatic changes at 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day, about twice the maximum recommended human oral daily dose [MRHD] on a mg/m^2 basis) and rats (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m^2 basis) provided no evidence of a carcinogenic potential for propafenone HCl.

Propafenone HCl tested negative for mutagenicity in the Ames (salmonella) test and in the in vivo mouse dominant lethal test. It tested negative for clastogenicity in the human lymphocyte chromosome aberration assay in vitro and in 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 HCl, 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 HCl, were seen at lethal or near lethal dose levels and were not seen in rats treated either orally or intravenously (see PRECAUTIONS, Impaired Spermatogenesis). Treatment of male rabbits for 10 weeks prior to mating at an oral dose of 120 mg/kg/day (about 2.4 times the MRHD on a mg/m^2 basis) or an intravenous dose of 3.5 mg/kg/day (a spermatogenesis-impairing dose) did not result in evidence of impaired fertility. Nor was there evidence of impaired fertility when propafenone HCl was administered orally to male and female rats at dose levels up to 270 mg/kg/day (about 3 times the MRHD on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C.*** Propafenone HCl has been shown to be embryotoxic (decreased survival) in rabbits and rats when given in oral maternally toxic doses of 150 mg/kg/day (about 3 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and 600 mg/kg/day (about 6 times the MRHD on a mg/m^2 basis), respectively. Although maternally tolerated doses (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m^2 basis) produced no evidence of embryotoxicity in rats, post-implantation loss was elevated in all rabbit treatment groups (doses as low as 15 mg/kg/day, about 1/3 the MRHD on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. RYTHMOL SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects: In a study in which female rats received daily oral doses of propafenone HCl from mid-gestation through weaning of their offspring, doses as low as 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis) produced increases in maternal deaths. Doses of 360 or more mg/kg/day (4 or more times the MRHD on a mg/m^2 basis) resulted in reductions in neonatal survival, body weight gain, and 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: Propafenone is excreted in human milk. Caution should be exercised when RYTHMOL SR is administered to a nursing mother.

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

Geriatric Use: Of the total number of subjects in Phase III clinical studies of RYTHMOL SR 45.7 percent were 65 and older, while 15.7 percent were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals at higher doses cannot be ruled out. The effect of age on the pharmacokinetics and pharmacodynamics of propafenone has not been studied.

ADVERSE REACTIONS

The data described below reflect exposure to RYTHMOL SR 225 mg twice daily in 126 patients, to RYTHMOL SR 325 mg twice daily in 135 patients, to RYTHMOL SR 425 mg twice daily in 136 patients, and to placebo in 126 patients for up to 39 weeks in a placebo-controlled

trial (RAFT) conducted in the US. The most commonly reported adverse events in the trial included dizziness, chest pain, palpitations, taste disturbance, dyspnea, nausea, constipation, anxiety, fatigue, upper respiratory tract infection, influenza, first-degree heart block, and vomiting. The frequency of discontinuation due to adverse events was highest during the first 14 days of treatment. The majority of the patients with serious adverse events who withdrew or were discontinued recovered without sequelae.

Adverse events occurring in 2% or more of the patients in any of the RAFT propafenone SR treatment groups and more common with propafenone than with placebo, excluding those that are common in the population and those not plausibly related to drug therapy, are listed in Table 2.

Table 2. Most Common Adverse Events (≥2.0% in any RAFT Propafenone SR Treatment Group and More Common on Propafenone Than on Placebo)

	RYTHMOL SR			
MeDRA Body System/Preferred Term	225 mg twice daily (N = 126) n (%)	325 mg twice daily (N = 135) n (%)	425 mg twice daily (N = 136) n (%)	Placebo (N = 126) n (%)
Mean exposure (days)	124	149	141	91
Cardiac disorders				
Angina pectoris	0 (0)	0 (0)	3 (2)	0 (0)
Atrial flutter	3 (2)	2 (1)	0 (0)	1 (1)
AV block first degree	3 (2)	3 (2)	4 (3)	0 (0)
Bradycardia	4 (3)	4 (3)	6 (4)	1 (1)
Cardiac failure congestive	0 (0)	1 (1)	3 (2)	1 (1)
Cardiac murmur	2 (2)	3 (2)	6 (4)	0 (0)
Edema	6 (5)	18 (13)	10 (7)	8 (6)
Eye disorders				
Vision blurred	1 (1)	1 (1)	5 (4)	0 (0)
Gastrointestinal disorders				
Constipation	10 (8)	19 (14)	16 (12)	3 (2)
Diarrhea	2 (2)	3 (2)	5 (4)	3 (2)
Dry mouth	1 (1)	1 (1)	5 (4)	1 (1)
Flatulence	3 (2)	3 (2)	1 (1)	0 (0)
Nausea	11 (9)	15 (11)	23 (17)	11 (9)
Vomiting	1 (1)	0 (0)	8 (6)	3 (2)
General disorder and administration site				
Fatigue	14 (11)	17 (13)	17 (13)	7 (6)

Weakness	4 (3)	6 (4)	6 (4)	3 (2)
Infections and infestations				
Upper respiratory tract infection	11 (9)	16 (12)	11 (8)	7 (6)
Investigations				
Blood alkaline phosphatase increased	0 (0)	0 (0)	4 (3)	0 (0)
Cardioactive drug level above therapeutic	1 (1)	1 (1)	3 (2)	1 (1)
Hematuria	2 (2)	2 (1)	4 (3)	3 (2)
Musculoskeletal, connective tissue and bone				
Muscle weakness	1 (1)	5 (4)	1 (1)	0 (0)
Nervous system disorders				
Dizziness (excluding vertigo)	29 (23)	28 (21)	29 (21)	18 (14)
Headache	8 (6)	12 (9)	14 (10)	11 (9)
Taste disturbance	7 (6)	18 (13)	30 (22)	1 (1)
Tremor	2 (2)	0 (0)	3 (2)	1 (1)
Somnolence	1 (1)	1 (1)	4 (3)	0 (0)
Psychiatric disorders				
Anxiety	12 (10)	17 (13)	16 (12)	13 (10)
Depression	1 (1)	4 (3)	0 (0)	2 (2)
Respiratory, thoracic and mediastinal disorder				
Dyspnea	16 (13)	23 (17)	17 (13)	9 (7)
Rales	2 (2)	1 (1)	3 (2)	0 (0)
Wheezing	0 (0)	0 (0)	3 (2)	0 (0)
Skin and subcutaneous tissue disorders				
Ecchymosis	2 (2)	3 (2)	5 (4)	0 (0)

No clinically important differences in incidence of adverse reactions were noted by age, or gender. Too few non-white patients were enrolled to assess adverse events according to race. Adverse events occurring in 2% or more of the patients in any of the ERAFT propafenone SR treatment groups and not listed in Table 2 include the following: bundle branch block left, bundle branch block right, conduction disorders, sinus bradycardia, and hypotension.

Other adverse events reported with propafenone clinical trials not already listed in Table 2 include the following adverse events by body and preferred term.

Blood and Lymphatic System Disorders: Anemia, lymphadenopathy, spleen disorder, thrombocytopenia.

Cardiac Disorders: Angina unstable, arrhythmia, atrial hypertrophy, atrioventricular block, bundle branch block, bunch branch block left, bundle branch block right, cardiac arrest, cardiac disorder, conduction disorder, coronary artery disease, extrasystoles, myocardial infarction, nodal arrhythmia, palpitations, pericarditis, sinoatrial block, sinus arrest, sinus arrhythmia, sinus bradycardia, supraventricular extrasystoles, supraventricular tachycardia, ventricular arrhythmia, ventricular extrasystoles, ventricular hypertrophy.
Ear and Labyrinth Disorders: Hearing impaired, tinnitus, vertigo.
Eye Disorders: Eye hemorrhage, eye inflammation, eyelid ptosis, miosis, retinal disorder, visual acuity reduced.
Gastrointestinal Disorders: Abdominal distension, abdominal pain, dry throat, duodenitis, dyspepsia, dysphagia, eructation, gastritis, gastroesophageal reflux disease, gingival bleeding, glossitis, glossodynia, gum pain, halitosis, intestinal obstruction, melena, mouth ulceration, pancreatitis, peptic ulcer, rectal bleeding, sore throat.
General Disorders and Administration Site Conditions: Chest pain, feeling hot, hemorrhage, malaise, pain, pyrexia.
Hepatobiliary Disorders: Hepatomegaly.
Investigations: Abnormal electrocardiogram, abnormal heart sounds, abnormal liver function tests, abnormal pulse, carotid bruit, decreased blood chloride, decreased blood pressure, decreased blood sodium, decreased hemoglobin, decreased neutrophil count, decreased platelet count, decreased prothrombin level, decreased red blood cell count, decreased weight, electrocardiogram QT prolonged, glycosuria present, heart rate irregular, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, increased blood cholesterol, increased blood creatinine, increased blood glucose, increased blood lactate dehydrogenase, increased blood pressure, increased blood prolactin, increased blood triglycerides, increased blood urea, increased blood uric acid, increased eosinophil count, increased gamma-glutamyltransferase, increased monocyte count, increased prostatic specific antigen, increased prothrombin level, increased weight, increased white blood cell count, ketonuria present, proteinuria present.
Metabolism and Nutrition Disorders: Anorexia, dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypokalemia.
Musculoskeletal, Connective Tissue and Bone Disorders: Arthritis, bursitis, collagen-vascular disease, costochondritis, joint disorder, muscle cramps, muscle spasms, myalgia, neck pain, pain in jaw, sciatica, tendonitis.
Nervous System Disorders: Amnesia, ataxia, balance impaired, brain damage, cerebrovascular accident, dementia, gait abnormal, hypertonia, hypothesia, insomnia, paralysis, paresthesia, peripheral neuropathy, speech disorder, syncope, tongue hypoesthesia.
Psychiatric Disorders: Decreased libido, emotional disturbance, mental disorder, neurosis, nightmare, sleep disorder.
Renal and Urinary Disorders: Dysuria, nocturia, oliguria, pyuria, renal failure, urinary casts, urinary frequency, urinary incontinence, urinary retention, urine abnormal.

Reproductive System and Breast Disorders: Breast pain, impotence, prostatism.
Respiratory, Thoracic and Mediastinal Disorders Disorders: Atelectasis, breath sounds decreased, chronic obstructive airways disease, cough, epistaxis, hemoptysis, lung disorder, pleural effusion, pulmonary congestion, rales, respiratory failure, rhinitis, throat tightness.
Skin and Subcutaneous Tissue Disorders: Alopecia, dermatitis, dry skin, erythema, nail abnormality, petechiae, pruritis, sweating increased, urticaria.
Vascular Disorders: Arterial embolism limb, deep limb venous thrombosis, flushing, hematoma, hypertension, hypertensive crisis, hypotension, labile blood pressure, pallor, peripheral coldness, peripheral vascular disease, thrombosis.
Laboratory: *Electrocardiograms:* Propafenone prolongs the PR and QRS intervals in patients with atrial and ventricular arrythmias. Prolongation of the QRS interval makes it difficult to interpret the effect of propafenone on the QT interval.

Table 3. Mean Change in 12-Lead Electrocardiogram Results (RAFT)

	RYTHMOL SR twice-daily dosing			
	225 mg	325 mg	425 mg	**Placebo**
	n = 126	n = 135	n = 136	n = 126
PR (ms)	9±22	12±23	21±24	1±16
QRS (ms)	4±14	6±15	6±15	-2±12
QTc* (ms)	2±30	5±36	6±37	5±35

* Calculated using Bazett's correction factor

In RAFT, the distribution of the maximum changes in QTc compared to baseline over the study in each patient was similar in the RYTHMOL SR 225 mg twice daily, 325 mg twice daily, and 425 mg twice daily and placebo dose groups. Similar results were seen in the ERAFT study.

Table 4. Number of Patients According to the Range of Maximum QTc Change Compared to Baseline Over the Study in Each Dose Group (RAFT Study)

Range maximum QTc change	RYTHMOL SR			Placebo
	225 mg twice daily	325 mg twice daily	425 mg twice daily	
	N = 119	N = 129	N = 123	N = 120
	n (%)	n (%)	n (%)	n (%)
>20%	1 (1%)	6 (5%)	3 (2%)	5 (4%)
10-20%	19 (16%)	28 (22%)	32 (26%)	24 (20%)
≤10%	99 (83%)	95 (74%)	88 (72%)	91 (76%)

OVERDOSAGE

The symptoms of overdosage 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 abnormal ventricular 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 hemodialysis 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 (>95%) and large volume of distribution.

DOSAGE AND ADMINISTRATION

The dose of RYTHMOL SR must be individually titrated on the basis of response and tolerance. Therapy should be initiated with RYTHMOL SR 225 mg given every 12 hours. Dosage may be increased at a minimum of 5-day interval to 325 mg given every12 hours. If additional therapeutic effect is needed, the dose of RYTHMOL SR may be increased to 425 mg given every 12 hours.

In patients with hepatic impairment or having significant widening of the QRS complex or second or third degree AV block, dose reduction should be considered.

RYTHMOL SR can be taken with or without food. Do not crush or further divide the contents of the capsule.

HOW SUPPLIED

RYTHMOL® SR (propafenone HCl) capsules are supplied as white, opaque, hard-gelatin capsules containing either 225 mg, 325 mg, or 425 mg of propafenone HCl and imprinted in red with Reliant PHARMACEUTICALS, INC. and strength. The 325-mg strength is also imprinted with a single red band

around ¾ of the circumference of the body; the 425-mg strength is imprinted with three bands around ¾ of the circumference of the body.

Capsule Strength	60 count bottle NDC
225 mg	0173-0786-01
325 mg	0173-0788-01
425 mg	0173-0789-01

Storage: Store at 25°C (77°F); excursions permitted to 15°to 30°C (59°to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

RYTHMOL is a registered trademark of G. Petrik used under license by Abbott Laboratories.

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Manufactured by:
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November 2008 RMS:2PI