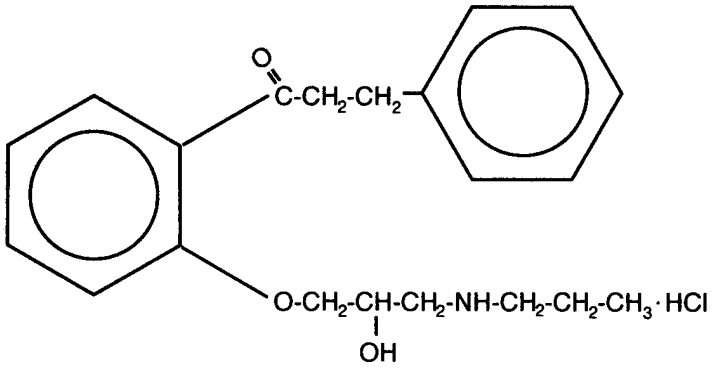
(Nos. 6134, 6135, 6136)
NEW

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:



$C_{21}H_{27}NO_3 \cdot HCl$ M.W. = 377.92

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

Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone HCl occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20ºC), chloroform and ethanol. Rythmol SR are capsules 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 µg/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 three to eight 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 in overall first pass metabolism (See **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 regimens of RYTHMOL SR approximates that of RYTHMOL immediate release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20-25% 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 BID), 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 two-compartment pharmacokinetic model. The average distribution half-life corresponding to the first phase was about five 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 0.5-2µg/mL. Protein binding decreases to about 88% in patients with severe hepatic dysfunction.

Metabolism
There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10-32 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 three to four 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 for to five days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The large intersubject 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-hydroxyproprafenone 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 60-70% 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 two randomized, double-blind, placebo controlled trials.

RAFT
In one US multicenter study (Rythmol SR Atrial Fibrillation Trial, RAFT), three doses of RYTHMOL SR (225 mg BID, 325 mg BID and 425 mg BID) 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. Over 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.

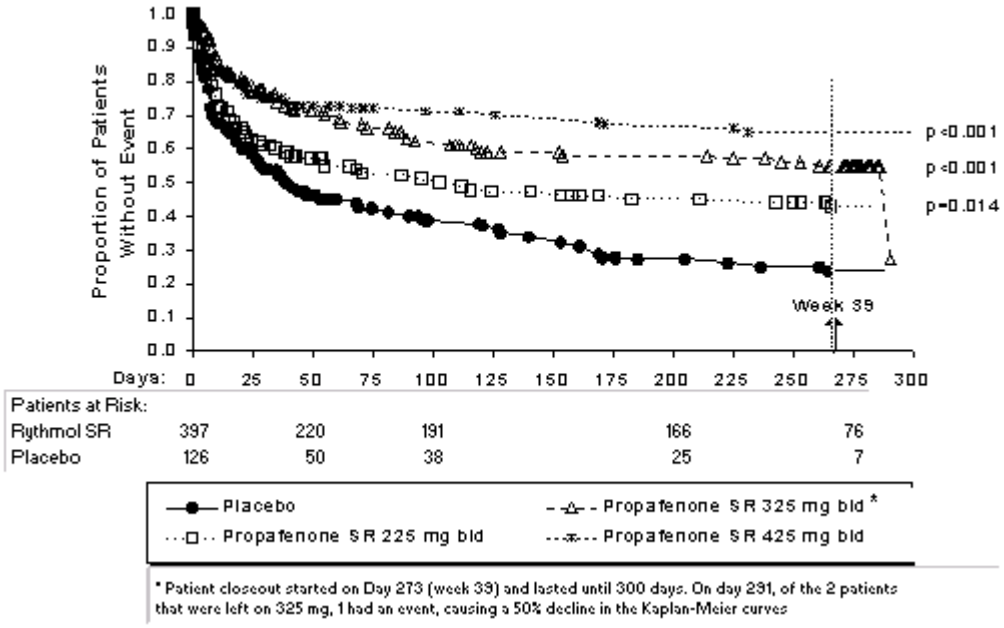
Table 1: Analysis of tachycardia-free period (days) from Day 1 of randomization

	RYTHMOL SR Dose			
Parameter	225 mg BID (N = 126) n (%)	325 mg BID (N = 135) n (%)	425 mg BID (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 BID, 325 mg BID, and 425 mg BID) 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)], two doses of RYTHMOL SR (325 mg BID and 425 mg BID) 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 four-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 lower 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 two RYTHMOL SR treatment groups 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 six days but less than two 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 ten months.

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) or other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be

avoided in patients with non-life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Proarrhythmic Effects:
Propafenone 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 Torsades 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 U.S. 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 nine patients, the ventricular tachycardia was of atrial origin. Six of the nine 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, Torsades de Pointes, asystole, and death.

In the RAFT study, there were five deaths, three in the pooled RYTHMOL SR group (0.8%) and two 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 five 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 U.S. 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 U.S. 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 two months of propafenone therapy and upon discontinuation of therapy, the white count usually normalized by 14 days. Unexplained fever and/or decrease in white cell count, particularly during the initial three months of therapy, warrant consideration of possible agranulocytosis 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 3-40% in patients with normal liver function when given RYTHMOL immediate release tablets. In eight patients with moderate to severe liver disease administered RYTHMOL immediate release tablets, the mean half-life was approximately nine 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 health care 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 health care provider of ongoing Rythmol SR therapy. Patients should also check with their health care 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, or vomiting, or loss of appetite or thirst, these conditions should be immediately reported to their health care 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 RYTHMOL administration 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 RYTHMOL immediate release tablet therapy.

Drug Interactions:
Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4 might lead to increased plasma levels of propafenone. When propafenone is co-administered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (see **CLINICAL PHARMACOLOGY**). The use of quinidine with propafenone is not recommended.
Local Anesthetics: Concomitant use of local anesthetics (i.e., during pacemaker implantations, surgery, or dental use) may increase the risks of central nervous system side effects.
Digitalis: RYTHMOL immediate release tablets have been shown to produce dose-related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day of RYTHMOL immediate release tablets 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 is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.
Beta-Antagonists: In a study involving healthy subjects, concomitant administration of RYTHMOL immediate release tablets and propranolol resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. Similar observations have been reported with metoprolol. Propafenone appears to inhibit the hydroxylation pathway for the two beta-antagonists (just as quinidine inhibits propafenone metabolism). Increased plasma concentrations of metoprolol could overcome its relative cardioselectivity. In RYTHMOL immediate release tablet clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects. While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.
Warfarin: In a study of eight healthy subjects receiving RYTHMOL immediate release tablets and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary.
Cimetidine: Concomitant administration of RYTHMOL immediate release tablets and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.
Desipramine: Concomitant administration of propafenone and desipramine may result in elevated serum desipramine levels. Both desipramine, a tricyclic antidepressant, and propafenone

are cleared by oxidative pathways of demethylation and hydroxylation carried out by the hepatic P-450 cytochrome.
Cyclosporin: Propafenone therapy may increase levels of cyclosporin.
Theophylline: Propafenone may increase theophylline concentration during concomitant therapy with the development of theophylline toxicity.
Rifampin: Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.

Renal and Hepatic Toxicity in Animals:
Renal changes have been observed in the rat following six months of oral administration of propafenone HCl at doses of 180 and 360 mg/kg/day (about two and four 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 six 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 three 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 three 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 three 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 three times the maximum recommended human dose [MRHD] on a mg/m^2

basis) and 600 mg/kg/day (about six times the MRHD on a mg/m^2 basis), respectively. Although maternally tolerated doses (up to 270 mg/kg/day, about three 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 (four 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 over, while 15.7 percent were 75 and over. 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 BID in 126 patients, to RYTHMOL SR 325 mg BID in 135 patients, to RYTHMOL SR 425 mg BID 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)

MedDRA Body System/Preferred Term	RYTHMOL SR 225 mg BID (N = 126) n (%)	RYTHMOL SR 325 mg BID (N = 135) n (%)	RYTHMOL SR 425 mg BID (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)

MedDRA Body System/Preferred Term	RYTHMOL SR 225 mg BID (N = 126) n (%)	RYTHMOL SR 325 mg BID (N = 135) n (%)	RYTHMOL SR 425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
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 & 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; *Hepato-biliary 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:* 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 arrhythmias. 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 BID 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 BID, 325 mg BID, and 425 mg BID 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 of maximum QTc change	RYTHMOL SR			Placebo
	225 mg BID	325 mg BID	425 mg BID	
	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 twelve hours. Dosage may be increased at a minimum of five day interval to 325 mg given every twelve hours. If additional therapeutic effect is needed, the dose of RYTHMOL SR may be increased to 425 mg given every twelve 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 ⓐ 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.

	NDC #0074-xxxx-yy	
	Abbo-Pac® Unit dose	Bottle of 100
225 mg	6134-11	6134-13
325 mg	6135-11	6135-13
425 mg	6136-11	6136-13

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

Rx Only

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Revised: NEW

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