

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RYTHMOL SR safely and effectively. See full prescribing information for RYTHMOL SR.

RYTHMOL SR® (propafenone hydrochloride) Extended Release Capsules
Initial U.S. Approval: 1989

WARNING: MORTALITY

See full prescribing information for complete boxed warning.

- An increased rate of death or reversed cardiac arrest rate was seen in patients treated with encainide or flecainide (Class IC antiarrhythmics) compared with that seen in patients assigned to placebo. At present it is prudent to consider any IC antiarrhythmic to have a significant risk of provoking proarrhythmic events 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.

RECENT MAJOR CHANGES

Dosage and Administration (2)	9/2010
Warnings and Precautions, Simultaneous use with Inhibitors of Cytochrome P450 2D6 and 3A4 (5.2)	9/2010

INDICATIONS AND USAGE

RYTHMOL SR is an antiarrhythmic indicated to prolong the time to recurrence of symptomatic atrial fibrillation (AF) in patients with episodic (most likely paroxysmal or persistent) AF who do not have structural heart disease. (1)

Usage Considerations:

- Use in patients with permanent atrial fibrillation or with atrial flutter or PSVT has not been evaluated. Do not use to control ventricular rate during atrial fibrillation. (1)
- In patients with atrial fibrillation and atrial flutter, use RYTHMOL SR with drugs that increase the atrioventricular nodal refractory period. (1)
- The effect of propafenone on mortality has not been determined. (1)

DOSAGE AND ADMINISTRATION

- Initiate therapy with 225 mg given every 12 hours. (2)
- Dosage may be increased at a minimum of 5 day intervals to 325 mg every 12 hours and, if necessary, to 425 mg every 12 hours. (2)
- Dose reduction should be considered in patients with hepatic impairment, significant widening of the QRS complex, or second or third degree AV block. (2)

DOSAGE FORMS AND STRENGTHS

Capsules: 225 mg, 325 mg, 425 mg. (3)

CONTRAINDICATIONS

- Heart failure (4)
- Cardiogenic shock (4)
- Sinoatrial, atrioventricular, and intraventricular disorders of impulse generation and/or conduction in the absence of pacemaker (4)
- Bradycardia (4)

- Marked hypotension (4)
- Bronchospastic disorders and severe obstructive pulmonary disease (4)
- Marked electrolyte imbalance (4)

WARNINGS AND PRECAUTIONS

- May cause new or worsened arrhythmias. Evaluate patients via ECG prior to and during therapy. (5.1)
- Avoid simultaneous use of propafenone with both a cytochrome P450 2D6 inhibitor and a 3A4 inhibitor. (5.2)
- Avoid use with other antiarrhythmic agents or other drugs that prolong the QT interval. (5.3)
- Patients with bronchospastic disease should not, in general, receive propafenone or other agents with beta-adrenergic-blocking activity.(5.4)
- May provoke overt heart failure. (5.5)
- May cause dose-related first degree AV block or other conduction disturbances. Should not be given to patients with conduction defects in absence of a pacemaker. (5.6)
- May affect artificial pacemakers. Pacemakers should be monitored during therapy. (5.7)
- Agranulocytosis: Patients should report signs of infection. (5.8)
- Administer cautiously to patients with impaired hepatic and renal function. (5.9, 5.10)
- Exacerbation of myasthenia gravis has been reported. (5.11)

ADVERSE REACTIONS

The most commonly reported adverse events with propafenone (>5% and greater than placebo) excluding those not reasonably associated with the use of the drug included the following: dizziness, palpitations, chest pain, dyspnea, taste disturbance, nausea, fatigue, anxiety, constipation, upper respiratory tract infection, edema, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibitors of CYP2D6, 1A2, and 3A4 may increase propafenone levels which may lead to cardiac arrhythmias. Simultaneous use with both a CYP3A4 and CYP2D6 inhibitor (or in a patient with CYP2D6 deficiency) should be avoided. (7.1)
- Propafenone may increase warfarin or digoxin levels. (7.2, 7.3)
- Concomitant use of lidocaine may increase central nervous system side effects. (7.3)
- Orlistat may reduce propafenone concentrations. Abrupt cessation of orlistat in patients stable on RYTHMOL SR has resulted in convulsions, atrioventricular block, and circulatory failure. (7.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2010

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WARNING: MORTALITY

1 INDICATIONS AND USAGE

RYTHMOL SR® IS INDICATED TO PROLONG THE TIME TO RECURRENCE OF SYMPTOMATIC ATRIAL FIBRILLATION (AF) IN PATIENTS WITH EPISODIC (MOST LIKELY PAROXYSMAL OR PERSISTENT) AF WHO DO NOT HAVE STRUCTURAL HEART DISEASE.

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: MORTALITY**

3 • In the National Heart, Lung and Blood Institute’s Cardiac Arrhythmia Suppression Trial
4 (CAST), a long-term, multi-center, randomized, double-blind study in patients with
5 asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction
6 more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac
7 arrest rate (7.7%; 56/730) was seen in patients treated with encainide or flecainide (Class IC
8 antiarrhythmics) compared with that seen in patients assigned to placebo (3.0%; 22/725). The
9 average duration of treatment with encainide or flecainide in this study was 10 months.

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

16 **1 INDICATIONS AND USAGE**

17 RYTHMOL SR[®] is indicated to prolong the time to recurrence of symptomatic atrial
18 fibrillation (AF) in patients with episodic (most likely paroxysmal or persistent) AF who do not
19 have structural heart disease.
20

21 **Usage Considerations:**

- 22 • The use of RYTHMOL SR in patients with permanent AF or in patients exclusively with
23 atrial flutter or paroxysmal supraventricular tachycardia (PSVT) has not been evaluated. Do
24 not use RYTHMOL SR to control ventricular rate during AF.
25 • Some patients with atrial flutter treated with propafenone have developed 1:1 conduction,
26 producing an increase in ventricular rate. Concomitant treatment with drugs that increase the
27 functional atrioventricular (AV) nodal refractory period is recommended.
28 • The effect of propafenone on mortality has not been determined [*see Boxed Warning*].

29 **2 DOSAGE AND ADMINISTRATION**

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

32 The dose of RYTHMOL SR must be individually titrated on the basis of response and
33 tolerance. Initiate therapy with RYTHMOL SR 225 mg given every 12 hours. Dosage may be
34 increased at a minimum of 5 day interval to 325 mg given every 12 hours. If additional
35 therapeutic effect is needed, the dose of RYTHMOL SR may be increased to 425 mg given every
36 12 hours.

37 In patients with hepatic impairment or those with significant widening of the QRS
38 complex or second or third degree AV block, consider reducing the dose.

39 The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6
40 inhibition with the simultaneous administration of propafenone may significantly increase the
41 concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse
42 events. Therefore, avoid simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and
43 a CYP3A4 inhibitor. [see Warnings and Precautions (5.2) and Drug Interactions (7.1)].

44 **3 DOSAGE FORMS AND STRENGTHS**

45 RYTHMOL SR (propafenone HCl) capsules are supplied as white, opaque, hard gelatin
46 capsules containing 225 mg, 325 mg, or 425 mg of propafenone HCl and imprinted in red with
47 the Reliant logo and strength. The 325 mg strength is also imprinted with a single red band
48 around $\frac{3}{4}$ of the circumference of the body; the 425 mg strength is imprinted with three bands
49 around $\frac{3}{4}$ of the circumference of the body.

50 **4 CONTRAINDICATIONS**

51 RYTHMOL SR is contraindicated in the following circumstances:

- 52 • Heart failure
- 53 • Cardiogenic shock
- 54 • Sinoatrial, atrioventricular and intraventricular disorders of impulse generation or conduction
55 (e.g., sick sinus node syndrome, AV block) in the absence of an artificial pacemaker
- 56 • Bradycardia
- 57 • Marked hypotension
- 58 • Bronchospastic disorders or severe obstructive pulmonary disease
- 59 • Marked electrolyte imbalance

60 **5 WARNINGS AND PRECAUTIONS**

61 **5.1 Proarrhythmic Effects**

62 Propafenone has caused new or worsened arrhythmias. Such proarrhythmic effects
63 include sudden death and life-threatening ventricular arrhythmias such as ventricular fibrillation,
64 ventricular tachycardia, asystole and Torsade de Pointes. It may also worsen premature
65 ventricular contractions or supraventricular arrhythmias, and it may prolong the QT interval. It is
66 therefore essential that each patient given RYTHMOL SR be evaluated electrocardiographically
67 prior to and during therapy, to determine whether the response to RYTHMOL SR supports
68 continued treatment. Because propafenone prolongs the QRS interval in the electrocardiogram,
69 changes in the QT interval are difficult to interpret [see Clinical Pharmacology (12.2)].

70 In the RAFT study [see Clinical Studies (14)], there were too few deaths to assess the
71 long term risk to patients. There were 5 deaths, 3 in the pooled RYTHMOL SR group (0.8%) and
72 2 in the placebo group (1.6%). In the overall RYTHMOL SR and RYTHMOL immediate release
73 database of 8 studies, the mortality rate was 2.5% per year on propafenone and 4.0% per year on

74 placebo. Concurrent use of propafenone with other antiarrhythmic agents has not been well
75 studied.

76 In a U.S. uncontrolled, open label multicenter trial using the immediate release
77 formulation in patients with symptomatic supraventricular tachycardia (SVT), 1.9% (9/474) of
78 these patients experienced ventricular tachycardia (VT) or ventricular fibrillation (VF) during the
79 study. However, in 4 of the 9 patients, the ventricular tachycardia was of atrial origin. Six of the
80 9 patients that developed ventricular arrhythmias did so within 14 days of onset of therapy.
81 About 2.3% (11/474) of all patients had recurrence of SVT during the study which could have
82 been a change in the patients' arrhythmia behavior or could represent a proarrhythmic event.
83 Case reports in patients treated with propafenone for atrial fibrillation/flutter have included
84 increased premature ventricular contractions (PVCs), VT, VF, Torsade de Pointes, asystole, and
85 death.

86 Overall in clinical trials with RYTHMOL immediate release (which included patients
87 treated for ventricular arrhythmias, atrial fibrillation/flutter, and PSVT), 4.7% of all patients had
88 new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was
89 an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who
90 had worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery
91 disease, and 68% had a prior myocardial infarction. The incidence of pro-arrhythmia in patients
92 with less serious or benign arrhythmias, which include patients with an increase in frequency of
93 PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy,
94 late events also were seen and the CAST study [*see Boxed Warning: Mortality*] suggests that an
95 increased risk of proarrhythmia is present throughout treatment.

96 **5.2 Drug Interactions: Simultaneous Use with Inhibitors of Cytochrome P450** 97 **Isoenzymes 2D6 and 3A4**

98 Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes.
99 Approximately 6% of Caucasians in the U.S. population are naturally deficient in CYP2D6
100 activity and to a somewhat lesser extent in other demographic groups. Drugs that inhibit these
101 CYP pathways (such as desipramine, paroxetine, ritonavir, sertraline for CYP2D6; ketoconazole,
102 erythromycin, saquinavir, and grapefruit juice for CYP3A4; and amiodarone and tobacco smoke
103 for CYP1A2) can be expected to cause increased plasma levels of propafenone.

104 Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated
105 beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4
106 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is
107 potentially hazardous. Therefore, avoid simultaneous use of RYTHMOL SR with both a
108 CYP2D6 inhibitor and a CYP3A4 inhibitor.

109 **5.3 Use with Drugs that Prolong the QT Interval and Antiarrhythmic Agents**

110 The use of RYTHMOL SR in conjunction with other drugs that prolong the QT interval
111 has not been extensively studied. Such drugs may include many antiarrhythmics, some
112 phenothiazines, tricyclic antidepressants, and oral macrolides. Withhold Class IA and III
113 antiarrhythmic agents for at least 5 half-lives prior to dosing with RYTHMOL SR. Avoid the use

114 of propafenone with Class IA and III antiarrhythmic agents (including quinidine and
115 amiodarone). There is only limited experience with the concomitant use of Class IB or IC
116 antiarrhythmics.

117 **5.4 Use in Patients with a History of Heart Failure**

118 Propafenone exerts a negative inotropic activity on the myocardium as well as beta
119 blockade effects and may provoke overt heart failure. In the U.S. trial (RAFT) in patients with
120 symptomatic AF, heart failure was reported in 4 (1.0%) patients receiving RYTHMOL SR (all
121 doses), compared to 1 (0.8%) patient receiving placebo. Proarrhythmic effects more likely occur
122 when propafenone is administered to patients with heart failure (NYHA III and IV) or severe
123 myocardial ischemia [*see Contraindications (4)*].

124 In clinical trial experience with RYTHMOL immediate release, new or worsened heart
125 failure has been reported in 3.7% of patients with ventricular arrhythmia. These events were
126 more likely in subjects with preexisting heart failure and coronary artery disease. New onset of
127 heart failure attributable to propafenone developed in <0.2% of patients with ventricular
128 arrhythmia and in 1.9% of patients with paroxysmal AF or PSVT.

129 **5.5 Conduction Disturbances**

130 Propafenone slows atrioventricular conduction and may also cause dose-related first
131 degree AV block. Average PR interval prolongation and increases in QRS duration are also
132 dose-related. Do not give propafenone to patients with atrioventricular and intraventricular
133 conduction defects in the absence of a pacemaker [*see Contraindications (4) and Clinical
134 Pharmacology (12.2)*].

135 In a U.S. trial (RAFT) in 523 patients with a history of symptomatic AF treated with
136 RYTHMOL SR, sinus bradycardia (rate <50 beats/min) was reported with the same frequency
137 with RYTHMOL SR and placebo.

138 **5.6 Effects on Pacemaker Threshold**

139 Propafenone may alter both pacing and sensing thresholds of implanted pacemakers and
140 defibrillators. During and after therapy, monitor and re-program these devices accordingly.

141 **5.7 Agranulocytosis**

142 Agranulocytosis has been reported in patients receiving propafenone. Generally, the
143 agranulocytosis occurred within the first 2 months of propafenone therapy and upon
144 discontinuation of therapy, the white count usually normalized by 14 days. Unexplained fever or
145 decrease in white cell count, particularly during the initial 3 months of therapy, warrant
146 consideration of possible agranulocytosis or granulocytopenia. Instruct patients to report
147 promptly any signs of infection such as fever, sore throat, or chills.

148 **5.8 Use in Patients with Hepatic Dysfunction**

149 Propafenone is highly metabolized by the liver. Severe liver dysfunction increases the
150 bioavailability of propafenone to approximately 70% compared to 3-40% in patients with normal
151 liver function when given RYTHMOL immediate release tablets. In 8 patients with moderate to
152 severe liver disease administered RYTHMOL immediate release tablets, the mean half-life was
153 approximately 9 hours. No studies have compared bioavailability of propafenone from

154 RYTHMOL SR in patients with normal and impaired hepatic function. Increased bioavailability
155 of propafenone in these patients may result in excessive accumulation. Carefully monitor
156 patients with impaired hepatic function for excessive pharmacological effects [*see Overdosage*
157 (*10*)].

158 **5.9 Use in Patients with Renal Dysfunction**

159 Approximately 50% of propafenone metabolites are excreted in the urine following
160 administration of RYTHMOL immediate release tablets. No studies have been performed to
161 assess the percentage of metabolites eliminated in the urine following the administration of
162 RYTHMOL SR capsules.

163 In patients with impaired renal function, monitor for signs of overdose [*see*
164 *Overdosage (10)*].

165 **5.10 Use in Patients with Myasthenia Gravis**

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

167 **5.11 Elevated ANA Titers**

168 Positive ANA titers have been reported in patients receiving propafenone. They have
169 been reversible upon cessation of treatment and may disappear even in the face of continued
170 propafenone therapy. These laboratory findings were usually not associated with clinical
171 symptoms, but there is one published case of drug-induced lupus erythematosus (positive
172 rechallenge); it resolved completely upon discontinuation of therapy. Carefully evaluate patients
173 who develop an abnormal ANA test and if persistent or worsening elevation of ANA titers is
174 detected, consider discontinuing therapy.

175 **5.12 Impaired Spermatogenesis**

176 Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and
177 rabbits after high dose intravenous administration of propafenone. Evaluation of the effects of
178 short-term RYTHMOL administration on spermatogenesis in 11 normal subjects suggested that
179 propafenone produced a reversible, short-term drop (within normal range) in sperm count.

180 **6 ADVERSE REACTIONS**

181 **6.1 Clinical Trials Experience**

182 Because clinical trials are conducted under widely varying conditions, adverse reaction
183 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
184 trials of another drug and may not reflect the rates observed in practice.

185 The data described below reflect exposure to RYTHMOL SR 225 mg BID in 126
186 patients, to RYTHMOL SR 325 mg BID in 135 patients, to RYTHMOL SR 425 mg BID in 136
187 patients, and to placebo in 126 patients for up to 39 weeks (mean 20 weeks) in a placebo-
188 controlled trial (RAFT) conducted in the US. The most commonly reported adverse events with
189 propafenone (>5% and greater than placebo), excluding those not reasonably associated with the
190 use of the drug or because they were associated with the condition being treated, were dizziness,
191 palpitations, chest pain, dyspnea, taste disturbance, nausea, fatigue, anxiety, constipation, upper
192 respiratory tract infection, edema, and influenza. The frequency of discontinuation due to

193 adverse events was 17%, and the rate was highest during the first 14 days of treatment.

194 Cardiac-related adverse events occurring in $\geq 2\%$ of the patients in any of the RAFT
195 propafenone SR treatment groups and more common with propafenone than with placebo,
196 excluding those that are common in the population and those not plausibly related to drug
197 therapy, included the following: angina pectoris, atrial flutter, AV block first degree,
198 bradycardia, congestive cardiac failure, cardiac murmur, edema, dyspnea, rales, wheezing, and
199 cardioactive drug level above therapeutic.

200 Propafenone prolongs the PR and QRS intervals in patients with atrial and ventricular
201 arrhythmias. Prolongation of the QRS interval makes it difficult to interpret the effect of
202 propafenone on the QT interval [*see Clinical Pharmacology (12.2)*].

203 Non-cardiac related adverse events occurring in $\geq 2\%$ of the patients in any of the RAFT
204 propafenone SR treatment groups and more common with propafenone than with placebo,
205 excluding those that are common in the population and those not plausibly related to drug
206 therapy, included the following: blurred vision, constipation, diarrhea, dry mouth, flatulence,
207 nausea, vomiting, fatigue, weakness, upper respiratory tract infection, blood alkaline phosphatase
208 increased, hematuria, muscle weakness, dizziness (excluding vertigo), headache, taste
209 disturbance, tremor, somnolence, anxiety, depression, ecchymosis.

210 No clinically important differences in incidence of adverse reactions were noted by age
211 or gender. Too few non-Caucasian patients were enrolled to assess adverse events according to
212 race.

213 Adverse events occurring in 2% or more of the patients in any of the ERAFT [*see*
214 *Clinical Studies (14)*] propafenone SR treatment groups and not listed above include the
215 following: bundle branch block left, bundle branch block right, conduction disorders, sinus
216 bradycardia, and hypotension.

217 Other adverse events reported with propafenone clinical trials not already listed
218 elsewhere in the prescribing information include the following adverse events by body and
219 preferred term.

220 **Blood and lymphatic system disorders:** Anemia, lymphadenopathy, spleen disorder,
221 thrombocytopenia.

222 **Cardiac disorders:** Unstable angina, atrial hypertrophy, cardiac arrest, coronary artery
223 disease, extrasystoles, myocardial infarction, nodal arrhythmia, palpitations, pericarditis,
224 sinoatrial block, sinus arrest, sinus arrhythmia, supraventricular extrasystoles, ventricular
225 extrasystoles, ventricular hypertrophy.

226 **Ear and labyrinth disorders:** Hearing impaired, tinnitus, vertigo.

227 **Eye disorders:** Eye hemorrhage, eye inflammation, eyelid ptosis, miosis, retinal
228 disorder, visual acuity reduced.

229 **Gastrointestinal disorders:** Abdominal distension, abdominal pain, duodenitis,
230 dyspepsia, dysphagia, eructation, gastritis, gastroesophageal reflux disease, gingival bleeding,
231 glossitis, glossodynia, gum pain, halitosis, intestinal obstruction, melena, mouth ulceration,
232 pancreatitis, peptic ulcer, rectal bleeding, sore throat.

233 General disorders and administration site conditions: Chest pain, feeling hot,
234 hemorrhage, malaise, pain, pyrexia.

235 Hepato-biliary disorders: Hepatomegaly.

236 Investigations: Abnormal heart sounds, abnormal pulse, carotid bruit, decreased blood
237 chloride, decreased blood pressure, decreased blood sodium, decreased hemoglobin, decreased
238 neutrophil count, decreased platelet count, decreased prothrombin level, decreased red blood cell
239 count, decreased weight, glycosuria present, increased alanine aminotransferase, increased
240 aspartate aminotransferase, increased blood bilirubin, increased blood cholesterol, increased
241 blood creatinine, increased blood glucose, increased blood lactate dehydrogenase, increased
242 blood pressure, increased blood prolactin, increased blood triglycerides, increased blood urea,
243 increased blood uric acid, increased eosinophil count, increased gamma-glutamyltransferase,
244 increased monocyte count, increased prostatic specific antigen, increased prothrombin level,
245 increased weight, increased white blood cell count, ketonuria present, proteinuria present.

246 Metabolism and nutrition disorders: Anorexia, dehydration, diabetes mellitus, gout,
247 hypercholesterolemia, hyperglycemia, hyperlipidemia, hypokalemia.

248 Musculoskeletal, connective tissue and bone disorders: Arthritis, bursitis, collagen-
249 vascular disease, costochondritis, joint disorder, muscle cramps, muscle spasms, myalgia, neck
250 pain, pain in jaw, sciatica, tendonitis.

251 Nervous system disorders: Amnesia, ataxia, balance impaired, brain damage,
252 cerebrovascular accident, dementia, gait abnormal, hypertonia, hypothermia, insomnia, paralysis,
253 paresthesia, peripheral neuropathy, speech disorder, syncope, tongue hypoesthesia.

254 Psychiatric disorders: Decreased libido, emotional disturbance, mental disorder,
255 neurosis, nightmare, sleep disorder.

256 Renal and urinary disorders: Dysuria, nocturia, oliguria, pyuria, renal failure, urinary
257 casts, urinary frequency, urinary incontinence, urinary retention, urine abnormal.

258 Reproductive system and breast disorders: Breast pain, impotence, prostatism.

259 Respiratory, thoracic and mediastinal disorders: Atelectasis, breath sounds
260 decreased, chronic obstructive airways disease, cough, epistaxis, hemoptysis, lung disorder,
261 pleural effusion, pulmonary congestion, rales, respiratory failure, rhinitis, throat tightness.

262 Skin and subcutaneous tissue disorders: Alopecia, dermatitis, dry skin, erythema,
263 nail abnormality, petechiae, pruritus, sweating increased, urticaria.

264 Vascular disorders: Arterial embolism limb, deep limb venous thrombosis, flushing,
265 hematoma, hypertension, hypertensive crisis, hypotension, labile blood pressure, pallor,
266 peripheral coldness, peripheral vascular disease, thrombosis.

267 **7 DRUG INTERACTIONS**

268 **7.1 CYP2D6 and CYP3A4 Inhibitors**

269 Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline) and
270 CYP3A4 (such as ketoconazole, ritonavir, saquinavir, erythromycin, and grapefruit juice) can be
271 expected to cause increased plasma levels of propafenone. The combination of CYP3A4

272 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with administration of
273 propafenone may increase the risk of adverse reactions, including proarrhythmia. Therefore,
274 simultaneous use of RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor
275 should be avoided [see *Warnings and Precautions (5.2) and Dosage and Administration (2)*].

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

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

281 **Fluoxetine:** Concomitant administration of propafenone and fluoxetine in extensive
282 metabolizers increased the S propafenone C_{max} and AUC by 39 and 50% and the R propafenone
283 C_{max} and AUC by 71 and 50%.

284 **Quinidine:** Small doses of quinidine completely inhibit the CYP2D6 hydroxylation
285 metabolic pathway, making all patients, in effect, slow metabolizers [see *Clinical Pharmacology*
286 *(12)*]. Concomitant administration of quinidine (50 mg three times daily) with 150 mg immediate
287 release propafenone three times daily decreased the clearance of propafenone by 60% in EM,
288 making them PM. Steady-state plasma concentrations increased by more than 2-fold for
289 propafenone, and decreased 50% for 5-OH-propafenone. A 100 mg dose of quinidine increased
290 steady state concentrations of propafenone 3-fold. Avoid concomitant use of propafenone and
291 quinidine.

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

300 **7.2 Digoxin**

301 Concomitant use of propafenone and digoxin increased steady-state serum digoxin
302 exposure (AUC) in patients by 60 to 270%, and decreased the clearance of digoxin by 31 to
303 67%. Monitor plasma digoxin levels of patients receiving propafenone and adjust digoxin dosage
304 as needed.

305 **7.3 Warfarin**

306 The concomitant administration of propafenone and warfarin increased warfarin plasma
307 concentrations at steady state by 39% in healthy volunteers and prolonged the prothrombin time
308 (PT) in patients taking warfarin. Adjust the warfarin dose as needed by monitoring INR
309 (international normalized ratio).

310 **7.4 Orlistat**

311 Orlistat may limit the fraction of propafenone available for absorption. In post marketing
312 reports, abrupt cessation of orlistat in patients stabilized on propafenone has resulted in severe
313 adverse events including convulsions, atrioventricular block and acute circulatory failure.

314 **7.5 Beta-Antagonists**

315 Concomitant use of propafenone and propranolol in healthy subjects increased
316 propranolol plasma concentrations at steady state by 113%. In 4 patients, administration of
317 metoprolol with propafenone increased the metoprolol plasma concentrations at steady state by
318 100-400%. The pharmacokinetics of propafenone was not affected by the coadministration of
319 either propranolol or metoprolol. In clinical trials using propafenone immediate release tablets,
320 patients who were receiving beta-blockers concurrently did not experience an increased
321 incidence of side effects.

322 **7.6 Lidocaine**

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

327 **8 USE IN SPECIFIC POPULATIONS**

328 **8.1 Pregnancy**

329 Pregnancy Category C. There are no adequate and well-controlled studies in pregnant
330 women. RYTHMOL SR should be used during pregnancy only if the potential benefit justifies
331 the potential risk to the fetus.

332 Animal Data: Teratogenic Effects: Propafenone has been shown to be embryotoxic
333 (decreased survival) in rabbits and rats when given in oral maternally toxic doses of
334 150 mg/kg/day (about 3 times the maximum recommended human dose [MRHD] on a mg/m²
335 basis) and 600 mg/kg/day (about 6 times the MRHD on a mg/m² basis), respectively. Although
336 maternally tolerated doses (up to 270 mg/kg/day, about three times the MRHD on a mg/m² basis)
337 produced no evidence of embryotoxicity in rats, post-implantation loss was elevated in all rabbit
338 treatment groups (doses as low as 15 mg/kg/day, about 1/3 the MRHD on a mg/m² basis).

339 Non-teratogenic Effects: In a study in which female rats received daily oral doses of
340 propafenone from mid-gestation through weaning of their offspring, doses as low as
341 90 mg/kg/day (equivalent to the MRHD on a mg/m² basis) produced increases in maternal
342 deaths. Doses of 360 or more mg/kg/day (four or more times the MRHD on a mg/m² basis)
343 resulted in reductions in neonatal survival, body weight gain and physiological development.

344 **8.2 Labor and Delivery**

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

348 **8.3 Nursing Mothers**

349 Propafenone is excreted in human milk. Because of the potential for serious adverse
350 reactions in nursing infants from propafenone, decide whether to discontinue nursing or to
351 discontinue the drug, taking into account the importance of the drug to the mother.

352 **8.4 Pediatric Use**

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

355 **8.5 Geriatric Use**

356 Of the total number of subjects in Phase 3 clinical studies of RYTHMOL SR
357 (propafenone hydrochloride) 46% were 65 and over, while 16% were 75 and over. No overall
358 differences in safety or effectiveness were observed between these subjects and younger
359 subjects, but greater sensitivity of some older individuals at higher doses cannot be ruled out.
360 The effect of age on the pharmacokinetics and pharmacodynamics of propafenone has not been
361 studied.

362 **10 OVERDOSAGE**

363 The symptoms of overdose may include hypotension, somnolence, bradycardia, intra-
364 atrial and intra-ventricular conduction disturbances, and rarely convulsions and high grade
365 ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have
366 been effective in controlling abnormal rhythm and blood pressure. Convulsions have been
367 alleviated with intravenous diazepam. General supportive measures such as mechanical
368 respiratory assistance and external cardiac massage may be necessary.

369 The hemodialysis of propafenone in patients with an overdose is expected to be of limited
370 value in the removal of propafenone as a result of both its high protein binding (>95%) and large
371 volume of distribution.

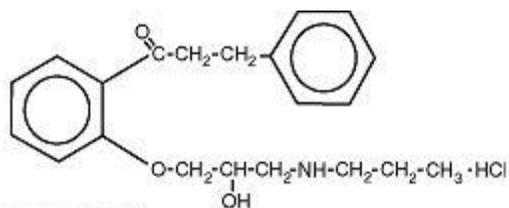
372 **11 DESCRIPTION**

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

375 Chemically, propafenone hydrochloride is 2'-[2-hydroxy-3-(propylamino)-propoxy]-3-
376 phenylpropiofenonehydrochloride, with a molecular weight of 377.92. The molecular formula
377 is $C_{21}H_{27}NO_3 \cdot HCl$.

378 Propafenone HCl has some structural similarities to beta-blocking agents. The structural
379 formula of propafenone HCl is given below:

380



383 Propafenone HCl occurs as colorless crystals or white crystalline powder with a very
384 bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. Rythmol SR capsules
385 are filled with cylindrical-shaped 2 x 2 mm microtablets containing propafenone and the
386 following inactive ingredients: antifoam, gelatin, hypromellose, red iron oxide, magnesium
387 stearate, shellac, sodium lauryl sulfate, sodium dodecyl sulfate, soy lecithin and titanium dioxide.

388 **12 CLINICAL PHARMACOLOGY**

389 **12.1 Mechanism of Action**

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

397 Studies in anesthetized dogs and isolated organ preparations show that propafenone has
398 beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing
399 isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-
400 adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials
401 with the immediate release formulation, resting heart rate decreases of about 8% were noted at
402 the higher end of the therapeutic plasma concentration range. At very high concentrations *in*
403 *vitro*, propafenone can inhibit the slow inward current carried by calcium, but this calcium
404 antagonist effect probably does not contribute to antiarrhythmic efficacy. Moreover, propafenone
405 inhibits a variety of cardiac potassium currents in *in vitro* studies (i.e. the transient outward, the
406 delayed rectifier, and the inward rectifier current). Propafenone has local anesthetic activity
407 approximately equal to procaine. Compared to propafenone, the main metabolite, 5-
408 hydroxypropafenone, has similar sodium and calcium channel activity, but about 10 times less
409 beta-blocking activity (N-depropylpropafenone has weaker sodium channel activity but
410 equivalent affinity for beta-receptors).

411 **12.2 Pharmacodynamics**

412 Electrophysiology: Electrophysiology studies in patients with ventricular tachycardia
413 have shown that propafenone prolongs atrioventricular conduction while having little or no effect
414 on sinus node function. Both atrioventricular nodal conduction time (AH interval) and His-
415 Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the
416 atrial functional refractory period, but AV nodal functional and effective refractory periods are
417 prolonged. In patients with Wolff-Parkinson-White syndrome, RYTHMOL immediate release
418 tablets reduce conduction and increase the effective refractory period of the accessory pathway
419 in both directions.

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

422

423 **Table 2. Mean Change ± SD in 12-Lead Electrocardiogram Results (RAFT)**

	RYTHMOL SR Twice-Daily Dosing			Placebo
	225 mg	325 mg	425 mg	
	n=126	n=135	n=136	
PR (ms)	9±22	12±23	21±24	1±16
QRS (ms)	4±14	6±15	6±15	-2±12
Heart rate	5±24	7±23	2±22	8±27
QTc* (ms)	2±30	5±36	6±37	5±35

424 *Calculated using Bazett's correction factor

425

426 In RAFT [see *Clinical Studies (14)*], the distribution of the maximum changes in QTc
 427 compared to baseline over the study in each patient was similar in the RYTHMOL SR 225 mg
 428 twice daily, 325 mg twice daily, and 425 mg twice daily and placebo dose groups. Similar results
 429 were seen in the ERAFT study.

430

431 **Table 3. Number of Patients According to the Range of Maximum QTc change compared**
 432 **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=100
	n (%)	n (%)	n (%)	n (%)
>20%	1 (1)	6 (5)	3 (2)	5 (4)
10-20%	19 (16)	28 (22)	32 (26)	24 (20)
0 ≤10%	99 (83)	95 (74)	88 (72)	91 (76)

433

434 Hemodynamics: Studies in humans have shown that propafenone exerts a negative
 435 inotropic effect on the myocardium. Cardiac catheterization studies in patients with moderately
 436 impaired ventricular function (mean C.I.=2.61 L/min/m²), utilizing intravenous propafenone
 437 infusions (loading dose of 2 mg/kg over 10 min+ followed by 2 mg/min for 30 min) that gave
 438 mean plasma concentrations of 3.0 µg/mL (a dose that produces plasma levels of propafenone
 439 greater than does recommended oral dosing), showed significant increases in pulmonary
 440 capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac
 441 output and cardiac index.

442 **12.3 Pharmacokinetics**

443 Absorption/Bioavailability: Maximal plasma levels of propafenone are reached between
444 3 to 8 hours following the administration of RYTHMOL SR. Propafenone is known to undergo
445 extensive and saturable presystemic biotransformation which results in a dose and dosage form
446 dependent absolute bioavailability; e.g., a 150 mg immediate release tablet had an absolute
447 bioavailability of 3.4%, while a 300 mg immediate release tablet had an absolute bioavailability
448 of 10.6%. Absorption from a 300 mg solution dose was rapid, with an absolute bioavailability of
449 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from
450 immediate release tablets increased still further.

451 Relative bioavailability assessments have been performed between RYTHMOL SR
452 capsules and RYTHMOL immediate release tablets. In extensive metabolizers, the
453 bioavailability of propafenone from the SR formulation was less than that of the immediate
454 release formulation as the more gradual release of propafenone from the prolonged-release
455 preparations resulted in an increase of overall first pass metabolism [*see Metabolism*]. As a
456 result of the increased first pass effect, higher daily doses of propafenone were required from the
457 SR formulation relative to the immediate release formulation, to obtain similar exposure to
458 propafenone. The relative bioavailability of propafenone from the 325 twice daily regimens of
459 RYTHMOL SR approximates that of RYTHMOL immediate release 150 mg three times daily
460 regimen. Mean exposure to 5-hydroxypropafenone was about 20-25% higher after SR capsule
461 administration than after immediate release tablet administration.

462 Food increased the exposure to propafenone 4-fold after single dose administration of
463 425 mg of RYTHMOL SR. However, in the multiple dose study (425 mg dose BID), the
464 difference between the fed and fasted state was not significant.

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

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

472 Metabolism: There are two genetically determined patterns of propafenone metabolism.
473 In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-
474 life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-
475 hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone
476 (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients,
477 metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is
478 minimally formed. In these patients, the estimated propafenone elimination half-life ranges from
479 10-32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated
480 with a diminished ability to metabolize debrisoquine and a variety of other drugs such as
481 encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6

482 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities
483 comparable to the levels occurring in extensive metabolizers.

484 As a consequence of the observed differences in metabolism, administration of
485 RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma
486 concentrations of propafenone, with slow metabolizers achieving concentrations about twice
487 those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences
488 are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than
489 extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway
490 (CYP2D6) results in greater-than-linear increases in plasma levels following administration of
491 RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics is linear. Because
492 the difference decreases at high doses and is mitigated by the lack of the active 5-
493 hydroxymetabolite in the slow metabolizers, and because steady-state conditions are achieved
494 after 4 to 5 days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is
495 the same for all patients. The larger inter-subject variability in blood levels require that the dose
496 of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence
497 of toxicity [see *Dosage and Administration (2)*].

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

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

511 ***Stereochemistry:*** RYTHMOL is a racemic mixture. The R- and S-enantiomers of
512 propafenone display stereoselective disposition characteristics. *In vitro* and *in vivo* studies have
513 shown that the R-isomer of propafenone is cleared faster than the S-isomer via the 5-
514 hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-
515 propafenone at steady state. Both enantiomers have equivalent potency to block sodium
516 channels; however, the S-enantiomer is a more potent β -antagonist than the R-enantiomer.
517 Following administration of RYTHMOL immediate release tablets or RYTHMOL SR capsules,
518 the S/R ratio for the area under the plasma concentration-time curve was about 1.7. The S/R
519 ratios of propafenone obtained after administration of 225, 325 and 425 mg RYTHMOL SR are
520 independent of dose. In addition, no difference in the average values of the S/R ratios is evident
521 between genotypes or over time.

522 Special Populations: Hepatic Impairment: Decreased liver function increases the
523 bioavailability of propafenone. Absolute bioavailability assessments have not been determined
524 for the RYTHMOL SR capsule formulation. Absolute bioavailability of RYTHMOL immediate
525 release tablets is inversely related to indocyanine green clearance, reaching 60-70% at clearances
526 of 7 mL/min and below. Protein binding decreases to about 88% in patients with severe hepatic
527 dysfunction. The clearance of propafenone is reduced and the elimination half-life increased in
528 patients with significant hepatic dysfunction [see Warnings and Precautions (5.8)].

529 **13 NONCLINICAL TOXICOLOGY**

530 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

531 Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day, about twice
532 the maximum recommended human oral daily dose [MRHD] on a mg/m² basis) and rats (up to
533 270 mg/kg/day, about 3 times the MRHD on a mg/m² basis) provided no evidence of a
534 carcinogenic potential for propafenone HCl.

535 Propafenone HCl tested negative for mutagenicity in the Ames (salmonella) test and in
536 the *in vivo* mouse dominant lethal test. It tested negative for clastogenicity in the human
537 lymphocyte chromosome aberration assay *in vitro* and in rat and Chinese hamster micronucleus
538 tests, and other *in vivo* tests for chromosomal aberrations in rat bone marrow and Chinese
539 hamster bone marrow and spermatogonia.

540 Propafenone HCl, administered intravenously to rabbits, dogs, and monkeys, has been
541 shown to decrease spermatogenesis. These effects were reversible, were not found following oral
542 dosing of propafenone HCl, were seen at lethal or near lethal dose levels and were not seen in
543 rats treated either orally or intravenously [see Warnings and Precautions (5.11)]. Treatment of
544 male rabbits for 10 weeks prior to mating at an oral dose of 120 mg/kg/day (about 2.4 times the
545 MRHD on a mg/m² basis) or an intravenous dose of 3.5 mg/kg/day (a spermatogenesis-impairing
546 dose) did not result in evidence of impaired fertility. Nor was there evidence of impaired fertility
547 when propafenone HCl was administered orally to male and female rats at dose levels up to
548 270 mg/kg/day (about 3 times the MRHD on a mg/m² basis).

549 **13.2 Animal Toxicology and/or Pharmacology**

550 Renal and Hepatic Toxicity in Animals: Renal changes have been observed in the rat
551 following 6 months of oral administration of propafenone HCl at doses of 180 and
552 360 mg/kg/day (about 2 and 4 times, respectively, the maximum recommended human daily
553 dose [MRHD] on a mg/m² basis). Both inflammatory and non-inflammatory changes in the renal
554 tubules, with accompanying interstitial nephritis, were observed. These changes were reversible,
555 as they were not found in rats allowed to recover for 6 weeks. Fatty degenerative changes of the
556 liver were found in rats following longer durations of administration of propafenone HCl at a
557 dose of 270 mg/kg/day (about 3 times the MRHD on a mg/m² basis). There were no renal or
558 hepatic changes at 90 mg/kg/day equivalent to the MRHD on a mg/m² basis).

559 **14 CLINICAL STUDIES**

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

563 RAFT: In one US multicenter study (Rythmol SR Atrial Fibrillation Trial, RAFT), 3
 564 doses of RYTHMOL SR (225 mg twice daily, 325 mg twice daily and 425 mg twice daily) and
 565 placebo were compared in 523 patients with symptomatic, episodic AF. The patient population
 566 in this trial was 59% male with a mean age of 63 years; 91% White and 6% Black. The patients
 567 had a median history of AF of 13 months, and documented symptomatic AF within 12 months of
 568 study entry. Over 90% were NYHA Class I, and 21% had a prior electrical cardioversion. At
 569 baseline, 24% were treated with calcium channel blockers, 37% with beta blockers, and 38%
 570 with digoxin. Symptomatic arrhythmias after randomization were documented by transtelephonic
 571 electrocardiogram and centrally read and adjudicated by a blinded adverse event committee.
 572 RYTHMOL SR administered for up to 39 weeks was shown to prolong significantly the time to
 573 the first recurrence of symptomatic atrial arrhythmia, predominantly AF, from Day 1 of
 574 randomization (primary efficacy variable) compared to placebo, as shown in Table 4.
 575

576 **Table 4: Analysis of Tachycardia-Free Period (Days) from Day 1 of Randomization**

Parameter	RYTHMOL SR Twice-Daily Dose			Placebo (N = 126) n (%)
	225 mg (N = 126) n (%)	325 mg (N = 135) n (%)	425 mg (N = 136) n (%)	
Patients completing with terminating event*	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier Media	112	291	NA [†]	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)	--

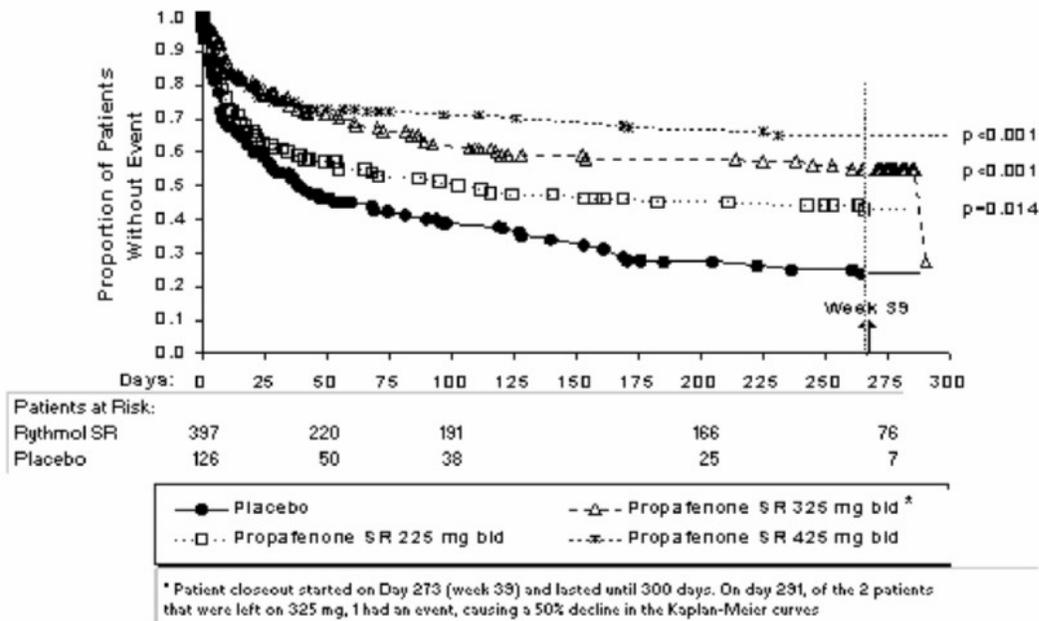
577 * Terminating events comprised 91% AF, 5% atrial flutter, and 4% PSVT.

578 † Not Applicable: Fewer than 50% of the patients had events. The median time is not calculable.

579

580 There was a dose response for RYTHMOL SR for the tachycardia-free period as shown
 581 in the proportional hazard analysis and the Kaplan-Meier curves presented in Figure 1.
 582

583 **Figure 1: RAFT Kaplan-Meier Analysis for the Tachycardia-free period from Day 1 of**
 584 **randomization:**
 585



586
 587
 588 In additional analyses, RYTHMOL SR (225 mg twice daily, 325 mg twice daily, and
 589 425 mg twice daily) was also shown to prolong time to the first recurrence of symptomatic AF
 590 from Day 5 (steady-state pharmacokinetics were attained). The antiarrhythmic effect of
 591 RYTHMOL SR was not influenced by age, gender, history of cardioversion, duration of AF,
 592 frequency of AF or use of medication that lowers heart rate. Similarly, the antiarrhythmic effect
 593 of RYTHMOL SR was not influenced by the individual use of calcium channel blockers, beta-
 594 blockers or digoxin. Too few non-White patients were enrolled to assess the influence of race on
 595 effects of RYTHMOL SR (propafenone hydrochloride).

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

598 **ERAFT:** In a European multicenter trial [(European Rythmonorm SR Atrial Fibrillation
 599 Trial (ERAFT)], 2 doses of RYTHMOL SR (325 mg twice daily and 425 mg twice daily) and
 600 placebo were compared in 293 patients with documented electrocardiographic evidence of
 601 symptomatic paroxysmal AF. The patient population in this trial was 61% male, 100% White
 602 with a mean age of 61 years. Patients had a median duration of AF of 3.3 years, and 61% were
 603 taking medications that lowered heart rate. At baseline, 15% of the patients were treated with
 604 calcium channel blockers (verapamil and diltiazem), 42% with beta-blockers and 8% with
 605 digoxin. During a qualifying period of up to 28 days, patients had to have 1 ECG-documented
 606 incident of symptomatic AF. The double-blind treatment phase consisted of a 4 day loading

607 period followed by a 91-day efficacy period. Symptomatic arrhythmias were documented by
608 electrocardiogram monitoring.

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

618 **16 HOW SUPPLIED/STORAGE AND HANDLING**

619 RYTHMOL SR (propafenone HCl) capsules are supplied as white, opaque, hard gelatin
620 capsules containing either 225 mg, 325 mg, or 425 mg of propafenone HCl and imprinted in red
621 with the Reliant logo and strength. The 325 mg strength is also imprinted with a single red band
622 around $\frac{3}{4}$ of the circumference of the body; the 425 mg strength is imprinted with three bands
623 around $\frac{3}{4}$ of the circumference of the body.

624

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

625

626 **Storage:** Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in a
627 tight container.

628

629 **17 PATIENT COUNSELING INFORMATION**

- 630
- 631 • Patients should be instructed to notify their health care providers of any change in over-the-
632 counter, prescription and supplement use. The health care provider should assess the patient's
633 medication history including all over-the-counter, prescription and herbal/natural
634 preparations for those that may affect the pharmacodynamics or kinetics of RYTHMOL SR
635 *[see Warnings and Precautions (5.2)]*.
 - 636 • Patients should also check with their health care providers prior to taking a new over-the-
637 counter medicine.
 - 638 • If patients experience symptoms that may be associated with altered electrolyte balance, such
639 as excessive or prolonged diarrhea, sweating, vomiting, or loss of appetite or thirst, these
640 conditions should be immediately reported to their health care provider.
 - 641 • Patients should be instructed NOT to double the next dose if a dose is missed. The next dose
642 should be taken at the usual time.

642
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