

**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)

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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- 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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- 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](http://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)

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Revised: 4/2011

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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<sup>®</sup> 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<sub>max</sub> and AUC by 39 and 50% and the R propafenone  
283 C<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> propafenone decreased by 84%, with a corresponding decrease  
299 in AUC and C<sub>max</sub> 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/m<sup>2</sup>  
335 basis) and 600 mg/kg/day (about 6 times the MRHD on a mg/m<sup>2</sup> basis), respectively. Although  
336 maternally tolerated doses (up to 270 mg/kg/day, about three times the MRHD on a mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> basis) produced increases in maternal  
342 deaths. Doses of 360 or more mg/kg/day (four or more times the MRHD on a mg/m<sup>2</sup> 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.

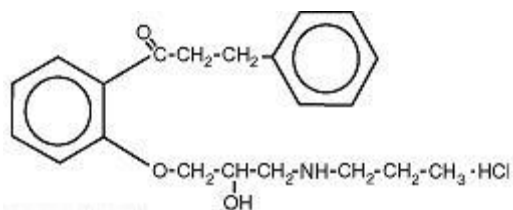
372 **11 DESCRIPTION**

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/m<sup>2</sup>), 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  $\beta$ -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/m<sup>2</sup> basis) and rats (up to  
533 270 mg/kg/day, about 3 times the MRHD on a mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> basis). There were no renal or  
558 hepatic changes at 90 mg/kg/day equivalent to the MRHD on a mg/m<sup>2</sup> 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**

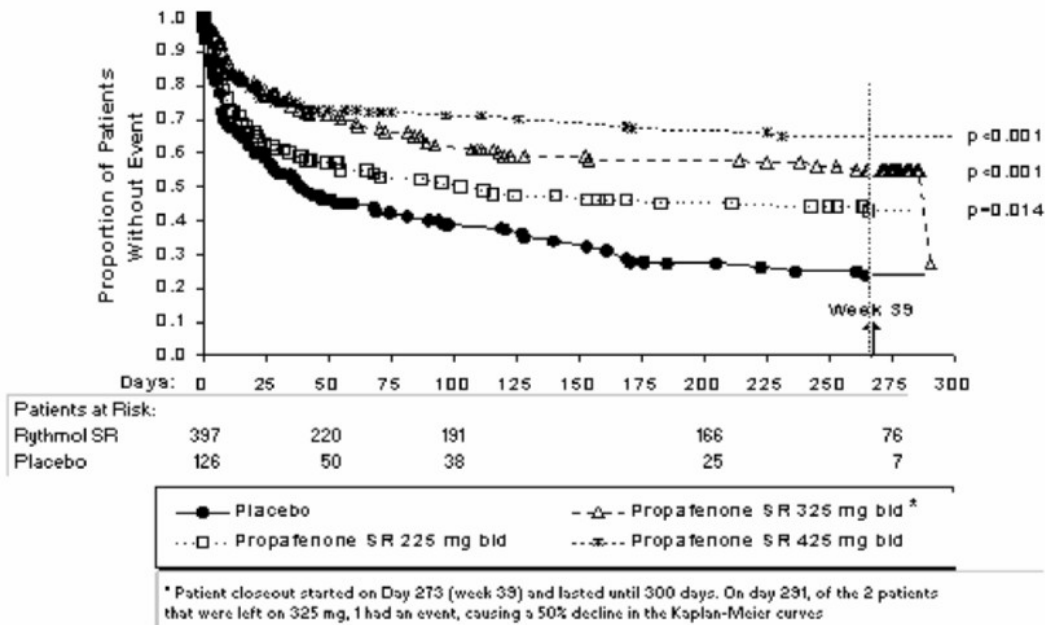
Parameter	RYTHMOL SR Twice-Daily Dose			Placebo (N = 126) n (%)
	225 mg (N = 126) n (%)	325 mg (N = 135) n (%)	425 mg (N = 136) n (%)	
Patients completing with terminating event*	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier Media	112	291	NA <sup>†</sup>	41
Range	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  
643 RYTHMOL SR is a registered trademark of G. Petrik used under license by Abbott Laboratories.

644  
645 Distributed by:



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652 Month Year  
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1 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

2 -----

3  
4 **PATIENT INFORMATION**  
5 **RYTHMOL SR® (RITH-Mall)**

6 **(propafenone hydrochloride) Extended Release Capsules**

7  
8 Read this Patient Information Leaflet before you start taking RYTHMOL SR and each  
9 time you get a refill. There may be new information. This information does not take  
10 the place of talking with your doctor about your medical condition or your  
11 treatment.

12  
13 **What is RYTHMOL SR?**

14 RYTHMOL SR is a prescription medicine that is used:

- 15 • in certain people who have a heart rhythm disorder called atrial fibrillation (AF)  
16 • to increase the amount of time between having symptoms of AF

17  
18 It is not known if RYTHMOL SR is safe and effective in children.

19  
20 **Who should not take RYTHMOL SR?**

21 Do not take RYTHMOL SR if you have:

- 22 • heart failure (weak heart)  
23 • had a recent heart attack  
24 • a heart rate that is too slow, and you do not have a pacemaker  
25 • very low blood pressure  
26 • certain breathing problems that make you short of breath or wheeze  
27 • certain abnormal body salt (electrolyte) levels in your blood

28  
29 Talk to your doctor before taking RYTHMOL SR if you think you have any of the  
30 conditions listed above.

31  
32 **What should I tell my doctor before taking RYTHMOL SR?**

33 Before you take RYTHMOL SR, tell your doctor if you:

- 34 • have liver or kidney problems  
35 • have breathing problems  
36 • have symptoms including diarrhea, sweating, vomiting, or loss of appetite or  
37 thirst that are severe. These symptoms may be a sign of abnormal electrolyte  
38 levels in your blood.  
39 • have myasthenia gravis  
40 • have lupus erythematosus

- 41 • have been told you have or had an abnormal blood test called Antinuclear  
42 Antibody Test or ANA Test
- 43 • are pregnant or plan to become pregnant. It is not known if RYTHMOL SR will  
44 harm your unborn baby.
- 45 • are breastfeeding or plan to breastfeed. RYTHMOL SR can pass into your milk  
46 and may harm your baby. You and your doctor should decide if you will  
47 breastfeed or take RYTHMOL SR. You should not do both.
- 48 • have any other medical conditions

49

50 **Tell your doctor about all the medicines you take**, including prescription and  
51 non-prescription medicines, vitamins, and herbal supplements. RYTHMOL SR and  
52 certain other medicines can affect each other and cause serious side effects.  
53 RYTHMOL SR may affect the way other medicines work, and other medicines may  
54 affect how RYTHMOL SR works.

55

56 **Especially tell your doctor if you take:**

- 57 • amiodarone or other medicines for your abnormal heart beats
- 58 • an antidepressant medicine
- 59 • a medicine to treat anxiety
- 60 • ritonavir (for example, KALETRA<sup>®</sup>, NORVIR<sup>®</sup>) or saquinavir (for example,  
61 INVIRASE<sup>®</sup>)
- 62 • an antibiotic medicine
- 63 • ketoconazole (for example, NIZORAL<sup>®</sup>)
- 64 • digoxin (LANOXIN<sup>®</sup>)
- 65 • warfarin sodium (for example, COUMADIN<sup>®</sup>, JANTOVEN<sup>®</sup>)

66

67 Know the medicines you take. Keep a list of them to show your doctor and  
68 pharmacist when you get a new medicine.

69

70 **How should I take RYTHMOL SR?**

- 71 • Take RYTHMOL SR exactly as prescribed. Your doctor will tell you how many  
72 capsules to take and how often to take them.
- 73 • To help reduce the chance of certain side effects, your doctor may start you with  
74 a low dose of RYTHMOL SR, and then slowly increase the dose.
- 75 • Do not open or crush the capsule.
- 76 • You may take RYTHMOL SR with or without food.
- 77 • You should not drink grapefruit juice during treatment with RYTHMOL SR.
- 78 • If you miss a dose of RYTHMOL SR, take your next dose at the usual time. Do  
79 not take 2 doses at the same time.

- 80 • If you take too much RYTHMOL SR, call your doctor or go to the nearest hospital  
81 emergency room right away.  
82 • Call your doctor if your heart problems get worse.  
83

84 **What are possible side effects of RYTHMOL SR?**

85 **RYTHMOL SR can cause serious side effects including:**

- 86
- 87 • **New or worsened abnormal heart beats, that can cause sudden death**  
88 **or be life-threatening.** Your doctor may do an electrocardiogram (ECG or  
89 EKG) before and during treatment to check your heart for these problems.  
90
  - 91 • **New or worsened heart failure. Tell your doctor about any changes in**  
92 **your heart symptoms, including:**
    - 93 ○ any new or increased swelling in your arms or legs
    - 94 ○ trouble breathing
    - 95 ○ sudden weight gain
  - 96
  - 97 • **Effects on pacemaker function.** RYTHMOL SR may affect how an  
98 implanted pacemaker or defibrillator works. Your doctor should check how  
99 your pacemaker or defibrillator is working during and after treatment with  
100 RYTHMOL SR. They may need to be re-programmed.  
101
  - 102 • **Very low white blood cell levels in your blood (agranulocytosis).** Your  
103 bone marrow may not produce enough of a certain type of white blood cells  
104 called neutrophils. If this happens, you are more likely to get infections. Tell  
105 your doctor right away if you have any of these symptoms, especially during  
106 the first 3 months of treatment:
    - 107 ○ fever
    - 108 ○ sore throat
    - 109 ○ chills
  - 110
  - 111 • **Worsening of myasthenia gravis in people who already have this**  
112 **condition.** Tell your doctor about any change in your symptoms.  
113
  - 114 • **RYTHMOL SR may cause lower sperm counts in men.** This could affect  
115 the ability to father a child. Talk to your doctor if this is a concern for you.  
116

117 Common side effects of RYTHMOL SR include:

- 118 • dizziness  
119 • fast or irregular heart beats

- 120 • chest pain
- 121 • trouble breathing
- 122 • taste changes
- 123 • nausea
- 124 • tiredness
- 125 • feeling anxious
- 126 • constipation
- 127 • upper respiratory infection or flu
- 128 • swelling

129

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

132 These are not all the possible side effects of RYTHMOL SR. For more information,  
133 ask your doctor or pharmacist.

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

136

#### 137 **How should I store RYTHMOL SR?**

- 138 • Store RYTHMOL SR at room temperature between 59°F to 86°F (15°C to 30°C).
- 139 • Keep the bottle tightly closed.

140

141 **Keep RYTHMOL SR and all medicines out of the reach of children.**

142

#### 143 **General information about RYTHMOL SR**

144 Medicines are sometimes prescribed for conditions other than those described in  
145 patient information leaflets. Do not use RYTHMOL SR for a condition for which it  
146 was not prescribed by your doctor. Do not give RYTHMOL SR to other people, even  
147 if they have the same symptoms you have. It may harm them.

148

149 This leaflet summarizes the most important information about RYTHMOL SR. If you  
150 would like more information, talk with your doctor. You can ask your doctor or  
151 pharmacist for information about RYTHMOL SR that is written for healthcare  
152 professionals. For more information about RYTHMOL SR, call 1-888-825-5249.

153

#### 154 **What are the ingredients in RYTHMOL SR?**

155 Active Ingredient: Propafenone hydrochloride

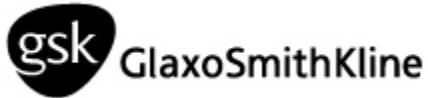
156

157 Inactive Ingredients: Antifoam, gelatin, hypromellose, red iron oxide, magnesium  
158 stearate, shellac, sodium lauryl sulfate, sodium dodecyl sulfate, soy lecithin and  
159 titanium dioxide.



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