

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use PROPAFENONE HYDROCHLORIDE EXTENDED RELEASE CAPSULES safely and effectively. See full prescribing information for PROPAFENONE HYDROCHLORIDE EXTENDED RELEASE CAPSULES.**

**PROPAFENONE HYDROCHLORIDE extended release capsules, for oral use**

**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.**

## INDICATIONS AND USAGE

Propafenone HCl Extended Release Capsules, USP 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 paroxysmal supraventricular tachycardia (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 propafenone ER capsules 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)
- Consider reducing the dose 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

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## FULL PRESCRIBING INFORMATION

### WARNING: MORTALITY

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

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

### 1 INDICATIONS AND USAGE

Propafenone HCl Extended Release Capsules, USP are 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.

### Usage Considerations:

- The use of propafenone ER capsules in patients with permanent AF or in patients exclusively with atrial flutter or paroxysmal supraventricular tachycardia (PSVT) has not been evaluated. Do not use

generation and/or conduction in the absence of pacemaker (4)

- Known Brugada Syndrome (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)
- Propafenone HCl Extended Release may unmask Brugada or Brugada-like Syndrome. Evaluate patients via ECG after initiation of therapy. (4, 5.2)
- Avoid use with other antiarrhythmic agents or drugs that prolong the QT interval. (5.3)
- Avoid simultaneous use of propafenone with both a cytochrome P450 2D6 (CYP2D6) inhibitor and a 3A4 inhibitor (CYP3A4). (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 (greater than 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 Par Pharmaceutical at 1-800-828-9393 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 patients with CYP2D6 deficiency) should be avoided. (7.1)
- Propafenone may increase digoxin or warfarin levels. (7.2, 7.3)
- Orlistat may reduce propafenone concentrations. Abrupt cessation of orlistat in patients stable on propafenone has resulted in convulsions, atrioventricular block, and circulatory failure. (7.4)
- Concomitant use of lidocaine may increase central nervous system side effects. (7.6)

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

**Revised: 10/2019**

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\*Sections or subsections omitted from the full prescribing information are not listed.

propafenone ER capsules to control ventricular rate during AF.

- Some patients with atrial flutter treated with propafenone have developed 1:1 conduction, producing an increase in ventricular rate. Concomitant treatment with drugs that increase the functional atrioventricular (AV) nodal refractory period is recommended.
- The effect of propafenone on mortality has not been determined **[see BOXED WARNING]**.

### 2 DOSAGE AND ADMINISTRATION

Propafenone HCl Extended Release Capsules, USP can be taken with or without food. Do not crush or further divide the contents of the capsule.

The dose of propafenone ER capsules must be individually titrated on the basis of response and tolerance. Initiate therapy with propafenone ER capsules 225 mg given every 12 hours. Dosage may be increased at a minimum of 5-day intervals to 325 mg given every 12 hours. If additional therapeutic effect is needed, the dose of propafenone ER capsules may be increased to 425 mg given every 12 hours.

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

The combination of cytochrome P450 3A4 (CYP3A4) inhibition and either cytochrome P450 2D6 (CYP2D6) deficiency or CYP2D6 inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. Therefore, avoid simultaneous use of propafenone ER capsules with both a CYP2D6 inhibitor and a CYP3A4 inhibitor **[see WARNINGS AND PRECAUTIONS (5.4) and DRUG INTERACTIONS (7.1)]**.

### 3 DOSAGE FORMS AND STRENGTHS

The 225 mg capsule is a white opaque cap and a white opaque body, imprinted with “par/209” on the cap and “par/209” on the body.

The 325 mg capsule is a orange opaque cap and a white opaque body, imprinted with “par/210” on the cap and “par/210” on the body.

The 425 mg capsule is a red opaque cap and a white opaque body, imprinted with “par/211” on the cap and “par/211” on the body.

### 4 CONTRAINDICATIONS

Propafenone ER capsules are contraindicated in the following circumstances:

- Heart failure
- Cardiogenic shock
- Sinoatrial, atrioventricular, and intraventricular disorders of impulse generation or conduction (e.g., sick sinus node syndrome, AV block) in the absence of an artificial pacemaker
- Known Brugada Syndrome
- Bradycardia
- Marked hypotension
- Bronchospastic disorders or severe obstructive pulmonary disease
- Marked electrolyte imbalance

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Proarrhythmic Effects

Propafenone has caused new or worsened arrhythmias. Such proarrhythmic effects include sudden death and life-threatening ventricular arrhythmias such as ventricular fibrillation, ventricular tachycardia, asystole, and torsade de pointes. It may also worsen premature ventricular contractions or supraventricular arrhythmias, and it may prolong the QT interval. It is therefore essential that each patient given propafenone be evaluated electrocardiographically prior to and during therapy to determine whether the response to propafenone ER capsules supports continued treatment. Because propafenone prolongs the QRS interval in the electrocardiogram, changes in the QT interval are difficult to interpret **[see CLINICAL PHARMACOLOGY (12.2)]**.

In the propafenone ER capsules Atrial Fibrillation Trial (RAFT) trial **[see CLINICAL STUDIES (14)]**, there were too few deaths to assess the long-term risk to patients. There were 5 deaths, 3 in the pooled group for propafenone ER capsules (0.8%), and 2 in the placebo group (1.6%). In the overall database of 8 trials of propafenone ER capsules and immediate release propafenone, the mortality rate was 2.5% per year on propafenone and 4.0% per year on placebo. Concurrent use of propafenone with other antiarrhythmic agents has not been well studied.

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

Overall in clinical trials with propafenone immediate release (which included patients treated for ventricular arrhythmias, atrial fibrillation/flutter, and PSVT), 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening or new appearance of VT or VF). Of the patients who had worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.8%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST trial **[see BOXED WARNING: MORTALITY]** suggests that an increased risk of proarrhythmia is present throughout treatment.

#### 5.2 Unmasking Brugada Syndrome

Brugada Syndrome may be unmasked after exposure to propafenone ER capsules. Perform an ECG after initiation of propafenone and discontinue the drug if changes are suggestive of Brugada Syndrome **[see CONTRAINDICATIONS (4)]**.

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

The use of propafenone ER capsules (propafenone hydrochloride) in conjunction with other drugs that prolong the QT interval has not been extensively studied. Such drugs may include many antiarrhythmics, some phenothiazines, tricyclic antidepressants, and oral macrolides. Withhold Class IA and III antiarrhythmic agents for at least 5 half-lives prior to dosing with propafenone ER capsules. Avoid the use of propafenone with Class IA and III antiarrhythmic agents (including quinidine and amiodarone). There is only limited experience with the concomitant use of Class IB or IC antiarrhythmics.

#### 5.4 Drug Interactions: Simultaneous Use with Inhibitors of Cytochrome P450 Isoenzymes 2D6 and 3A4

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

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

#### 5.5 Use in Patients with a History of Heart Failure

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

In clinical trial experience with propafenone immediate release, new or worsened congestive heart failure has been reported in 3.7% of patients with ventricular arrhythmia. These events were more likely in subjects with pre-existing heart failure and coronary artery disease. New onset of heart failure attributable to propafenone developed in less than 0.2% of patients with ventricular arrhythmia and in 1.9% of patients with paroxysmal AF or PSVT.

#### 5.6 Conduction Disturbances

Propafenone slows atrioventricular conduction and may also cause dose-related first-degree AV block. Average PR interval prolongation and increases in QRS duration are also dose-related. Do not give propafenone to patients with atrioventricular and intraventricular conduction defects in the absence of a pacemaker **[see CONTRAINDICATIONS (4), CLINICAL PHARMACOLOGY (12.2)]**.

In a U.S. trial (RAFT) in 523 patients with a history of symptomatic AF treated with propafenone ER capsules, sinus bradycardia (rate less than 50 beats/min) was reported with the same frequency with propafenone ER capsules and placebo.

#### 5.7 Effects on Pacemaker Threshold

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

#### 5.8 Agranulocytosis

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

#### 5.9 Use in Patients with Hypertic Dysfunction

Propafenone is highly metabolized by the liver. Severe liver dysfunction increases the bioavailability of propafenone to approximately 70% compared with 3% to 40% in patients with normal liver function when given propafenone immediate release tablets. In 8 patients with moderate to severe liver disease administered propafenone immediate release tablets, the mean half-life was approximately 9 hours. No trials have compared bioavailability of propafenone from propafenone ER capsules in patients with normal and impaired hepatic function. Increased bioavailability of propafenone in these patients may result in excessive accumulation. Carefully monitor patients with impaired hepatic function for excessive pharmacological effects **[see OVERDOSAGE (10)]**.

#### 5.10 Use in Patients with Renal Dysfunction

Approximately 50% of propafenone metabolites are excreted in the urine following administration of propafenone immediate release tablets. No trials have been performed to assess the percentage of metabolites eliminated in the urine following the administration of propafenone ER capsules.

In patients with impaired renal function, monitor for signs of overdosage **[see OVERDOSAGE (10)]**.

#### 5.11 Use in Patients with Myasthenia Gravis

Exacerbation of myasthenia gravis has been reported during propafenone therapy.

#### 5.12 Elevated ANA Titers

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

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

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

The data described below reflect exposure to propafenone ER capsules 225 mg twice daily in 126 patients, to propafenone ER capsules 325 mg twice daily in 135 patients, to propafenone ER capsules 425 mg twice daily in 136 patients, and to placebo in 126 patients for up to 39 weeks (mean, 20 weeks) in a placebo-controlled trial (RAFT) conducted in the U.S. The most commonly reported adverse events with propafenone (greater than 5% and greater than placebo) excluding those not reasonably associated with the use of the drug or because they were associated with the condition being treated, were dizziness, palpitations, chest pain, dyspnea, taste disturbance, nausea, fatigue, anxiety, constipation, upper respiratory tract infection, edema, and influenza. The frequency of discontinuation due to adverse events was 17%, and the rate was highest during the first 14 days of treatment.

Cardiac-related adverse events occurring in greater than or equal to 2% of the patients in any of the RAFT propafenone ER capsules treatment groups and more common with propafenone than with placebo, excluding those that are common in the population and those not plausibly related to drug therapy, included the following: angina pectoris, atrial flutter, AV block first-degree, bradycardia, congestive cardiac failure, cardiac murmur, edema, dyspnea, rales, wheezing, and cardioactive drug level above therapeutic.

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

Non-cardiac related adverse events occurring in greater than or equal to 2% of the patients in any of the RAFT propafenone ER capsules treatment groups and more common with propafenone than with placebo, excluding those that are common in the population and those not plausibly related to drug therapy, included the following: blurred vision, constipation, diarrhea, dry mouth, flatulence, nausea, vomiting, fatigue, weakness, upper respiratory tract infection, blood alkaline phosphatase increased, hemicrania, muscle weakness, dizziness (excluding vertigo), headache, taste disturbance, tremor, somnolence, anxiety, depression, ecchymosis.

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

Adverse events occurring in 2% or more of the patients in any of the ERAFT **[see CLINICAL STUDIES (14)]** propafenone ER capsules treatment groups and not listed above include the following: bundle branch block, bundle branch block right, conduction disorders, sinus bradycardia, and hypotension.

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

#### Blood and Lymphatic System

Anemia, lymphadenopathy, spleen disorder, thrombocytopenia.

#### Cardiac

Unstable angina, atrial hypertrophy, cardiac arrest, coronary artery disease, extrasystoles, myocardial infarction, nodal arrhythmia, palpitations, pericarditis, sinoatrial block, sinus arrest, sinus arrhythmia, supraventricular extrasystoles, ventricular extrasystoles, ventricular hypertrophy.

#### Ear and Labyrinth

Hearing impaired, tinnitus, vertigo.

#### Eye

Eye hemorrhage, eye inflammation, eyelid ptosis, miosis, retinal disorder, visual acuity reduced.

#### Gastrointestinal

Abdominal distension, abdominal pain, duodenitis, dyspepsia, dysphagia, eructation, gastritis, gastroesophageal reflux disease, gingival bleeding, glossitis, glossodynia, gum pain, halitosis, intestinal obstruction, melena, mouth ulceration, pancreatitis, peptic ulcer, rectal bleeding, sore throat.

#### General Disorders and Administration Site Conditions

Chest pain, feeling hot, hemorrhage, malaise, pain, pyrexia.

#### Hepatobiliary

Hepatomegaly.

#### Investigations

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

#### Metabolism and Nutrition

Anorexia, dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypokalemia.

#### Musculoskeletal, Connective Tissue, and Bone

Arthritis, bursitis, collagen-vascular disease, costochondritis, joint disorder, muscle cramps, muscle spasms, myalgia, neck pain, pain in jaw, sciatica, tendonitis.

#### Nervous System

Amnesia, ataxia, balance impaired, brain damage, cerebrovascular accident, dementia, gait abnormal, hypertension, hypothesia, insomnia, paralysis, paresthesia, peripheral neuropathy, speech disorder, syncope, tongue hypoesthesia.

#### Psychiatric

Decreased libido, emotional disturbance, mental disorder, neurosis, nightmare, sleep disorder.

#### Renal and Urinary

Dysuria, nocturia, oliguria, pyuria, renal failure, urinary casts, urinary frequency, urinary incontinence, urinary retention, urine abnormal.

#### Reproductive System and Breast

Breast pain, impotence, prostatism.

#### Respiratory, Thoracic, and Mediastinal

Atelectasis, breath sounds decreased, chronic obstructive airways disease, cough, epistaxis, hemoptysis, lung disorder, pleural effusion, pulmonary congestion, rales, respiratory failure, rhinitis, throat tightness.

#### Skin and Subcutaneous Tissue

Alopecia, dermatitis, dry skin, erythema, nail abnormality, petechiae, pruritus, sweating increased, urticaria.

#### Vascular

Arterial embolism limb, deep limb venous thrombosis, flushing, hematoma, hypertension, hypertensive crisis, hypotension, labile blood pressure, pallor, peripheral coldness, peripheral vascular disease, thrombosis.

### 7 DRUG INTERACTIONS

#### 7.1 CYP2D6 and CYP3A4 Inhibitors

Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline) and CYP3A4 (such as ketoconazole, ritonavir, saquinavir, erythromycin, grapefruit juice) can be expected to cause increased plasma levels of propafenone. The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with administration of propafenone may increase the risk of adverse reactions, including proarrhythmia. Therefore, simultaneous use of propafenone ER capsules with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided **[see WARNINGS and PRECAUTIONS (5.4), DOSAGE AND ADMINISTRATION (2)]**.

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

#### Cimetidine

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

#### Floxetine

## 8.5 Geriatric Use

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

## 10 OVERDOSAGE

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

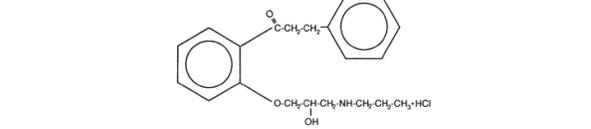
The hemodialysis of propafenone in patients with an overdose is expected to be of limited value in the removal of propafenone as a result of both its high protein binding (greater than 95%) and large volume of distribution.

## 11 DESCRIPTION

Propafenone Hydrochloride Extended Release Capsules, USP is an antiarrhythmic drug supplied in extended release capsules of 225 mg, 325 mg, and 425 mg for oral administration.

Chemically, propafenone hydrochloride is 2'-[2-hydroxy-3-(propylamino)-propoxy]-3-phenylprophe-none hydrochloride, with a molecular weight of 377.82. The molecular formula is C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub>·HCl.

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



Propafenone HCl occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform, and ethanol. Propafenone ER capsules are filled with granules containing the following inactive ingredients: ethylcellulose, lactose anhydrous, magnesium stearate and povidone. Each capsule contains Titanium dioxide and gelatin. In addition the 325 mg capsule also contains FD&C Blue No. 1, D&C Yellow No. 10 and FD&C Red No. 40 and the 425 mg capsule contains FD&C Blue No. 1, FD&C Red No. 40 and FD&C Yellow No. 6. The black ink consists of D&C Yellow No.10, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue No. 2, FD&C Red No. 40, FD&C Blue No. 1 and shellac glaze~45% (20% esterified) in ethanol.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Propafenone is a Class I<sub>C</sub> antiarrhythmic drug with local anesthetic effects and a direct stabilizing action on myocardial membranes. The electrophysiologic effect of propafenone manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and, to a lesser extent, myocardial fibers, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

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

### 12.2 Pharmacodynamics

**Cardiac Electrophysiology**

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

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

Table 1. Mean Change ± SD in 12-Lead Electrocardiogram Results (RAFT)	Propafenone HCl ER Capsules Twice-Daily Dosing				Placebo n = 126
	225 mg n=126	325 mg n=135	425 mg 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 <sup>a</sup> (ms)	2 ± 30	5 ± 36	6 ± 37	5 ± 35	

<sup>a</sup> Calculated using Bazett's correction factor.

In RAFT [see *CLINICAL STUDIES (14)*], the distribution of the maximum changes in QTc compared with baseline over the trial in each patient was similar in the groups receiving propafenone HCl extended release capsules 225 mg twice daily, 325 mg twice daily, and 425 mg twice daily, and placebo. Similar results were seen in the ERAFT trial.

Range Maximum QTc Change	Propafenone HCl ER Capsules				Placebo n = 100 n (%)
	225 mg Twice Daily n = 119 n (%)	325 mg Twice Daily n = 129 n (%)	425 mg Twice Daily n = 123 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)	

### Hemodynamics

Trials in humans have shown that propafenone exerts a negative inotropic effect on the myocardium. Cardiac catheterization trials in patients with moderately impaired ventricular function (mean Cl: 2.61 L/min/m<sup>2</sup>) utilizing intravenous propafenone infusions (loading dose of 2 mg/kg over 10 min + followed by 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 mg/mL (a dose that produces plasma levels of propafenone greater than recommended oral dosing) showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances, and depression of cardiac output and cardiac index.

### 12.3 Pharmacokinetics

**Absorption/Bioavailability**

Maximal plasma levels of propafenone are reached between 3 to 8 hours following the administration of propafenone ER capsules. Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose-dependent and dosage-form-dependent absolute bio-availability; e.g., a 150-mg immediate release tablet had an absolute bioavailability of 3.4%, while a 300-mg immediate release tablet had an absolute bioavailability of 10.8%. Absorption from a 300-mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate-release tablets increased still further.

Relative bioavailability assessments have been performed between propafenone ER capsules cap-sules and propafenone immediate release tablets. In extensive metabolizers, the bioavailability of

propafenone from the ER formulation was less than that of the immediate release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase of overall first-pass metabolism (*see Metabolism*). As a result of the increased first-pass effect, higher daily doses of propafenone were required from the ER formulation relative to the immediate release formulation to obtain similar exposures to propafenone. The relative bioavailability of propafenone from the 325-mg twice-daily regimen of propafenone ER capsules approximates that of propafenone immediate release 150-mg 3-times-daily regimen. Mean exposure to 5-hydroxypropafenone was about 20% to 25% higher after ER capsule administration than after immediate release tablet administration.

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

### Distribution

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

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

### Metabolism

There are 2 genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2 to 10 hours. These patients metabolize propafenone into 2 active metabolites: 5-hydroxypropafenone, which is formed by CYP2D6, and N-depropylpropafenone (norpropafenone), which is formed by both CYP3A4 and CYP1A2.

In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs, such as encaimide, melorolol, and dextromethorphan, whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.

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

The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiology properties similar to propafenone *in vitro*. In man after administration of propafenone ER capsules, the 5-hydroxy-propafenone metabolite is usually present in concentrations less than 40% of propafenone. The nor-propafenone metabolite is usually present in concentrations less than 10% of propafenone.

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

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

### Specific Populations

*Patients with Hepatic Impairment:* Decreased liver function increases the bioavailability of propa-fenone. Absolute bioavailability assessments have not been determined for the capsule formulation of propafenone ER. Absolute bioavailability of propafenone HCl immediate-release tablets is inversely related to indocyanine green clearance, reaching 60% to 70% at clearances of 7 mL/min and below. Protein binding decreases to about 88% in patients with severe hepatic dysfunction. The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction [*see WARNINGS AND PRECAUTIONS (5.9)*].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day, approximately twice the MRHD on a mg/m<sup>2</sup> basis) and rats (up to 270 mg/kg/day, approximately 3 times the MRHD on a mg/m<sup>2</sup> basis) provided no evidence of a carcinogenic potential for propafenone.

Propafenone was not mutagenic in the Ames (salmonella) test and the *in vivo* mouse dominant lethal test in rabbits (≥5 mg/kg/day) or at near-threshold doses in monkeys and dogs (≤5 mg/kg/day); doses were less than the MRHD on a mg/m<sup>2</sup> basis. These effects were reversible and did not impair fertility in rabbits at an intravenous dose of 3.5 mg/kg/day (a spermatogenesis-impairing dose). Effects on spermatogenesis were not found when propafenone was administered to rats either orally or intravenously up to 360 mg/kg/day or 6 mg/kg/day, respectively, or in dogs at oral doses up to 240 mg/kg/day (up to approximately 4 or 9 times the MRHD on a mg/m<sup>2</sup> basis in rats and dogs, respectively). Treatment of male rabbits for 10 weeks prior to mating at an oral dose of 120 mg/kg/day (approximately 2 times the MRHD on a mg/m<sup>2</sup> basis) did not result in evidence of impaired fertility. Nor was there evidence of impaired fertility when propafenone was administered orally to male and female rats at dose levels up to 270 mg/kg/day (approximately 3 times the MRHD on a mg/m2 basis) for 10 weeks (males) or 2 weeks (females) prior to mating through mating.

**13.2 Animal Toxicology and/or Pharmacology**
Renal changes have been observed in the rat following 6 months of oral administration of propafenone HCl at doses of 180 and 360 mg/kg/day (about 2 and 4 times, respectively, the MRHD on a mg/m<sup>2</sup> basis). Both inflammatory and non-inflammatory changes in the renal tubules, with accompanying interstitial nephritis, were observed. These changes were reversible, as they were not found in rats allowed to recover for 6 weeks. Fatty degenerative changes of the liver were found in rats following longer durations of administration of propafenone HCl at a dose of 270 mg/kg/day (about 3 times the MRHD on a mg/m<sup>2</sup> basis). There were no renal or hepatic changes at 90 mg/kg/day equivalent to the MRHD on a mg/m<sup>2</sup> basis).

### 14 CLINICAL STUDIES

Propafenone ER capsules have been evaluated in patients with a history of electrocardiographically documented recurrent episodes of symptomatic AF in 2 randomized, double-blind, placebo-controlled trials.

### RAFT

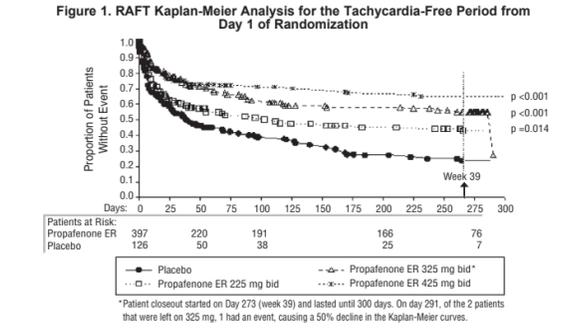
In one U.S. multicenter trial (RAFT), 3 doses of propafenone ER capsules (225 mg twice daily, 325 mg twice daily, and 425 mg twice daily) and placebo were compared in 523 patients with symp-tomatic, episodic AF. The patient population in this trial was 59% male with a mean age of 63 years, 91% white, and 6% black. The patients had a median history of AF of 13 months and documented symptomatic AF within 12 months of trial entry. Over 90% were NYHA Class I, and 21% had a prior electrical cardioversion. At baseline, 24% were treated with calcium channel blockers, 37% with beta-blockers, and 38% with digoxin. Symptomatic arrhythmias after randomization were documented by transtelephonic electrocardiogram and centrally read and adjudicated by a blinded adverse event committee. Propafenone ER capsules administered for up to 39 weeks was shown to prolong signifi-cantly the time to the first recurrence of symptomatic atrial arrhythmia, predominantly AF, from Day 1 of randomization (primary efficacy variable) compared with placebo, as shown in **Table 3**.

Parameter	Dose of Propafenone HCl ER Capsules			Placebo (N = 126) n (%)
	225 mg Twice Daily (N = 126) n (%)	325 mg Twice Daily (N = 135) n (%)	425 mg Twice Daily (N = 136) n (%)	
Patients completing with terminating event <sup>a</sup>	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier Media	112	291	NA <sup>b</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 with placebo	0.67	0.43	0.35	--
95% CI for Hazard Ratio	(0.49, 0.93)	(0.31, 0.61)	(0.24, 0.51)	--

<sup>a</sup> Terminating events comprised 91% AF, 5% atrial flutter, and 4% PSVT.

<sup>b</sup> Not Applicable: Fewer than 50% of the patients had events. The median time is not calculable.

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



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

No difference in the average heart rate during the first recurrence of symptomatic arrhythmia between propafenone ER capsules and placebo was observed.

### ERAFT

In a European multicenter trial (European Rythmonorm SR Atrial Fibrillation Trial (ERAFT)), 2 doses of propafenone ER capsules (325 mg twice daily and 425 mg twice daily) and placebo were compared in 293 patients with documented electrocardiographic evidence of symptomatic paroxysmal AF. The patient population in this trial was 61% male, 100% white with a mean age of 61 years. Patients had a median duration of AF of 3.3 years, and 61% were taking medications that lowered heart rate. At baseline, 15% of the patients were treated with calcium channel blockers (verapamil and diltiazem), 42% with beta-blockers, and 8% with digoxin. During a qualifying period of up to 28 days, patients had to have 1 ECG-documented incident of symptomatic AF. The double-blind treatment phase consisted of a 4-day loading period followed by a 91-day efficacy period. Symptomatic arrhythmias were documented by electrocardiogram monitoring.

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Propafenone Hydrochloride Extended Release Capsules, USP, 225 mg are available as hard gelatin capsules containing 225 mg of propafenone HCl. The capsule is a white opaque cap printed "par/209" in black ink and white opaque body printed "par/209" in black ink.

NDC 49884-113-02 Bottles of 60 capsules  
NDC 49884-113-09 Bottles of 90 capsules  
NDC 49884-113-01 Bottles of 100 capsules  
NDC 49884-113-05 Bottles of 500 capsules  
NDC 49884-113-10 Bottles of 1000 capsules

Propafenone Hydrochloride Extended Release Capsules, USP, 325 mg are available as hard gelatin capsules containing 325 mg of propafenone HCl. The capsule is an orange opaque cap printed "par/210" in black ink and white opaque body printed "par/210" in black ink.

NDC 49884-210-02 Bottles of 60 capsules  
NDC 49884-210-09 Bottles of 90 capsules  
NDC 49884-210-01 Bottles of 100 capsules  
NDC 49884-210-05 Bottles of 500 capsules  
NDC 49884-210-10 Bottles of 1000 capsules

Propafenone Hydrochloride Extended Release Capsules, USP, 425 mg are available as hard gelatin capsules containing 425 mg of propafenone HCl. The capsule is a red opaque cap printed "par/211" in black ink and white opaque body printed "par/211" in black ink.

NDC 49884-211-02 Bottles of 60 capsules  
NDC 49884-211-09 Bottles of 90 capsules  
NDC 49884-211-01 Bottles of 100 capsules  
NDC 49884-211-05 Bottles of 500 capsules  
NDC 49884-211-10 Bottles of 1000 capsules

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

## 17 PATIENT COUNSELING INFORMATION

*Advise the patient to read the FDA-approved patient labeling (Patient Information).*

- Instruct patients to notify their healthcare providers of any change in over-the-counter, prescrip-tion, and supplement use.
- Instruct patients to report symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, vomiting, or loss of appetite or thirst.
- Instruct patients not to double the next dose if a dose is missed. The next dose should be taken at the usual time.

## PATIENT INFORMATION

## PROPAFENONE HYDROCHLORIDE EXTENDED RELEASE CAPSULES, USP

### What is propafenone HCl ER capsules?

- Propafenone HCl ER capsules is a prescription medicine that is used:
- in certain people who have a heart rhythm disorder called atrial fibrillation (AF)
- to increase the amount of time between having symptoms of AF

It is not known if propafenone HCl ER capsules is safe and effective in children.

## Who should not take propafenone HCl ER capsules?

Do not take propafenone HCl ER capsules if you have:

- heart failure (weak heart)
- had a recent heart attack
- a heart condition called Brugada Syndrome
- a heart rate that is too slow, and you do not have a pacemaker
- very low blood pressure
- certain breathing problems that make you short of breath or wheeze
- certain abnormal body salt (electrolyte) levels in your blood

Talk to your doctor before taking propafenone HCl ER capsules if you think you have any of the conditions listed above.

## What should I tell my doctor before taking propafenone HCl ER capsules?

Before you take propafenone HCl ER capsules, tell your doctor if you:

- have liver or kidney problems
- have breathing problems
- have symptoms including diarrhea, sweating, vomiting, or loss of appetite or thirst that are severe. These symptoms may be a sign of abnormal electrolyte levels in your blood.
- have myasthenia gravis
- have lupus erythematosus
- have been told you have or had an abnormal blood test called Antinuclear Antibody Test or ANA Test
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed. Propafenone HCl ER capsules can pass into your milk. You and your doctor should discuss the best way to feed your baby during this time.
- have any other medical conditions

**Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Propafenone HCl ER capsules and certain other medicines can affect each other and cause serious side effects. Propafenone HCl ER capsules may affect the way other medicines work, and other medicines may affect how propafenone HCl ER capsules work.

## Especially tell your doctor if you take:

- amiodarone or other medicines for your abnormal heart beats
- an antidepressant medicine
- a medicine to treat anxiety
- ritonavir (for example, KALETRA, NORVIR) or saquinavir (for example, INVIRASE)
- an antibiotic medicine
- ketoconazole (for example, NIZORAL)
- digoxin (LANOXIN)
- warfarin sodium (for example, COUMADIN, JANTOVEN)

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

## How should I take propafenone HCl ER capsules?

- Take propafenone HCl ER capsules exactly as prescribed. Your doctor will tell you how many capsules to take and how often to take them.
- To help reduce the chance of certain side effects, your doctor may start you with a low dose of propafenone HCl ER capsules, and then slowly increase the dose.
- Do not open or crush the capsule.
- You may take propafenone HCl extended release capsules with or without food.
- You should not drink grapefruit juice during treatment with propafenone HCl ER capsules.
- If you miss a dose of propafenone HCl ER capsules, take your next dose at the usual time. Do not take 2 doses at the same time.
- If you take too much propafenone HCl ER capsules, call your doctor or go to the nearest hospital emergency room right away.
- Call your doctor if your heart problems get worse.

## What are possible side effects of propafenone HCl ER capsules?

**Propafenone HCl ER capsules can cause serious side effects including:**
**New or worsened abnormal heart beats, that can cause sudden death or be life-threatening.** Your doctor may do an electrocardiogram (ECG or EKG) before and during treatment to check your heart for these problems.

- **New or worsened heart failure. Tell your doctor about any changes in your heart symptoms, including:**
  - any new or