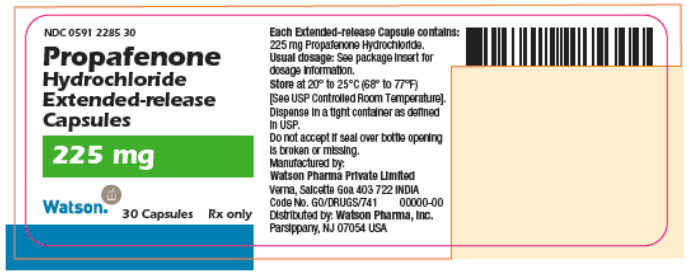
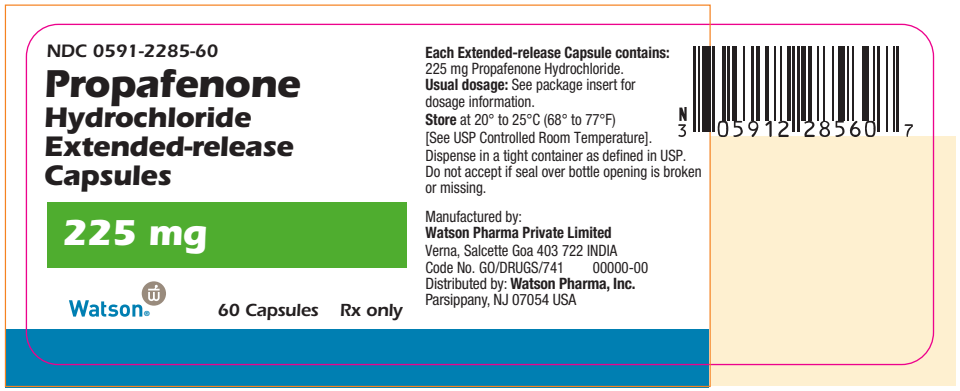
Artwork prepared for Watson, Goa, INDIA



Skip-Varnish area:
30 mm (L) x 25 mm (H)

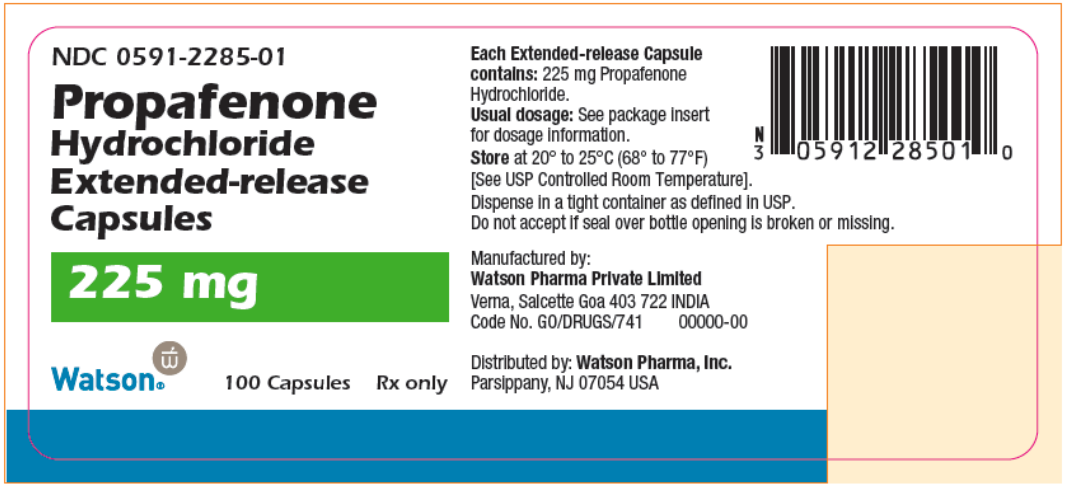
LABEL SIZE: 89 mm by 32 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



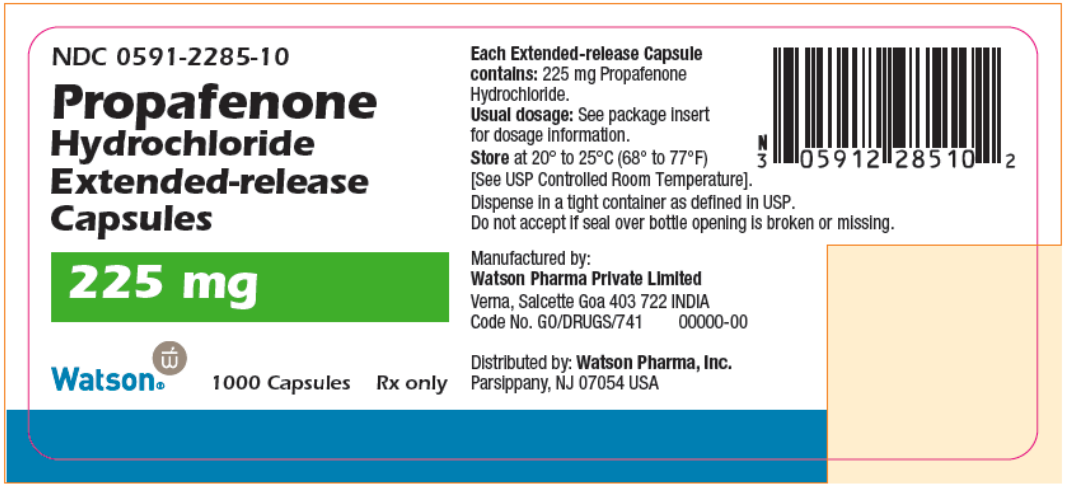
LABEL SIZE: 120 mm by 45 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



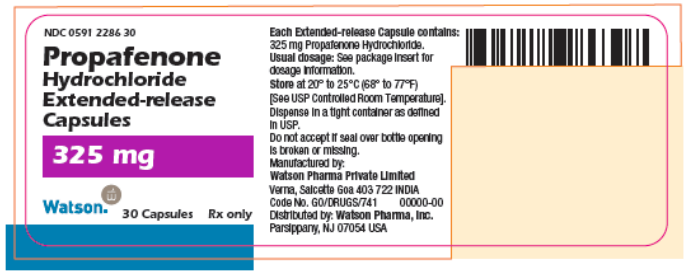
LABEL SIZE: 140 mm by 60 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



LABEL SIZE: 140 mm by 60 mm
COLORS: (b) (4)

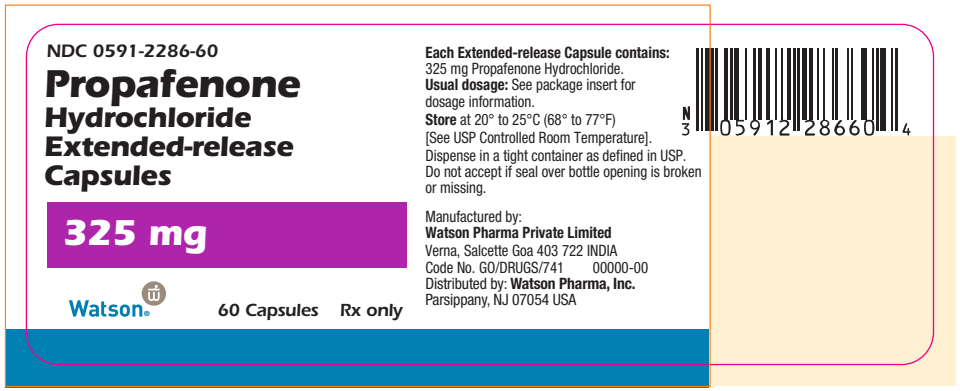
Artwork prepared for Watson, Goa, INDIA



Skip-Varnish area:
30 mm (L) x 25 mm (H)

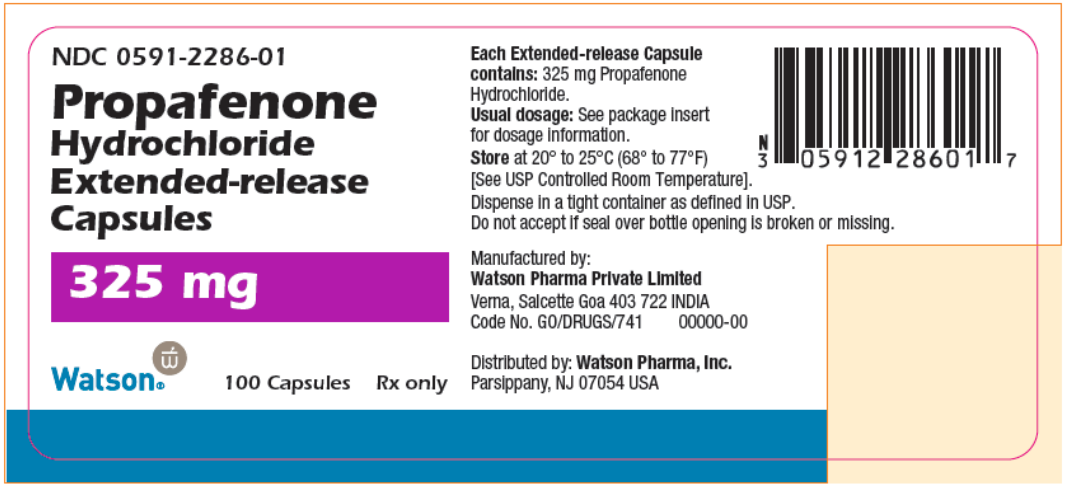
LABEL SIZE: 89 mm by 32 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



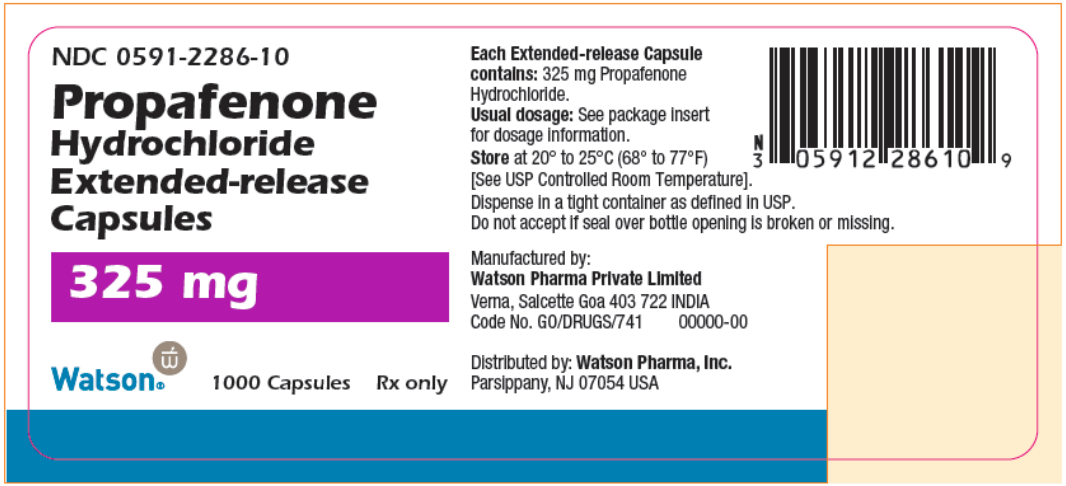
LABEL SIZE: 120 mm by 45 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



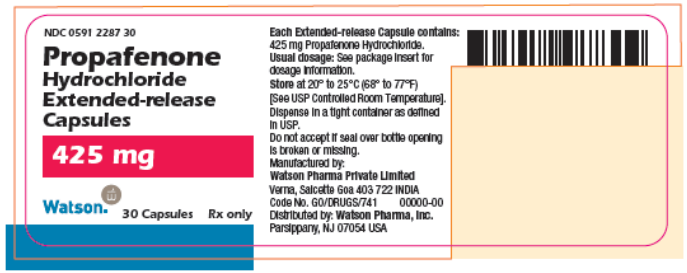
LABEL SIZE: 140 mm by 60 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



LABEL SIZE: 140 mm by 60 mm
COLORS: (b) (4)

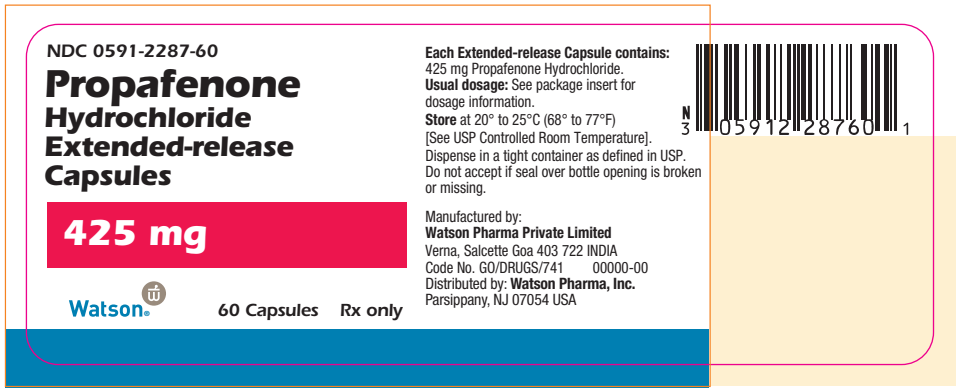
Artwork prepared for Watson, Goa, INDIA



Skip-Varnish area:
30 mm (L) x 25 mm (H)

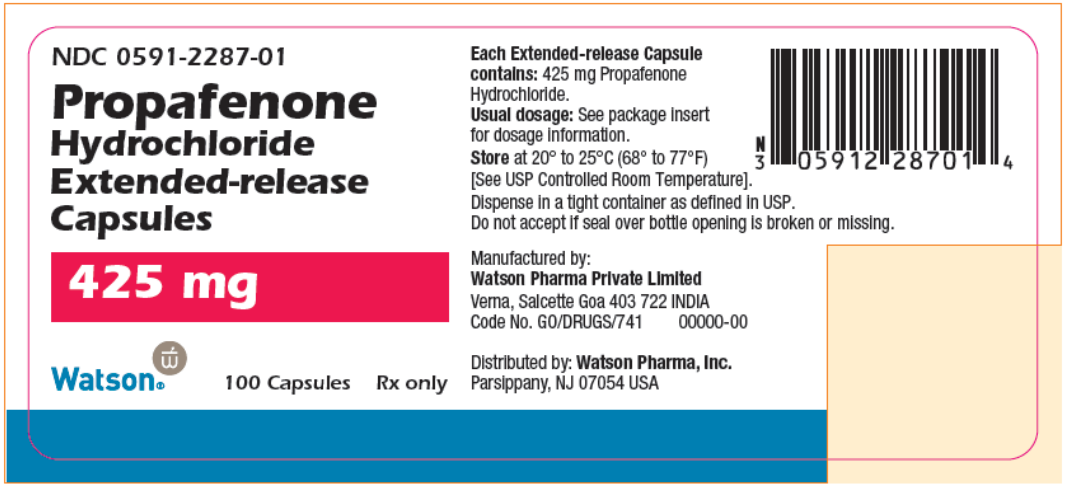
LABEL SIZE: 89 mm by 32 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



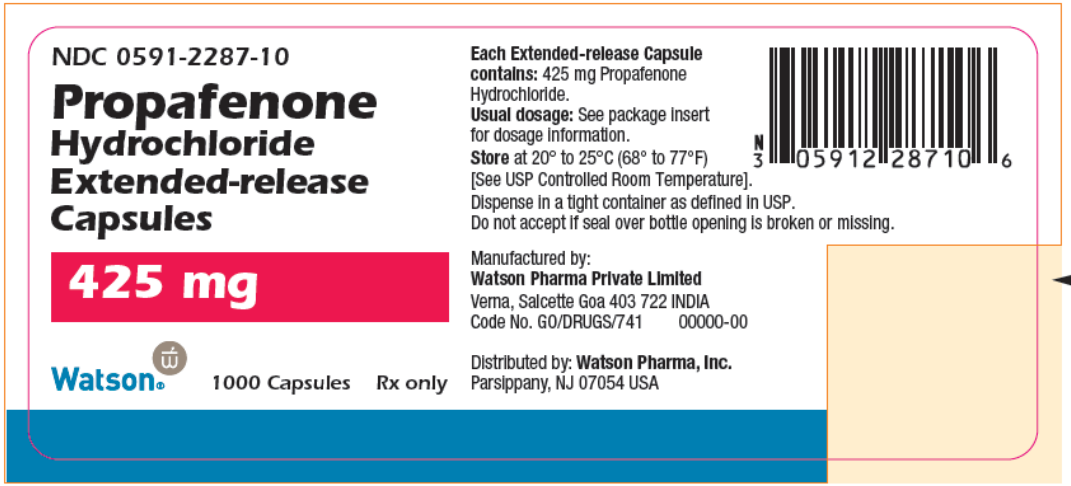
LABEL SIZE: 120 mm by 45 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



LABEL SIZE: 140 mm by 60 mm
COLORS: (b) (4)

Artwork prepared for Watson, Goa, INDIA



LABEL SIZE: 140 mm by 60 mm
COLORS: (b) (4)

Propafenone Hydrochloride Extended-release Capsules
Revised: April 2015
2001475-00 Rx only

Propafenone Hydrochloride Extended-release Capsules
Rx only
2001475-00
Revised: April 2015

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 antiarrhythic 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-lifethreatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

----------RECENT MAJOR CHANGES----------

Contraindications (4)	02/2013
Warnings and Precautions, Unmasking Brugada Syndrome (5.2)	02/2013

----------INDICATIONS AND USAGE----------

Propafenone hydrochloride extended-release capsules are 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 propafenone hydrochloride extended-release capsules with drugs that increase the atrioventricular nodal refractory period. (1)
- The effect of propafenone on mortality has not been determined. (1)

----------DOSAGE AND ADMINSTRATION----------
- 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)

----------CONTRINDICATIONS----------
- Heart failure (4)
- Cardiogenic shock (4)
- Sinoatrial, atrioventricular, and intraventricular disorders of impulse 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 hydrochloride extended-release capsules 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 other drugs that prolong the QT interval. (5.3)
- Avoid simultaneous use of propafenone with both a cytochrome P450 2D6 inhibitor and a 3A4 inhibitor. (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 Watson Laboratories, Inc at 1-800-272-5525 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 hydrochloride extended-release capsules 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: 04/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: MORTALITY
- **In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest rate (7.7%; 56/730) was seen in patients treated with encainide or flecainide (Class 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 study was 10 months.**
- **The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) or other antiarrhythmic drugs is uncertain, but at present, it is prudent to consider any 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 hydrochloride extended-release capsules 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 hydrochloride extended-release 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 propafenone hydrochloride extended-release 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 hydrochloride extended-release capsules can be taken with or without food. Do not crush or further divide the contents of the capsule.

The dose of propafenone hydrochloride extended-release capsules must be individually titrated on the basis of response and tolerance. Initiate therapy with propafenone hydrochloride extended-release capsules 225 mg given every 12 hours. Dosage may be increased at a minimum of 5 day interval to 325 mg given every 12 hours. If additional therapeutic effect is needed, the dose of propafenone hydrochloride extended-release 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 CYP3A4 inhibition and either 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 hydrochloride extended-release 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

Propafenone hydrochloride extended-release capsules are supplied as opaque white capsules containing 225 mg, 325 mg or 425 mg of propafenone HCl. The 225 mg capsule is printed with **"WPI"** on cap and **"2285"** on body in black ink. The 325 mg capsule is printed with **"WPI"** on cap and **"2286"** on body in black ink. The 425 mg capsule is printed with **"WPI"** on cap and **"2287"** on body in black ink. The capsules are filled with white circular biconvex minitablets plain on both sides.

4 CONTRAINDICATIONS

Propafenone hydrochloride extended-release 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 hydrochloride extended-release capsules be evaluated electrocardiographically prior to and during therapy, to determine whether the response to propafenone hydrochloride extended-release 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 RAFT study *[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 propafenone hydrochloride extended-release group (0.8%) and 2 in the placebo group (1.6%). In the overall propafenone hydrochloride extended-release and propafenone hydrochloride immediate release database of 8 studies, 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 study. However, in 4 of the 9 patients, the ventricular tachycardia was of atrial origin. Six of the 9 patients that developed ventricular arrhythmias did so within 14 days of onset of therapy. About 2.3% (11/474) of all patients had recurrence of SVT during the study which could have been a change in the patients' arrhythmia behavior or could represent a proarrhythmic event. Case reports in patients treated with 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 hydrochloride 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 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study *[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 hydrochloride extended-release capsules. Perform an ECG after initiation of propafenone hydrochloride extended-release capsules 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 hydrochloride extended-release capsules 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 hydrochloride extended-release 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 to a somewhat lesser extent in other demographic groups. 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 hydrochloride extended-release 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 hydrochloride extended-release capsules (all doses), compared to 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 hydrochloride immediate-release, new or worsened heart failure has been reported in 3.7% of patients with ventricular arrhythmia. These events were more likely in subjects with preexisting 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) and Clinical Pharmacology (12.2)]*.

In a U.S. trial (RAFT) in 523 patients with a history of symptomatic AF treated with propafenone hydrochloride extended-release capsules, sinus bradycardia (rate less than 50 beats/min) was reported with the same frequency with propafenone hydrochloride extended-release 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 Hepatic Dysfunction

Propafenone is highly metabolized by the liver. Severe liver dysfunction increases the bioavailability of propafenone to approximately 70% compared to 3 to 40% in patients with normal liver function when given propafenone hydrochloride immediate-release tablets. In 8 patients with moderate to severe liver disease administered propafenone hydrochloride immediate-release tablets, the mean half-life was approximately 9 hours. No studies have compared bioavailability of propafenone from propafenone hydrochloride extended-release 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 hydrochloride immediate-release tablets. No studies have been performed to assess the percentage of metabolites eliminated in the urine following the administration of propafenone hydrochloride extended-release 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 erythematosis (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.

5.13 Impaired Spermatogenesis

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

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 to 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 hydrochloride extended-release capsules 225 mg twice daily in 126 patients, to propafenone hydrochloride extended-release capsules 325 mg twice daily in 135 patients, to propafenone hydrochloride extended-release 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 US. 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 extended-release 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 SR treatment groups and more common with propafenone than with placebo, excluding those that are common in the population and those not plausibly related to drug therapy, included the following: blurred vision, constipation, diarrhea, dry mouth, flatulence, nausea, vomiting, fatigue, weakness, upper respiratory tract infection, blood alkaline phosphatase increased, hematuria, 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 SR treatment groups and not listed above include the following: bundle branch block left, bundle branch block right, conduction disorders, sinus bradycardia, and hypotension.

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

Blood and Lymphatic System Disorders: Anemia, lymphadenopathy, spleen disorder, thrombocytopenia.
Cardiac Disorders: 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 Disorders: Hearing impaired, tinnitus, vertigo.
Eye Disorders: Eye hemorrhage, eye inflammation, eyelid ptosis, miosis, retinal disorder, visual acuity reduced.
Gastrointestinal Disorders: Abdominal distension, abdominal pain, duodenitis, dyspepsia, dysphagia, eructation, gastritis, gastroesophageal reflux disease, gingival bleeding, glossitis, glossodynia, gum pain, halitosis, intestinal obstruction, melena, mouth ulceration, pancreatitis, peptic ulcer, rectal bleeding, sore throat.
General Disorders and Administration Site Conditions: Chest pain, feeling hot, hemorrhage, malaise, pain, pyrexia.
Hepatobiliary Disorders: Hepatomegaly.
Investigations: Abnormal 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 Disorders: Anorexia, dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypokalemia.
Musculoskeletal, Connective Tissue and Bone Disorders: Arthritis, bursitis, collagen-vascular disease, costochondritis, joint disorder, muscle cramps, muscle spasms, myalgia, neck pain, pain in jaw, sciatica, tendonitis.
Nervous System Disorders: Amnesia, ataxia, balance impaired, brain damage, cerebrovascular accident, dementia, gait abnormal, hypertonia, hypothesia, insomnia, paralysis, paresthesia, peripheral neuropathy, speech disorder, syncope, tongue hypoesthesia.
Psychiatric Disorders: Decreased libido, emotional disturbance, mental disorder, neurosis, nightmare, sleep disorder.
Renal and Urinary Disorders: Dysuria, nocturia, oliguria, pyuria, renal failure, urinary casts, urinary frequency, urinary incontinence, urinary retention, urine abnormal.
Reproductive System and Breast Disorders: Breast pain, impotence, prostatism.
Respiratory, Thoracic and Mediastinal Disorders: Atelectasis, breath sounds decreased, chronic obstructive airways disease, cough, epistaxis, hemoptysis, lung disorder, pleural effusion, pulmonary congestion, rales, respiratory failure, rhinitis, throat tightness.
Skin and Subcutaneous Tissue Disorders: Alopecia, dermatitis, dry skin, erythema, nail abnormality, petechiae, pruritus, sweating increased, urticaria.
Vascular Disorders: Arterial embolism limb, deep limb venous thrombosis, flushing, hematoma, hypertension, hypertensive crisis, hypotension, labile blood pressure, pallor, peripheral coldness, peripheral vascular disease, thrombosis.

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, and 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 hydrochloride extended-release capsules with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided *[see Warnings and Precautions (5.4) and 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.
Fluoxetine: Concomitant administration of propafenone and fluoxetine in extensive metabolizers increased the S propafenone Cmax and AUC by 39 and 50% and the R propafenone Cmax and AUC by 71 and 50%.
Quinidine: Small doses of quinidine completely inhibit the CYP2D6 hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers *[see Clinical Pharmacology (12)]*. Concomitant administration of quinidine (50 mg three times daily) with 150 mg immediate-release propafenone three times daily decreased the clearance of propafenone by 60% in extensive metabolizers, making them poor metabolizers. Steady-state plasma concentrations increased by more than 2-fold for propafenone, and decreased 50% for 5-OH-propafenone. A 100 mg dose of quinidine increased steady state concentrations of propafenone 3-fold. Avoid concomitant use of propafenone and quinidine.
Rifampin: Concomitant administration of rifampin and propafenone in extensive metabolizers decreased the plasma concentrations of propafenone by 67% with a corresponding decrease of 5-OH-propafenone by 65%. The concentrations of norpropafenone increased by 30%. In poor metabolizers, there was a 50% decrease in propafenone plasma concentrations and increased the AUC and Cmax of norpropafenone by 74 and 20%, respectively. Urinary excretion of propafenone and its metabolites decreased significantly. Similar results were noted in elderly patients: Both the AUC and Cmax propafenone decreased by 84%, with a corresponding decrease in AUC and Cmax of 5-OH-propafenone by 69 and 57%.

7.2 Digoxin

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

7.3 Warfarin

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

7.4 Orlistat

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

7.5 Beta-Antagonists

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

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION
Propafenone Hydrochloride
(proe-PA-fen-one HYE-droe-KLOR-ide)
Extended-release Capsules

Read this Patient Information Leaflet before you start taking propafenone hydrochloride extended-release capsules and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What are propafenone hydrochloride extended-release capsules?

Propafenone hydrochloride extended-release capsules are 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 hydrochloride extended-release capsules are safe and effective in children.

Who should not take propafenone hydrochloride extended-release capsules?

Do not take propafenone hydrochloride extended-release capsules if you have:
- heart failure (weak heart)
- had a recent heart attack
- have 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 hydrochloride extended-release capsules if you think you have any of the conditions listed above.

What should I tell my doctor before taking propafenone hydrochloride extended-release capsules?

Before you take propafenone hydrochloride extended-release 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 erythematosis
- 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. It is not known if propafenone hydrochloride will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Propafenone hydrochloride can pass into your milk and may harm your baby. You and your doctor should decide if you will breastfeed or take propafenone hydrochloride extended-release capsules. You should not do both.
- have any other medical conditions

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Propafenone hydrochloride extended-release capsules and certain other medicines can affect each other and cause serious side effects. Propafenone hydrochloride extended-release capsules may affect the way other medicines work, and other medicines may affect how propafenone hydrochloride extended-release 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 hydrochloride extended-release capsules?

- Take propafenone hydrochloride extended-release 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 hydrochloride extended-release capsules and then slowly increase the dose.
- Do not open or crush the capsule.
- You may take propafenone hydrochloride extended-release capsules with or without food.
- You should not drink grapefruit juice during treatment with propafenone hydrochloride extended-release capsules
- If you miss a dose of propafenone hydrochloride extended-release capsules, take your next dose at the usual time. Do not take 2 doses at the same time.
- If you take too many propafenone hydrochloride extended-release capsules, call your doctor or go to the nearest hospital emergency room right away.
- Call your doctor if your heart problems get worse.

Open Size: 415 x 381 mm Folding Size: 32 x 30 mm Paper: 40 gsm Bible Paper Date: 19.10.2012

415 mm

381 mm

192 mm (1st fold)

30 mm

30 mm

32 mm

What are possible side effects of propafenone hydrochloride extended-release capsules?

Propafenone hydrochloride extended-release 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 increased swelling in your arms or legs
  - trouble breathing
  - sudden weight gain
- **Effects on pacemaker function.** Propafenone hydrochloride extended-release capsules may affect how an implanted pacemaker or defibrillator works. Your doctor should check how your pacemaker or defibrillator is working during and after treatment with propafenone hydrochloride extended-release capsules. They may need to be re-programmed.
- **Very low white blood cell levels in your blood (agranulocytosis).** Your bone marrow may not produce enough of a certain type of white blood cells called neutrophils. If this happens, you are more likely to get infections. Tell your doctor right away if you have any of these symptoms, especially during the first 3 months of treatment:
  - fever
  - sore throat
  - chills
- **Worsening of myasthenia gravis in people who already have this condition.** Tell your doctor about any change in your symptoms.
- **Propafenone hydrochloride extended-release capsules may cause lower sperm counts in men.** This could affect the ability to father a child. Talk to your doctor if this is a concern for you.

Common side effects of propafenone hydrochloride extended-release capsules include:

- dizziness
- fast or irregular heart beats
- chest pain
- trouble breathing
- taste changes
- nausea
- tiredness
- feeling anxious
- constipation
- upper respiratory infection or flu
- swelling

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

These are not all the possible side effects of propafenone hydrochloride extended-release capsules. For more information, ask your doctor or pharmacist.

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

How should I store propafenone hydrochloride extended-release capsules?

- Store propafenone hydrochloride extended-release capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the bottle tightly closed.

Keep propafenone hydrochloride extended-release capsules and all medicines out of the reach of children.

General information about propafenone hydrochloride extended-release capsules

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use propafenone hydrochloride extended-release capsules for a condition for which it was not prescribed by your doctor. Do not give propafenone hydrochloride extended-release capsules to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about propafenone hydrochloride extended-release capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about propafenone hydrochloride extended-release capsules that is written for healthcare professionals. For more information about propafenone hydrochloride extended-release capsules call 1-800-272-5525.

What are the ingredients in propafenone hydrochloride extended-release capsules?

Active Ingredient: Propafenone hydrochloride

Inactive Ingredients: black iron oxide, gelatin, hypromellose, magnesium stearate, potassium hydroxide, propylene glycol, shellac, sodium lauryl sulfate, talc, and titanium dioxide.

*Brands listed are trademarks of their respective owners and are not trademarks of Watson Laboratories, Inc. The makers of these brands are not affiliated with and do not endorse Watson Laboratories, Inc. or its products.

Manufactured by:
Watson Pharma Private Ltd.
Verna, Goa INDIA

Distributed by:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: April 2015

7.6 Lidocaine

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Propafenone hydrochloride extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data:

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

Non-teratogenic Effects: In a study in which female rats received daily oral doses of propafenone from mid-gestation through weaning of their offspring, doses as low as 90 mg/kg/day (equivalent to the MRHD on a mg/m² basis) produced increases in maternal deaths. Doses of 360 or more mg/kg/day (4 or more times the MRHD on a mg/m² basis) resulted in reductions in neonatal survival, body weight gain and physiological development.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

10 OVERDOSAGE

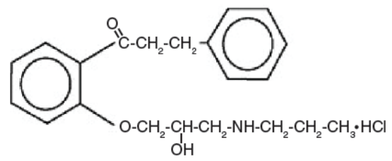
The symptoms of overdosage may include hypotension, somnolence, bradycardia, intra-atrial and intra-ventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling abnormal 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 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-phenylpropiophenone hydrochloride, with a molecular weight of 377.92. The molecular formula is $C_{21}H_{27}NO_3$•HCl.

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



Propafenone HCl occurs as a white powder. It is soluble in methanol and hot water. Propafenone hydrochloride extended-release capsules are filled with circular biconvex minitablets containing propafenone and the following inactive ingredients: black iron oxide, gelatin, hypromellose, magnesium stearate, potassium hydroxide, propylene glycol, shellac, sodium lauryl sulfate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Propafenone is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

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

12.2 Pharmacodynamics

Electrophysiology: Electrophysiology studies 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 Hydrochloride Extended-release Capsules Twice Daily Dosing			
	225 mg n=126	325 mg n=135	425 mg n=136	Placebo n=126
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

*Calculated using Bazett's correction factor

In RAFT *[see Clinical Studies (14)]*, the distribution of the maximum changes in QTc compared to baseline over the study in each patient was similar in the propafenone hydrochloride extended-release capsules 225 mg twice daily, 325 mg twice daily, and 425 mg twice daily and placebo dose groups. Similar results were seen in the ERAFT study.

Table 2. Number of Patients According to the Range of Maximum QTc Change Compared to Baseline Over the Study in Each Dose Group (RAFT Study).

Range maximum QTc change	Propafenone Hydrochloride Extended-release Capsules			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)

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

12.3 Pharmacokinetics

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

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

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

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

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

Metabolism: There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2 to10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxymetabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.

As a consequence of the observed differences in metabolism, administration of propafenone hydrochloride extended-release capsules to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of propafenone hydrochloride extended-release capsules. In slow metabolizers, 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 hydrochloride extended-release capsules is the same for all patients. The larger inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity *[see Dosage and Administration (2)]*.

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

Inter-Subject Variability: With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of propafenone hydrochloride extended-release 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 hydrochloride is a racemic mixture. The R- and S-enantiomers of propafenone display stereoselective disposition characteristics. *In vitro* and *in vivo* studies have shown that the R-isomer of propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-propafenone at steady state. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent β-antagonist than the R-enantiomer. Following administration of propafenone hydrochloride immediate-release tablets or propafenone hydrochloride extended-release 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 hydrochloride extended-release 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.

Special Populations: ***Hepatic Impairment:*** Decreased liver function increases the bioavailability of propafenone. Absolute bioavailability assessments have not been determined for the propafenone hydrochloride extended-release capsule formulation. Absolute bioavailability of propafenone hydrochloride 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, about twice the maximum recommended human oral daily dose [MRHD] on a mg/m² basis) and rats (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m² basis) provided no evidence of a carcinogenic potential for propafenone HCl.

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

Propafenone HCl, administered intravenously to rabbits, dogs, and monkeys, has been shown to decrease spermatogenesis. These effects were reversible, were not found following oral dosing of propafenone HCl, were seen at lethal or near lethal dose levels and were not seen in rats treated either orally or intravenously *[see Warnings and Precautions (5.13)]*. Treatment of male rabbits for 10 weeks prior to mating at an oral dose of 120 mg/kg/day (about 2.4 times the MRHD on a mg/m² basis) or an intravenous dose of 3.5 mg/kg/day (a spermatogenesis-impairing dose) did not result in evidence of impaired fertility. Nor was there evidence of impaired fertility when propafenone HCl was administered orally to male and female rats at dose levels up to 270 mg/kg/day (about 3 times the MRHD on a mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

Renal and Hepatic Toxicity in Animals: Renal changes have been observed in the rat following 6 months of oral administration of propafenone HCl at doses of 180 and 360 mg/kg/day (about 2 and 4 times, respectively, the MRHD on a mg/m² 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/m² basis). There were no renal or hepatic changes at 90 mg/kg/day equivalent to the MRHD on a mg/m² basis.

14 CLINICAL STUDIES

Propafenone hydrochloride extended-release 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 US multicenter study (propafenone hydrochloride extended-release capsules Atrial Fibrillation Trial, RAFT), 3 doses of propafenone hydrochloride extended-release capsules (225 mg twice daily, 325 mg twice daily and 425 mg twice daily) and placebo were compared in 523 patients with symptomatic, 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 study entry. Over 90% were NYHA Class I, and 21% had a prior electrical cardioversion. At baseline, 24% were treated with calcium channel blockers, 37% with beta blockers, and 38% with digoxin. Symptomatic arrhythmias after randomization were documented by transtelephonic electrocardiogram and centrally read and adjudicated by a blinded adverse event committee. Propafenone hydrochloride extended-release capsules administered for up to 39 weeks was shown to prolong significantly the time to the first recurrence of symptomatic atrial arrhythmia, predominantly AF, from Day 1 of randomization (primary efficacy variable) compared to placebo, as shown in Table 3.

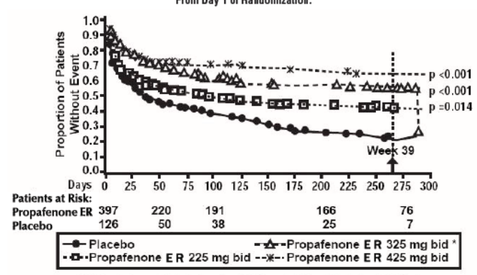
Table 3: Analysis of Tachycardia-Free Period (Days) from Day 1 of Randomization

	Propafenone Hydrochloride Extended-release Capsules Twice-Daily Dose			
Parameter	225 mg twice daily (N = 126) n (%)	325 mg twice daily (N = 135) n (%)	425 mg twice daily (N = 136) n (%)	Placebo (N = 126) n (%)
Patients completing with terminating event*	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier Media	112	291	NA†	41
Range	0 to 285	0 to 293	0 to 300	0 to 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)	--

* Terminating events comprised 91% AF, 5% atrial flutter, and 4% PSVT.
† Not Applicable: Fewer than 50% of the patients had events. The median time is not calculable.

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

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



* Patient closeout started on Day 273 (week 39) and lasted until 300 days. On day 291, of the 2 patients that were left on 325 mg, 1 had an event, causing a 50% decline in the Kaplan-Meier curves

In additional analyses, propafenone hydrochloride extended-release capsules (225 mg twice daily, 325 mg twice daily, and 425 mg twice daily) were 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 hydrochloride extended-release capsules 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 hydrochloride extended-release 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 hydrochloride.

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

ERAFT: In a European multicenter trial [(European Rythmonorm SR Atrial Fibrillation Trial (ERAFT)], 2 doses of propafenone hydrochloride extended-release 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 hydrochloride extended-release capsules were shown to prolong the time to the first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization (primary efficacy analysis). The proportional hazard analysis revealed that both propafenone hydrochloride extended-release capsules doses 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 hydrochloride extended-release capsules. There was a slight increase in the incidence of centrally diagnosed asymptomatic AF or atrial flutter in each of the 2 propafenone hydrochloride extended-release treatment groups compared to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Propafenone hydrochloride extended-release capsules are supplied as opaque white capsules containing either 225 mg, 325 mg or 425 mg of propafenone HCl. The 225 mg capsule is printed with "**WPI**" on cap and "**2285**" on body in black ink. The 325 mg capsule is printed with "**WPI**" on cap and "**2286**" on body in black ink. The 425 mg capsule is printed with "**WPI**" on cap and "**2287**" on body in black ink. The capsules are filled with white circular biconvex minitablets plain on both sides.

Capsule Strength	Bottle Count	NDC
225 mg	30	0591-2285-30
225 mg	60	0591-2285-60
225 mg	100	0591-2285-01
225 mg	1000	0591-2285-10
325 mg	30	0591-2286-30
325 mg	60	0591-2286-60
325 mg	100	0591-2286-01
325 mg	1000	0591-2286-10
425 mg	30	0591-2287-30
425 mg	60	0591-2287-60
425 mg	100	0591-2287-01
425 mg	1000	0591-2287-10

Storage: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight container.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

17.1 Information for Patients

- Patients should be instructed to notify their health care providers of any change in over-the-counter, prescription and supplement use. The health care provider should assess the patient's medication history including all over-the-counter, prescription and herbal/natural preparations for those that may affect the pharmacodynamics or kinetics of propafenone hydrochloride extended-release capsules *[see Warnings and Precautions (5.4)]*.
- Patients should also check with their health care providers prior to taking a new over-the-counter medicine.
- If patients experience symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, vomiting, or loss of appetite or thirst, these conditions should be immediately reported to their health care provider.
- Patients should be instructed NOT to double the next dose if a dose is missed. The next dose should be taken at the usual time.

Manufactured by:
Watson Pharma Private Ltd.
Verna, Goa INDIA

Distributed by:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: April 2015 2001475-00