DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21416/S-007

SUPPLEMENT APPROVAL

GlaxoSmithKline LLC
Attention: Robert J. Bohinski
Associate Director, Global Regulatory Affairs, CVM
2711 Centerville Road, Suite 400
Wilmington, DE 19808

Dear Mr. Bohinski:

Please refer to your Supplemental New Drug Application (sNDA) dated June 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rythmol SR Extended-Release Capsules, 225, 325, and 425 mg.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. The labeling has been revised to the PLR format.

2. The INDICATIONS AND USAGE section has been changed from:

INDICATIONS AND USAGE
RYTHMOL SR is indicated to prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease.

The use of RYTHMOL SR in patients with permanent atrial fibrillation or in patients exclusively with atrial flutter or PSVT has not been evaluated. RYTHMOL SR should not be used to control ventricular rate during atrial fibrillation.

The effect of RYTHMOL SR on mortality has not been determined (see black box WARNINGS).

To:

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

Usage Considerations:

- The use of RYTHMOL SR in patients with permanent AF or in patients exclusively with atrial flutter or paroxysmal supraventricular tachycardia (PSVT) has not been evaluated. Do not use RYTHMOL SR 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]*.

4. The following text has been added as the fourth paragraph of the DOSAGE AND ADMINISTRATION section:

   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 RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor. *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)]*.

5. Under CONTRAINDICATIONS, "Bronchospastic disorders" has been changed to "Bronchospastic disorders or severe obstructive pulmonary disease."

6. The following text has been added to the WARNINGS AND PRECAUTIONS/Proarrhythmic Effects section as the final paragraph of the section:

   Overall in clinical trials with RYTHMOL 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 pro-arrhythmia 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.

7. The following has been added as a new section under WARNINGS AND PRECAUTIONS:

   5.2 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 RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor.

8. Under WARNINGS AND PRECAUTIONS, the Use in Patients with a History of Bronchospasm section has been deleted.

9. The following has been added as the second paragraph under WARNINGS AND PRECAUTIONS/Use in Patients with a History of Heart Failure:

In clinical trial experience with RYTHMOL 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 <0.2% of patients with ventricular arrhythmia and in 1.9% of patients with paroxysmal AF or PSVT.

10. The WARNINGS AND PRECAUTIONS/Conduction Disturbances section has been changed from:

    Propafenone causes dose-related first degree AV block. Average PR interval prolongation and increases in QRS duration are also dose-related.

    Propafenone should not be given to patients with atrioventricular and intraventricular conduction defects in the absence of a pacemaker (see CONTRAINDICATIONS).

    In a U.S. trial (RAFT) in 523 patients with a history of symptomatic atrial fibrillation treated with RYTHMOL SR, electrocardiograms obtained in response to symptoms were associated with no patients having sinus rhythm with Mobitz Type I (Wenckenbach) second degree AV block, sinus rhythm with Mobitz Type II second degree AV block, or third degree AV block. Sinus bradycardia (rate <50 beats/min) was reported with the same frequency with RYTHMOL SR and placebo.

    To:

    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 RYTHMOL SR, sinus bradycardia (rate <50 beats/min) was reported with the same frequency with RYTHMOL SR and placebo.

11. The WARNINGS AND PRECAUTIONS/Effects of Pacemaker Threshold section has been changed from:

    Propafenone may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

    To:

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

12. The WARNINGS AND PRECAUTIONS/Hematologic section has been changed from:

    Hematologic Disturbances:
    Agranulocytosis (fever, chills, weakness, and neutropenia) has been reported in patients receiving propafenone. Generally, the agranulocytosis occurred within the first two months of propafenone therapy and upon discontinuation of therapy, the white count usually normalized by 14 days. Unexplained fever and/or decrease in white cell count, particularly during the initial three months of therapy, warrant consideration of possible agranulocytosis or granulocytopenia. Patients should be

instructed to report promptly the development of any signs of infection such as fever, sore throat, or chills.

To:

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.

13. The WARNINGS AND PRECAUTIONS/Use in Patients with Hepatic Dysfunction section has been changed from:

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

    Until further data are available, RYTHMOL SR should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

    To:

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

14. Under WARNINGS AND PRECAUTIONS/Impaired Spermatogenesis, the following sentence has been deleted:

    Subsequent evaluations in 11 patients receiving RYTHMOL chronically have found no effect of propafenone on sperm count.

15. The ADVERSE REACTIONS section has been substantially revised in order to comply with FDA Guidance and/or regulation, for increased clarity and ease of use, and to eliminate information available elsewhere in the label (the large RAFT adverse event table has been deleted).

16. The Drug Interactions section has been substantially revised from:

    Propafenone is metabolized by CYP2D6 (major pathway) and CYP1A2 and CYP3A4. Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline), CYP1A2 (such as amiodarone), and CYP3A4 (such as ketaconazole, ritonavir, saquinavir, erythromycin, and grapefruit juice) can be expected to cause increased plasma levels of propafenone. Appropriate monitoring is

recommended when RYTHMOL SR is used together with such drugs. In addition, propafenone is an inhibitor of CYP2D6. Coadministration of propafenone with drugs metabolized by CYP2D6 (such as desipramine, imipramine, haloperidol, venlafaxine) might lead to increased plasma concentrations of these drugs. The effect of propafenone on the P-Glycoprotein transporter has not been studied.

Quinidine: Small doses of quinidine completely inhibit the CYP2D6 hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (see CLINICAL PHARMACOLOGY). Concomitant administration of quinidine (50 mg TID) with 150 mg immediate release propafenone TID decreased the clearance of propafenone by 60% in EM, making them PM. Steady-state plasma concentrations increased by more that 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. Concomitant use of propafenone and quinidine is not recommended.

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%. Plasma digoxin levels of patients receiving propafenone should be monitored and digoxin dosage adjusted as needed.

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 have been reported to increase the risks of central nervous system side effects of lidocaine.

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 100-400%. 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.

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 in patients taking warfarin. Adjustment of the warfarin dose should be guided by monitoring of the prothrombin time.

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.

Rifampin: Concomitant administration of rifampin and propafenone in extensive metabolizers decreased the plasma concentrations of propafenone by 67% with a corresponding decrease of 5OH-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 5OH-propafenone by 69 and 57%.

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%.

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

To:

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 RYTHMOL SR with both a CYP2D6 inhibitor and a CYP3A4 inhibitor should be avoided *[see Warnings and Precautions (5.2) 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 C_{max} and AUC by 39 and 50% and the R propafenone C_{max} 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 EM, making them PM. Steady-state plasma concentrations increased by more that 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 5OH-propafenone by 65%. The concentration of norpropafenone increased by 30%. In poor metabolizers, there was a 50% decrease in propafenone plasma concentrations and increased the AUC and C_{max} 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 C_{max} propafenone decreased by 84%, with a corresponding decrease in AUC and C_{max} of 5OH-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 100-400%. 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.

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.

17. The Nursing Mothers section (now under USE IN SPECIFIC POPULATIONS) has been changed from:

    Propafenone is excreted in human milk. Caution should be exercised when RYTHMOL SR is administered to a nursing mother.

    To:

    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.

18. Table 2 [Mean Change ± SD in 12-Lead Electrocardiogram Results (RAFT)] has been revised to include information on heart rate.

19. Minor editorial changes have been made throughout the labeling.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon Labeling Text

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
10/29/2010