DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-416/S-001

Reliant Pharmaceuticals, LLC
Attention: Mr. Robert Mandetta
110 Allen Road
Liberty Corner, NJ 07938

Dear Mr. Mandetta:

Please refer to your supplemental new drug application dated September 18, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Rythmol SR (propafenone HCl) 225, 325 and 425 mg extended release Capsules.

We acknowledge receipt of your submission dated June 22, 2004, which constituted a complete response to our March 22, 2004 action letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. The **PRECAUTIONS/Drug Interactions** section has been substantially revised and now reads as follows:

   Drug Interactions:
   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 ketoconazole, 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, venalafaxine) 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 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. 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 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.

2. A new **Post Marketing Reports** section has been added after the **Drug Interactions** section and reads as follows:

   Post Marketing Reports:
   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.

3. The last sentence of the second paragraph of the **CLINICAL PHARMACOLOGY/Metabolism** section, a hyphen has been added to the word “inter-subject.”

We have completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on June 22, 2004.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

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

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

/s/

Norman Stockbridge

9/13/04 03:25:28 PM