DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Ernest Mario, Ph.D.
Chief Executive Officer
Reliant Pharmaceuticals, Inc.
110 Allen Road
Liberty Corner, NJ 07938

RE: NDA # 21-416
Rythmol® SR (propafenone HCl) extended release Capsules
MACMIS ID # 14383

WARNING LETTER

Dear Dr. Mario:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two promotional pieces, identified as RYTH-2026 and RYTH-1028, for Rythmol® SR (propafenone HCl) extended release Capsules (Rythmol SR) submitted by Reliant Pharmaceuticals, Inc. (Reliant) under cover of Form FDA 2253. These pieces are false or misleading because they fail to communicate any risk information for Rythmol SR and broaden the indication for the product. Therefore, these pieces misbrand Rythmol SR in violation of sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i). These violations concern us from a public health perspective because they suggest that the product is effective in a broader range of conditions and is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Rythmol SR:

> 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**).

The PI also contains the following safety information, in pertinent part:

Black box **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 six days but less than two 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 1C 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 ten 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 1C antiarrhythmic to have a significant 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.

CONTRAINDICATIONS

RYTHMOL SR is contraindicated in the presence of congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, electrolyte imbalance, or hypersensitivity to the drug.

WARNINGS

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 RYTHMOL SR be evaluated electrocardiographically prior to and during therapy, to determine whether the response to RYTHMOL SR supports continued treatment….

Use with Drugs that Prolong the QT Interval and Antiarrhythmic Agents:
The use of RYTHMOL SR (propafenone hydrochloride) in conjunction with other drugs that prolong the QT interval has not been extensively studied and is not recommended. Such drugs may include many antiarrhythmics, some phenothiazines, cisapride, bepridil, tricyclic

antidepressants and oral macrolides….The use of propafenone with Class Ia and III antiarrhythmic agents (including quinidine and amiodarone) is not recommended….

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema):
Patients with bronchospastic disease should not, in general, receive propafenone or other agents with beta-adrenergic-blocking activity.

Congestive Heart Failure:
Propafenone exerts a negative inotropic activity on the myocardium as well as beta blockade effects and may provoke overt congestive heart failure….

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

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

Hematologic Disturbances:
Agranulocytosis (fever, chills, weakness, and neutropenia) has been reported in patients receiving propafenone….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.

PRECAUTIONS

Hepatic Dysfunction:
Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function….

Renal Dysfunction:
Approximately 50% of propafenone metabolites are excreted in the urine following administration of RYTHMOL immediate release tablets….Until further data are available, RYTHMOL SR should be administered cautiously to patients with impaired renal function….

ADVERSE REACTIONS

The most commonly reported adverse events….included dizziness, chest pain, palpitations, taste disturbance, dyspnea, nausea, constipation, anxiety, fatigue, upper respiratory tract infection, influenza, first degree heart block and vomiting….

Omission of Risk Information

The promotional pieces RYTH-2026 and RYTH-1028 are misleading because they make numerous representations about the dosing of Rythmol SR and its use for atrial fibrillation, but fail to provide <u>any</u> information about the risks of the product. By omitting the most serious and frequently occurring risks

associated with the drug, these pieces misleadingly suggest that Rythmol SR is safer than has been demonstrated by substantial evidence or substantial clinical experience. We note the inclusion of a reference to the "full Prescribing Information, including Boxed Warning," at the bottom of each piece; this statement, however, is not sufficient to provide appropriate qualification or pertinent information for claims made in the pieces. *Cf*. 21 CFR 202.1(e)(3)(i).

Broadening of Indication

The promotional pieces RYTH-2026 and RYTH-1028 are also misleading because they suggest that Rythmol SR is safe and effective for use in a broader patient population or under broader conditions than has been demonstrated by substantial evidence or substantial clinical experience. These pieces contain numerous representations that promote the use of Rythmol SR to treat the broad population of patients with "atrial fibrillation" or "AFib." For example, the pieces claim:

- "….demand for Rythmol SR is expected to continue as increasing numbers of aging Americans are being diagnosed with atrial fibrillation,"
- "**More atrial fibrillation cases are being diagnosed**…." and
- "Don't make your AFib patients wait! Make sure you are stocked and ready with new Rythmol SR…." (emphasis in original)

The PI identifies limitations to the use of Rythmol SR for atrial fibrillation. Specifically, according to the Indications and Usage section, "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." By failing to identify the limitations to its indication, these claims imply that Rythmol SR is useful for the treatment of all patients with atrial fibrillation when this is not the case.

Conclusion and Requested Action

The promotional pieces identified as RYTH-2026 and RYTH-1028 omit risk information for Rythmol SR and broaden the indication for the product. Therefore, these pieces misbrand Rythmol SR in violation of the Act. 21 U.S.C. §§ 352(a) & 321(n); *cf*. 21 CFR 202.1(e)(3)(i).

DDMAC requests that Reliant immediately cease the dissemination of violative promotional materials for Rythmol SR such as those described above. Please submit a written response to this letter on or before September 30, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Rythmol SR such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 14383 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Rythmol SR comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams

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