DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-151/S-005 & S-009

Abbott Laboratories
Attention: Ms. Marylou Reed
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, IL 60064-6157

Dear Ms. Reed:

Please refer to your supplemental new drug applications dated August 27, 1998 and June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rythmol (propafenone HCl) 150, 225 and 300 mg Tablets.

We acknowledge receipt of your submissions to S-005 dated September 10, 1998, April 23, June 29, 1999, August 8, December 12, 2001, June 20, November 1, 2002; and to S-009 dated June 20, and November 1, 2002. The November 1, 2002 submission constituted a complete response to our January 12, 1999 and August 28, 2000 approvable letters.

These supplemental new drug applications provide final printed labeling revised to read as follows:

1. The following editorial changes are noted:

    a. Throughout, the parenthetical "(propafenone HCl)" has either been added or removed after the word "RYTHMOL" or the words "RYTHMOL (propafenone HCl)" have been changed to either "RYTHMOL" or "propafenone HCl" or the words "propafenone HCl" or "propafenone" have been replaced by "RYTHMOL" and vice versa.

    b. Throughout, references to other sections have been bolded where appropriate.

    c. The following abbreviations have been spelled out on their initial use: AV, WPW, PAF, PSVT and SVT.

    d. In the first paragraph under **CLINICAL PHARMACOLOGY/Electrophysiology**, the words "dose related" are hyphenated.

    e. In the fourth paragraph (in both the second and third sentences) under **ADVERSE REACTIONS**, the words "dose related" are hyphenated.

2. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism**,

    a. The third paragraph has been changed from:

        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 2-10

hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone and N-depropylpropafenone.
In vitro preparations have shown these two metabolites to have antiarrhythmic activity comparable to propafenone but in man they both are usually present in concentrations less than 20% of propafenone. Nine additional metabolites have been identified, most only in trace amounts. It is the saturable hydroxylation pathway that is responsible for nonlinear pharmacokinetic disposition.

To the following two paragraphs:

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 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone which is formed by both CYP3A4 and CYP1A2.

In vitro preparations have shown these two metabolites to have antiarrhythmic activity comparable to propafenone but in man they both are usually present in concentrations less than 20% of propafenone. Nine additional metabolites have been identified, most only in trace amounts. It is the saturable hydroxylation pathway that is responsible for nonlinear pharmacokinetic disposition.

b. The following paragraph has been added to the end of the **CLINICAL PHARMACOLOGY/ Pharmacokinetics and Metabolism** section:

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 during steady state.

3. In the boxed Warning under **WARNINGS,** the word "rate" has been added after "reversed cardiac arrest" in the first sentence.

4. Under the **WARNINGS/Conduction Disturbances** subsection**,** the words "ventricular arrhythmia" have been added in the third sentence after "…AV block observed in 2,127."

5. Under **PRECAUTIONS,**

a. The following has been added as the last two sentences under **Drug Interactions/Other**:

Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4 might lead to increased plasma levels of propafenone. When propafenone is administered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

b. The **"Animal Toxicology"** subsection has been re-titled **"Renal and Hepatic Toxicity in Animals"** and is now listed before the **"Carcinogenesis, Mutagenesis, Impairment of Fertility"** subsection. The text has been changed from:

Renal changes have been observed in the rat following 6 months of oral administration of propafenone at doses of 180 and 360 mg/kg/day (12-24 times the maximum recommended human dose) but not 90 mg/kg/day. Both inflammatory and non-inflammatory changes in the renal tubules with accompanying interstitial nephritis were observed. These lesions were reversible, in that they were not found in rats treated at these dosage levels and allowed to recover for 6 weeks. Fatty degenerative changes of the liver were found in rats following

chronic administration of propafenone at dose levels 19 times the maximum recommended human dose.

To:

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 maximum recommended human daily dose [MRHD] on a mg/m^2 basis). Both inflammatory and non-inflammatory changes in the renal tubules, with accompanying interstitial nephritis, were observed. These changes were reversible, as they were not found in rats allowed to recover for 6 weeks. Fatty degenerative changes of the liver were found in rats following longer durations of administration of propafenone HCl at a dose of
270 mg/kg/day (about 3 times the MRHD on a mg/m^2 basis.) There were no renal or hepatic changes at 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

c. The **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection has been changed from:

Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone.

RYTHMOL was not mutagenic when assayed for genotoxicity in 1) mouse Dominant Lethal test, 2) rat bone marrow Chromosome Analysis, 3) Chinese hamster bone marrow and spermatogonia chromosome analysis, 4) Chinese hamster micronucleus test, and 5) Ames bacterial test.

Propafenone 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, were seen only at lethal or sublethal dose levels and were not seen in rats treated either orally or intravenously (see PRECAUTIONS, Impaired Spermatogenesis). Propafenone did not affect fertility rates when administered orally to male and female rats at doses of 270 mg/kg/day or when administered orally or intravenously to male rabbits at doses of 120 mg/kg/day or 3.5 mg/kg/day, respectively. On a body weight basis, the above noted oral doses in rat and rabbit are 18 times and 8 times, respectively, the maximum recommended daily human dose of 900 mg (based on a 60 kg human body weight).

To:

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/m^2 basis) and rats (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m^2 basis) provided no evidence of a carcinogenic potential for propafenone HCl.

Propafenone HCl tested negative for mutagenicity in the Ames (salmonella) test and the mouse dominant lethal test, and tested negative for clastogenicity in the Chinese hamster micronucleus test, 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 **PRECAUTIONS, Impaired Spermatogenesis**). 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/m^2 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/m^2 basis).

d. The **Pregnancy-Teratogenic Effects/Pregnancy-Nonteratogenic Effects** sections have been changed from:

Pregnancy-Teratogenic Effects:
Pregnancy Category C:
Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well-controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Pregnancy-Nonteratogenic Effects:
In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

To:

Pregnancy
Teratogenic Effects: *Pregnancy Category C.* Propafenone HCl 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/m^2 basis) and 600 mg/kg/day (about 6 times the MRHD on a mg/m^2 basis), respectively. Although maternally tolerated doses (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m^2 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/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Rythmol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects:
In a study in which female rats received daily oral doses of propafenone HCl from mid-gestation through weaning of their offspring, doses as low as 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis) produced increases in maternal deaths. Doses of 360 or more mg/kg/day (4 or more times the MRHD on a mg/m^2 basis) resulted in reductions in neonatal survival, body weight gain and physiological development.

e. The Geriatric Use subsection has been changed from:

There do not appear to be any age related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, RYTHMOL should be used with caution. The effective dose may be lower in these patients.

To:

Clinical studies of RYTHMOL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

6. Under **ADVERSE REACTIONS,**

   a. In the second sentence of the third paragraph under **ADVERSE REACTIONS**, the word "in" was changed to "for" so that the sentence now reads as follows:

      Adverse reactions reported for ≥ 1% of the patients receiving propafenone as shown, unless they were more frequent on placebo than propafenone.

   b. In the table entitled **"Adverse Reactions Reported for ≥ 1% of Ventricular Arrhythmia Patients,"** the symbol "-" listed for "Anorexia" in the "Prop. (N=53)"column under "Prop./Quinidine Trials" has been changed to "0%."

   c. Under the **Gastrointestinal** subsection, the word "foreign" has been deleted from between the words "reported in" and "post-marketing" in the first sentence so that it now reads as follows:

      A number of patients with liver abnormalities associated with propafenone therapy have been reported in post-marketing experience.

7. Under **DOSAGE AND ADMINISTRATION**, the words "ventricular arrhythmia" have been added in the second paragraph after "…in the elderly or in."

8. Under **HOW SUPPLIED/Storage**, the storage statement has been changed from:

   Storage: Store at controlled room temperature 15°-30°C (59°- 86°F). Dispense in a tight, light-resistant container as defined in the U.S.P.

   To:

   Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Dispense in a tight, light-resistant container as defined in the USP.

   Rx Only

We completed our review of these supplemental new drug applications. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 1, 2002.

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}

Douglas C. Throckmorton, M.D.
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/

Doug Throckmorton

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