CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-416

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-416

Abbott Laboratories
Ms. Marilou Reed
D-491/AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Reed:

Please refer to your new drug application (NDA) dated March 15, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rythmol SR (propafenone hydrochloride) 225, 325 and 425 mg Capsules.

We acknowledge receipt of your submissions dated January 20, 31 (two), February 17, May 23, June 2, and August 14 and 15, 2003. The August 15, 2003 submission constituted a complete response to our January 15, 2003 action letter.

This new drug application provides for the use of Rythmol SR (propafenone hydrochloride) Capsules to prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon electronic labeling text. The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-416.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing commitment agreed to in your submission dated January 31, 2003. This commitment is listed below.

1. Submit a supplemental NDA to update the Drug Interactions section of the labeling within 2 weeks of the date of this letter.

All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", **or** "**Postmarketing Study Correspondence.**"

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore,

we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We note that you have already submitted your proposed introductory promotional materials to the Division of Drug Marketing, Advertising and Communications.

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 contact:

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

Sincerely,

/S/

{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

Enclosure

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
9/4/03 11:21:42 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-416

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-416

Abbott Laboratories
Ms. Marilou Reed
D-491/AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Reed:

Please refer to your new drug application (NDA) dated March 15, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rythmol (propafenone) 225, 325 and 425 mg Extended Release Capsules.

We acknowledge receipt of your submissions dated March 22, April 26, May 8 (two), June 24, July 1, 2, 11, 15, 17, 29, August 29, September 4, 19, December 3, 19, and 20, 2002.

We completed our review of this application, as amended, and it is approvable. Before the application can be approved the following deficiencies will need to be addressed satisfactorily. Additionally, we will need to have agreement on the content of final labeling. Proposed language updating specific parts of the label is requested from you, and is subject to our review and comment. These items are identified as notes to you in the appended proposed labeling.

Clinical

1. Additional information is needed in the label on the effect of CYP3A4 inhibition on the pharmacokinetics of propafenone and its two major metabolites, 5-hydroxypropafenone and norpropafenone. Such data should be provided for both in a population who are poor and those who are extensive metabolizers by the CYP 2D6 route. This information may be derived from literature sources, but will require additional clinical investigation if adequate information is not otherwise available.

2. Information in the approved label on the electrophysiologic effects of propafenone and its metabolites, especially the effects on the QT interval, needs to be updated.

3. The safety data from the ERAFT study need to be incorporated into the approved labeling.

Packaging Issues

4. To effectively differentiate this product from the immediate-release product, the dosage statement on all container labels should include the following: "See enclosure for full prescribing information", along with an amendment of the dosing statement to include "every twelve hours."

5. All unit dose and physician carton labeling should contain the boxed statement, "This package for households without young children." It is not clear whether you intend to distribute this product in child resistant cartons and/or containers. If the carton is not child resistant and could be dispensed for outpatient use, the carton should state that the unit dose package is not child resistant, and the medication should be

dispensed in a child resistant container. In the latter case, the carton should also include the following: "This unit dose package is not child resistant."

Dissolution Specifications

6. To assess dissolution of the drug product more adequately, modify your proposed dissolution method and specifications as follows:

Apparatus Type	Type 2 (Paddle), 50 RPM
Medium	Phosphate buffer (pH 6.8)
Temperature, Volume	37°C, 900 mL
Specification	Q[ ]% at 2 hour, Q[ ]% at 4 hours and Q[ ]% at 12 hours.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

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

Sincerely,

/S/

{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
1/15/03 04:58:54 PM

16 pages redacted from this section of the approval package consisted of draft labeling