CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-972

Approval Letter(s)

DEC 24 1985

NDA 18-972

Sanofi Pharmaceuticals, Inc.
c/o Ives Laboratories Inc.
Attention: Robert H. Harris, Ph.D.
685 Third Avenue
New York, NY 10017

Dear Dr. Harris:

Please refer to your March 14, 1983 new drug application resubmitted on June 28, 1983 and April 4, 1984 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets.

We also acknowledge receipt of your amendments dated May 6 and 10, 1983; June 28, 1983; August 31, 1983; September 1 (two), and 16, 1983; January 9, 17, 24 and 27, 1984; February 9 and 28, 1984; March 28, 1984; April 2, 6, 27 and 30, 1984; May 25, 1984 (two); June 12, 1984; July 31, 1984; August 17 and 22, 1984; September 19, 1984; October 4, 1984; November 2 and 13 (two), 1984; December 18, 1984; February 11, 1985; May 3, 10 and 17, 1985; an undated letter we received on October 23, 1985; and December 23, 1985.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the application is approved. Prior to marketing, however, please submit twelve copies of the final printed labeling that are identical to the enclosed draft. Please individually mount seven copies of the labeling on heavy weight paper or similar material.

We also recommend that repeat teratology (Segment II) studies be conducted with amiodarone in two species according to FDA Guidelines for Reproduction Studies in order to be in a position to defend broadening of indications. For the population currently indicated, such studies are not required.

It is also our understanding that you have agreed to pursue the following diligently:

1. The Mason survey. The survey initiated by Jay Mason and members of his group constitutes a data base that, given the individuals involved, is of potentially very high quality; it reflects a larger long term experience than is otherwise available in detail. Its analysis should be completed. I have spoken to Dr. Mason, who assures me that he is eager to work with Ives to complete the analysis and evaluation of these data. He would make the raw data (the responses to the survey) available to Ives so that they can carry out their own analysis. I believe that these and other arrangements can be worked out readily if there is a desire to do so and I would be happy to serve as a "broker" between the two parties.

2. There are a number of groups carrying out detailed evaluations of pulmonary function and pulmonary toxicity in patients receiving amiodarone. Preliminary reports that appeared in the most recent American Heart Association meeting suggest, at least the possibility, that monitoring of diffusion capacity may give early warning of patients at risk for serious pulmonary disease, perhaps allowing dosage adjustment or even trials of therapy, such as corticosteroids. It is important to attempt to get the underlying data from these studies and evaluate them.

3. We expect you to continue to review regularly all published clinical literature on amiodarone, as well as any other data of interest, so that the labeling can be modified and updated as needed. We would expect to see a review of new literature approximately quarterly with recommendations for labeling revision as needed.

4. Approved labeling does not allow claims related to atrial arrhythmias but the potential usefulness of amiodarone in these arrhythmias is widely recognized. Controlled clinical trials in patients with atrial arrhythmias need to be conducted.

The objectives of such trials would include dose-response, efficacy and safety, with an emphasis on defining the range of useful doses in at least the different classes of atrial arrhythmias. Development of such a program will require careful thought. Consult with the Division of Cardio-Renal Drug Products as often as you wish during your efforts in designing the program.

5. It will almost certainly prove difficult to carry out randomized controlled trials in patients with life threatening arrhythmias, but there are populations in whom randomized trials are reasonable and the outcomes potentially very important. High risk post infarction patients (patients with relatively frequent ventricular premature beats and low ejection fractions) would be highly suitable candidates for a clinical trial and have no present identified effective therapy. It should be possible and desirable to carry out a trial of amiodarone vs placebo in these patients. An alternative would be to compare amiodarone to individualized alternative therapy, although the possibility that these treatments are actually detrimental must be explored; CAPS results may prove helpful in this. We are eager to discuss the kinds of trials that might be carried out at your earliest convenience.

6. The effects of amiodarone on thyroid function and TSH levels in man are not completely defined at present. Clarification and a change in labeling to include new information is also expected at your earliest convenience.

We would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second copy, along with the package insert, directly to the Director, Division of Drug Advertising and Labeling (HFN-240). Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

We understand that you have agreed not to advertise or market this product until your advertising material and promotional plan have been reviewed by the Division of Drug Advertising and the Office of Drug Research and Review and have been approved.

Please submit one market package of the drug when available.

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:

Ms. Cathy Heald
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

R Temple

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
~~Original NDA~~
HFN-110
HFN-110/CSO
HFN-83
HFN-240 (with labeling)
HFN-100/Dr. Temple
HFN-232 (with labeling)
HFN-110/CHeald/12/18/85;12/18/85/12/23/85
sb/12/18/85;12/20/85/2559s
klb/12-20-85;sh/12/23/85
R/D: RLipicky/12/19/85/12/20/85
MCommarato/12/20/85
CResnick/12/20/85
PLMartese/12/20/85
CHeald/12/20/85
RWolters/12/20/85
NMorgenstern/12/20/85 pem 12/23/85

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NCGlocke 12-24-85