CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 18-972/S-015, S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 18-972/S-015, S-017

Trade Name: CORDARONE TABLETS, 200 mg

Generic Name:(amiodarone HCl)

Sponsor: Wyeth Laboratories

Approval Date: January 5, 1999

Indication: S-015 provides for final printed labeling revised to add text to the PRECAUTIONS/Surgery section regarding the monitoring of patients receiving Cordarone therapy who undergo anesthesia with volatile anesthetic agents, specific FiO2 recommendations. S-017 provides for revised text in the WARNING/Mortality subsection based on safety findings from the European Infarct Amiodarone Trial (IMIAT) and the Canadian Myocardial Infarct Amiodarone Trial (CAMIAT).

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18-972/S-015, S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-972/ S-015
S-017

JAN 5 999

Wyeth Laboratories
Attention: Ms. Roberta A. Acchione
170 North Radnor-Chester Road
St. David's, PA 19087-5221

Dear Ms. Acchione:

Please refer to your supplemental new drug applications dated January 17, 1996 (S-015) and April 24, 1997 (S-017) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets, 200 mg.

We acknowledge receipt of your submission dated November 12, 1998.

Supplemental application 015, as amended, provides for final printed labeling revised to add text to the **PRECAUTIONS/Surgery** section regarding the monitoring of patients receiving Cordarone therapy who undergo anesthesia with volatile anesthetic agents, specific FiO_2 recommendations. In addition, text has been added that refers to volatile anesthetics in the **PRECAUTIONS/Drug Interactions** section. The April 29, 1996 approvable letter requested changes to the **Carcinogenesis, Mutagenesis, Impairment of Fertility**, **Pregnancy: Pregnancy Category D**, and **Neonatal hypo- or hyperthyroidism** subsections.

Supplemental application 017, as amended, provides for revised text in the **WARNINGS/Mortality** subsection based on safety findings from the European Infarct Amiodarone Trial (IMIAT) and the Canadian Myocardial Infarct Amiodarone Trial (CAMIAT).

We have completed the review of these supplemental applications, as amended, 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 final printed labeling included in your November 12, 1998 submission. Accordingly, these supplemental applications are approved effective on the date of this letter.

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. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

1/5/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 18-972
~~HFD-110/Div. Files~~
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE
HFD-110/D.Willard/12/4/98;12/18/98 D. Willard 12/30/98
sb/12/7/98;12/22/98
Initialed by: N Stockbridge/12/22/98
N Morgenstern/12/22/98
filename: 18972s015ap.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18-972/S-015, S-017

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-972/S-015

APR 29 1996

Wyeth-Ayerst Laboratories
Attention: Joseph L. Morrison, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Morrison:

Please refer to your January 17, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets.

We acknowledge receipt of your amendment dated January 30, 1996.

The supplemental application provides for draft labeling revised by adding text to the **PRECAUTIONS/Surgery** section regarding the monitoring of patients receiving Cordarone therapy who undergo general anesthesia with volatile anesthetic agents, as well as text regarding a lack of substantial data to support specific FiO_2 recommendations. In addition, text has been added that refers to volatile anesthetics in the **PRECAUTIONS/Drug Interactions** section.

We have completed the review of this supplemental application as submitted with draft labeling. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft and incorporate the changes noted in the **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY, PREGNANCY:** ***Pregnancy Category D*** and **NEONATAL HYPO- OR HYPERTHYROIDISM** sections. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Please submit sixteen copies of the printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

These changes may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Coordinator
Telephone: (301) 594-5311

Sincerely yours,

/S/ 4/24/96

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
~~HFD-80~~
HFD-110
HFD-110/Project Manager
HFD-735/DBarash (with labeling)
HFD-110/DWillard/3/18/96;3/20/96;4/25/96
sb/3/18/96;4/11/96;4/23/96
R/D: PGill-Kumar
CResnick/3/22/96
SChen/4/9/96
NMorgenstern/4/9/96
GBuehler for NMorgenstern/4/25/96

Approval Date: December 24, 1985

APPROVABLE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-972/S-016
S-017

SEP 19 1997

Wyeth-Ayerst Laboratories
Attention: Mr. Timothy K. Ressler
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Ressler:

Please refer to your April 16 (S-016) and 24 (S-017), 1997 supplemental new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) 200 mg Tablets.

Your April 16 supplemental application provides for draft labeling revised under **Warnings**, **Precautions**, and **Adverse Reactions** to modify or expand the text on optic disorders in these sections. Additionally, text pertaining to patient monitoring in the **Precautions**/SURGERY/ Adult Respiratory Distress Syndrome subsection has been revised. "Angioedema" has been added to the **Adverse Reactions** section.

Your April 24 supplemental application provides for draft labeling revised under **Warnings**/MORTALITY to incorporate text regarding safety findings from the European Myocardial Infarct Amiodarone Trial and the Canadian Myocardial Infarct Amiodarone Trial.

We have completed the review of these supplemental applications as submitted with draft labeling and they are approvable. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft and should also incorporate the changes to the CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY, PREGNANCY: Pregnancy Category D, and NEONATAL HYPO- OR HYPERTHYROIDISM subsections under **Precautions** outlined in our April 26, 1996 approvable letter for your January 17, 1996 supplemental application. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Please submit sixteen copies of the printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw these supplemental applications.

The changes proposed in your April 24 supplemental application may not be implemented until you have been notified in writing that this application is approved.

Should you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
Telephone: (301) 594-5311

Sincerely yours,

/S/ 9/19/97

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-92
HFD-110
DISTRICT OFFICE
HFD-40/DDMAC (with labeling)
HFD-110/DWillard/6/4/97;9/15/97
sb/6/9/97;9/17/97
R/D: NStockbridge/9/16/97
NMorgenstern/9/16/97

Approval Date: December 24, 1985

APPROVABLE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-972/S-015
S-017

JUL 1 1998

Wyeth-Ayerst Laboratories
Attention: Ms. Diane Mitrione
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your January 17, 1996 (S-015) and April 24, 1997 (S-017) supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets.

We acknowledge receipt of your submission dated February 26, 1998.

Supplemental application 015 provides for changes to the **Precautions** section of the labeling relative to the possible mechanism of Adult Respiratory Distress Syndrome coincident with Cordarone therapy and for text regarding specific FiO_2 recommendations. This supplement also provides for revision of the **Precautions/PEDIATRIC USE** subsection to replace the word "children" with the term "pediatric patients." In addition, the April 29, 1996 approvable letter for this supplement requested changes to the **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy: Pregnancy Category D,** and **Neonatal hypo- or hyperthyrodism** subsections.

Supplemental application 017 provides for revised text in the **WARNINGS**/Mortality subsection based on safety findings from the European Infarct Amiodarone Trial (EMIAT) and the Canadian Myocardial Infarct Amiodarone Trial (CAMIAT).

We have completed the review of these applications as submitted with draft labeling, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

to:

In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term multi-centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

Cordarone therapy was evaluated in two multi-centered, randomized, double-blind, placebo-controlled trials involving 1202 (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CAMIAT) and 1486 (European Myocardial Infarction Amiodarone Trial; EMIAT) post-MI patients followed for up to 2 years. Patients in CAMIAT qualified with ventricular arrhythmias, and those randomized to amiodarone received weight- and response-adjusted doses of 200 to 400 mg/day. Patients in EMIAT qualified with ejection fraction <40%, and those randomized to amiodarone received fixed doses of 200 mg/day. Both studies had weeks-long loading dose schedules. Intent-to-treat all-cause mortality results were as follows:

	Placebo		Amiodarone		Relative Risk	
	N	Deaths	N	Deaths		95% CI
EMIAT	743	102	743	103	0.99	0.76-1.31
CAMIAT	596	68	606	57	0.88	0.58-1.16

These data are consistent with the results of a pooled analysis of smaller, controlled studies involving patients with structural heart disease (including post-myocardial infarction).

2. The **WARNINGS/Pregnancy: Pregnancy Category D** subsection should be deleted. This subsection stated:

3. A third paragraph should be added under **WARNINGS/Neonatal hypo- or hyperthyroidism** that states:

4. Under **PRECAUTIONS/Surgery**, the following text should be added following the **Surgery** heading:

Volatile Anesthetic Agents : Close perioperative monitoring is recommended in patients undergoing general anesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction effects of halogenated inhalational anesthetics.

5. Under **PRECAUTIONS/Drug Interactions**, the following text should be added preceding the table entitled "Summary of drug interactions with Cordarone":

Volatile Anesthetic Agents (See **"PRECAUTIONS, Surgery,** Volatile Anesthetic Agents.")

6. The **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility**, subsection should be changed from:

to:

Amiodarone HCl was associated with a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control even at the lowest dose level tested, i.e., 5 mg/kg/day (approximately .08 times the maximum recommended human maintenance dose*).

Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with Cordarone were negative.

In a study in which amiodarone HCl was administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*).

*600 mg in a 50 kg patient (dose compared on a body surface area basis)

7. Under **PRECAUTIONS**, the **Pregnancy: Pregnancy Category D** subsection should be changed from:

to:

See "**WARNINGS, Neonatal hypo- or hyperthyroidism.**"

8. The third sentence in the first paragraph under **OVERDOSAGE** should be changed from:

to:

The acute oral LD_{50} of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.

9. Under **HOW SUPPLIED,** should be changed to "Rx only."

Please submit 20 copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

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

Within 10 days after the date of this letter, you are required to amend these applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw these application.

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
Telephone: (301) 594-5311

Sincerely yours,

/S/ 7/1/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-92/DDM-DIAB
DISTRICT OFFICE
HFD-40/DDMAC (with labeling)
HFD-110/DWillard/5/18/98;5/26/98;6/18/98 D. Willard 6/24/98
sb/5/18/98;6/26/98
R/D: PGill-Kumar/6/2/98;6/19/98
CResnick/6/19/98
NStockbridge/6/19/98
NMorgenstern/6/25/98

Approval Date: December 24, 1985

APPROVABLE (AE)