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

ADMINISTRATIVE DOCUMENTS

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RHPM Review of Final Printed Labeling
NDA 18-972/S-015 and S-017

Sponsor: Wyeth Laboratories

Product: Cordarone (amiodarone HCl) Tablets

Submission Date: November 12, 1998

Receipt Date: November 13, 1998

Type of Submission: Final Printed Labeling

Background: S-015, submitted January 17, 1996, provides for revisions to the **PRECAUTIONS/ Surgery** subsection of the labeling 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 FiO2 recommendations. In addition, text was added that refers to volatile anesthetics in the **PRECAUTIONS/Drug Interactions** subsection. An approvable letter, issued April 29, 1996, requested that the sponsor submit FPL "identical in content to the enclosed marked-up draft" and that the FPL should "incorporate the changes noted in the **Carcinogenesis, Mutagenesis, Impairment of Fertility**, **Pregnancy: Pregnancy Category D, and Neonatal hypo- or hyperthyroidism** subsections." In a February 26, 1998 submission for S-015 and S-017, Wyeth proposed alternative numbers for the **Carcinogenesis, Mutagenesis, Impairment of Fertility**, **gnancy: Pregnancy Category D, and Neonatal hypo- or hyperthyroidism** subsections.

S-017, submitted with draft labeling on April 24, 1997, 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). An approvable letter issued for S-017 (and S-016) on September 19, 1997. This letter stated that when FPL is submitted for S-017 (and S-016), the changes to the subsections under **PRECAUTIONS/ Carcinogenesis, Mutagenesis, Impairment of Fertility**, **Pregnancy: Pregnancy Category D**, and **Neonatal hypo- or hyperthyroidism** outlined in the Division's April 29, 1996 approvable letter for S-015 should be incorporated into the FPL.

The July 1, 1998 approvable letter for S-015 and S-017 (attached) requested changes to the **Mortality**, **Pregnancy: Pregnancy Category D**, and **Neonatal hypo- or hyperthyroidism** subsections under **WARNINGS**. In addition, changes were requested under **PRECAUTIONS** in the **Surgery**, **Drug Interactions**, **Carcinogenesis, Mutagenesis, Impairment of Fertility**, and **Pregnancy: Pregnancy Category D** subsections and in the **OVERDOSAGE** and **HOW SUPPLIED** sections.

Evaluation: When compared with the most recently approved labeling (S-016 and S-018: both approved on June 15, 1998), the following changes were noted:

Under **WARNINGS**,

a) The second paragraph of the **Mortality** subsection has been changed from:

to:

Cordarone therapy was evaluated in two multi-centered, randomized, double-blind, placebo-controlled trials involving 1202 (Canadian Amiodarone Myocardial Infarction Arrhythmia; 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 infarction).

b) The **Pregnancy: Pregnancy Category D** subsection has been deleted. This subsection stated:

c) A third paragraph has been added at the end of the **Neonatal Hypo- or Hyperthyroidism** subsection states:

Neonatal Hypo- or Hyperthyroidism
In pregnant rats and rabbits, amiodarone HCl in doses of 25 mg/kg/day (approximately 0.4 and 0.9 times, respectively, the maximum recommended human maintenance dose*) had no adverse effects on the fetus. In the rabbit, 75 mg/kg/day caused abortions in greater than 90% of the animals. In the rat, doses of 50 mg/kg/day or more were associated with slight displacement of the testes and an increased incidence of incomplete ossification of some skull and digital bones; at 100 mg/kg/day or more, fetal body weights were reduced; at 200 mg/kg/day, there was an increased incidence of fetal resorption. (These doses in the rat are approximately 0.8, 1.6 and 3.2 times the maximum recommended human maintenance dose.*) Adverse effects on fetal growth and survival also were noted in one of two strains of mice at a dose of 5 mg/kg/day (approximately 0.04 times the maximum recommended human maintenance dose*).
*600 mg in a 50 kg patient (doses compared on a body surface area basis)

2) Under **PRECAUTIONS**,

a) A new subsection has been added under **Surgery**. This subsection states:

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.

b) In the first sentence under **Surgery**/Adult Respiratory Distress Syndrome (ARDS), the word has been deleted. This sentence has been changed from:

to:

Postoperatively, occurrences of ARDS have been reported in patients receiving Cordarone therapy who have undergone either cardiac or noncardiac surgery.

c) A new subsection has been added under **Drug Interactions** after the Antiarrhythmic Agents subsection. This subsection states:

d) The **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection has been changed from:

to:

Amiodarone HCl was associated with a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma an/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 0.08 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)

e) The **Pregnancy: Pregnancy Category D** subsection has been changed from:

to:

See **"WARNINGS, Neonatal Hypo- or Hyperthyroidism."**

3) Under **OVERDOSAGE**, the third sentence of the first paragraph has been changed from:

to:

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

4) Under **HOW SUPPLIED**, the
statement has been changed to

Comments/Recommendations: The changes made under 1a, 1b, 2a, 2c, 2d, 2e, 3, and 4 are changes requested in the July 1, 1998 approvable letter for these supplements.

The values that issued with the July 1, 1998 approvable letter for Supplements 015 and 017 retained the values submitted in the February 26, 1998 draft labeling submission. These were not the values that were subsequently agreed to by the Division in an April 22, 1998 facsimile transmission (FAX). The changes under 1c above, with the exception of one value, are the values agreed upon in the April 22, 1998 FAX to Wyeth from the Division. The one exception was agreed upon, after consultation with Dr. Resnick, during an April 27, 1998 telephone conversation between Ms. Jean Lassen of Wyeth and Ms. Willard.

During a December 4, 1998 conversation between Dr. Stockbridge and Ms. Willard, Dr. Stockbridge stated that the change under 2b above is acceptable.

An approval letter should issue for these supplements.

/S/

Diana Willard
Regulatory Health Project Manager

cc: original
HFD-110
HFD-110/Dwillard
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JUL 1 1998

RHPM Review of Draft Labeling
NDA 18-972/S-015 and S-017

Sponsor: Wyeth-Ayerst Laboratories

Product: Cordarone (amiodarone HCl) Tablets, 200 mg

Submission Date: February 26, 1998

Receipt Date: February 27, 1998

Type of Submission: Draft Labeling

Background: The January 17, 1996 cover letter for Supplement 015 states that before final printed labeling (FPL) is prepared as requested in the October 18, 1995 approval letter for S-014, Wyeth would like to make two revisions to the Cordarone Tablet labeling. S-015 provides for revisions to the **PRECAUTIONS/Surgery** subsection of the labeling 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** subsection. An approvable letter, issued April 29, 1996, requested that the sponsor submit FPL "identical in content to the enclosed marked-up draft' that should " incorporate the changes noted in the **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy: Pregnancy Category D,** and **Neonatal hypo- or hyperthyroidism** subsections." In this February 26, 1998 submission, Wyeth proposes alternative numbers for the **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy: Pregnancy Category D,** and **Neonatal hypo- or hyperthyroidism.**

Supplement 017, submitted with draft labeling on April 24, 1997, provides for revised text in the **WARNINGS/Mortality** subsection based on safety finding from the European Infarct Amiodarone Trial (EMIAT) and the Canadian Myocardial Infarct Amiodarone Trial (CAMIAT). An approvable letter issued for S-017 (and S-016) on September 19, 1997. This letter stated that when FPL is submitted for S-017 (and S-016), the changes to the subsections under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy: Pregnancy Category D,** and **Neonatal hypo- or hyperthyrodism** outlined in the Division's April 29, 1996 approvable letter for S-015 (Attachment 1) should be incorporated into the FPL.

Evaluation: When compared with the draft labeling issued with the September 19, 1997 approvable letter for S-016 and S-017 the following changes were noted:

1) Under **WARNINGS**,

a) In the first sentence of the second paragraph in the MORTALITY subsection, the number has been changed to 1846 and the word has been deleted from
The sentence has been changed to:

b) The **Surgery** subsection has been deleted. This subsection stated:

c) Under **Loss of Vision**, the statement
has not been deleted as requested in the Division's September 19, 1997 approvable letter for S-107 (and S-016).

d) The **Pregnancy: Pregnancy Category D** subsection has been deleted as requested in the Division's approvable letter of April 29, 1996 for S-015.

e) In the third paragraph of the **Neonatal hypo- or hyperthyroidism** subsection, all the numbers for the maximum human maintenance dose have been recalculated to reflect a change from to 600 mg in a 50 kg basis. This paragraph has been changed from:

to:

2) Under **PRECAUTIONS**,

a) i) A **Surgery**/Volatile Anesthetic Agents subsection has been added that states:

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.

i i) The **Surgery**/Adult Respiratory Distress Syndrome (ARDS) subsection has not been deleted as was requested in the September 17, 1997 approvable letter for S-016 and S-017. **Note:** this was a change requested by the Division for S-016.

b) A **Drug Interactions**/Volatile Anesthetic Agents subsection has been added that states:
(See "**PRECAUTIONS, Surgery**, Volatile Anesthetic Agents.")

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

to:

d) Under **Pregnancy:** ***Pregnancy Category D***, the Pregnancy Category D has not been changed to lower case and italicized as requested in the approvable letter of September 17, 1998.

Comments/Recommendations: Dr. Shaw Chen signed off on Supplement 015 on April 16, 1996 (on the review transmittal sheet). The April 29, 1996 approvable letter to S-015 requested that the changes noted under 2ai and 2b above be incorporated into FPL.

Dr. Gill-Kumar disagreed with several of the sponsor's changes for the **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy: Pregnancy Category D,** and **Neonatal hypo- or hyperthyrodism** subsections made in the February 26, 1998 submission. Dr. Gill-Kumar's changes were FAXed to the sponsor on April 22, 1998 and a reply received from Wyeth on April 27, 1998 (attached). The changes requested by Dr. Gill-Kumar and agreed to by Wyeth are incorporated into the enclosed marked-up draft.

Dr. Stockbridge's August 14, 1997 review of S-017 recommended alternative language regarding the EMIAT and CAMIAT trials than that proposed by the sponsor for the **WARNINGS/Mortality** subsection. This alternative language was included in the September 19, 1997 approvable. The sponsor incorporated these changes into the February 26, 1998 submission.

The sponsor should be requested to change the third sentence in the first paragraph under **OVERDOSAGE** from

to "The acute oral LD_{50} of amiodarone in mice, rats, and dogs is greater than 3,000 mg/kg" as recommended in Dr. Resnick's March 19, 1996 review.

The statement under **How Supplied** should be changed to "Rx only" as provided for under the FDA Modernization Act of 1997.

An approvable letter should issue for these supplements.

/S/

Diana M. Willard
Regulatory Health Project Manager

cc: original file
HFD-110
HFD-110/DWillard
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