SEP 22 1997

RHPM Review of Labeling
NDA 18-972/S-016 and S-017

Sponsor: Wyeth-Ayerst Laboratories

Product: Cordarone (amiodarone HCl) Tablets, 200 mg

Submission Dates: April 16, 1997 (S-016)
April 24, 1997 (S-017)

Receipt Dates: April 21, 1997 (S-016)
April 30, 1997 (S-017)

Type of Submission: Special Supplement - Changes Being Effected (S-016)
Draft Labeling (S-017)

Background: Supplement 016, submitted with final printed labeling as a Special Supplement - Changes Being Effected on April 16, 1997, provides for changes to the **Warnings**, **Precautions**, and **Adverse Reactions** sections of the labeling to strengthen the safety information regarding optic disorders. The supplement also provides for revised text pertaining to patient monitoring in the **Precautions**/SURGERY/Adult Respiratory Distress Syndrome (ARDS) subsection. In addition, was added to the **Adverse Reactions** section.

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).

Evaluation: When compared with the most recently approved package insert dated October 18, 1995, the following changes were noted:

1) The **Warnings**, the following changes were noted:

   a) The MORTALITY subsection has been changed from:

to:

In the National Heart, Lung and Bloods 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. The applicability of these results to other populations (e.g., those without recent myocardial infarctions) is uncertain.

Cordarone therapy was evaluated in two definitive, 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 for up to 2 years. The results of both studies demonstrated no excess in all-cause mortality in amiodarone-treated patients (CAMIAT: 57/606 amiodarone-treated patients vs. 68/596 placebo patients; EMIAT: 103/743 amiodarone-treated patients vs. 102/743 placebo patients).

These data confirm the results of a pooled analysis of small, controlled studies involving patients with structural heart disease (including post-myocardial infarction) where there was no excess mortality in the Cordarone-treated population.

b) A LOSS OF VISION subsection has been added between the subsections LIVER INJURY and PREGNANCY: PREGNANCY CATEGORY D. This subsection states:

Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and/or neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. If symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral vision, prompt ophthalmic examination is recommended. Appearance of optic neuropathy and/or neuritis calls for re-evaluation of Cordarone therapy. The risks and complications of antiarrhythmic therapy with Cordarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including fundoscopy and slit-lamp examination, is recommended during administration of Cordarone. (See **"Adverse Reactions."**)

2) Under **Precautions**, The following changes were noted:

a) The subsection CORNEAL MICRODEPOSITS/IMPAIRMENT OF VISION has been changed from:

to:

IMPAIRMENT OF VISION
Optic Neuropathy and/or Neuritis
Cases of optic neuropathy and optic neuritis have been reported (see "**Warnings**").

Corneal Microdeposits
Corneal microdeposits appear in the majority of adults treated with Cordarone. They are usually discernible only by slit-lamp examination, but give rise to symptoms such as visual halos or blurred vision in as many as 10% of patients. Corneal microdeposits are reversible upon reduction of dose or termination of treatment. Asymptomatic microdeposits alone are not a reason to reduce dose or discontinue treatment (see "**Adverse Reactions**").

NOTE: The word "alone" has been added to the last sentence in the IMPAIRMENT OF VISION/*Corneal Microdeposits* subsection.

b) The subsection SURGERY/Adult Respiratory Distress Syndrome (ARDS) has been changed from:

to:

Postoperatively, rare occurrences of ARDS have been reported in patients receiving Cordarone therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FiO2 and the determinants of oxygen delivery to the tissues (e.g., SaO_2, PaO_2) be closely monitored in patients on Cordarone.

3) Under **Adverse Reactions,** the following changes were noted:

a) The words have been deleted from the third sentence of the first paragraph. The sentence has been changed from:

to:

They are often reversible with dose reduction or cessation of Cordarone treatment.

b) The following paragraph has been added after the third paragraph of this section:

Ophthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness, papilledema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities, and macular degeneration have been reported. (See "**Warnings.**")

c) The following paragraph has been added after the sixth paragraph in this section:

Hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudotumor cerebri, thrombocytopenia, and angioedema also have been reported in patients receiving Cordarone.

NOTE: This paragraph was moved from a different place under **Adverse Reactions** and the word "angioedema" has been added.

d) The second paragraph under in this section has been deleted.

This paragraph stated:

Comments/Recommendations: Supplement 014, submitted with draft labeling on April 24, 1995, provided 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. The supplement also provided for revising the **Precautions**/ PEDIATRIC USE subsection to replace the word with the term "pediatric patients." The approval letter for this supplement, issued October 18, 1995, requested final printed labeling (FPL) identical to the draft labeling included with the April 24, 1995 submission. No FPL has been submitted for this supplement.

The cover letter for Supplement 015 states that before 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 provided 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 was added that referred to volatile anesthetics in the **Precautions**/DRUG INTERACTIONS subsection. The approvable letter that issued for this supplement on April 26, 1996 requested FPL incorporating changes noted in the CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY, PREGNANCY: Pregnancy Category D, and NEONATAL HYPO- OR HYPERTHYROIDISM subsections under **Precautions**. No FPL has been submitted for this supplement.

When FPL is submitted for S-016 and S-017, the approval letter should acknowledge that this is also FPL for S-014 and S-015.

The word "angioedema" in the eighth paragraph under **Adverse Reactions** was added in response to a supplement request letter dated February 11, 1997.

An approvable letter with marked-up draft labeling that incorporates the changes recommended in Dr. Stockbridge's reviews for S-014 (Attachment 1) and S-017 (Attachment 2) should issue for these supplements. Dr. Stockbridge's mark-up of the draft labeling submitted with S-016 (Attachment 3) should also be incorporated into the marked-up draft labeling.

/S/

Diana M. Willard
Regulatory Health Project Manager

cc: original file
HFD-110
HFD-110/DWillard
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Attachment 1

Norman Stockbridge, M.D., Ph.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
Rockville, MD 20857

5600 Fishers Lane
Tel (301) 594-5329 FAX: (301) 594-5494

Memorandum

N Stockbridge 8/4/97

O.K. Let's do it
Lipsky
8/7/97

DATE: 4 August 1997

TO: NDA 18-972

RE: S-014

SUBJECT: Amiodarone and risk of ARDS.

The sponsor was proposed a change in the labeling for amiodarone.

The current label has a section under PRECAUTIONS as follows:

> *Adult Respiratory Distress Syndrome (ARDS): Postoperatively, rare occurrences of ARDS have been reported in patients receiving Cordarone therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. One possible mechanism of the deleterious effect may be the generation of superoxide radicals during oxygenation; therefore, the operative FiO2 should be kept as close to room air as possible.*

The sponsor wishes to amend this paragraph to read:

> *Adult Respiratory Distress Syndrome (ARDS): Postoperatively, rare occurrences of ARDS have been reported in patients receiving Cordarone therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FiO2 and the determinants of oxygen delivery to the tissues (e.g., SaO2, PaO2) be closely monitored in patients on Cordarone.*

MEDLINE searches were performed to look for (a) amiodarone & ARDS, and (b) amiodarone & free radicals.

The first search turned up two retrospective series looking at the incidence of ARDS in surgical patients on amiodarone.

Hawthorne et al. (1993)* reviewed 99 consecutive cases of patients going to surgery for implantable defibrillators at one academic center over a 5-year period. Of 60 patients not on amiodarone pre-operatively, none developed ARDS post-operatively. Of 39 patients on amiodarone pre-operatively, 10 developed ARDS post-operatively.

Greenspan et al. (1991)† reviewed cases of 67 patients who underwent either defibrillator implantation (n=43) or subendocardial resection (n=24). Seventeen of these patients (6 receiving a defibrillator and 13 undergoing endocardial resection) were on amiodarone with two weeks of surgery. Nine of these patients developed ARDS post-operatively. Of 44 subjects not receiving amiodarone, none developed ARDS post-operatively.

These series suggest that, contrary to the current label, post-operative ARDS is not rare.

The second search uncovered reports by a Hungarian group‡ and a group at Yale** all of which describe studies in animals consistent with a role of oxygen free radicals in the toxicity of amiodarone. These reports were not reviewed in detail and no

* Hawthorne HR, Wood MA, Stambler BS, et al. Can amiodarone pulmonary toxicity be predicted in patients undergoing implantable cardioverter defibrillator implantation?, Pacing Clin Electrophysiol. (1993) 16(12):2241-2249.

† Greenspan AJ, Kidwell GA et al. Amiodarone-related postoperative adult respiratory distress syndrome. Circulation (1991) 84(5 suppl):III407-415.

‡ Vereckei A et al. The role of free radicals in the pathogenesis of amiodarone toxicity. J Cardiovasc Electrophysiol (1993) 4(2):161-177; Siminiak T, et al. The effect of selected antiarrhythmic drugs on neutrophil free oxygen radicals production measured by chemiluminescence. Basic Res Cardiol (1991) 86(4):355-362.

pharmacology consult was requested.

No doubt, the data cannot support a strong assertion of mechanism here, much less a strong assertion of appropriate remedial therapy. However, the current label seems suitably circumspect, and offers reasonable and specific action, missing from the sponsor's proposed changes, consistent with what appears to be the most likely mechanism.

It is recommended that the current paragraph be replaced as follows:

Perhaps, it would be appropriate to place this paragraph under WARNINGS rather than PRECAUTIONS.

** Zitnik RJ et al. Effects of in vitro amiodarone exposure on alveolar macrophage inflammatory mediator production. Am J Med Sci (1992) 304(6):352-356.

Attachment 2

Norman Stockbridge, M.D., Ph.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
Rockville, MD 20857

5600 Fishers Lane
Tel (301) 594-5329 FAX: (301) 594-5494

Memorandum

8/5/97

DATE: 5 August 1997

TO: NDA 18-972

RE: S-017

SUBJECT: Amiodarone's CAST warning.

O.K. let's do it.
Spilsbury
8/7/97

The sponsor was proposed a change in the labeling for amiodarone.

The current label has a section under WARNINGS as follows:

> *MORTALITY*
>
> *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.*
>
> *The applicability of these results to other populations (e.g., those without recent myocardial infarctions) or to Cordarone-treated patients is uncertain. While definitive controlled trials with Cordarone are in progress, pooled analysis of small controlled studies in patients with structural heart disease (including post-myocardial infarction) have not shown excess mortality in the Cordarone-treated population.*

On the basis of results from two recently reported studies, the sponsor wishes to amend this section to read:

> *MORTALITY*
>
> *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 definitive, multi-centered, randomized, double-blind, placebo-controlled trials involving 1202 (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CAMIAT) and 1486 (European Myocardial Infraction Amiodarone Trial; EMIAT) post-MI patients for up to 2 years. The results of both studies demonstrated no excess in all-cause mortality in amiodarone-treated patients (CAMIAT: 57/606 amiodarone-treated patients vs. 68/596 placebo patients; EMIAT: 103/743 amiodarone-treated patients vs. 102/743 placebo patients).*
>
> *These data confirm the results of a pooled analysis of small, controlled studies involving patients with structural heart disease (including post-myocardial infarction) where there was no excess mortality in the Cordarone-treated population.*

In support of the changes, the sponsor provided published reports for each of the studies. No other materials (protocol, datasets, or case report forms) were provided.

EMIAT* recruited from European hospital CCUs between 1990 and 1995. Eligible subjects were 5 days out from a myocardial infarction, age 18 to 75, with LVEF <40% by MUGA. Exclusions were (1) childbearing potential, (2) exposure to amiodarone

* Julian DG et al. Randomised trail of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet (1997) 349:667-674.

within 6 months, (3) HR <50 bpm, (4) second- or third-degree A-V block, (5) long sinus pauses without a pacemaker, (6) clinically significant hepatic disease, (7) thyroid dysfunction, (8) long-QT syndrome, (9) severe, refractory angina or heart failure, (10) need for antiarrhythmics other than beta-blockers or digoxin, (11) imminent cardiac surgery, or (12) labelled contraindications to amiodarone. Subjects were stratified by EF and randomized to placebo or amiodarone (800 mg x 14 days, 400 mg x 14 weeks, then 200 mg/day). Minimum follow-up was 1 year. Follow-up continued for subjects withdrawn for any reason. The primary end point was all-cause mortality. The study was powered to detect a 15% treatment effect at 2 years. Population characteristics included NYHA I 50%, prior MI 30%, on beta-blocker 45%, on ACE inhibitor 59%, on diuretic 38%. Withdrawal rates were 39% on amiodarone and 21% on placebo. Two subjects were lost to follow-up. The intent-to-treat analysis for mortality showed 102/743 deaths on placebo and 103/743 on amiodarone (RR=0.99; 95% CI 0.76-1.31). The on-treatment analysis gave similar results.

CAMIAT* recruited from Canadian hospital CCUs between 1990 and 1995. Eligible subjects were 6 to 45 days out from a myocardial infarction, age >19, with >10 VPDs per hour or one run of VT on 24-hour ambulatory monitoring. Exclusions were (1) previous intolerance to amiodarone, (2) HR <50 bpm, (3) first-, second-, or third-degree A-V block, (4) QTc >480 ms, (5) moderate or severe peripheral neuropathy, (6) acute or chronic hepatitis, (7) interstitial fibrosis, (8) hypo- or hyperthyroidism, (9) asthma, (10) childbearing potential, (11) need for antiarrhythmics other than beta-blockers or digoxin, (12) need for tricyclic antidepressants, phenytoin, or sotolol, (13) NYHA IV heart failure, angian, hypotension, uncorrected hypokalemia, or (14) other concomitant disease leading to life expectancy <2 years. Subjects were randomized to placebo or amiodarone (10 mg/kg x 14 days, then 300 to 400 mg/day). Subjects with arrhythmia suppression at 4 or 8 months had their dose reduced to 200 to 300 mg/day. Minimum follow-up was 1 year. Follow-up continued for subjects withdrawn for any reason. The primary end point was resuscitated VF or arrhythmic death. The study was powered to detect a 50% treatment effect at 2 years; it was underpowered to detect an expected 25% reduction in all-cause mortality. The primary analysis was on-treatment or within 3 months of treatment. Three interim analyses were planned with asymmetric stopping rules. Population characteristics included smoking 79%, hypotension 42%, diabetes 16%, previous myocardial infarction 34%, heart failure 23%, on aspirin 83%, on beta-blocker 60%, and on ACE inhibitor 31%. No subjects were lost to follow-up. Withdrawal rates were 36% on amiodarone and 25% on placebo. The intent-to-treat analysis for all-cause mortality showed 68/596 deaths on placebo and 57/606 on amiodarone (risk reduction=0.18; 95% CI -0.16 to 0.42). The on-treatment analysis gave similar results, and, as predicted, the primary effect appeared to be reductions in arrhythmic deaths.

Although not reviewable in great detail, the results of these studies seem straightforward. Interpretation of these results is, however, much easier if the confidence limits are included in the trial description. The following is proposed as an alternative to the sponsor's changes:

MORTALITY

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-

* Cairns JA, et al. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations:CAMIAT. Lancet (1997) 349:675-682.

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).

CSO Review of Draft Labeling
NDA 18-972/S-015

APR 29 1996

Sponsor: Wyeth-Ayerst Laboratories

Product: Cordarone (amiodarone HCl) Tablets, 200 mg

Submission Date: January 17, 1996

Receipt Date: January 18, 1996

Type of Submission: Draft Labeling

Background: Supplement 014, submitted with draft labeling on April 24, 1995, provided 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. The supplement also provided for revising the **Precautions/PEDIATRIC USE** subsection to replace the word with the term "pediatric patients." The approval letter for this supplement, issued October 18, 1995, requested final printed labeling identical to the draft labeling included with the April 24, 1995 submission.

The cover letter for Supplement 015 states that before 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.

Evaluation: Changes made from the draft labeling approved on October 18, 1995 are:

1) Under **Precautions/SURGERY,** the following text has been added:

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.

2) Under **Precautions/DRUG INTERACTION**, the following text has been added preceding the table summarizing drug interactions with Cordarone:

Volatile Anesthetic Agents (See "**Precautions, SURGERY,** *Volatile Anesthetic Agents*.")

Comments/Recommendations: Dr. Chen signed off with "approval" for this supplement on February 16, 1996.

Dr. Resnick, in a review dated March 19, 1996, made several recommended revisions to the current labeling for this NDA. These revisions have been incorporated into the marked-up draft to be sent with the approvable letter.

An approvable letter should issue for this supplement.

/S/

Diana M. Willard
Consumer Safety Officer

cc: original file
HFD-110
HFD-111/DWillard
HFD-111/SBenton