

CENTER FOR DRUG EVALUATION AND RESEARCH

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

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 18-972 (amiodarone)

Sponsor: Wyeth-Ayerst.

Submission: Correspondence on supplements S-015, S-016, and S-017, dated 26 February 1998 and subsequent draft RHPM Review of Draft Labeling, undated.

Review date: 10 April 1998.

Reviewer: N. Stockbridge, M.D., Ph.D.

Comments follow along the draft RHPM Review of Draft Labeling.

Under **Warnings**, the sponsor proposes minor corrections to wording describing CAMIAT and EMIAT trials. The medical officer concurs.

Also under **Warnings**, the sponsor proposes that the Division's proposed paragraph describing risks of subacute pulmonary toxicity in surgery be moved to **Precautions** and reworded. There are several issues here. One is a reasonable description of the phenomenon and the second is a reasonable placement in the label.

With regard to the description of the phenomenon, the Division's description probably overstates the risk of post-operative ARDS, as the sponsor cites larger series and lower rates. The Division's paragraph proposed that superoxide radical formation was a possible mechanism and that therefore high FiO₂ should be avoided. The Division's assigned pharmacologist's review of this issue is attached. A review of the literature undertaken by the medical officer suggests the following: (1) There probably are different mechanisms contributing to chronic pulmonary toxicity (viz accumulation) and subacute toxicity. (2) Subacute pulmonary toxicity cases cited by Donica et al. (1996)¹ led them to study an animal model consistent with toxicity dependent upon oxygen. Various cases can be reviewed, but a brief survey suggests that oxygen-dependent toxicity is not much at issue. (3) Somewhat more controversial appears to be the role of a mechanism dependent upon oxygen free radicals; e.g., compare Leeder et al (1996)² and Futamura (1996)³. The sponsor's proposed description, however, goes too far in implicitly denying oxygen as a risk factor and recommending merely that "oxygen delivery...be closely monitored...." The medical reviewer now recommends the following, to appear under **Warnings** rather than **Precautions**:

The sponsor proposes to retain the statement under LOSS OF VISION:

The Division has asked that statement be removed. The sponsor might submit an expert report containing the estimated background rate for non-drug-related loss of vision from optic neuritis and alternative explanations or pertinent confounding factors in each of the reported cases on amiodarone. The Division's current position is to have the label be mute on the relationship between these events and amiodarone, but a more detailed analysis could support a more definitive statement.

The medical officer has no comment on proposed changes in the sections on NEONATAL HYPO- OR HYPERTHYROIDISM, CARCINOGENESIS, or PREGNANCY.

¹ Donica SK, et al., 1996. Danger of amiodarone therapy and elevated inspired oxygen concentrations in mice. *Am J. Cardiol* 77(1): 109-110.

² Leeder RG, et al. 1996. Evaluation of reactive oxygen species involvement in amiodarone pulmonary toxicity in vivo and in vitro. *J. Biochem. Toxicol.* 11(3):147-160.

³ Futamura Y. Toxicity of amiodarone on mouse pulmonary endothelial cells cultured with or without alveolar macrophages. *J Toxicol. Sci.* 21(4):253-267.

/S/

N. Stockbridge, M.D., Ph.D.

cc: NDA 18-972
HFD-110
HFD-110/CSO
HFD-110/Pharmacologist
HFD-110/Stockbridge

CENTER FOR DRUG EVALUATION AND RESEARCH

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

CHEMISTRY REVIEW(S)

FEB 2 1996

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 18-972
3. Name and Address of Applicant (City & State) Wyeth-Ayerst Laboratories P.O. Box 8299 Philadelphia, PA 19101-1245		4. Supplement(s) Number(s) Date(s) S-015 1/17/96 (LR)	
5. Drug Name Cordarone	6. Nonproprietary Name Amiodarone hydrochloride		8. Amendments & Other (reports, etc) - Dates 1/24/96
7. Supplement Provides For: Labeling changes.			
9. Pharmacological Category Antiarrhythmic	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/NDA(s)/DMF(s)
12. Dosage Form(s) Tablet (pink)	13. Potency(ies) 200 mg		
14. Chemical Name and Structure			15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No
16. Comments: SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED Labeling is satisfactory for DESCRIPTION and HOW SUPPLIED sections. Changes are being made in Precautions/SURGERY and Precautions/DRUG INTERACTIONS subsections.			
17. Conclusions and Recommendations: Satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
18. REVIEWER			
Name Danute G. Cunningham	Signature <i>DS</i>		Date Completed January 29, 1996
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO <input type="checkbox"/> District			

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DS 2/1/96

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MAY 7 1997

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 18-972
3. Name and Address of Applicant (City & State) Wyeth-Ayerst Laboratories P.O. Box 8299 Philadelphia, PA 19101-1245		4. Supplement(s) Number(s) Date(s) S-017 4/24/97 (LR)	
5. Drug Name Cordarone	6. Nonproprietary Name Amiodarone hydrochloride		8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Labeling.			
9. Pharmacological Category Antiarrhythmic	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/NDA(s)/DMF(s)
12. Dosage Form(s) Tablet (pink)	13. Potency(ies) 200 mg		
14. Chemical Name and Structure			15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No
16. Comments: Labeling change is under WARNINGS-Mortality subsection. No changes in DESCRIPTION and HOW SUPPLIED sections.			
17. Conclusions and Recommendations: Satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
18. REVIEWER			
Name Danute G. Cunningham	Signature <i>DS</i>		Date Completed May 7, 1997
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO <input type="checkbox"/> District			

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5/17/97

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NOV 25 1998

CHEMIST'S REVIEW		1. ORGANIZATION HFD-110	2. NDA Number 18-972
3. Name and Address of Applicant (City & State) Wyeth Laboratories 170 North Radnor-Chester Rd. St. Davids, PA 19087-5221		4. Supplement(s) Number(s) Date(s) SLR-015&SLR-017(AF) SLR-014, SLR-016, SLR-018 (SNC) 11/12/98	
5. Drug Name Cordarone	6. Nonproprietary Name Amiodarone hydrochloride		8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Final printed labeling.			
9. Pharmacological Category Antiarrhythmic	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC		11. Related IND(s)/NDA(s)/DMF(s)
12. Dosage Form(s) Tablet (pink)	13. Potency(ies) 200 mg		
14. Chemical Name and Structure 2-Butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride			15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No
16. Comments: Attachment 1 - includes the copy of division approval letter dated 6/15/98 (S-014, S-016, S-018). Attachment 2 - includes the copy of the division approvable letter dated 7/1/98. Attachment 3 - empty. FPL distributed as mounted samples in the Archival Copy. Attachment 4 - Guide to revisions in the FPL showing sections that were changed as indicated by strike-outs and shading. Attachment 5 - a copy of the currently approved Cordarone Tablets labeling. Insert - Cl 4662-4 Revised February 20, 1998 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
17. Conclusions and Recommendations: Satisfactory for DESCRIPTION and HOW SUPPLIED sections.			
18. REVIEWER			
Name Danute G. Cunningham	Signature <i>[Signature]</i>		Date Completed November 23, 1998
Distribution: <input checked="" type="checkbox"/> Original Jacket <input type="checkbox"/> Reviewer <input type="checkbox"/> Division File <input type="checkbox"/> CSO			

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11/23-98