



NDA 18-972/S-031

Wyeth Pharmaceuticals, Inc.
Attention: Caroline Henesey, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Henesey:

Please refer to your supplemental new drug application dated March 10, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) 200 mg Tablets.

This "Changes Being Effected" supplemental new drug application provides for labeling revised as follows:

1. The following text and graphics have been added to the beginning of the labeling:

	This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.	
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2. Under **DESCRIPTION**, the generic name (amiodarone HCl) has been added parenthetically after the first use of the Cordarone name. All subsequent uses of the parenthetical generic name after Cordarone uses have been deleted.
3. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following has been added as a new third paragraph:

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines.

4. Under **PRECAUTIONS/Drug Interactions**, the second and third sentences have been changed from:

Amiodarone is also a known inhibitor of CYP3A4. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4.

To:

Amiodarone is an inhibitor of CYP3A4 and p-glycoprotein. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4 and substrates of p-glycoprotein.

5. Under **PRECAUTIONS/Drug Interactions/Other substances**, the second paragraph has been changed from:

Amiodarone may suppress certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A4. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes. Reported examples of this interaction include the following:

To:

Amiodarone inhibits p-glycoprotein and certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A4. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes or are substrates of p-glycoprotein. Reported examples of this interaction include the following:

6. Under **PRECAUTIONS/Drug Interactions**, the title of the *HMG CoA Reductase inhibitors* subsection has been bolded.
7. Under **ADVERSE REACTIONS/Postmarketing Reports**, the following reported events have been added:
 - acute renal failure
 - renal impairment
 - renal insufficiency
 - agranulocytosis
8. The document number and revision date have been updated.
9. The reference to the physician insert has been removed from the Medication Guide.

We have completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on March 10, 2005.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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