



NDA 20-377/S-018

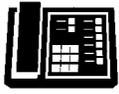
Wyeth Pharmaceuticals, Inc.
Attention: Caroline Henesey, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

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) Intravenous, 50 mg/ml.

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

1. The following text and graphics have been 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 following text has been added:

Cordarone I.V. contains polysorbate 80, which is known to leach di-(2-ethylhexyl)phthalate (DEHP) from polyvinylchloride (PVC) (see **DOSAGE AND ADMINISTRATION**).

3. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism**, the second paragraph has been changed from:

N-desethylamiodarone (DEA) is the major active metabolite of amiodarone in humans. DEA serum concentrations above 0.05 mg/L are not usually seen until after several days of continuous infusion but with prolonged therapy reach approximately the same concentration as amiodarone. The enzymes responsible for the N-deethylation are believed to be the cytochrome P-450 3A (CYP3A) subfamily, principally CYP3A4. This isozyme is present in both the liver and intestines. The highly variable systemic availability of oral amiodarone may be attributed potentially to large interindividual variability in CYP3A4 activity.

To:

N-desethylamiodarone (DEA) is the major active metabolite of amiodarone in humans. DEA serum concentrations above 0.05 mg/L are not usually seen until after several days of continuous infusion but with prolonged therapy reach approximately the same concentration as amiodarone. 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. The highly variable systemic availability of oral amiodarone may be attributed potentially to large interindividual variability in CYP3A4 activity.

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

Amiodarone is also known to be an 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/Pregnancy**, the parenthetical amiodarone HCl has been removed from the fourth paragraph.
7. Under **ADVERSE REACTIONS/Postmarketing Reports**, the following reported events have been added:
- acute renal failure
 - renal impairment
 - renal insufficiency
 - agranulocytosis

8. Under **DOSAGE AND ADMINISTRATION**, the tenth and eleventh paragraphs have been changed from:

It is well known that amiodarone adsorbs to polyvinyl chloride (PVC) tubing and the clinical trial dose administration schedule was designed to account for this adsorption. All of the clinical trials were conducted using PVC tubing and its use is therefore recommended. The concentrations and rates of infusion provided in **DOSAGE AND ADMINISTRATION** reflect doses identified in these studies. It is important that the recommended infusion regimen be followed closely.

Cordarone I.V. has been found to leach out plasticizers, including DEHP [di-(2-ethylhexyl)phthalate] from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing Cordarone I.V. at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION**.

To:

It is well known that amiodarone adsorbs to polyvinyl chloride (PVC) tubing and the clinical trial dose administration schedule was designed to account for this adsorption. All of the clinical trials were conducted using PVC tubing and its use is therefore recommended. The concentrations and rates of infusion provided in **DOSAGE AND ADMINISTRATION** reflect doses identified in these studies. Cordarone I.V. has been found to leach out plasticizers, including DEHP [di-(2-ethylhexyl)phthalate] from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing Cordarone I.V. at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION**. In addition, polysorbate 80, a component of Cordarone I.V., is also known to leach DEHP from PVC (see **DESCRIPTION**). Therefore, it is important that the recommendations in **DOSAGE AND ADMINISTRATION** be followed closely.

9. The document number and revision date have been updated.
10. The Wyeth name and signature line have been update.

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 electronic labeling 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, 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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
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