DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-377/S-007, 008 and 015

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 applications dated June 7, 2001 (S-007), November 5, 2001 (S-008) and November 7, 2003 (S-015), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Intravenous 50 mg/ml.

We acknowledge receipt of your submissions dated March 8 (two, S-007) and September 24, 2002 (S-007), November 7, 2003 (S-007, S-008 and S-015), and September 14, 2004 (S-007, S-008 and S-015). The September 14, 2004 submissions constituted a complete response to our May 21, 2004 action letter.

These "Changes Being Effected" supplemental new drug applications provide for labeling revised as follows:

1. The word "micellar" has been added to the third sentence of the second paragraph in the **DESCRIPTION** section so that it now reads:

   Cordarone I.V. is a sterile clear, pale-yellow micellar solution visually free from particulates.

2. The **CONTRAINDICATIONS** section has been updated to include iodine, so that it now reads as follows:

   Cordarone I.V. is contraindicated in patients with known hypersensitivity to any of the components of Cordarone I.V., including iodine, or in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block unless a functioning pacemaker is available.

3. Under **PRECAUTIONS/Liver Enzyme Elevations**, the second paragraph have been revised and now reads as follows:

   Acute, centrolobular confluent hepatocellular necrosis leading to hepatic coma, acute renal failure, and death has been associated with the administration of Cordarone I.V. at a much higher loading dose concentration and much faster rate of infusion than recommended in **DOSAGE AND ADMINISTRATION**. Therefore, ***the initial concentration and rate of infusion should be monitored closely and should not exceed that prescribed in*** **DOSAGE AND ADMINISTRATION** (see **DOSAGE AND ADMINISTRATION**).

4. Under **PRECAUTIONS/Proarrhythmia**, the following has been added to the end of the first paragraph:

   Combination of amiodarone with other antiarrhythmic therapy that prolongs the QTc should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent.

   The need to co-administer amiodarone with any other drug known to prolong the QTc interval must be based on a careful assessment of the potential risks and benefits of doing so for each patient.

A careful assessment of the potential risks and benefits of administering Cordarone I.V. must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia, which may result in death, in these patients.

5. Under **PRECAUTIONS**, the format and content of the **Drug Interactions** subsection has been substantially revised, and now reads as follows:

Drug Interactions
Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochromes P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines (see **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism**). 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. While only a limited number of *in vivo* drug-drug interactions with amiodarone have been reported, chiefly with the oral formulation, the potential for other interactions should be anticipated. This is especially important for drugs associated with serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured. In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone.

Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone. Reported examples include the following:

Protease Inhibitors:
Protease inhibitors are known to inhibit CYP3A4 to varying degrees. A case report of one patient taking amiodarone 200 mg and indinavir 800 mg three times a day resulted in increases in amiodarone concentrations from 0.9 mg/L to 1.3 mg/L. DEA concentrations were not affected. There was no evidence of toxicity. Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy should be considered.

Histamine H_2 antagonists:
Cimetidine inhibits CYP3A4 and can increase serum amiodarone levels.

Other substances:
Grapefruit juice given to healthy volunteers increased amiodarone AUC by 50% and C_{max} by 84%, resulting in increased plasma levels of amiodarone. Grapefruit juice should not be taken during treatment with oral amiodarone. This information should be considered when changing from intravenous amiodarone to oral amiodarone (see **DOSAGE AND ADMINISTRATION, Intravenous to Oral Transition**).

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:

Immunosuppressives:
Cyclosporine (CYP3A4 substrate) administered in combination with oral amiodarone has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

HMG-CoA Reductase Inhibitors:

Simvastatin (CYP3A4 substrate) in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis.

Cardiovasculars:
Cardiac glycosides: In patients receiving **digoxin** therapy, administration of oral amiodarone regularly results in an increase in serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. Amiodarone taken concomitantly with digoxin increases the serum digoxin concentration by 70% after one day. **On administration of oral amiodarone, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.

Antiarrhythmics: Other antiarrhythmic drugs, such as **quinidine, procainamide, disopyramide,** and **phenytoin,** have been used concurrently with amiodarone. There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. Phenytoin decreases serum amiodarone levels. Amiodarone taken concomitantly with quinidine increases quinidine serum concentration by 33% after two days. Amiodarone taken concomitantly with procainamide for less than seven days increases plasma concentrations of procainamide and n-acetyl procainamide by 55% and 33%, respectively. Quinidine and procainamide doses should be reduced by one-third when either is administered with amiodarone. Plasma levels of **flecainide** have been reported to increase in the presence of oral amiodarone; because of this, the dosage of flecainide should be adjusted when these drugs are administered concomitantly. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring. Combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to oral amiodarone, the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of oral amiodarone (see **DOSAGE AND ADMINISTRATION, Intravenous to Oral Transition**). The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as amiodarone is continued. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Antihypertensives: Amiodarone should be used with caution in patients receiving **β-receptor blocking agents** (e.g., propranolol, a CYP3A4 inhibitor) or **calcium channel antagonists** (e.g., verapamil, a CYP3A4 substrate, and diltiazem, a CYP3A4 inhibitor) because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, amiodarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

Anticoagulants: Potentiation of **warfarin**-type (CYP2C9 and CYP3A4 substrate) anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone increases the prothrombin time by 100% after 3 to 4 days, **the dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A4 (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy. Reported examples of this interaction include the following:

Antibiotics:

Rifampin is a potent inducer of CYP3A4. Administration of rifampin concomitantly with oral amiodarone has been shown to result in decreases in serum concentrations of amiodarone and desethylamiodarone.

Other substances, including herbal preparations:
St. John's Wort (Hypericum perforatum) induces CYP3A4. Since amiodarone is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving amiodarone could result in reduced amiodarone levels.

Other reported interactions with amiodarone:
Fentanyl (CYP3A4 substrate) in combination with amiodarone may cause hypotension, bradycardia, and decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with **lidocaine** (CYP3A4 substrate) given for local anesthesia. Seizure, associated with increased lidocaine concentrations, has been reported with concomitant administration of intravenous amiodarone.

Dextromethorphan is a substrate for both CYP2D6 and CYP3A4. Amiodarone inhibits CYP2D6.

Cholestyramine increases enterohepatic elimination of amiodarone and may reduce its serum levels and $t_{1/2}$.

Disopyramide increases QT prolongation which could cause arrhythmia.

Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with **propranolol, diltiazem,** and **verapamil**.

Volatile Anesthetic Agents: (see **PRECAUTIONS, Surgery**).

In addition to the interactions noted above, chronic (> 2 weeks) ***oral*** Cordarone administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.

6. Under **PRECAUTIONS/Nursing Mothers**, the first sentence has been changed from:

(b)(4)

To:

Amiodarone and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug.

7. Under **OVERDOSAGE**, the first sentence has been changed to read as follows:

There have been cases, some fatal, of amiodarone overdose. Effects of an inadvertent overdose of Cordarone I.V. include hypotension, cardiogenic shock, bradycardia, AV block, and hepatotoxicity.

8. Under **DOSAGE AND ADMINISTRATION**, "…at room temperature" has been added to the comments column for both container types in the AMIONDARONE HCl SOLUTION STABILITY chart.

9. Under **DOSAGE AND ADMINISTRATION/Intravenous to Oral Transition**, the following two new paragraphs have been added after the first paragraph:

Since there are some differences between the safety and efficacy profiles of the intravenous and oral formulations, the prescriber is advised to review the package insert for oral amiodarone when switching from intravenous to oral amiodarone therapy.

Since grapefruit juice is known to inhibit CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone; grapefruit juice should not be taken during treatment with oral amiodarone (see **PRECAUTIONS, Drug Interactions**).

10. The document number and date have been updated.

We have completed our review of these supplemental new drug applications. They are approved, effective on the date of this letter, for use as recommended in the labeling submitted on September 14, 2004. We note that you are no longer manufacturing Cordarone Intravenous, and therefore have not provided final printed labeling. Should you resume manufacture in the future, we request that you submit final printed labeling identical in content to the labeling submitted on September 14, 2004

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

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/s/

Norman Stockbridge

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