DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-972/S-022 and S-027

Wyeth Pharmaceuticals, Inc.
Attention: Ms. Diane Mitrione
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your supplemental new drug applications dated November 16, 2001 (S-022) and November 19, 2003 (S-027), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets 200 mg.

We acknowledge receipt of your submission date November 19, 2003 (S-022 and S-027).

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

1. In the final sentence of the second paragraph of the **CLINICAL PHARMACOLOGY/Pharmacokinetics** section, "class III" has been changed to "Class III."

2. In the first paragraph of the **INDICATIONS AND USAGE** section, the spelling of "antiarrhthymics" has been changed to "antiarrhythmics."

3. In the first paragraph of the **CONTRAINDICATIONS** section, "second- and third-degree atrioventricular block" has been changed to "second- or third-degree atrioventricular block."

4. Under **CONTRAINDICATIONS**, the second paragraph has been changed from:

   Cordarone is contraindicated in patients with a known hypersensitivity to the drug.

   To:

   Cordarone is contraindicated in patients with a known hypersensitivity to the drug or to any of its components, including iodine.

5. Under **WARNINGS/Worsened Arrhythmia**, the following two paragraphs have been added to the end of the section:

   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 must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia in these patients.

6. Under **WARNINGS/Loss of Vision**, the spelling of "fundoscopy" in the last sentence has been changed to "funduscopy."

7. Under **PRECAUTIONS/Thyroid Abnormalities**, in the second sentence of the third paragraph has been changed from:

   Cordarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation.

   To:

   Cordarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation, which may result in death.

8. The format and content of the **PRECAUTIONS/Drug Interactions** section has been updated to read as follows:

   Drug Interactions
   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 (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, 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 CYP3A4 may decrease the metabolism and increase serum concentrations 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%, and decreased DEA to unquantifiable concentrations. Grapefruit juice inhibits CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone; therefore, 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**").

   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 the 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 initiation 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 oral 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 amiodarone the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of amiodarone, when arrhythmia suppression should be beginning. 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 t½.

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**, *Volatile Anesthetic Agents*.")

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

9. The **PRECAUTIONS/Electrolyte Disturbances** section has been changed from:

   Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting Cordarone therapy.

   To:

   Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting and during Cordarone therapy. Use caution when co-administering Cordarone with drugs which may induce hypokalemia and/or hypomagnesemia.

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

    Cordarone is excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug.

To:

Cordarone 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.

11. Under **ADVERSE REACTIONS/Postmarketing Reports**, muscle weakness and pruritus have been added, so that the end of the list now reads as follows:

    …myopathy, muscle weakness, rhabdomyolysis, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, and pruritus, also have been reported in patients receiving Cordarone.

12. Under **OVERDOSAGE**, the first paragraph has been changed from:

    There have been a few reported cases of Cordarone overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. The acute oral LD_{50} of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.

    To:

    There have been cases, some fatal, of Cordarone overdose.

13. Under **OVERDOSAGE**, the following has been added as a new third paragraph:

    The acute oral LD_{50} of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.

14. Under **DOSAGE AND ADMINISTRATION**, the period at the end of the second paragraph has been changed to a colon.

15. Under **DOSAGE AND ADMINISTRATION**, the following has been added as a new fourth paragraph:

    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**").

16. The document number and date have been updated.

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the final printed labeling submitted on November 19, 2003.

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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact:

Mr. Russell Fortney
Regulatory 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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