DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-972/S-032

Wyeth Pharmaceuticals, Inc.
Attention: Brian Schlag
Manager, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Schlag:

Please refer to your supplemental new drug application dated October 27, 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. Under **CONTRAINDICATIONS**, the following text has been added to the first paragraph:

   patients with cardiogenic shock;

2. Under **WARNINGS/Pulmonary Toxicity**, the second sentence of the first paragraph has been changed from:

   Findings have included pulmonary infiltrates on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia.

   To:

   Findings have included pulmonary infiltrates and/or mass on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia.

3. Under **PRECAUTIONS/Thyroid Abnormalities**, the following new paragraph has been added as the last paragraph:

   There have been postmarketing reports of thyroid nodules/thyroid cancer in patients treated with Cordarone. In some instances hyperthyroidism was also present (see "**WARNINGS**" and "**ADVERSE REACTIONS**").

4. Under **PRECAUTIONS**, the following section has been added following the **SURGERY** section:

   Corneal Refractive Laser Surgery
   Patients should be advised that most manufacturers of corneal refractive laser surgery devices contraindicate that procedure in patients taking Cordarone.

5. Under **PRECAUTIONS/Drug Interactions**, the following new sections have been added:

   Histamine H_1 antagonists:
   Loratadine, a non-sedating antihistaminic, is metabolized primarily by CYP3A4. QT interval prolongation

and torsade de pointes have been reported with the co-administration of loratadine and amiodarone.

Antidepressants:
Trazodone, an antidepressant, is metabolized primarily by CYP3A4. QT interval prolongation and torsade de pointes have been reported with the co-administration of trazodone and amiodarone.

6. Under **PRECAUTIONS/Drug Interactions**/*Anticoagulants,* the following has been added as a new second paragraph:

   Clopidogrel, an inactive thienopyridine prodrug, is metabolized in the liver by CYP3A4 to an active metabolite. A potential interaction between clopidogrel and Cordarone resulting in ineffective inhibition of platelet aggregation has been reported.

7. Under ADVERSE REACTIONS, the Postmarketing Reports has been changed from:

   Postmarketing Reports
   In postmarketing surveillance, sinus arrest, hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, impotence, vasculitis, pseudotumor cerebri, syndrome of inappropriate antidiuretic hormone secretion (SIADH), acute renal failure, renal impairment, renal insufficiency, thrombocytopenia, angioedema, bronchiolitis obliterans organizing pneumonia (possibly fatal), bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest, and ARDS), fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates, pleuritis, pancreatitis, toxic epidermal necrolysis (sometimes fatal), myopathy, muscle weakness, rhabdomyolysis, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, agranulocytosis, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pruritus, hallucination, confusional state, disorientation, and delirium also have been reported in patients receiving Cordarone.

   To:

   Postmarketing Reports
   In postmarketing surveillance, hypotension (sometimes fatal), sinus arrest, anaphylactic/anaphylactoid reaction (including shock), angioedema, hepatitis, cholestatic hepatitis, cirrhosis, pancreatitis, renal impairment, renal insufficiency, acute renal failure, bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest, and ARDS), bronchiolitis obliterans organizing pneumonia (possibly fatal), fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates and/or mass, pleuritis, pseudotumor cerebri, syndrome of inappropriate antidiuretic hormone secretion (SIADH), thyroid nodules/thyroid cancer, toxic epidermal necrolysis (sometimes fatal), erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, skin cancer, vasculitis, pruritus, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, thrombocytopenia, agranulocytosis, granuloma, myopathy, muscle weakness, rhabdomyolysis, hallucination, confusional state, disorientation, delirium, epididymitis, and impotence, also have been reported with amiodarone therapy.

8. In the **HOW SUPPLIED** section, reference to the Redipak has been deleted as that presentation has been discontinued.

9. In the **HOW SUPPLIED** section, the package code has been added to the NDC for completeness.

10. In the **HOW SUPPLIED** section, the storage information has been changed from:

    Keep tightly closed.
    Store at room temperature, approximately 25°C (77°F).
    Protect from light.
    Dispense in a light-resistant, tight container.

Use carton to protect contents from light.

To:

Keep tightly closed.
Store at Controlled Room Temperature, 20° to 25°C (68° to 77°F).
Protect from light.
Dispense in a light-resistant, tight container.

11. The document number and revision date have been updated.

The Medication Guide has been revised as follows:

12. The following bullet point has been added to the section under the section titled "**Tell your doctor about all the medicines you take including…:**"

    - loratadine (for example: Claritin®, Alavert®), a medicine for allergy symptoms

13. The first sentence of the bullet for **thyroid problems**, in the "Some other serious side effects of Cordarone Tablets include" section has been changed from:

    Cordarone Tablets can cause hypothyroidism or hyperthyroidism.

    To:

    Cordarone Tablets can cause thyroid problems, including hypothyroidism or hyperthyroidism.

We have completed our review of this application, and it is approved, effective on the date of this letter, for use as recommended in the labeling submitted on February 28, 2006.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted February 28, 2006).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 18-972/S-032**." Approval of this submission by FDA is not required before the labeling is used.

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
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 Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal 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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