DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-972/S-033

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 February 28, 2006, 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 **WARNINGS**, the following new section has been added following the **Worsened Arrhythmia** section:

   Thyrotoxicosis
   Cordarone-induced hyperthyroidism may result in thyrotoxicosis and/or the possibility of arrhythmia breakthrough or aggravation. There have been reports of death associated with amiodarone-induced thyrotoxicosis. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED (see "**PRECAUTIONS, Thyroid Abnormalities**").

2. Under **PRECAUTIONS/Thyroid Abnormalities**, the third paragraph has been changed from:

   Hyperthyroidism occurs in about 2% of patients receiving Cordarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. 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. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED.

   To:

   Hyperthyroidism occurs in about 2% of patients receiving Cordarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of thyrotoxicosis and/or arrhythmia breakthrough or aggravation, all of which may result in death. There have been reports of death associated with amiodarone-induced thyrotoxicosis. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED.

3. Under **PRECAUTIONS/Thyroid Abnormalities**, the following sentence has been deleted from the fifth paragraph:

   Experience with thyroid surgery in this setting is extremely limited, and this form of therapy runs the theoretical risk of inducing thyroid storm.

4. Under **PRECAUTIONS/Thyroid Abnormalities**, the following parenthetical reference has been added to the end of the fifth paragraph:

   (see "**WARNINGS, Thyrotoxicosis**").

5. Under **PRECAUTIONS/Thyroid Abnormalities**, the following has been added as a new sixth paragraph:

   When aggressive treatment of amiodarone-induced thyrotoxicosis has failed or amiodarone cannot be discontinued because it is the only drug effective against the resistant arrhythmia, surgical management may be an option. Experience with thyroidectomy as a treatment for amiodarone-induced thyrotoxicosis is limited, and this form of therapy could induce thyroid storm. Therefore, surgical and anesthetic management require careful planning.

The Medication Guide has been revised as follows:

6. A new bullet for "thyroid problems" has been added to first set of bullets under the "What is the most important information I should know about Cordarone Tablets" section.

7. Under "Call your doctor or get medical help right away if you have any symptoms such as the following:" the following has been added as the last bullet:

   - weakness, weight loss or weight gain, heat or cold intolerance, hair thinning, sweating, changes in your menses, swelling of your neck (goiter), nervousness, irritability, restlessness, decreased concentration, depression in the elderly, or tremor.

8. The paragraph under the "**What are the possible or reasonably likely side effects of Cordarone Tablets?**" section has been changed from:

   Cordarone Tablets can cause serious side effects that lead to death including lung damage, liver damage, and worse heartbeat problems. See "**What is the most important information I should know about Cordarone Tablets?**"

   To:

   Cordarone Tablets can cause serious side effects that lead to death including lung damage, liver damage, worse heartbeat problems, and thyroid problems. See "**What is the most important information I should know about Cordarone Tablets?**"

9. Under "**Some other serious side effects of Cordarone Tablets include**:" the "thyroid problems" bullet has been changed from:

   - **thyroid problems.** Cordarone Tablets can cause thyroid problems, including hypothyroidism or hyperthyroidism. Your doctor may arrange regular blood tests to check your thyroid function during treatment with Cordarone. Call your doctor if you have weight loss or weight gain, restlessness, weakness, heat or cold intolerance, hair thinning, sweating, changes in your menses, or swelling of your neck (goiter).

   To:

   - **thyroid problems.** Cordarone Tablets can cause thyroid problems, including low thyroid function or overactive thyroid function. Your doctor may arrange regular blood tests to check your thyroid function during treatment with Cordarone. Call your doctor if you have weakness, weight loss or weight gain, heat or cold intolerance, hair thinning, sweating, changes in your menses, swelling of your neck (goiter), nervousness, irritability, restlessness, decreased concentration, depression in the

elderly, or tremor.

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

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-033**." 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

8/28/2006 10:00:35 AM