DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-377/S-010 and S-012

Wyeth Pharmaceuticals, Inc.
Attention: Ms. Patricia Kuker Staub
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Kuker Staub:

Please refer to your supplemental new drug applications dated May 10 (S-010) and November 6, 2002 (S-012), 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 submission dated April 10, 2003, which constituted a complete response to our December 19, 2002 action letter.

These supplemental new drug applications provide for final printed labeling revised to read as follows:

1. The paragraph under **WARNINGS/Hypotension** has been changed from:

> Hypotension is the most common adverse effect seen with Cordarone I.V. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with Cordarone I.V. Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and was not dose related, but appeared to be related to the rate of infusion. Hypotension necessitating alterations in Cordarone I.V. therapy was reported in 3% of patients, with permanent discontinuation required in less than 2% of patients. Hypotension should be treated initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. ***The initial rate of infusion should be monitored closely and should not exceed that prescribed in*** **DOSAGE AND ADMINISTRATION**.
>
> To:
>
> Hypotension is the most common adverse effect seen with Cordarone I.V. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with Cordarone I.V. Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and was not dose related, but appeared to be related to the rate of infusion. Hypotension necessitating alterations in Cordarone I.V. therapy was reported in 3% of patients, with permanent discontinuation required in less than 2% of patients.
>
> Hypotension should be treated initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. ***The initial rate of infusion should be monitored closely and should not exceed that prescribed in*** **DOSAGE AND ADMINISTRATION.**
>
> In some cases, hypotension may be refractory resulting in fatal outcome (see **ADVERSE REACTIONS, Postmarketing Reports**).

2. Under **PRECAUTIONS/Pulmonary Disorders**, the following has been added as the new first sub-heading:

   Early-onset pulmonary toxicity
   There have been postmarketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with Cordarone I.V. Findings have included pulmonary infiltrates on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure and/or death.

3. Under **PRECAUTIONS/Pulmonary Disorders/***ARDS*, "involving 48 hours of therapy" has been added to the end of the first sentence.

4. Under **PRECAUTIONS/Pulmonary Disorders/***ARDS,* the last sentence of the of the first paragraph has been changed from:

   It is not possible to determine what role, if any, Cordarone I.V. played in causing or exacerbating the pulmonary disorder in those patients.

   To:

   There have been postmarketing reports of ARDS in Cordarone I.V. patients. Cordarone I.V. may play a role in causing or exacerbating pulmonary disorders in those patients.

5. Under **PRECAUTIONS/Drug Interactions**, the following new subsection has been added after the ***Immunosuppressives*** subsection:

   HMG-CoA Reductase Inhibitors:
   Simvastatin (CYP3A4 substrate) in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis.

6. The **ADVERSE REACTIONS/Postmarketing Reports** section has been changed from:

   In postmarketing surveillance, sinus arrest, pseudotumor cerebri, toxic epidermal necrolysis, exfoliative dermatitis, pancytopenia, neutropenia, erythema multiforme, angioedema, bronchospasm, and anaphylactic shock also have been reported with amiodarone therapy.

   To:

   In postmarketing surveillance, hypotension (sometimes fatal), sinus arrest, pseudotumor cerebri, toxic epidermal necrolysis, exfoliative dermatitis, pancytopenia, neutropenia, erythema multiforme, angioedema, bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest, and ARDS), fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates and anaphylactic/anaphylactoid reaction (including shock) also have been reported with amiodarone therapy.

   Also, in patients receiving recommended dosages, there have been postmarketing reports of the following injection site reactions: pain, erythema, edema, pigment changes, venous thrombosis, phlebitis, thrombophlebitis, cellulitis, necrosis, and skin sloughing (see **DOSAGE AND ADMINISTRATION**).

7. Under **DOSAGE AND ADMINISTRATION**, a cross-reference to the **ADVERSE REACTIONS/Postmarketing Reports** section has been added to the paragraph regarding phlebitis.

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 final printed labeling (FPL) submitted on April 10, 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, HF-2
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}

Douglas C. Throckmorton, M.D.
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/

Doug Throckmorton
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