DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-377/S-004
/S-005

Wyeth Laboratories
Attention: Ms. Mary Alice Dankulich
170 North Radnor Chester Road
St. Davids, PA 19087

Dear Ms. Dankulich:

Please refer to your supplemental new drug applications dated August 27, 1998 (S-004) and June 9, 1999 (S-005) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Intravenous.

We acknowledge receipt of your submissions dated November 15, 2000 and February 2 and May 18, 2001. Your submissions of November 15, 2000 constituted a complete response to our December 8, 1998 and October 8, 1999 approvable letters.

These supplemental applications, as amended, provide for final printed labeling revised as follows:

Supplement 004

S-004 provides for the addition of a **PRECAUTIONS/Geriatric Use** subsection as follows:

> **Geriatric Use**
> Clinical studies of Cordarone I.V. did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

We note that the structural formula has been included under the **DESCRIPTION** section.

Supplement 005

S-005 provides for revisions in the **WARNINGS/Neonatal Hypo- or Hyperthyroidism** subsection, **PRECAUTIONS/Pulmonary Disorders/***ARDS*, **Carcinogenesis, Mutagenesis, Impairment of Fertility**, and **Pregnancy** subsections, and the **ADVERSE REACTIONS** section as follows:

> Under the **WARNINGS/Neonatal Hypo- or Hyperthyroidism** subsection, the first sentence was changed to:
>
> > Although Cordarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with its oral administration.

Under the **PRECAUTIONS** section,

(1) At the end of the **Pulmonary Disorders**/*ARDS* subsection, the following paragraph was added:

> Postoperatively, occurrences of ARDS have been reported in patients receiving ***oral*** Cordarone therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FiO_2 and the determinants of oxygen delivery to the tissues (e.g., SaO_2, PaO_2) be closely monitored in patients on Cordarone.

(2) Under the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the 2nd, 3rd, and 6th sentences have been changed to:

> No carcinogenicity studies were conducted with Cordarone I.V. However, ***oral*** Cordarone caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors in rats was greater than the incidence in controls even at the lowest dose level tested, i.e., 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).
>
> Mutagenicity studies conducted with amiodarone HCl (Ames, micronucleus, and lysogenic induction tests) were negative.
>
> No fertility studies were conducted with Cordarone I.V. However, in a study in which amiodarone HCl was orally administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*). *600 mg in a 50 kg patient (doses compared on a body surface area basis)

(3) Under the **Pregnancy** subsection, the word "and" was replaced by a comma in the statement "See **WARNINGS and Neonatal Hypo- or Hyperthyroidism**" so that the statement now reads: "See **WARNINGS, Neonatal Hypo- or Hyperthyroidism**."

Under the **ADVERSE REACTIONS** section, the last sentence has been changed to:

> In postmarketing surveillance, toxic epidermal necrolysis, pancytopenia, neutropenia, angioedema, and anaphylactic shock also have been reported with amiodarone therapy.

We note that the words "**Rx only**" have been added above the **DESCRIPTION** section.

Changes Being Effected

We note that you included changes that qualify as "Changes Being Effected" in your November 15, 2000 submission of final printed labeling as well as a "Dear Health Professional" letter in your submissions of February 2 and May 18, 2001 relating to these "Changes Being Effected". This letter highlighted additional safety language added to the package insert.

Under the **PRECAUTIONS/Pediatric Use** subsection you included information on the benzyl alcohol content of the drug product and under the **DOSAGE AND ADMINISTRATION** section, information on the leaching of plasticizers into intravenous tubing as follows:

Under the **PRECAUTIONS/Pediatric Use** subsection, the following paragraph was added:

> Cordarone I.V. contains the preservative benzyl alcohol (see **DESCRIPTION**). There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Under the **DOSAGE AND ADMINISTRATION** section, the following paragraph was added:

> Cordarone I.V. has been found to leach out plasticizers, including DEHP [di-(2-ethylhexyl)phthalate] from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing Cordarone I.V. at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION**.

Additionally, we note the following changes that were made since the last approved labeling:

Under **PRECAUTIONS/Surgery**, the word "effects" was replaced by the word "defects" so that the sentence now reads:

> Close perioperative monitoring is recommended in patients undergoing general anesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction defects of halogenated inhalational anesthetics.

We also note that several minor editorial changes were made throughout the package insert**.**

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your November 15, 2000 submission). Accordingly, these supplemental applications are approved effective on the date of this letter.

Please make the following change at the time of your next printing: under **CLINICAL PHARMACOLOGY/Mechanisms of Action**, in the table entitled "**EFFECTS OF INTRAVENOUS AND ORAL CORDARONE ON ELECTROPHYSIOLOGIC PARAMETERS**", the word "Qtc" should be restored to "QTc". These changes may be reported in the next annual report.

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:

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Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
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