DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 12-796/S-049

Wyeth-Ayerst Laboratories
Division of American Home Products
Attention: Ms. Mary Alice Dankulich
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Dankulich:

Please refer to your supplemental new drug application dated August 27, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Quinidex Extentabs (quinidine sulfate extended-release tablets), 300 mg.

We acknowledge receipt of your submission dated December 7, 2000 that constitutes a complete response to our February 3, 1999 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

In accordance with 21 CFR 201.57(f)(10), under **PRECAUTIONS**, the **Geriatric Use** subsection has been moved so that it follows the **Pediatric Use** subsection and has been revised from the single statement:

> Safety and efficacy of quinidine in elderly patients have not been systematically studied.

to:

> Clinical studies of quinidine generally were not adequate to determine if significant safety or efficacy differences exist between elderly patients (65 years or older) and younger patients.
>
> Quinidine clearance is apparently independent of age (**see CLINICAL PHARMACOLOGY-Pharmacokinetics**). However, renal or hepatic dysfunction causes the elimination of quinidine to be slowed (see **WARNINGS-Pharmacokinetic Considerations**), and since these conditions are more common in the elderly, appropriate dosing reductions should be considered in these individuals.

Under **PRECAUTIONS**, the heading of the **Drug Interactions** subsection has been changed to **Drug and Diet Interactions** and the following paragraphs were added so that they are the last paragraphs under **PRECAUTIONS/Drug and Diet Interactions**/*Altered pharmacokinetics of quinidine*:

Grapefruit juice inhibits P450 3A4-mediated metabolism of quinidine to 3-hydroxyquinidine. Although the clinical significance of this interaction is unknown, grapefruit juice should be avoided.

The rate and extent of quinidine absorption may be affected by changes in **dietary salt** intake; a decrease in dietary salt intake may lead to an increase in plasma quinidine concentrations

Under **OVERDOSAGE**, the following paragraph was added after the first paragraph:

A case of tablet ingestion by a 16-month-old infant has been reported in which a concretion or bezoar was formed in the stomach, resulting in nondeclining toxic levels of quinidine. The mass was only dimly visible on plain radiographs, but a gastric aspirate revealed quinidine levels approximately 50 times higher than those in plasma. In cases of massive overdose with prolonged high plasma levels, diagnostic/therapeutic endoscopy may be appropriate.

Under **HOW SUPPLIED**, modifications made to the last approved labeling supplement, approved June 24, 1998 (package insert dated January 26, 1998), were not retained in this supplement. The storage statement has been changed from:

Store at controlled room temperature, between 20° and 25°C (68° and 77°F).

to:

Store tablets at controlled room temperature, 20° -25°C (68° -77°F).

We note that under **WARNINGS**, the word "heart" has been restored in the subsection heading "**Paradoxical Increase in Ventricular Heart Rate in Atrial Flutter/Fibrillation**" in the final printed labeling.

In addition, we note the following changes made since the last approved package insert:

Throughout the **PRECAUTIONS/Drug and Diet Interactions**/*Altered pharmacokinetics of quinidine* and *Altered pharmacokinetics of other drugs* subsections, the nomenclature referring to cytochrome P450 enzymes has been updated.

Under **HOW SUPPLIED**, the statement "Caution: Federal law prohibits dispensing without prescription." has been changed to "**Rx only**."

We have completed the review of this supplemental application, 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 December 7, 2000 submission). Accordingly, the supplemental application is approved effective on the date of this letter.

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:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, 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/

Raymond Lipicky
8/16/01 08:52:41 AM