CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-972/S-030

Administrative/Correspondence Reviews

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 27, 2004

TO: Norman Stockbridge, M.D., Acting Director
Division of Cardio-Renal Drug Products
HFD-110

VIA: Russell Fortney, Regulatory Health Project Manager,
Division of Cardio-Renal Drug Products
HFD-110

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Medication Guide for Cordarone (amiodarone HCL) Tablets, NDA 18-972/S-030

The attached Medication Guide represents the revised patient risk communication materials for Cordarone (amiodarone HCL) Tablets, NDA 18-972/S-030. The Medication Guide has been reviewed by DSRCS and by DDMAC. We have simplified the wording, made it consistent with the prescribing information, removed promotional and other unnecessary information and put it in the format that is specified under 21 CFR § 208.20, *Content and format of a Medication Guide*.

These revisions are based on current labeling (prescribing information or PI) approved May 21, 2004. The Medication Guide should always be consistent with the PI. All relevant future changes to the PI should also be reflected in the Medication Guide.

We also have the following comment:
The PI is missing the Information for Patients subsection under the PRECAUTIONS section. This subsection should contain information given to patients for the safe and effective use of the product (21 CFR 201.57(f)(2).]

Comments to the review Division are bolded, italicized, and underlined. We can provide

marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

Appears This Way
On Original

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
9/27/04 11:48:24 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
9/27/04 01:17:58 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-972/S-030

Wyeth Pharmaceuticals, Inc.
Attention: Caroline M. Henesey, Ph.D.
500 Arcola Road
Collegeville, PA 19426

Dear Dr. Henesey:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Cordarone® (amiodarone hydrochloride) 200 mg Tablets
NDA Number:	18-972
Supplement number:	030
Date of supplement:	August 20, 2004
Date of receipt:	August 23, 2004

This supplemental application proposes a draft Medication Guide for Cordarone® (amiodarone hydrochloride) 200 mg tablets based on the currently in-use labeling.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 22, 2004, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

/S/

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
9/10/04 02:07:57 PM

RHPM Review of Labeling

Application:	NDA 18-972/S-030
	Cordarone (amiodarone HCl) Tablets 200 mg
Applicant:	Wyeth Pharmaceuticals
Supplement Date:	August 20, 2004
Supplement Receipt Date:	August 26, 2004
Supplement Type:	Prior Approval

Background:

During a November, 2003 teleconference, the Division requested that Wyeth develop a medication guide for Cordarone. On August 20, 2004, Wyeth submitted a supplemental NDA containing the requested medication guide. The content and format of the medication guide was reviewed by both the Division and the Office of Drug Safety. The changes requested by the Division and ODS were communicated to Wyeth in an email on October 5, 2004.

Wyeth submitted the requested changes, along with additional changes, on October 25, 2004. ODS indicated their approval of Wyeth's additional changes in an email dated November 11, 2004. Dr. Stockbridge reviewed the submission and requested additional minor revisions. These revisions were communicated to Wyeth in an email dated November 17, 2004. In a telephone call on November 23, 2004, Wyeth agreed to those revisions.

Review:

Wyeth has added a medication guide to the labeling for Cordarone. This medication guide will be distributed to patients each time a prescription for Cordarone is filled (or refilled). In addition, generic manufacturers of oral amiodarone must also add the medication guide to the labeling for their products.

The agreed-upon text of the medication guide is as follows:

Medication Guide

Cordarone® 'KOR-DU-RŌN Tablets

(amiodarone HCl)

Rx only

Read the Medication Guide that comes with Cordarone Tablets before you start taking them and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Cordarone Tablets?

Cordarone Tablets can cause serious side effects that can lead to death including:

- **lung damage**
- **liver damage**
- **worse heartbeat problems**

Call your doctor or get medical help right away if you have any symptoms such as the following:

- shortness of breath, wheezing, or any other trouble breathing; coughing, chest pain, or spitting up of blood
- nausea or vomiting; passing brown or dark-colored urine; feel more tired than usual; your skin and whites of your eyes get yellow; or have stomach pain
- heart pounding, skipping a beat, beating very fast or very slowly; feel light-headed or faint

Because of these possible side effects, Cordarone Tablets should only be used in adults with life-threatening heartbeat problems called ventricular arrhythmias, for which other treatments did not work or were not tolerated.

Cordarone Tablets can cause other serious side effects. See "**What are the possible or reasonably likely side effects of Cordarone Tablets?**" for more information.

If you get serious side effects during treatment with Cordarone Tablets you may need to stop Cordarone Tablets, have your dose changed, or get medical treatment. Talk with your doctor before you stop taking Cordarone Tablets.

You may still have side effects after stopping Cordarone Tablets because the medicine stays in your body months after treatment is stopped.

Tell all your healthcare providers that you take or took Cordarone Tablets. This information is very important for other medical treatments or surgeries you may have.

What are Cordarone Tablets?

Cordarone is a medicine used in adults to treat life-threatening heartbeat problems called ventricular arrhythmias, for which other treatment did not work or was not tolerated. Cordarone Tablets have not been shown to help people with life-threatening heartbeat problems live longer. Treatment with Cordarone Tablets should be started in a hospital to monitor your condition. You should have regular check-ups, blood tests, chest x-rays, and eye exams before and during treatment with Cordarone Tablets to check for serious side effects.

Cordarone Tablets have not been studied in children.

Who should not take Cordarone Tablets?

Do not take Cordarone Tablets if you:

- **have certain heart conditions** (heart block, very slow heart rate, or slow heart rate with dizziness or lightheadedness)

- **have an allergy to amiodarone, iodine, or any of the other ingredients in Cordarone Tablets.** See the end of this Medication Guide for a complete list of ingredients in Cordarone Tablets.

What should I tell my doctor before starting Cordarone Tablets?

Tell your doctor about all of your medical conditions including if you:

- **have lung or breathing problems**
- **have liver problems**
- **have or had thyroid problems**
- **have blood pressure problems**
- **are pregnant or planning to become pregnant.** Cordarone can harm your unborn baby. Cordarone can stay in your body for months after treatment is stopped. Therefore, talk with your doctor before you plan to get pregnant.
- **are breastfeeding.** Cordarone passes into your milk and can harm your baby. You should not breast feed while taking Cordarone. Also, Cordarone can stay in your body for months after treatment is stopped.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Cordarone Tablets and certain other medicines can interact with each other causing serious side effects. Sometimes the dose of Cordarone Tablets or other medicines must be changed when they are used together. Especially, tell your doctor if you are taking:

- antibiotic medicines used to treat infections
- depression medicines
- blood thinner medicines
- HIV or AIDS medicines
- cimetidine (Tagamet®), a medicine for stomach ulcers or indigestion
- seizure medicines
- diabetes medicines
- cyclosporine, an immunosuppressive medicine
- dextromethorphan, a cough medicine
- medicines for your heart, circulation, or blood pressure
- water pills (diuretics)
- high cholesterol or bile medicines
- narcotic pain medicines
- St. John's Wort

Know the medicines you take. Keep a list of them with you at all times and show it to your doctor and pharmacist each time you get a new medicine. Do not take any new medicines while you are taking Cordarone Tablets unless you have talked with your doctor.

How should I take Cordarone Tablets?

- **Take Cordarone Tablets exactly as prescribed by your doctor.**

- The dose of Cordarone Tablets you take has been specially chosen for you by your doctor and may change during treatment. Keep taking your medicine until your doctor tells you to stop. Do not stop taking it because you feel better. Your condition may get worse. Talk with your doctor if you have side effects.
- Your doctor will tell you to take your dose of Cordarone Tablets with or without meals. Make sure you take Cordarone Tablets the same way each time.
- **Do not drink grapefruit juice during treatment with Cordarone Tablets.** Grapefruit juice affects how Cordarone is absorbed in the stomach.
- Taking too many Cordarone Tablets can be dangerous. If you take too many Cordarone Tablets, call your doctor or go to the nearest hospital right away. You may need medical care right away.
- If you miss a dose, do not take a double dose to make up for the dose you missed. Continue with your next regularly scheduled dose.

What should I avoid while taking Cordarone Tablets?

- **Do not drink grapefruit juice during treatment with Cordarone Tablets.** Grapefruit juice affects how Cordarone is absorbed in the stomach.
- **Avoid exposing your skin to the sun or sun lamps.** Cordarone Tablets can cause a photosensitive reaction. Wear sun-block cream or protective clothing when out in the sun.
- **Avoid pregnancy during treatment with Cordarone Tablets.** Cordarone can harm your unborn baby.
- **Do not breastfeed while taking Cordarone Tablets.** Cordarone passes into your milk and can harm your baby.

What are the possible or reasonably likely side effects of Cordarone Tablets?

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?"**

Some other serious side effects of Cordarone Tablets include:

- **vision problems that may lead to permanent blindness.** You should have regular eye exams before and during treatment with Cordarone Tablets. Call your doctor if you have blurred vision, see halos, or your eyes become sensitive to light.
- **nerve problems.** Cordarone Tablets can cause a feeling of "pins and needles" or numbness in the hands, legs, or feet, muscle weakness, uncontrolled movements, poor coordination, and trouble walking.
- **thyroid problems.** Cordarone Tablets can cause 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).
- **skin problems.** Cordarone Tablets can cause your skin to be more sensitive to the sun or to turn a bluish-gray color. In most patients, skin color slowly returns to normal after stopping Cordarone Tablets. In some patients, skin color does not return to normal.

Other side effects of Cordarone Tablets include nausea, vomiting, constipation, and loss of appetite.

Call your doctor about any side effect that bothers you.

These are not all the side effects with Cordarone Tablets. For more information, ask your doctor or pharmacist.

How should I store Cordarone Tablets?

- Store Cordarone Tablets at room temperature. Protect from light. Keep Cordarone Tablets in a tightly closed container.
- Safely dispose of Cordarone Tablets that are out-of-date or no longer needed.
- **Keep Cordarone Tablets and all medicines out of the reach of children.**

General information about Cordarone Tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Cordarone Tablets for a condition for which it was not prescribed. Do not share Cordarone with other people, even if they have the same symptoms that you have. It may harm them.

If you have any questions or concerns about Cordarone Tablets, ask your doctor or healthcare provider. This Medication Guide summarizes the most important information about Cordarone Tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Cordarone Tablets that was written for healthcare professionals.

This Medication Guide may have been revised after this copy was produced. For more information and the most current Medication Guide, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

What are the ingredients in Cordarone Tablets?

Active Ingredient: amiodarone HCl
Inactive Ingredients: colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and FD&C Red 40.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rx only

Manufactured for

Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101

by Sanofi Winthrop Industrie
1, rue de la Vierge
33440 Ambares, France

Last Revised: August 2004

[PPI number]

Based on Physician Insert W10427C005

Cordarone is a registered trademark of Sanofi-Synthelabo.

Tagamet is a registered trademark of SmithKline Beecham Pharmaceuticals Co.

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(End of medication guide)

In addition, the following subsection has been added to the **PRECAUTIONS** section of the package insert labeling:

> **Information for Patients**
> Patients should be instructed to read the accompanying Medication Guide each time they refill their prescription. The complete text of the Medication Guide is reprinted at the end of this document.

The carton and container labels have also been revised to add a reference to the medication guide.

Comments/Recommendations:

No other changes were noted in a line-by-line comparison of the revised package insert labeling with the last approved version (the addition of the reference to the medication guide in the **PRECAUTIONS** section is the only change).

The addition of the reference to the medication guide to the carton and container labels is acceptable to ODS.

An approval letter will be drafted for Dr. Stockbridge's signature.

/S/

Russell Fortney
Regulatory Health Project Manager

rf-11/24/04

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/s/

Russell Fortney
12/3/04 01:20:50 PM
CSO

Teleconference Minutes

Date:	May 5, 2004
Application	NDA 18,972
Drug:	Cordarone (amiodarone) Tablets
Sponsor:	Wyeth Pharmaceuticals
Date Requested:	April 28, 2004
Date Confirmed:	April 28, 2004
Briefing package received:	N/A
Purpose:	Discuss Progress of Medication Guide for Cordarone

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Russell Fortney	Regulatory Health Project Manager

Wyeth Pharmaceuticals Participants:

John J. Savarese, Ph.D.	Worldwide Regulatory Affairs
Anne Williamson, Pharm.D.	Global Labeling Division
Karen Riddick, M.S.	Global Labeling Division

Background:

Wyeth Pharmaceuticals is the owner of the NDA for Cordarone (amiodarone) Tablets. On December 19, 2003, the Agency issued a letter to Wyeth formally requesting the development of a Medication Guide for Cordarone. This teleconference was scheduled to discuss the timeline for the completion of the Medication Guide.

Teleconference:

Dr. Stockbridge asked the sponsor for an update on the development of the Medication Guide for Cordarone. The sponsor said that they have completed the first draft and expect to have a completed version in six months.

Dr. Stockbridge said that the Division has also been working on a version, and offered to share that version with the sponsor in order to expedite the process. The sponsor agreed to review the Division's version, and will consider completing the Medication Guide a priority.

Minutes preparation: /S/
Russell Fortney

Concurrence, Chair: /S/
Norman Stockbridge, M.D., Ph.D.

draft: 5/13/04 final: 5/13/04

reviewed: NS 5/13/04

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/s/

Russell Fortney
5/13/04 01:43:09 PM

Norman Stockbridge
5/13/04 05:28:11 PM

Teleconference Minutes

Date:	November 25, 2003
Application	NDA 18,972
Drug:	Cordarone (amiodarone) Tablets
Sponsor:	Wyeth Pharmaceuticals
Date Requested:	October 23, 2003
Date Confirmed:	October 23, 2003
Briefing package received:	N/A
Purpose:	Discussion of Medication Guide for Cordarone

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products
Mike Johnston, R.Ph.	Safety Evaluator, Office of Drug Safety
Russell Fortney	Regulatory Health Project Manager

Wyeth Pharmaceuticals Participants:

Diane Mitrione	Assistant Vice-President, Worldwide Regulatory Affairs
Dr. Brenda Cooperstone	Assistant Vice-President, Global Medical Affairs
Dr. Ajay Singh	Senior Director, Global Safety Surveillance and Epidemiology
Mora Harrison	Senior Coordinator, Worldwide Regulatory Affairs

Background:

Wyeth Pharmaceuticals is the owner of the NDA for Cordarone (amiodarone) Tablets. Recently, there has been discussion within the Agency of the potential need for a Medication Guide for amiodarone. This teleconference was scheduled to discuss the need for a Medication Guide for Cordarone.

Teleconference:

After introductions, Dr. Throckmorton said that despite efforts to strengthen the safety information in the Cordarone label, the Agency continues to receive complaints that patients feel they have not been adequately warned regarding the toxicities associated with amiodarone use. The Division, as well as more senior management within the Center, agree that a Medication Guide is an appropriate next step to provide patients with additional information to manage risk.

The sponsor asked that the Division provide and official request for a Medication Guide in writing. Dr. Throckmorton agreed to do that. The sponsor asked if the Agency has identified new toxicities that need to be addressed. Dr. Throckmorton said that the Medication Guide is not meant to describe new toxicities, rather it is meant to be another method of conveying the known toxicities to patients.

The sponsor said that they expect a Medication Guide to be quite lengthy because of litigation concerns. Dr. Throckmorton said he is sensitive to those concerns, and asked that the sponsor work with the Office of Drug Safety regarding the content and format of the Medication Guide. He said the first draft should be submitted to the Division of Cardio-Renal Drug Products and to the Office of Drug Safety.

The sponsor expressed a concern that they are being asked to develop the Medication Guide for the entire amiodarone market, Mr. Johnston agreed to investigate this issue for the sponsor.

The sponsor said they are concerned with using a Medication Guide to communicate directly with patients instead of going through a healthcare provider. Dr. Throckmorton said that the Medication Guide could encourage discussion with healthcare providers, while at the same time inform patients about serious safety concerns. He referred the sponsor to a current Medication Guide for bosentan, which is similarly formatted.

The sponsor said that they expect that they will have to hire outside contractors to develop the Medication Guide, and thus they expect that it will take a number of months to complete. Dr. Throckmorton said he understands the sponsor's position, but that he hopes to be able to work together in completing the Medication Guide in a reasonable time frame.

Minutes preparation: /S/
Russell Fortney

Concurrence, Chair: /S/
Douglas C. Throckmorton, M.D.

draft: 11/26/03 final: 12/2/03

reviewed:
M.Johnston-12/1/03
N.Stockbridge-12/2/03
D.Throckmorton-12/2/03

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/s/

Russell Fortney
12/2/03 12:37:20 PM

Doug Throckmorton
12/3/03 08:15:38 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-972

Wyeth Pharmaceuticals Inc.
Attention: Diane Mitrione
Assistant Vice President, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) 200 mg Tablets.

Thank you for agreeing to meet with the Division on November 25, 2003. During the meeting, we would like to discuss the general content and timelines for the creation of a Medication Guide for amiodarone, to provide important information to patients regarding its safe use in its approved indication.

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

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/s/

Doug Throckmorton
10/28/03 04:34:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-972

Wyeth Pharmaceuticals Inc.
Attention: Ms. Diane Mitrione
Assistant Vice President, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) 200 mg Tablets.

The Division of Cardio-Renal Drug Products is interested in working with you on a Medication Guide for Cordarone. The intent of such a Medication Guide would be to facilitate Cordarone's safe use by alerting patients to the need for appropriate physician monitoring while using amiodarone as well as informing patients about its observed toxicities. We invite you to discuss the format and content of a Medication Guide with the appropriate individuals within the Division of Cardio-Renal Drug Products, as well as the Office of Drug Safety, and request that you provide us an estimate as to the timeline for its completion.

If you have any questions, please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

{See appended electronic signature page}

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robert Temple
12/19/03 07:15:04 PM