CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18972/S019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 18-972/S-019
S-020

OCT 8 1999

Wyeth Laboratories
Attention: Ms. Roberta R. Acchione
170 North Radnor-Chester Road
St, David's, PA 19087-5221

Dear Ms. Acchione:

Please refer to your supplemental new drug applications dated August 27, 1998 (S-019) and December 23, 1998 (S-020), received August 28, 1998 and December 28, 1998, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets, 200 mg.

We acknowledge receipt of your submissions dated March 9 (S-020), May 3, July 14, and August 31, 1999 (S-019 and S-020).

Supplemental application 019 provides for final printed labeling revised to add a **Geriatric Use** subsection under **PRECAUTIONS** section of the labeling. In addition, revisions have been made in the **CLINICAL PHARMACOLOGY/Pharmacokinetics** subsection to bring Cordarone Tablet labeling into accord with the Cordarone I.V. labeling.

The changes in supplemental application 020 are contained in the same final printed labeling as 019 and provides for revised text under the **CLINICAL PHARMACOLOGY/ Pharmacokinetics** subsection and the **DOSAGE AND ADMINISTRATION** section to incorporate results of the effect of food on the oral administration of amiodarone.

The following changes in the labeling have been made:

1. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics,**

   a. The following has been added at the end of the first paragraph:

      Food increases the rate and extent of absorption of Cordarone. The effects of food upon the bioavailability of Cordarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (T_{max}) by 37%. The mean AUC and mean Cmax of desethylamiodarone increased by 55% (range 58 to 101%) and 32% (range 4 to 84%), respectively, but there was no change in the T_{max} in the presence of food.

b. The third and fourth sentences of the second paragraph in the **Pharmacokinetics** subsection have been deleted and replaced with three other sentences. This paragraph has been changed from:

to:

Cordarone has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of Cordarone, desethylamiodarone (DEA), has been identified in man; it accumulates to an even greater extent in almost all tissues. No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral Cordarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation.

c. The third paragraph of the **Pharmacokinetics** subsection has been changed from:

to: [redacted]

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable.

In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 mL/hr/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of intravenous amiodarone in cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower concentrations (about 100 ml/hr/kg) than younger subjects (about 150 ml/hr/kg) and an increase in $t_{1/2}$ from about 20 to 47 days.

In patients with severe left ventricular disposition the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition $t_{1/2}$ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

d. The following has been added at the beginning of the fifth paragraph:

Following single dose administration in 12 healthy subjects, Cordarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA).

2. Under **PRECAUTIONS**, a new Geriatric Use subsection has been added that states:

Geriatric Use
Clinical studies of Cordarone Tablets 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.

3. Following the second sentence of the second paragraph under **DOSAGE AND ADMINISTRATION**, the statement that "Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals (see '**Clinical Pharmacology**')" has been added. The second paragraph now states:

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Cordarone has not been determined. Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals (see "**Clinical Pharmacology**") Individual patient titration is suggested according to the following guidelines.

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 August 31, 1999 submission). Accordingly, these supplemental applications are 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.

NDA 18-972/S-019
S-020

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Project Manager
(301) 594-5311

Sincerely yours,

/S/ 10/8/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S019

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-972/S-019

JAN 12 1999

Wyeth Laboratories
Attention: Ms. Roberta R. Acchione
170 North Radnor-Chester Road
St. David's, PA 19087-5221

Dear Ms. Acchione:

Please refer to your supplemental new drug application dated August 27, 1998, received August 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets, 200 mg.

This supplement provides for draft labeling revised under **CLINICAL PHARMACOLOGY/ PHARMACOKINETICS** with text changes to bring Cordarone Tablet labeling into accord with the Cordarone I.V. label. A **Geriatric Use** subsection has been added to the **PRECAUTIONS** section of the labeling.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. The structural formula should be included under the **DESCRIPTION** section.

2. The **PRECAUTIONS/Geriatric Use** subsection should be changed from:

to:

Geriatric Use
Clinical studies of Cordarone Tablets 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.

Please consider a revised storage statement that reads as follows:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

/S/ 1/12/95

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment 3
WILLARD

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-972/S-020

FEB 12 1999

Wyeth-Ayerst Laboratories
Attention: Ms. Diana Mitrione
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your supplemental new drug application dated December 23, 1998, received December 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets.

We acknowledge receipt of your submissions dated January 15 and 21, 1999.

This supplemental application provides for draft labeling revised under **CLINICAL PHARMACOLOGY/ Pharmacokinetics** and **DOSAGE AND ADMINISTRATION** sections to incorporate results of the effect of food on the oral administration of amiodarone.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics,**

   a. The following statement should be changed from:

   [redacted]

   to:

   Food increases the rate and extent of absorption of Cordarone. The effects of food upon the bioavailability of Cordarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (Cmax) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (Tmax) by 37%. The AUC and Cmax of desethylamiodarone increased by 55% (range 58 to 101%) and 32% (range 4 to 84%), respectively, but there was no change in the Tmax in the presence of food.

b. The following statement should be changed from:

to:

> Following single dose administration in 12 healthy subjects, Cordarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA).

The following change proposed under **DOSAGE AND ADMINISTRATION** is acceptable:

1. Following the second sentence of the second paragraph the statement that "Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals. (see '**Clinical Pharmacology**')" has been added. The second paragraph now states:

> In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Cordarone has not been determined. Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals. (see "**Clinical Pharmacology**") Individual patient titration is suggested according to the following guidelines.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 18-972
HFD-110/Div. Files
HFD-95/DDMS
DISTRICT OFFICE
HFD-110/D.Willard;2/10/99
sb/2/8/99;2/11/99
Initialed by: E Fadiran/2/10/99
P Marroum/2/10/99
N Stockbridge/2/10/99
N Morgenstern/2/10/99
filename: 18972s020ae.doc

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S019

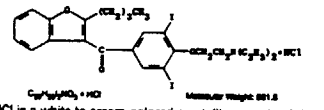
FINAL PRINTED LABELING

Cordarone®
(amiodarone HCl)
TABLETS

DESCRIPTION

Cordarone is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects, available for oral administration as pink, scored tablets containing 200 mg of amiodarone hydrochloride. The inactive ingredients present are colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and FD&C Red 40. Cordarone is a benzofuran derivative: 2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride. It is not chemically related to any other available antiarrhythmic drug.

The structural formula is as follows:



$C_{25}H_{29}I_2NO_3 \cdot HCl$ Molecular Weight: 681.8

Amiodarone HCl is a white to cream-colored crystalline powder. It is slightly soluble in water, soluble in alcohol, and freely soluble in chloroform. It contains 37.3% iodine by weight.

CLINICAL PHARMACOLOGY

Electrophysiology/Mechanisms of Action

In animals, Cordarone is effective in the prevention or suppression of experimentally-induced arrhythmias. The antiarrhythmic effect of Cordarone may be due to at least two major properties: 1) a prolongation of the myocardial cell-action potential duration and refractory period and 2) noncompetitive α- and β-adrenergic inhibition.

Cordarone prolongs the duration of the action potential of all cardiac fibers while causing minimal reduction of dV/dt (maximal upstroke velocity of the action potential). The refractory period is prolonged in all cardiac tissues. Cordarone increases the cardiac refractory period without influencing resting membrane potential, except in automatic cells where the slope of the prepotential is reduced, generally reducing automaticity. These electrophysiologic effects are reflected in a decreased sinus rate of 15 to 20%, increased PR and QT intervals of about 10%, the development of U-waves, and changes in T-wave contour. These changes should not require discontinuation of Cordarone as they are evidence of its pharmacological action, although Cordarone can cause marked sinus bradycardia or sinus arrest and heart block. On rare occasions, QT prolongation has been associated with worsening of arrhythmia (see **"WARNINGS"**).

Hemodynamics

In animal studies and after intravenous administration in man, Cordarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. After oral dosing, however, Cordarone produces no significant change in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF. After acute intravenous dosing in man, Cordarone may have a mild negative inotropic effect.

Pharmacokinetics

Following oral administration in man, Cordarone is slowly and variably absorbed. The bioavailability of Cordarone is approximately 50%, but has varied between 35 and 65% in various studies. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100 to 600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day. These means, however, include considerable individual variability. Food increases the rate and extent of absorption of Cordarone. The effects of food upon the bioavailability of Cordarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (T_{max}) by 37%. The mean AUC and mean C_{max} of desethylamiodarone increased by 55% (range 58 to 101%) and 32% (range 4 to 84%), respectively, but there was no change in the T_{max} in the presence of food.

Cordarone has a very large but variable volume of distribution, averaging about 66 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of Cordarone, desethylamiodarone (DEA), has been identified in man; it accumulates to an even greater extent in almost all tissues. No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral Cordarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation.

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable.

In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 ml/hr/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of intravenous amiodarone in cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower clearances (about 100 ml/hr/kg) than younger subjects (about 150 ml/hr/kg) and an increase in $t_{1/2}$ from about 20 to 47 days. In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition $t_{1/2}$ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

Following single dose administration in 12 healthy subjects, Cordarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA). In patients, following discontinuation of chronic oral therapy, Cordarone has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26 to 107 days, with a mean of approximately 53 days and most patients in the 40- to 55-day range. In the absence of a loading-dose period, steady-state plasma concentrations, at constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat.

The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of Cordarone should be based on individual patient requirements (see **"DOSAGE AND ADMINISTRATION"**).

Cordarone and its metabolite have a limited transplacental transfer of approximately 10 to 50%. The parent drug and its metabolite have been detected in breast milk.

Cordarone is highly protein-bound (approximately 96%).

Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of Cordarone, effects on abnormal rhythms are not seen before 2 to 3 days and usually require 1 to 3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods still. There is evidence that the time to effect is shorter when a loading-dose regimen is used.

Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after Cordarone is discontinued, but the time of recurrence is variable and unpredictable. In general, when the drug is resumed after recurrence of the arrhythmia, control is established relatively rapidly compared to the initial response, presumably because tissue stores were not wholly depleted at the time of recurrence.

Pharmacodynamics

There is no well-established relationship of plasma concentration to effectiveness, but it does appear that concentrations much below 1 mg/L are often ineffective and that levels above 2.5 mg/L are generally not needed. Within individuals dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control. Plasma-concentration measurements can be used to identify patients whose levels are unusually low, and who might benefit from a dose increase, or unusually high, and who might have dosage reduction in the hope of minimizing side effects. Some observations have suggested a plasma concentration, dose, or dose/duration relationship for side effects such as pulmonary fibrosis, liver-enzyme elevations, corneal deposits and facial pigmentation, peripheral neuropathy, gastrointestinal and central nervous system effects.

Monitoring Effectiveness

Predicting the effectiveness of any antiarrhythmic agent in long-term prevention of recurrent ventricular tachycardia and ventricular fibrillation is difficult and controversial, with highly qualified investigators recommending use of ambulatory monitoring, programmed electrical stimulation with various stimulation regimens, or a combination of these, to assess response. There is no present consensus on many aspects of how best to assess effectiveness, but there is a reasonable consensus on some aspects:

1. If a patient with a history of cardiac arrest does not manifest a hemodynamically unstable arrhythmia during electrocardiographic monitoring prior to treatment, assessment of the effectiveness of Cordarone requires some provocative approach, either exercise or programmed electrical stimulation (PES).
2. Whether provocation is also needed in patients who do manifest their life-threatening arrhythmia spontaneously is not settled, but there are reasons to consider PES or other provocation in such patients. In the fraction of patients whose PES-inducible arrhythmia can be made noninducible by Cordarone (a fraction that has varied widely in various series from less than 10% to almost 40%, perhaps due to different stimulation criteria), the prognosis has been almost uniformly excellent, with very low recurrence (ventricular tachycardia or sudden death) rates. More controversial is the meaning of continued inducibility. There has been an impression that continued inducibility in Cordarone patients may not foretell a poor prognosis but, in fact, many observers have found greater recurrence rates in patients who remain inducible than in those who do not. A number of criteria have been proposed, however, for identifying patients who remain inducible but who seem likely nonetheless to do well on Cordarone. These criteria include increased difficulty of induction (more stimuli or more rapid stimuli), which has been reported to predict a lower rate of recurrence, and ability to tolerate the induced ventricular tachycardia without severe symptoms, a finding that has been reported to correlate with better survival but not with lower recurrence rates. While these criteria require confirmation and further study in general, *easier* inducibility or *poorer* tolerance of the induced arrhythmia should suggest consideration of a need to revise treatment.

Several predictors of success not based on PES have also been suggested, including complete elimination of all nonsustained ventricular tachycardia on ambulatory monitoring and very low premature ventricular-beat rates (less than 1 VPB/1,000 normal beats).

While these issues remain unsettled for Cordarone, as for other agents, the prescriber of Cordarone should have access to (direct or through referral), and familiarity with, the full range of evaluatory procedures used in the care of patients with life-threatening arrhythmias.

It is difficult to describe the effectiveness rates of Cordarone, as these depend on the specific arrhythmia treated, the success criteria used, the underlying cardiac disease of the patient, the number of drugs tried before resorting to Cordarone, the duration of follow-up, the dose of Cordarone, the use of additional antiarrhythmic agents, and many other factors. As Cordarone has been studied principally in patients with refractory life-threatening ventricular arrhythmias, in whom drug therapy must be selected on the basis of response and cannot be assigned arbitrarily, randomized comparisons with other agents or placebo have not been possible. Reports of series of treated patients with a history of cardiac arrest and mean follow-up of one year or more have given mortality (due to arrhythmia) rates that were highly variable, ranging from less than 5% to over 30%, with most series in the range of 10 to 15%. Overall arrhythmia-recurrence rates (fatal and nonfatal) also were highly variable (and, as noted above, depended on response to PES and other measures), and depend on whether patients who do not seem to respond initially are included. In most cases, considering only patients who seemed to respond well enough to be placed on long-term treatment, recurrence rates have ranged from 20 to 40% in series with a mean follow-up of a year or more.

INDICATIONS AND USAGE

Because of its life-threatening side effects and the substantial management difficulties associated with its use (see **"WARNINGS"** below), Cordarone is indicated only for the treatment of the following documented, life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated.

1. Recurrent ventricular fibrillation
2. Recurrent hemodynamically unstable ventricular tachycardia

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of Cordarone favorably affects survival.

Cordarone should be used only by physicians familiar with and with access to (directly or through referral) the use of all available modalities for treating recurrent life-threatening ventricular arrhythmias, and who have access to appropriate monitoring facilities, including in-hospital and ambulatory continuous electrocardiographic monitoring and electrophysiologic techniques. Because of the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of the arrhythmia, initiation of therapy with Cordarone should be carried out in the hospital.

CONTRAINDICATIONS

Cordarone is contraindicated in severe sinus-node dysfunction, causing marked sinus bradycardia; second- and third-degree atrioventricular block; and when episodes of bradycardia have caused syncope (except when used in conjunction with a pacemaker).

Cordarone is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2 to 5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2 to 5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

Mortality

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

Cordarone therapy was evaluated in two multi-centered, randomized, double-blind, placebo-controlled trials involving 1202 (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial: CAMIAT) and 1486 (European Myocardial Infarction Amiodarone Trial: EMIAT) post-MI patients followed for up to 2 years. Patients in CAMIAT qualified with ventricular arrhythmias, and these randomized to amiodarone received weight- and response-adjusted doses of 200 to 400 mg/day. Patients in EMIAT qualified with ejection fraction <40%, and these randomized to amiodarone received fixed doses of 200 mg/day. Both studies had weeks-long loading dose schedules. Intent-to-treat all-cause mortality results were as follows:

	Placebo		Amiodarone		Relative Risk	
	N	Deaths	N	Deaths		95%CI
EMIAT	743	102	743	103	0.98	0.76-1.31
CAMIAT	596	68	606	57	0.68	0.58-1.16

These data are consistent with the results of a pooled analysis of smaller, controlled studies involving patients with structural heart disease (including myocardial infarction).

Pulmonary Toxicity

Cordarone may cause a clinical syndrome of cough and progressive dyspnea accompanied by functional, radiographic, gallium-scan, and pathological data consistent with pulmonary toxicity, the frequency of which varies from 2 to 7% in most published reports, but is as high as 10 to 17% in some reports. Therefore, when Cordarone therapy is initiated, a baseline chest X ray and pulmonary-function tests, including diffusion capacity, should be performed. The patient should return for a history, physical exam, and chest X ray every 3 to 6 months.

Preexisting pulmonary disease does not appear to increase the risk of developing pulmonary toxicity; however, these patients have a poorer prognosis if pulmonary toxicity does develop.

Pulmonary toxicity secondary to Cordarone seems to result from either indirect or direct toxicity as represented by hypersensitivity pneumonitis or interstitial/alveolar pneumonitis, respectively.

Hypersensitivity pneumonitis usually appears earlier in the course of therapy, and rechallenging these patients with Cordarone results in a more rapid recurrence of greater severity. Bronchoalveolar lavage is the procedure of choice to confirm this diagnosis, which can be made when a T suppressor/cytotoxic (CD8-positive) lymphocytosis is noted. Steroid therapy should be instituted and Cordarone therapy discontinued in these patients.

Interstitial/alveolar pneumonitis may result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), due to inhibition of phospholipase, will be present in most cases of Cordarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on Cordarone therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of Cordarone-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the Cordarone to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone-induced pulmonary toxicity was usually noted within the first week, and a clinical improvement was greatest in the first two to three weeks. Chest X ray changes usually resolve within two to four months. According to some experts, steroids may prove beneficial. Prednisone in doses of 40 to 60 mg/day or equivalent doses of other steroids have been given and tapered over the course of several weeks depending upon the condition of the patient. In some cases rechallenge with Cordarone at a lower dose has not resulted in return of toxicity. Recent reports suggest that the use of lower loading and maintenance doses of Cordarone are associated with a decreased incidence of Cordarone-induced pulmonary toxicity.

In a patient receiving Cordarone, any new respiratory symptoms should suggest the possibility of pulmonary toxicity, and the history, physical exam, chest X ray, and pulmonary-function tests (with -diffusion capacity) should be repeated and evaluated. A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as the decrease in diffusion capacity approaches 30%, the sensitivity decreases but the specificity increases. A gallium-scan also may be performed as part of the diagnostic workup.

Fatalities, secondary to pulmonary toxicity, have occurred in approximately 10% of cases. However, in patients with life-threatening arrhythmias, discontinuation of Cordarone therapy due to suspected drug-induced pulmonary toxicity should be undertaken with caution, as the most common cause of death in these patients is sudden cardiac death. Therefore, every effort should be made to rule out other causes of respiratory impairment (i.e., congestive heart failure with Swan-Ganz catheterization if necessary, respiratory infection, pulmonary embolism, malignancy, etc.) before discontinuing Cordarone in these patients. In addition, bronchoalveolar lavage, transbronchial lung biopsy and/or open lung biopsy may be necessary to confirm the diagnosis, especially in those cases where no acceptable alternative therapy is available.

If a diagnosis of Cordarone-induced hypersensitivity pneumonitis is made, Cordarone should be discontinued, and treatment with steroids should be instituted. If a diagnosis of Cordarone-induced interstitial/alveolar pneumonitis is made, steroid therapy should be instituted and, preferably, Cordarone discontinued or, at a minimum, reduced in dosage. Some cases of Cordarone-induced interstitial/alveolar pneumonitis may resolve following a reduction in Cordarone dosage in conjunction with the administration of steroids. In some patients, rechallenge at a lower dose has not resulted in return of interstitial/alveolar pneumonitis; however, in some patients (perhaps because of severe alveolar damage) the pulmonary lesions have not been reversible.

Worsened Arrhythmia

Cordarone, like other antiarrhythmics, can cause serious exacerbation of the presenting arrhythmia, a risk that may be enhanced by the presence of concomitant antiarrhythmics. Exacerbation has been reported in about 2 to 5% in most series, and has included new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia associated with QT prolongation (Torsade de Pointes). In addition, Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2 to 4% of patients.

Liver Injury

Elevations of hepatic enzyme levels are seen frequently in patients exposed to Cordarone and in most cases are asymptomatic. If the increase exceeds three times normal, or doubles in a patient with an elevated baseline, discontinuation of Cordarone or dosage reduction should be considered. In a few cases in which biopsy has been done, the histology has resembled that of alcoholic hepatitis or cirrhosis. Hepatic failure has been a rare cause of death in patients treated with Cordarone.

Loss of Vision

Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and/or neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. If symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral

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Tablets
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vision, prompt ophthalmic examination is recommended. Appearance of optic neuropathy and/or neuritis calls for re-evaluation of Cordarone® therapy. The risks and complications of antiarrhythmic therapy with Cordarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including fundoscopy and slit-lamp examination, is recommended during administration of Cordarone. (See "**ADVERSE REACTIONS**").

Neonatal Hypo- or Hyperthyroidism

Cordarone can cause fetal harm when administered to a pregnant woman. Although Cordarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If Cordarone is used during pregnancy, or if the patient becomes pregnant while taking Cordarone, the patient should be apprised of the potential hazard to the fetus.

In general, Cordarone should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus.

In pregnant rats and rabbits, amiodarone HCl in doses of 25 mg/kg/day (approximately 0.4 and 0.9 times, respectively, the maximum recommended human maintenance dose*) had no adverse effects on the fetus. In the rabbit, 75 mg/kg/day (approximately 2.7 times the maximum recommended human maintenance dose*) caused abortions in greater than 90% of the animals. In the rat, doses of 50 mg/kg/day or more were associated with slight displacement of the testes and an increased incidence of incomplete ossification of some skull and digital bones; at 100 mg/kg/day or more, fetal body weights were reduced; at 200 mg/kg/day, there was an increased incidence of fetal resorption. (These doses in the rat are approximately 0.8, 1.6 and 3.2 times the maximum recommended human maintenance dose.*) Adverse effects on fetal growth and survival also were noted in one of two strains of mice at a dose of 5 mg/kg/day (approximately 0.04 times the maximum recommended human maintenance dose*).

*600 mg in a 50 kg patient (doses compared on a body surface area basis)

PRECAUTIONS

Impairment of Vision

Optic Neuropathy and/or Neuritis

Cases of optic neuropathy and optic neuritis have been reported (see "**WARNINGS**").

Corneal Microdeposits

Corneal microdeposits appear in the majority of adults treated with Cordarone. They are usually discernible only by slit-lamp examination, but give rise to symptoms such as visual halos or blurred vision in as many as 10% of patients. Corneal microdeposits are reversible upon reduction of dose or termination of treatment. Asymptomatic microdeposits alone are not a reason to reduce dose or discontinue treatment (see "**ADVERSE REACTIONS**").

Neurologic

Chronic administration of oral amiodarone in rare instances may lead to the development of peripheral neuropathy that may resolve when amiodarone is discontinued, but this resolution has been slow and incomplete.

Photosensitivity

Cordarone has induced photosensitization in about 10% of patients; some protection may be afforded by the use of sun-barrier creams or protective clothing. During long-term treatment, a blue-gray discoloration of the exposed skin may occur. The risk may be increased in patients of fair complexion or those with excessive sun exposure, and may be related to cumulative dose and duration of therapy.

Thyroid Abnormalities

Cordarone inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine levels, decreased T_3 levels, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. It is also a potential source of large amounts of inorganic iodine. Because of its release of inorganic iodine, or perhaps for other reasons, Cordarone can cause either hypothyroidism or hyperthyroidism. Thyroid function should be monitored prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of the slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for several weeks or even months following Cordarone withdrawal.

Hypothyroidism has been reported in 2 to 4% of patients in most series, but in 8 to 10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Hypothyroidism is best managed by Cordarone dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue Cordarone in some patients.

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. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Hyperthyroidism is best identified by relevant clinical symptoms and signs, accompanied usually by abnormally elevated levels of serum T_3 RIA, and further elevations of serum T_4, and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of Cordarone. The institution of antithyroid drugs, β-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism. Experience with thyroid surgery in this setting is extremely limited, and this form of therapy runs the theoretical risk of inducing thyroid storm. Cordarone-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

Surgery

Volatile Anesthetic Agents: 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 effects of halogenated inhalational anesthetics.

Hypotension Postbypass: Rare occurrences of hypotension upon discontinuation of cardiopulmonary bypass during open-heart surgery in patients receiving Cordarone have been reported. The relationship of this event to Cordarone therapy is unknown.

Adult Respiratory Distress Syndrome (ARDS): Postoperatively, occurrences of ARDS have been reported in patients receiving 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.

Laboratory Tests

Elevations in liver enzymes (SGOT and SGPT) can occur. Liver enzymes in patients on relatively high maintenance doses should be monitored on a regular basis. Persistent significant elevations in the liver enzymes or hepatomegaly should alert the physician to consider reducing the maintenance dose of Cordarone or discontinuing therapy.

Cordarone alters the results of thyroid-function tests, causing an increase in serum T_4 and serum reverse T_3, and a decline in serum T_3 levels. Despite these biochemical changes, most patients remain clinically euthyroid.

Drug Interactions

Although only a small number of drug-drug interactions with Cordarone have been explored formally, most of these have shown such an interaction. The potential for other interactions should be anticipated, particularly for drugs with potentially serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured.

In view of the long and variable half-life of Cordarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of Cordarone.

Cyclosporine

Concomitant use of amiodarone and cyclosporine has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

Digitalis

Administration of Cordarone to patients receiving digoxin therapy regularly results in an increase in the serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. **On initiation of Cordarone, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.

Anticoagulants

Potentiation of warfarin-type anticoagulant response is almost always seen in patients receiving Cordarone and can result in serious or fatal bleeding. **The dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

Antiarrhythmic Agents

Other antiarrhythmic drugs, such as quinidine, procainamide, disopyramide, and phenytoin, have been used concurrently with Cordarone.

There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with Cordarone. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring.

In general, combination of Cordarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to Cordarone. During transfer to Cordarone the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of Cordarone, when arrhythmia suppression should be beginning. The continued need for the other antiarrhythmic agent should be reviewed after the effects of Cordarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as Cordarone is continued. In Cordarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Cordarone should be used with caution in patients receiving β-blocking agents or calcium antagonists because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, Cordarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

Volatile Anesthetic Agents (See "**PRECAUTIONS**, **Surgery**, *Volatile Anesthetic Agents.*")

SUMMARY OF DRUG INTERACTIONS WITH CORDARONE

Concomitant Drug	Interaction: Onset (days)	Interaction: Magnitude	Recommended Dose Reduction of Concomitant Drug
Warfarin	3 to 4	increases prothrombin time by 100%	↓ 1/3 to 1/2
Digoxin	1	increases serum concentration by 70%	↓ 1/2
Quinidine	2	increases serum concentration by 33%	↓ 1/3 to 1/2 (or discontinue)
Procainamide	<7	increases plasma concentration by 55%; NAPA* concentration by 33%	↓ 1/3 (or discontinue)

*NAPA = n-acetyl procainamide.

Electrolyte Disturbances
Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting Cordarone therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Amiodarone HCl was associated with a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control 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 (Ames, micronucleus, and lysogenic tests) with Cordarone were negative.
In a study in which amiodarone HCl was 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 (dose compared on a body surface area basis)

Pregnancy: Pregnancy Category D
See **"WARNINGS, Neonatal Hypo- or Hyperthyroidism."**

Labor and Delivery
It is not known whether the use of Cordarone during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect of Cordarone on the duration of gestation or on parturition.

Nursing Mothers
Cordarone is excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered Cordarone have been shown to be less viable and have reduced body-weight gains. Therefore, when Cordarone therapy is indicated, the mother should be advised to discontinue nursing.

Pediatric Use
The safety and effectiveness of Cordarone in pediatric patients have not been established.

Geriatric Use
Clinical studies of Cordarone Tablets 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.

ADVERSE REACTIONS

Adverse reactions have been very common in virtually all series of patients treated with Cordarone for ventricular arrhythmias with relatively large doses of drug (400 mg/day and above), occurring in about three-fourths of all patients and causing discontinuation in 7 to 18%. The most serious reactions are pulmonary toxicity, exacerbation of arrhythmia, and rare serious liver injury (see **"WARNINGS"**), but other adverse effects constitute important problems. They are often reversible with dose reduction or cessation of Cordarone treatment. Most of the adverse effects appear to become more frequent with continued treatment beyond six months, although rates appear to remain relatively constant beyond one year. The time and dose relationships of adverse effects are under continued study.
Neurologic problems are extremely common, occurring in 20 to 40% of patients and including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy; they are rarely a reason to stop therapy and may respond to dose reductions or discontinuation (see **"PRECAUTIONS"**).
Gastrointestinal complaints, most commonly nausea, vomiting, constipation, and anorexia, occur in about 25% of patients but rarely require discontinuation of drug. These commonly occur during high-dose administration (i.e., loading dose) and usually respond to dose reduction or divided doses.
Ophthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness, papilledema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities, and macular degeneration have been reported. (See **"WARNINGS."**)
Asymptomatic corneal microdeposits are present in virtually all adult patients who have been on drug for more than 6 months. Some patients develop eye symptoms of halos, photophobia, and dry eyes. Vision is rarely affected and drug discontinuation is rarely needed.
Dermatological adverse reactions occur in about 15% of patients, with photosensitivity being most common (about 10%). Sunscreen and protection from sun exposure may be helpful, and drug discontinuation is not usually necessary.
Prolonged exposure to Cordarone occasionally results in a blue-gray pigmentation. This is slowly and occasionally incompletely reversible on discontinuation of drug but is of cosmetic importance only.
Cardiovascular adverse reactions, other than exacerbation of the arrhythmias, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dosage reduction but may require a pacemaker for control. CHF rarely requires drug discontinuation. Cardiac conduction abnormalities occur infrequently and are reversible on discontinuation of drug.
Hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudotumor cerebri, thrombocytopenia, angioedema, bronchiolitis obliterans organizing pneumonia (possibly fatal), pleuritis, pancreatitis, toxic epidermal necrolysis, pancytopenia, and neutropenia also have been reported in patients receiving Cordarone.
The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

The following side effects were each reported in 10 to 33% of patients:
Gastrointestinal: Nausea and vomiting.

The following side effects were each reported in 4 to 9% of patients:
Dermatologic: Solar dermatitis/photosensitivity.
Neurologic: Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias.
Gastrointestinal: Constipation, anorexia.
Ophthalmologic: Visual disturbances.
Hepatic: Abnormal liver-function tests.
Respiratory: Pulmonary inflammation or fibrosis.

The following side effects were each reported in 1 to 3% of patients:
Thyroid: Hypothyroidism, hyperthyroidism.
Neurologic: Decreased libido, insomnia, headache, sleep disturbances.
Cardiovascular: Congestive heart failure, cardiac arrhythmias, SA node dysfunction.
Gastrointestinal: Abdominal pain.
Hepatic: Nonspecific hepatic disorders.
Other: Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

The following side effects were each reported in less than 1% of patients:
Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities.
In surveys of almost 5,000 patients treated in open U.S. studies and in published reports of treatment with Cordarone, the adverse reactions most frequently requiring discontinuation of Cordarone included pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, congestive heart failure, and elevation of liver enzymes. Other symptoms causing discontinuations less often included visual disturbances, solar dermatitis, blue skin discoloration, hyperthyroidism, and hypothyroidism.

OVERDOSAGE

There have been a few reported cases of Cordarone overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. The acute oral LD_{50} of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.
In addition to general supportive measures, the patient's cardiac rhythm and blood pressure should be monitored, and if bradycardia ensues, a β-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither Cordarone nor its metabolite is dialyzable.

DOSAGE AND ADMINISTRATION

BECAUSE OF THE UNIQUE PHARMACOKINETIC PROPERTIES, DIFFICULT DOSING SCHEDULE, AND SEVERITY OF THE SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, CORDARONE SHOULD BE ADMINISTERED ONLY BY PHYSICIANS WHO ARE EXPERIENCED IN THE TREATMENT OF LIFE-THREATENING ARRHYTHMIAS WHO ARE THOROUGHLY FAMILIAR WITH THE RISKS AND BENEFITS OF CORDARONE THERAPY, AND WHO HAVE ACCESS TO LABORATORY FACILITIES CAPABLE OF ADEQUATELY MONITORING THE EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT.
In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Cordarone has not been determined. Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals (see **"CLINICAL PHARMACOLOGY"**). Individual patient titration is suggested according to the following guidelines.
For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia: Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1,600 mg/day are required for 1 to 3 weeks (occasionally longer) until initial therapeutic response occurs. (Administration of Cordarone in divided doses with meals is suggested for total daily doses of 1,000 mg or higher, or when gastrointestinal intolerance occurs.) If side effects become excessive, the dose should be reduced. Elimination of recurrence of ventricular fibrillation and tachycardia usually occurs within 1 to 3 weeks, along with reduction in complex and total ventricular ectopic beats.
Upon starting Cordarone therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs (see section on **"Drug Interactions"**). When adequate arrhythmia control is achieved, or if side effects become prominent, Cordarone dose should be reduced to 600 to 800 mg/day for one month and then to the maintenance dose, usually 400 mg/day (see **"CLINICAL PHARMACOLOGY–Monitoring Effectiveness"**). Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses. Cordarone may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a b.i.d. dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation and by patient tolerance. Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity (see **"CLINICAL PHARMACOLOGY"**).
The lowest effective dose should be used to prevent the occurrence of side effects. In all instances, the physician must be guided by the severity of the individual patient's arrhythmia and response to therapy.
When dosage adjustments are necessary, the patient should be closely monitored for an extended period of time because of the long and variable half-life of Cordarone and the difficulty in predicting the time required to attain a new steady-state level of drug. Dosage suggestions are summarized below:

	Loading Dose (Daily)	Adjustment and Maintenance Dose (Daily)	
Ventricular Arrhythmias	1 to 3 weeks	~1 month	usual maintenance
	800 to 1,600 mg	600 to 800 mg	400 mg

HOW SUPPLIED

Cordarone® (amiodarone HCl) Tablets are available in bottles of 60 tablets and in Redipak® cartons containing 100 tablets (10 blister strips of 10) as follows:
200 mg, NDC 0008-4188, round, convex-faced, pink tablets with a raised "C" and marked "200" on one side, with reverse side scored and marked "WYETH" and "4188."

Keep tightly closed.
Store at room temperature, approximately 25°C (77°F).
Protect from light.
Dispense in a light-resistant, tight container.
Use carton to protect contents from light.

℞ only

Manufactured for
Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

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

CI 6036-1 Issued August 26,1999 Printed in USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S019

CHEMISTRY REVIEW(S)

SEP 7 1999

CHEMIST'S REVIEW	1.ORGANIZATION HFD-110	2. NDA Number 18-972
3. Name and Address of Applicant (City & State) Wyeth-Ayerst Research. P.O. Box-8299 Philadelphia, PA 19101-8299		4. Supplement(s) Number(s) Date(s) SLR-019 & SLR-020 (AF) 8/31/99
5. Drug Name Cordarone	6. Nonproprietary Name Amiodarone hydrochloride	8. Amendments & Other (reports, etc) Dates
7. Supplement Provides For: Final printed labeling.		
9. Pharmacological Category Antiarrhythmic	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablet (pink)	13. Potency(ies) 200 mg	
14. Chemical Name and Structure 2-Butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments:

Insert - Cl 6036-1 Issued August 26, 1999 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	September 3, 1999

Distribution: [ ] Original Jacket [ ] Reviewer [X] Division File [ ] CSO

18972S20.AM2

/S/
9-3-99

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AUG - 6

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 18-972
3. Name and Address of Applicant (City & State) Wyeth Laboratories 170 North Radnor-Chester Rd. St. Davids, PA 19087-5221		4. Supplement(s) Number(s) Date(s) SLR-019 (AF) & SLR-020 (AF) 5/3/99
5. Drug Name Cordarone	6. Nonproprietary Name Amiodarone hydrochloride	8. Amendments & Other (reports, etc) - Dates SLR-019(BF) & SLR-020(BF) 7/14/99
7. Supplement Provides For: Final printed labeling.		
9. Pharmacological Category Antiarrhythmic	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablet (pink)	13. Potency(ies) - 200 mg	
14. Chemical Name and Structure 2-Butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Insert - Cl 6036-1 Issued June 7, 1999 - satisfactory for DESCRIPTION and HOW SUPPLIED sections. (It has the molecular formula and molecular weight written underneath the structural formula.)

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	July 20, 1999

Distribution: ☐ Original Jacket ☐ Reviewer ☒ Division File ☐ CSO

18972S20.AM1

/S/
8-5-99

MAY 25 1999

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 18-972
3. Name and Address of Applicant (City & State) Wyeth Laboratories 170 North Radnor-Chester Rd. St. Davids, PA 19087-5221		4. Supplement(s) Number(s) Date(s) SLR-019(AF) & SLR-020(AF) 5/3/99
5. Drug Name Cordarone	6. Nonproprietary Name Amiodarone hydrochloride	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Final printed labeling.		
9. Pharmacological Category Antiarrhythmic	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablet (pink)	13. Potency(ies) 200 mg	
14. Chemical Name and Structure 2-Butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Attachment 1 - contained summary of the labeling changes proposed en each supplement.
Attachment 2a-2d - copies of the reference documents cited in the labeling change summary.
Attachment 3 - one sample of mounted FPL.
Attachment 4 - word-processor copy of the FPL illustrating by shading or strike-out the changes that are reflected in the FPL.
Attachment 5 - one copy of the currently approved labeling.

Insert - C1-6036-1 Issued April 28, 1999 - satisfactory for DESCRIPTION and HOW SUPPLIED section. (The company retained the historic storage temperature statement. Reason is presented under S-019).

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER		
Name Danute G. Cunningham	Signature /S/	Date Completed May 11, 1999

Distribution: ☐ Original Jacket ☐ Reviewer ☒ Division File ☐ CSO

18972S20.SUP

/S/
5-24-99

DF

OCT 23 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 18-972
3. Name and Address of Applicant (City & State) Wyeth Laboratories 170 North Radnor-Chester Rd. St. Davids, PA 19087-5221		4. Supplement(s) Number(s) Date(s) SLR-019 8/27/98
5. Drug Name Cordarone	6. Nonproprietary Name Amiodarone hydrochloride	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Geriatric labeling supplement.		
9. Pharmacological Category Antiarrhythmic	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablet (pink)	13. Potency(ies) 200 mg	
14. Chemical Name and Structure 2-Butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments:

Added to the labeling Geriatric Use subsection in PRECAUTIONS section. Additional text changes appear in the CLINICAL PHARMACOLOGY section Pharmacokinetics subsection.

No changes were made in DESCRIPTION and HOW SUPPLIED sections. DESCRIPTION section - satisfactory. Please consider revision of the storage statement to: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION section. HOW SUPPLIED section request the firm to consider the statement as above.

18. REVIEWER		
Name Danute G. Cunningham	Signature /S/	Date Completed September 3, 1998
Distribution: [ ] Original Jacket [ ] Reviewer [X] Division File [ ] CSO		

18972S19.SUP

/S/ 10-22-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S019

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 21 1999 C-020 DF

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 18-972 (SNC to B006 , B007 & B008) **SUBMISSION DATE: October 23, 1998**
Cordarone® (Amiodarone HCL) Tablets **December 23, 1998**
January 15, 1999
January 21, 1999

Wyeth-Ayerst Research **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: FOOD EFFECT STUDY REPORT

BACKGROUND:
Amiodarone is a class III antiarrhythmic used in the treatment of angina pectoris and cardiac arrhythmias. The sponsor has conducted a food effect study on the bioavailability of amiodarone and has submitted the report as well as a labeling up-date based on the results of the study. The sponsor has also requested a meeting with the Agency to discuss the effect of food on the oral administration of amiodarone (meeting scheduled for 02/05/99).

SYNOPSIS:
This was an open-label, single-dose, randomized, two-period, crossover study in 30 healthy volunteers and a washout period of 9 weeks. Each subject received 600 mg amiodarone (3 x 200 mg Cordarone tablet) under fasting and fed conditions.
Administration of Cordarone tablets with a high-fat meal resulted in: (i) 3.7 fold increase (2.7 – 4.4 fold range) in Cmax and 2.3-fold increase (1.7 – 3.6 fold range) in the AUC_{0-t} of amiodarone; (ii) a decrease in the Tmax of amiodarone from 7.1 to 4.5 hours; (iii) a 32% increase (range 4 – 84%) in the Cmax and 55% increase (range 58 – 101%) in the AUC_{0-t} of desethylamiodarone (DEA) but no change in the Tmax of DEA. The half-life (Mean ± SD) of amiodarone is 58 ± 43 days (range 15-142 days) while that of DEA is 36 ± 19 days (range 14-75 days).
A summary of the review of the preliminary report and the proposed labeling submitted by the sponsor are attached.

COMMENTS ~~TO~~ BE SENT TO THE SPONSOR:
1. Labeling comments: Recommendations for labeling up-date

Clinical Pharmacology Section, Pharmacokinetic Sub-Section:

The above statement should be changed to:

"Food increases the rate and extent of absorption of Cordarone. The effects of food upon the bioavailability of Cordarone have been studied in thirty healthy subjects who received a single 600 mg dose immediately after consuming a *high fat* meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (Cmax) of amiodarone *increased* by as 2.3 *(range 1.7 to 3.6)* and 3.8 *(range 2.7 to 4.4)* times respectively, in the presence of food. Food also increased the rate of absorption *of amiodarone*, decreasing the time to peak plasma concentration (Tmax) by 37%. The *AUC and Cmax of desethylamiodarone (DEA) increased by 55% (range 58 to 101%) and 32% (range 4 to 84%) respectively but there was no change in the Tmax, in the presence of food".*

Clinical Pharmacology Section, Pharmacokinetic Sub-Section:

The above statement should be changed to:
"Following single dose administration in *twelve* healthy subjects, Cordarone exhibits multi-compartmental pharmacokinetics with mean apparent plasma terminal elimination half-life of 58 days *(range 15 to 142 days)* for *amiodarone and 36 days (range 14 to 75 days)* for the active metabolite *(DEA)".*

Dosage and Administration Section

"In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Cordarone has not been determined. Because of the food effect on the absorption of Cordarone, administration of Cordarone should be consistent with regard to meals. (see "**Clinical Pharmacology**") Individual patient titration is suggested according to the following guidelines."

The above proposed statement for dosage and administration is acceptable.

RECOMMEDATION:
The Division of Pharmaceutical Evaluation I has reviewed the sponsor's report of the amiodarone food effect study and recommends that the labeling for Cordarone Tablets should be up-dated with the results of this study. Please, forward the above comments to the sponsor.

CONCLUSION:

The above comments should be incorporated into the sponsor's proposed labeling up-date for Cordarone Tablets.

/S/ 1/26/99

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by P. Marroum, Ph.D. /S/ 1/27/1999

cc: NDA 18-972, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy)

FOOD EFFECT STUDY

PROTOCOL 585B1-104-CA

INVESTIGATOR AND LOCATION:

STUDY DATE: March to October 1998

STUDY OBJECTIVE: To compare the oral bioavailability of Cordarone tablets in the fed and fasting states, and to more clearly define the terminal disposition half-lives of the drug and its major active metabolite, desthylamiodarone (DEA).

DRUG ADMINISTRATION:
200 mg Cordarone tablets, Lot # 9961595

STUDY DESIGN:
This was an open-label, single-dose, randomized, two-period, crossover study in 30 healthy volunteers and a washout period of 9 weeks. Each subject received 600 mg amiodarone (3 x 200 mg Cordarone tablet) under fasting and fed conditions (after ingestion of a standard high-fat breakfast). Blood samples (sufficient to yield 3ml of plasma) were collected from each subject at 0 (baseline, just prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, 168, 336, 504, 672, 840, and 1008 hours post dosing with study drug. Additional samples were collected from a subgroup of 12 subjects throughout the 9-week washout interval at 0 hour on days 53, 63, 73, 83, 93, and 103.
The high fat meal consisted of 2 eggs fried in butter, 2 pieces of bacon, 2 pieces of toast with butter, 4 ounces of hashed brown potatoes cooked in butter and 8 ounces of whole milk.

ASSAYS:

DATA ANALYSIS:
Plasma concentrations were used to determine pharmacokinetic parameters (AUC, Cmax, Tmax, and Kel).

RESULTS: Tables 1-2 and Figures 1-2 summarize the pharmacokinetic data obtained from the study.

Table 1:

SINGLE-DOSE PHARMACOKINETIC PROFILES OF AMIODARONE AND DEA IN 30 SUBJECTS RECEIVING 3×200-MG CORDARONE TABLES WITH AND WITHOUT A HIGH-FAT MEAL [a]

Treatment	C_{max} (ng/mL)[b]		t_{max} (h)[b]		AUC_T (ng·h/mL)[b]	
	Amiodarone	DEA	Amiodarone	DEA	Amiodarone	DEA
Fasting	380±196 (346)	75.8±25.6 (71.7)	7.1±1.4	17±17	14024±5923 (13138)	17698±5254 (17018)
Fed	1402±583 (1305)	99.7±21.2 (97.6)	4.5±1.3	16±11	32951±10990 (31507)	27468±6643 (26789)
Treatment p-values from an analysis of variance for two-period crossover						
p-Value	<0.001	<0.001	<0.001	0.825	<0.001	<0.001
Ratios of Means and 90% Confidence Intervals (C.I.) [c]						
Ratio of means	376%	136%	63%	96%	239%	157%
90% C.I.	332-426%	123-150%	56-71%	69-124%	218-263%	143-172%

[a] Mean ± SD (geometric mean)
[b] The estimates were obtained based on the amiodarone and DEA concentration-time data at 0 through 1008 hours.
[c] The 90% confidence intervals about the ratio of the fed-to-fasting means were calculated using the least squares means from the analysis of variance.

Table 2: Half-lives of amiodarone and DEA

	Mean ±SD (Days)	Range (Days)
Amiodarone	58 ± 43	15 - 142
DEA	36 ± 19	14 - 75

Figure 1

Mean±SE of Plasma Concentrations of Amiodarone in Normal Subjects Receiving a 600-mg Dose of Cordarone in the Fed and Fasting States

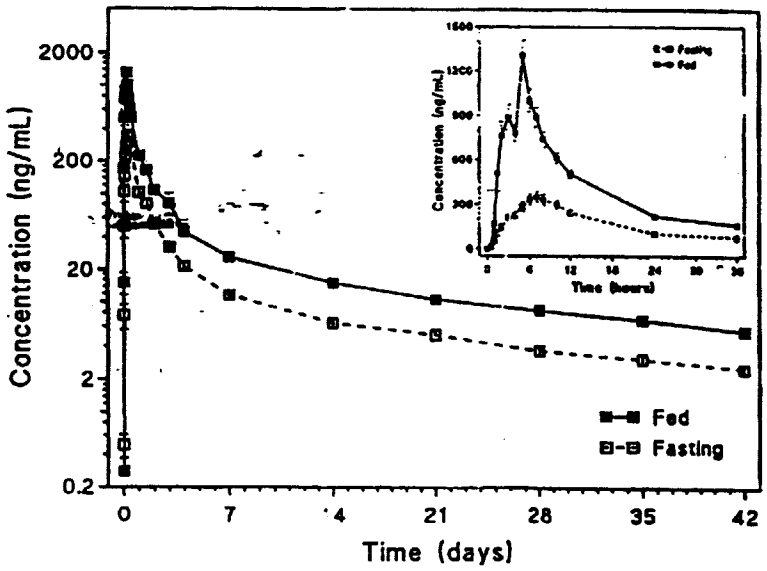
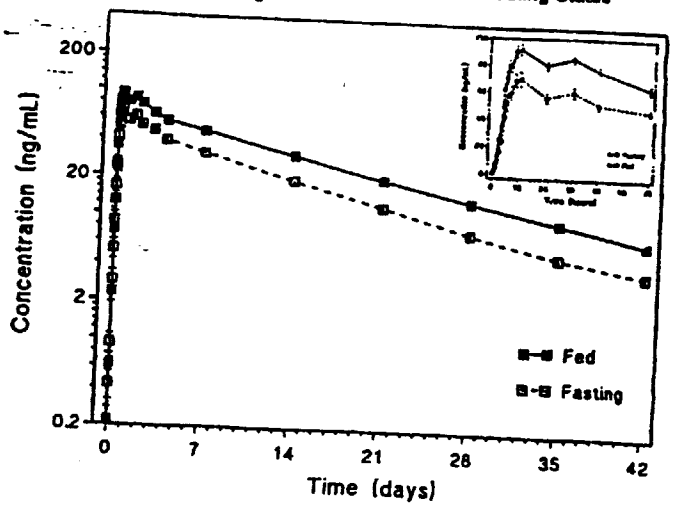


Figure 2

Mean±SE of Plasma Concentrations of DEA in Normal Subjects Receiving a 600-mg Dose of Cordarone in the Fed and Fasting States



CONCLUSIONS:

Administration of Cordarone tablets with a high-fat meal resulted in: (i) 3.7 fold increase (2.7 – 4.4 fold range) in Cmax and 2.3-fold increase (1.7 – 3.6 fold range) in the AUC_{0-t} of amiodarone; (ii) a decrease in the Tmax of amiodarone from 7.1 to 4.5 hours; (iii) a 32% increase (range 4 – 84%) in the Cmax and 55% increase (range 58 – 101%) in the AUC_{0-t} of desethylamiodarone (DEA) but no change in the Tmax of DEA. The half-life (Mean ± SD) of amiodarone is 58 ± 43 days (range 15-142 days) while that of DEA is 36 ± 19 days (range 14-75 days).

The labeling for Cordarone Tablets should be up-dated with the results of this study.

DF

DEC - 7 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA: 18972
Cordarone® Tablets, SLR-019
Wyeth-Ayerst Research

Submission Date: August 27, 1998

Reviewer: Gabriel J. Robbie

Type of Submission: This is a geriatric labeling supplement for Cordarone® (amiodarone hydrochloride) tablets

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BACKGROUND:

Cordarone® tablets contain 200 mg of amiodarone hydrochloride intended for use as an antiarrhythmic. The sponsor intends to revise the existing information on pharmacokinetics and also incorporate information pertaining to Cordarone® use in geriatric population in compliance with the Final Rule published in the Federal Register (August 27, 1998) requiring geriatric labeling information.

AMENDMENT:

The existing information under "Pharmacokinetics" in the CLINICAL PHARMACOLOGY, which the sponsor intends to delete is italicized, and the revised information is in presented in Bold.

The pharmacological activity of this metabolite, however, is not known. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one.

The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. However, its kinetics in patients with hepatic insufficiency have not been elucidated. Cordarone has a very low plasma clearance with negligible renal excretion, so that it does not appear necessary to modify the dose in patients with renal failure. In patients with renal impairment, the plasma concentration of Cordarone is not elevated. Neither Cordarone nor its metabolite is dialyzable.

No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral Cordarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation.

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable.

In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 ml/hr/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA.

Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of intravenous amiodarone in cirrhotic patients, significantly lower Cmax and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower clearances (about 100 ml/hr/kg) than younger subjects (about 150 ml/hr/kg) and an increase in t1/2 from about 20 to 47 days. In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition t1/2 of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

The sponsor also intends to incorporate the following information under GERIATRIC USE.

GERIATRIC USE

Clinical studies of Cordarone were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients; however, greater sensitivity to Cordarone cannot be ruled out.

Age does not appear to have a clinically significant effect on amiodarone pharmacokinetics. Elimination half-life may be prolonged in the elderly. (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, do not appear to have a clinically significant effect on amiodarone pharmacokinetics (see "CLINICAL PHARMACOLOGY, Pharmacokinetics"). Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients. The lowest effective dose should be used to prevent the occurrence of side effects (see **"DOSAGE AND ADMINISTRATION"**).

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics finds the proposed amendments to GERIATRIC USE and CLINICAL PHARMACOLOGY sections of the label acceptable. The medical officer is requested to review the efficacy and safety aspects of the GERIATRIC USE section of the label

/S/ Robbie 12/7/98

Gabriel J. Robbie, Ph. D.

RD/FT by Patrick J. Marroum, Ph. D. /S/ 12/7/1998

Cc: NDA 18972, HFD 110, HFD 860 (Robbie), CDER document room: Attn: Barbara Murphy

DF

D. Willard

JUN 17 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:18-972
Submission Date: 5/1/97
Amiodarone HCl (CORDARONE) Tablets, 200 mg
Sponsor: Wyeth Ayerst
Reviewer: Ameeta Parekh, Ph.D.
Type of Submission: Consult on rationale for ANDA BE study with food

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Background: Amiodarone is a Class III antiarrhythmic which is slightly soluble in water. Cordarone oral tablets are available as scored 200 mg tablets. Loading doses of 800-1600 mg/day are recommended until initial therapeutic response occurs; once this is achieved, the dose is recommended to be gradually reduced to a lower maintenance dose (600 mg or 400 mg/day, depending on patient response). Administration of Cordarone in divided doses with meals is suggested for total daily doses of 1000 mg or higher or when GI intolerance occurs. Information on magnitude of pharmacokinetic change upon coadministration with meals is not available from either the labeling or the original NDA review document (review 2/88 by Medical Reviewer; review not undertaken by Division of Biopharmaceutics).

Plasma concentrations for patients on amiodarone are useful in evaluating nonresponsiveness or unexpectedly severe toxicity. Both, amiodarone and its des-methyl metabolite contribute significantly to the antiarrhythmic activity. Due to the long t1/2 (ranging from 26-107 days for parent and about 61 days for metabolite), the effect is not instantaneous and long term monitoring is needed to individually stabilize patients to safe and effective doses. Generally, plasma concentrations between 1-2.5 ug/ml are considered effective (trough concentrations above 2 ug/ml showed a significant reduction in PVCs as compared to lower trough levels).

In the email sent to Dr. Lipicky by Dr. Mhatre of Division of Bioequivalence (DOB), a scientific opinion was requested regarding the need for comparable food-effects on pharmacokinetics of generic and reference products. The current practice of DOB is to require a fasted bioequivalence study for approval of ANDAs. Studies under fed conditions are required based on information in the innovator labeling regarding food-effects and administration. DOB states the following reasons for not requiring comparison of innovator and ANDA products under fed conditions:

1. Length of washout periods required between treatments due to long t1/2 of drug and metabolite

2. Toxicity shown by relatively large doses (400 mg/day and above)

3. Need for close monitoring of patients during loading doses.

DOB has received an ANDA with a food-effect study that shows almost doubling of AUC and Cmax for amiodarone when taken with meals. Metabolite levels were comparable. There were no adverse events reported.

Recommendation: (Discussed with Dr. Stockbridge, Medical Officer, on 5/23/97). Comment 1 pertains to the rationale for ANDA study with food, Comment 2 is a suggestion for request for data from the NDA sponsor:

1. Based on the analysis of plasma concentration relation to side effects, it appears (from the medical review) that:

- Adverse events are more common when plasma levels are maintained for a prolonged duration (18 months to 2 years). There is, however, considerable overlap of plasma concentrations between patients with and without adverse events.

- It seems prudent to assure same or similar plasma profiles under switchability situations, e.g. when a patient has been titrated up to a dose to achieve an individualized steady state plasma level for control of arrhythmia using the reference drug (whether the patient is taking it with meals or without), and the patient is switched to another formulation (generic).

Since higher doses are to be in divided daily doses and likely to be taken with meals, assurance of similarity should be considered for drug approval. Confirming similarity with meals, in addition to standard fasted BE study, will assure switchability for multi-source formulations.

2. The NDA sponsor should be requested to provide information on food-effect for their product. If not available, the label should state so.

/S/

Ameeta Parekh, PhD. 6/17/97
DPE1/OCPB

FT Initialed by Patrick Marroum, Ph.D. P.M. 6/17/1997
cc: NDA 18-972, HFD-110 (Willard), HFD-860 (Parekh), CDR (Attn. Barbara Murphy), HFD-340 (Vish)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S019

ADMINISTRATIVE DOCUMENTS

OCT 8 1999

RHPM Review of Final Printed Labeling
NDA 18-972/S-019 and S-020

Sponsor: Wyeth Laboratories

Product: Cordarone (amiodarone HCl) Tablets, 200 mg

Submission Date: August 31, 1999

Receipt Date: September 1, 1999

Type of Submission: Final Printed Labeling

Background:

Supplement 019

Supplement 019 provides for information regarding the use of Cordarone Tablets in the geriatric population. It was submitted on August 27, 1998 in response to a Federal Register Notice of August 27, 1997 that amended the regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and over) and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling. Additionally, revisions were made in the **CLINICAL PHARMACOLOGY/Pharmacokinetics** subsection "to bring the Tablet insert into accord with the I.V. product labeling."

An approvable letter issued January 12, 1999 (Attachment 1) requesting revisions under the **DESCRIPTION** section and the **PRECAUTIONS/Geriatric Use** subsection. The sponsor was also requested to consider a revision in the storage statement.

Supplement 020

A May 1, 1997 E-mail from Dr. Mhatre in the Division of Bioequivalence requested Dr. Lipicky's "expert opinion on the issue of 'if a food study is needed for approval in a bioequivalence study of a generic amiodarone tablet?' " Dr. Mhatre's E-mail lists the reasons for not requiring a comparison of the innovator (Cordarone Tablets) and generic amiodarone products under fed conditions. Dr. Parekh's June 17, 1997 review of Dr. Mhatre's E-mail states that the "sponsor should be requested to provide information on food-effect for their product. If not available, the label should so state." On July 29, 1997, a letter signed by Dr. Lipicky issued requesting that Wyeth-Ayerst "submit, if available, clinical data in support of and your proposed revision of the Cordarone Tablets labeling to reflect the increase in oral bioavailability when ingested with a high fat meal." On March 13, 1998, Wyeth-Ayerst submitted a proposal for a Cordarone IV food effect study.

Supplement 020, submitted on December 23, 1998, provides for draft labeling revised under **CLINICAL PHARMACOLOGY/Pharmacokinetics** and **DOSAGE AND ADMINISTRATION** to incorporate results of the effect of food on the oral administration of amiodarone.

An approvable letter for Supplement 020 issued February 12, 1999 (Attachment 2) requesting that final printed labeling (FPL) containing the revisions under **CLINICAL PHARMACOLOGY/Pharmacokinetics** noted in the letter be submitted.

S-019 and S-020

An amendment containing FPL for both S-019 and S-020 was submitted on May 3, 1999.

An amendment submitted for both S-019 and S-020 on July 14, 1999 states that after the May 3, 1999 submission of FPL was made, Wyeth "discovered errors in the Description section of the FPL...." The purpose of the July 14, 1999 submission was to correct the errors contained in the FPL submitted May 3, 1999.

During an August 25, 1999 telephone conversation between Ms. Lassen from Wyeth-Ayerst and Ms. Willard, Ms. Willard noted that an omission had been made under **ADVERSE REACTIONS** in the FPL submitted July 14, 1999. An amendment containing FPL revised under **ADVERSE REACTIONS** was submitted August 31, 1999 in response to the August 25, 1999 telephone conversation.

Evaluation: When compared with the most recently approved labeling (S-015 and S-017, approved January 5, 1999), the following changes were noted:

1. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics,**

   a. The following has been added at the end of the first paragraph:

      Food increases the rate and extent of absorption of Cordarone. The effects of food upon the bioavailability of Cordarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (T_{max}) by 37%. The mean AUC and mean Cmax of desethylamiodarone increased by 55% (range 58 to 101%) and 32% (range 4 to 84%), respectively, but there was no change in the T_{max} in the presence of food.

   b. The third and fourth sentences of the second paragraph in the **Pharmacokinetics** subsection have been deleted and replaced with three other sentences. This paragraph has been changed from:

to:

Cordarone has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of Cordarone, desethylamiodarone (DEA), has been identified in man; it accumulates to an even greater extent in almost all tissues. No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral Cordarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation.

c. The third paragraph of the **Pharmacokinetics** subsection has been changed from:

to:

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable.

In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 mL/hr/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a

single dose of intravenous amiodarone in cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower concentrations (about 100 ml/hr/kg) than younger subjects (about 150 ml/hr/kg) and an increase in $t_{1/2}$ from about 20 to 47 days. In patients with severe left ventricular disposition the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition $t_{1/2}$ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

d. The following has been added at the beginning of the fifth paragraph:

Following single dose administration in 12 healthy subjects, Cordarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA).

2. Under **PRECAUTIONS**, a new Geriatric Use subsection has been added that states:

Geriatric Use
Clinical studies of Cordarone Tablets 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.

3. Following the second sentence of the second paragraph under **DOSAGE AND ADMINISTRATION**, the statement that "Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals (see '**Clinical Pharmacology**')" has been added. The second paragraph now states:

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of Cordarone has not been determined. Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals (see "**Clinical Pharmacology**") Individual patient titration is suggested according to the following guidelines.

Comments/Recommendations: The changes under 1a and 1d above reflect the revisions requested in the February 12, 1999 approvable letter to S-020. The February 12, 1999 letter further stated that the change under 3 above is acceptable.

The changes under 1b and 1c above were found acceptable in the January 12, 1999 approvable letter to S-019.

Regarding 2 above, Dr. Lipicky requested at rounds on December 16, 1998 that the **Geriatric Use** subsection be changed from the wording submitted by the sponsor on August 27, 1998 to the wording under 21 CFR 201.57(f)(10)(ii)(A). The FPL submitted August 31, 1999 reflects Dr. Lipicky's request for this subsection.

The chemists' October 23, 1998 review for S-019 states that the firm should be requested to consider..." a revised storage statement as follows:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

This revised storage statement was requested in the January 12, 1999 approvable letter for S-019. Wyeth has chosen not to revise the storage statement for Cordarone Tablets.

The chemists September 7, 1999 review for S-019 and S-020 states that the labeling submitted August 31, 1999 is "Satisfactory for DESCRIPTION and HOW SUPPLIED."

An approval letter should issue for these supplements.

/S/

Diana Willard
Regulatory Health Project Manager

cc: original [redacted]
HFD-110
HFD-110/DWillard
HFD-110/ABlount

FEB 12 1999

RHPM Review of Draft Labeling
NDA 18-972/S-020

Sponsor: Wyeth Laboratories

Product: Cordarone (amiodarone HCl) Tablets, 200 mg

Submission Date: December 23, 1998

Receipt Date: December 28, 1998

Type of Submission: Draft Labeling

Background: A May 1, 1997 E-mail from Dr. Mhatre in the Division of Bioequivalence requested Dr. Lipicky's "expert opinion on the issue of 'if a food study is needed for approval in a bioequivalence study of a generic amiodarone tablet?' " Dr. Mhatre's E-mail lists the reasons for not requiring a comparison of the innovator (Cordarone Tablets) and generic amiodarone products under fed conditions. Dr. Parekh's June 17, 1997 review of Dr. Mhatre's E-mail (attached) states that the "sponsor should be requested to provide information on food-effect for their product. If not available, the label should so state." On July 29, 1997, a letter signed by Dr. Lipicky issued requesting that Wyeth-Ayerst "submit, if available, clinical data in support of and your proposed revision of the Cordarone Tablets labeling to reflect the increase in oral bioavailability when ingested with a high fat meal." On March 13, 1998, Wyeth-Ayerst submited a proposal for a Cordarone IV food effect study. The results of that food effect study were submitted on December 23, 1998 as Supplement 020.

Supplement 020 provides for draft labeling revised under **CLINICAL PHARMACOLOGY/Pharmacokinetics** and **DOSAGE AND ADMINISTRATION** to incorporate results of the effect of food on the oral administration of amiodarone.

Evaluation:

1) Under **CLINICAL PHARMACOLOGY/Pharmacokinetics,**

2) Under **DOSAGE AND ADMINISTRATION**, Wyeth-Ayers proposed to add the sentence "Because of the food effect on absorption, Cordarone should be administered consistently with regard to meals. (see '**Clinical Pharmacology**')" following the second sentence of the second paragraph. The second paragraph would state:

Comments/Recommendations: In his January 27, 1999 review, the clinical pharmacology/biopharmaceutics reviewer states that the proposed labeling under 1a above should be changed to:

> Food increases the rate and extent of absorption of Cordarone. The effects of food upon the bioavailability of Cordarone have been studied in thirty healthy subjects who received a single 600 mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (Cmax) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (Tmax) by 37%. The AUC and Cmax of desethylamiodarone (DEA) increased by 55% (range 58 to 101%) and 32% (range 4 to 84%), respectively, but there was no change in the Tmax in the presence of food.

The clinical pharmacology/biohparmaceutics reviewer recommends that the labeling under 1b above be changed to:

> Following single dose administration in twelve healthy subjects, Cordarone exhibits multi-compartmental pharmacokinetics with mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA).

The clinical pharmacology/biopharmaceutics reviewer further states that the proposed statement under **DOSAGE AND ADMINISTRATION** is acceptable.

An approvable letter that incorporates the recommendations of the clinical pharmacology/biopharmaceutics reviewer should issue.

/S/

Diana Willard
Regulatory Health Project Manager

cc: original
HFD-110
HFD-110/DWillard
HFD-110/SBenton

DF

JAN 12 1999

RHPM Review of Draft Labeling
NDA 18-972/S-019

Sponsor: Wyeth Laboratories

Product: Cordarone (amiodarone HCl) Tablets, 200 mg

Submission Date: August 27, 1998

Receipt Date: August 28, 1998
Type of Submission: Draft Labeling

Background: This supplement provides for information regarding the use of Cordarone Tablets in the geriatric population. It was submitted in response to a Federal Register Notice of August 27, 1997 that amended the regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and over) and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling. Additionally, revisions were made in **the CLINICAL PHARMACOLOGY/ Pharmacokinetics** subsection "to bring the Tablet insert into accord with the I.V. product labeling."

Evaluation: When compared with the most recently approved labeling (S-016 and S-018 approved June 15, 1998), the following changes were noted:

1) Under **DESCRIPTION**, the structural formula was omitted.

2) Under **CLINICAL PHARMACOLOGY**,

   a) The third and fourth sentences of the second paragraph in the **Pharmacokinetics** subsection have been deleted and replaced with three other sentences. This paragraph has been changed from:

[redacted]

to:

Cordarone has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially

adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of Cordarone, desethylamiodarone (DEA), has been identified in man; it accumulates to an even greater extent in almost all tissues. No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral Cordarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation.

b) The third paragraph of the **Pharmacokinetics** subsection has been changed from:

to:

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable.

In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 mL/hr/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA.

Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of intravenous amiodarone in cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects (about 150 mL/hr/kg) and an increase in $t_{1/2}$ from about 20 to 47 days. In patients with severe left ventricular disposition $t_{1/2}$ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

3) Under **PRECAUTIONS**, a new Geriatric Use subsection has been added that states:

Geriatric Use
Clinical studies of Cordarone were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects. Other reported clinical exsperience has not identified differences in response between the elderly and younger patients; however, greater sensitivity to Cordarone cannot be ruled out.

Age does not appear to have a clinically significant effect on amiodarone pharmacokinetics. Elimination half-life may be prolonged in the elderly. (see "**CLINICAL PHARMACOLOGY, Pharmacokinetics**").

Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, do not appear to have a clinically significant effect on amiodarone pharmacokinetics (see "**CLINICAL PHARMACOLOGY, Pharmacokinetics**"). Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with Cordarone, close clinical monitoring is prudent for elderly patients. The lowest effective dose should be used to prevent the occurrence of side effects (see "**DOSAGE AND ADMINISTRATION**").

4) Under **HOW SUPPLIED**, has been changed to "Rx only."

Comments/Recommendations: The medical officers hand-written September 4, 1998 note on the review transmittal form states that the first sentence of the second paragraph and the last sentence of the third paragraph should be deleted from the proposed geriatric labeling.

The Biopharmaceutists' December 7, 1998 review states that "The Office of Clinical Pharmacology and Biopharmaceutics finds the proposed amendments to GERIATRIC USE and CLINICAL PHARMACOLOGY sections of the label acceptable."

The chemists' October 23, 1998 review states that the labeling is "satisfactory for DESCRIPTION section. HOW SUPPLIED section request the firm to consider..." a revised storage statement as follows:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

The change under 4 above is provided for under the FDA Modernization Act of 1997.

Dr. Lipicky requested at rounds on December 16, 1998 that the Geriatric Use subsection be changed to the wording under 21 CFR 201.57(f)(10)(ii)(A).

An approvable letter that incorporates Dr. Lipicky's and the chemists' requests as well as instructions to include the structural formula should issue.

/S/

Diana Willard
Regulatory Health Project Manager

cc: original
HFD-110
HFD-110/Dwillard
HFD-110/SBenton

DF

MAR 16 1999

Memo to the File
March 16, 1999

Application: NDA 18-972/S-020
Cordarone (amiodarone HCl) Tablets

Sponsor: Wyeth-Ayerst Laboratories

A May 1, 1997 E-mail from Dr. Mhatre in the Division of Bioequivalence requested Dr. Lipicky's "expert opinion on the issue of 'if a food study is needed for approval in a bioequivalence study of a generic amiodarone tablet?' " Dr. Mhatre's E-mail lists the reasons for not requiring a comparison of the innovator (Cordarone Tablets) and generic amiodarone products under fed conditions. Dr. Parekh's June 17, 1997 review of Dr. Mhatre's E-mail (attached) states that the "sponsor should be requested to provide information on food-effect for their product. If not available, the label should so state." On July 29, 1997, a letter signed by Dr. Lipicky issued requesting that Wyeth-Ayerst "submit, if available, clinical data in support of and your proposed revision of the Cordarone Tablets labeling to reflect the increase in oral bioavailability when ingested with a high fat meal." On March 13, 1998, Wyeth-Ayerst submitted a proposal for a Cordarone food effect study. The results of that food effect study were submitted on December 23, 1998 as Supplement 020. An approvable letter for S-020 issued on February 12, 1999.

At the end of a March 1, 1999 teleconference requested by Wyeth-Ayerst to discuss the wording requested in the February 12, 1999 approvable letter, Wyeth stated that alternative labeling to that proposed by the Division (in the February 12, 1999 approvable letter) would be submitted for review: Wyeth's proposed revised wording was submitted on March 9, 1999.

Wyeth's proposed wording for the amiodarone food effect in the March 9, 1999 submission was discussed with Drs. Lipicky, Stockbridge, and Fadiran on March 16, 1999. Dr. Lipicky's handwritten comments were conveyed to Ms. Diane Mitrione of Wyeth-Ayerst on March 16, 1999. Ms. Mitrione will consult with Wyeth-Ayerst staff to determine if they will pursue this issue further.

/S/
Diana Willard

cc: original
HFD-110
JFD860/EFadiran
HFD-110/DWillard

Minutes of a Teleconference
March 1, 1999

MAR 1 - 1999

Application: NDA 18-972/S-020
Cordarone (amiodarone HCl) Tablets

Sponsor: Wyeth-Ayerst Laboratories

Attending:

Wyeth-Ayerst:

Diane Mitrione	Senior Director, US Regulatory Affairs
Mark Koyne	Associate Director, Product Information and Labeling
Dr. XU Meng	Associate Director, Clinical Pharmacology
Dr. Ira Weinryb	Senior Director, Clinical Pharmacology
Dr. Paul Minella	Manager, Product Information and Labeling

FDA:

Emmanuel Fadiran, Ph.D.	Clinical Pharmacologist/Biopharmaceutist, HFD-860
Diana Willard	Regulatory Health Project Manager, HFD-110

Background: A May 1, 1997 E-mail from Dr. Mhatre in the Division of Bioequivalence requested Dr. Lipicky's "expert opinion on the issue of 'if a food study is needed for approval in a bioequivalence study of a generic amiodarone tablet?' " Dr. Mhatre's E-mail lists the reasons for not requiring a comparison of the innovator (Cordarone Tablets) and generic amiodarone products under fed conditions. Dr. Parekh's June 17, 1997 review of Dr. Mhatre's E-mail (attached) states that the "sponsor should be requested to provide information on food-effect for their product. If not available, the label should so state." On July 29, 1997, a letter signed by Dr. Lipicky issued requesting that Wyeth-Ayerst "submit, if available, clinical data in support of and your proposed revision of the Cordarone Tablets labeling to reflect the increase in oral bioavailability when ingested with a high fat meal." On March 13, 1998, Wyeth-Ayerst submitted a proposal for a Cordarone food effect study. The results of that food effect study were submitted on December 23, 1998 as Supplement 020. An approvable letter for S-020 issued on February 12, 1999. Wyeth-Ayerst requested this teleconference to discuss the wording requested for the labeling in the approvable letter.

Teleconference: Ms. Mitrione began by referring to the February 24, 1999 facsimile transmission Wyeth-Ayerst sent to the Division regarding the wording in the February 12, 1999 approvable letter for S-020. Specifically, the FAX stated that Wyeth "can not link the proposed ranges to the information provided in our report text, nor to the analyses that we performed."

Dr. Fadiran referred Wyeth to the tables on pages 85 and 107 of their January 21, 1999 submission that provide the mean, minimum and maximum for the AUC and C_{max} of the parent drug amiodarone and the active metabolite desethylamiodarone. It is from the data in these two tables that the ranges for the changes in AUC and C_{max} of amiodarone and desethylamiodarone were derived. Wyeth questioned how Dr. Fadiran arrived at the conclusion that the minimum and maximum measurements for both AUC and C_{max} in these tables were from the same subject. Wyeth stated that the minimum and maximum for both AUC and C_{max} were calculated for each individual and then those numbers were pooled to arrive at a "collective" mean. Dr. Fadiran reiterated that the numbers in the February 12, 1999 approvable letter were derived from the data Wyeth submitted on January 21, 1999. Wyeth stated their preference for use of the means of the ratios of AUC and C_{max}. Dr. Fadiran stated that this approach would provide a nearly identical result to using the means of AUCs and C_{max}.

Wyeth asked for a rationale for the Division's decision to insert ranges for the AUC and C_{max} into the labeling. Noting that this issue had been discussed internally at a meeting with Dr. Lipicky, Dr. Fadiran stated that the Division believes the addition of the ranges to Wyeth's proposed labeling is essential to accurately portray to the clinician the wide variability observed in the data obtained from the study. The use of confidence intervals or ranges as well as other options was discussed with Dr. Lipicky. The Division believes that providing the range for the change in AUC and C_{max} in the labeling is the best choice in this case. The Agency has in the past utilized various methods to reflect variability in data in product labeling. The decision on what to use, i.e., confidence intervals, ranges, or some other option, has depended on the nature of the data. In this case the level of variability is very high and the Division believes that providing the range most accurately reflects the data.

Wyeth expressed the concern that using range for a collection of results is always an exaggeration due to "outliers." Wyeth does not believe that use of range is a reasonable approach to portray the data for C_{max} and AUC in this case: use of confidence intervals should be the preferred method.

Dr. Fadiran stated he would review any different approach Wyeth submitted for analysis of the data. Wyeth stated that a counter proposal to the labeling requested in the February 12, 1999 approvable letter will be submitted.

Signature, Minutes Prepare /S/ Diana Willard

Concurrence, Meeting Chair /S/ Emmanuel Fadiran, Ph.D.

DF

FEB 26 1999

MEMORANDUM

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

DATE: FEB 26 1999

S-020

FROM: Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Amiodarone Food Effect

TO: Director, Office of Generic Drugs, HFD-600

In response to a May 1, 1997 E-mail from Dr. Ramakant Mhatre (attachment 1), please see the attached review by Dr. Emmanuel Fadiran (attachment 2). The Division believes that a food study is needed for approval in a bioequivalence study of a generic amiodarone tablet.

A letter that issued to Wyeth-Ayerst on February 12, 1999 (attachment 3) outlined the labeling revisions for Cordarone Tablets that will incorporate results of the effect of food on the oral administration of amiodarone.

/S/

Raymond J. Lipicky, M.D.

Attachments

cc: NDA 18-972
Division Files
HFD-860/E Fadiran
HFD-110/D Willard

Attachment 1

E L E C T R O N I C M A I L M E S S A G E

Date: 01-May-1997 07:57am EDT
From: Ramakant Mhatre
MHATRE
Dept: HFD-658 MPN2 130
Tel No: 301-594-0345 FAX 301-594-0181

O: Raymond Lipicky (LIPICKY)

C: Nicholas Fleischer (FLEISCHERN)
C: Rabindra Patnaik (PATNAIK)
C: Yih Chain Huang (HUANGY)
C: Shriniwas Nerurkar (NERURKAR)

ubject: Amiodarone and Food Study

Dr. Lipicky,

The Division of Bioequivalence would like to have your expert opinion on the issue of " if a food study is needed for approval in a bioequivalence study of a generic amiodarone tablet ?" The following information will be helpful for your decision.

A. Amiodarone was approved on 12/24/85 for 200 mg tablet (NDA 18972). Wyeth Ayerst is the innovator.

B. Division of Biopharmaceutics did not review the study since the Division of Cardio-Renal had already approved the NDA.

C. The only reference to food in the 48th, 49th, 50th and 51st PDRs states that administration of Cordarone in divided doses with meals is suggested for total daily doses of 1000 mg or higher, or when gastrointestinal intolerance occurs.

D. The Division of Bioequivalence requires a fasting study with 200 mg dose (marketed strength). We did not require a food study.

E. Our reasons for NOT requiring food study are:
a. the parent drug and the metabolite have a very long half life. The mean half life of the parent drug is approximately 53 days and for the metabolite it is approximately 61 days. The washout period is at least 8 weeks.

b. substantial toxicity such as marked sinus bradycardia or sinus arrest and heart block, pulmonary toxicity seen with relatively large doses of drug (400 mg/day and above).

c. life -threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia need close monitoring of the patients during loading doses.

F. We have received an ANDA in which the sponsor conducted a food study (eventhough not required). The results indicated that the AUCinf and Cmax for amiodarone in food study was much higher than the one seen in fasting study (completing 2 or more phases).

AUCinf	(Fasting)	12832 ng.hr/ml
AUCinf	(Food)	20718 ng.hr/ml
Cmax	(Fasting)	459 ng/ml
Cmax	(Food)	1101 ng/ml

Completing 3 phases

AUCinf	(Fasting)	12832 ng.hr/ml
AUCinf	(Food)	21120 ng.hr/ml
Cmax	(Fasting)	459 ng/ml
Cmax	(Food)	1087 ng/ml

The levels of the metabolite desethylamiodarone were comparable and did not show much of a change when AUCinf and Cmax were compared during fasting and non-fasting states. No clinically significant adverse reactions were reported.

The above study did not show significant adverse effects even though there were significant increases in AUC and Cmax. We do not have more studies to compare. Knowing that the icreased levels of amiodarone may cause marked sinus bradycardia or sinus arrest and heart block should we ask for a nonfasting study or should we continue our policy of no nonfasting study. YOUR ADVICE WILL BE GREATLY APPRECIATED IN CORRECTING OUR POLICY, IF NECESSARY.

I know this is a very long e-mail but I wanted to give you the background necessary to help us out. Thank you very much.

Ram Mhatre