CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18972/S018

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-972/S-014
S-016
S-018

JUN 15 1998

Wyeth-Ayerst Laboratories
Attention: Ms. Diane Mitrione
P.O. Box 8299
Philadelphia, PA 19101-829

Dear Ms. Mitrione:

Please refer to your April 24, 1995 (S-014), April 16, 1997 (S-016), and April 17, 1998 (S-018) supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) Tablets.

We acknowledge receipt of your submission dated February 26, 1998 (S-016).

Supplemental application 016, as amended, provides for final printed labeling revised under the **Warnings**, **Precautions**, and **Adverse Reactions** sections to strengthen the safety information regarding optic disorders. Text pertaining to patient monitoring has also been revised in the **Precautions**/SURGERY/Adult Respiratory Distress Syndrome (ARDS) subsection. In addition, "angioedema" was added to the **Adverse Reactions** section.

Supplemental application 018 provides for final printed labeling revised under the **Precautions** and **Adverse Reactions** sections to add information on the possible development of peripheral neuropathy and the potential for resolution of this condition. Under **Adverse Reactions**, the new terms bronchiolitis obliterans organizing pneumonia, pleuritis, pancreatitis, toxic epidermal necrolysis, pancytopenia, and neutropenia have also been added.

We have completed the review of supplemental applications 016 and 018 and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included with your April 17, 1998 submission. Accordingly, these supplemental applications are approved effective on the date of this letter.

Supplemental application 014 was approved on October 18, 1995 based on draft labeling submitted. We consider the final printed labeling submitted April 17, 1998 with supplemental application 018 as the final printed labeling for supplemental application 014.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

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

Sincerely yours,

/S/ 6/12/98

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

cc:
Original NDA
HFD-110
HF-2/MedWatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
DISTRICT OFFICE
HFD-810/ONDC Division Director
HFI-20/Press Office (with labeling)
HFD-110/DWillard/5/18/98;5/20/98 DWillard 6/5/98
sb/5/18/98;6/1/98
R/D: NStockbridge/5/28/98
NMorgenstern/5/29/98

Approval Date: December 24, 1985

APPROVAL (AP) - S-016 and S-018
ACKNOWLEDGE AND RETAIN (AR) - S-014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S018

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DF

NDA 18-972/S-016
S-017

SEP 19 1997

Wyeth-Ayerst Laboratories
Attention: Mr. Timothy K. Ressler
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Ressler:

Please refer to your April 16 (S-016) and 24 (S-017), 1997 supplemental new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cordarone (amiodarone HCl) 200 mg Tablets.

Your April 16 supplemental application provides for draft labeling revised under **Warnings**, **Precautions**, and **Adverse Reactions** to modify or expand the text on optic disorders in these sections. Additionally, text pertaining to patient monitoring in the **Precautions**/SURGERY/ Adult Respiratory Distress Syndrome subsection has been revised. "Angioedema" has been added to the **Adverse Reactions** section.

Your April 24 supplemental application provides for draft labeling revised under **Warnings**/MORTALITY to incorporate text regarding safety findings from the European Myocardial Infarct Amiodarone Trial and the Canadian Myocardial Infarct Amiodarone Trial.

We have completed the review of these supplemental applications as submitted with draft labeling and they are approvable. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft and should also incorporate the changes to the CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY, PREGNANCY: Pregnancy Category D, and NEONATAL HYPO- OR HYPERTHYROIDISM subsections under **Precautions** outlined in our April 26, 1996 approvable letter for your January 17, 1996 supplemental application. In addition, all previous revisions as reflected in the most recently approved package insert 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.

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

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

Within 10 days after the date of this letter, you are required to amend these supplemental applications, 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 such action, FDA may take action to withdraw these supplemental applications.

The changes proposed in your April 24 supplemental application may not be implemented until you have been notified in writing that this application is approved.

Should you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
Telephone: (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

Enclosure

cc:
Original NDA
HFD-92
HFD-110
DISTRICT OFFICE
HFD-40/DDMAC (with labeling)
HFD-110/DWillard/6/4/97;9/15/97
sb/6/9/97;9/17/97
R/D: NStockbridge/9/16/97
NMorgenstern/9/16/97

Approval Date: December 24, 1985

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S018

FINAL PRINTED LABELING

Labeling: Original
NDA No: 18-972 Rc'd. 4-20-98
Reviewed by: _____

APPROVED
JUN 15 1998

CODE INSERTED HERE

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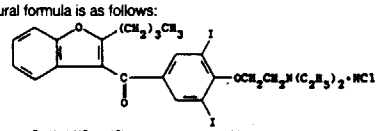
Cordarone®
(amiodarone HCl)
Tablets
CI 4662-4

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.

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, has been identified in man; it accumulates to an even greater extent in almost all tissues. 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.

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.

The applicability of these results to other populations (e.g., those without recent myocardial infarctions) or to Cordarone-treated patients is uncertain. While definitive controlled trials with Cordarone are in progress, pooled analysis of small controlled studies in patients with structural heart disease (including post-myocardial infarction) have not shown excess mortality in the Cordarone-treated population.

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 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."**)

Pregnancy: Pregnancy Category D

growth retardation) in the rat when given orally at a dose of 200 mg/kg/day (18 times the maximum recommended maintenance dose). Similar findings have been noted in one strain of mice at a dose of 5 mg/kg/day (approximately 1/2 the maximum recommended maintenance dose) and higher, but not in a second strain nor in the rabbit at doses up to 100 mg/kg/day (9 times the maximum recommended maintenance dose).

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.

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

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, rare 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.

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

Cordarone reduced fertility of male and female rats at a dose level of 90 mg/kg/day (8 x highest recommended human maintenance dose).

Cordarone caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control even at the lowest dose level of Cordarone tested, i.e., 5 mg/kg/day or approximately equal to 1/2 the highest recommended human maintenance dose. Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with Cordarone were negative.

Pregnancy: Pregnancy Category D

See **"WARNINGS."**

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.

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. Animal studies indicate that Cordarone has a high oral LD_{50} (>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. 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.
Caution: Federal law prohibits dispensing without prescription.

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 4662-4 Revised February 20,1998 Printed in USA

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Labeling: Original
NDA No: 18-972 Rc'd. 4-20-98
Reviewed by: _____

APPRO
JUN 15 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S018

MEDICAL REVIEW(S)

APR 10 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 18-972 (amiodarone)

Sponsor: Wyeth-Ayerst.

Submission: Correspondence on supplements S-015, S-016, and S-017, dated 26 February 1998 and subsequent draft RHPM Review of Draft Labeling, undated.

Review date: 10 April 1998.

Reviewer: N. Stockbridge, M.D., Ph.D.

Comments follow along the draft RHPM Review of Draft Labeling.

Under **Warnings**, the sponsor proposes minor corrections to wording describing CAMIAT and EMIAT trials. The medical officer concurs.

Also under **Warnings**, the sponsor proposes that the Division's proposed paragraph describing risks of subacute pulmonary toxicity in surgery be moved to **Precautions** and reworded. There are several issues here. One is a reasonable description of the phenomenon and the second is a reasonable placement in the label.

With regard to the description of the phenomenon, the Division's description probably overstates the risk of post-operative ARDS, as the sponsor cites larger series and lower rates. The Division's paragraph proposed that superoxide radical formation was a possible mechanism and that therefore high FiO_2 should be avoided. The Division's assigned pharmacologist's review of this issue is attached. A review of the literature undertaken by the medical officer suggests the following: (1) There probably are different mechanisms contributing to chronic pulmonary toxicity (viz accumulation) and subacute toxicity. (2) Subacute pulmonary toxicity cases cited by Donica et al. (1996)[1] led them to study an animal model consistent with toxicity dependent upon oxygen. Various cases can be reviewed, but a brief survey suggests that oxygen-dependent toxicity is not much at issue. (3) Somewhat more controversial appears to be the role of a mechanism dependent upon oxygen free radicals; e.g., compare Leeder et al (1996)[2] and Futamura (1996)[3]. The sponsor's proposed description, however, goes too far in implicitly denying oxygen as a risk factor and recommending merely that "oxygen delivery...be closely monitored...." The medical reviewer now recommends the following, to appear under **Warnings** rather than **Precautions**:

"**Warnings**: SURGERY/*Adult Respiratory Distress Syndrome (ARDS)*: Onset of ARDS has been reported in patients receiving Cordarone therapy who have undergone cardiac or non-cardiac surgery. High FiO_2 administered during such procedures may be a risk factor. Patients developing post-operative ARDS have usually responded well to vigorous respiratory therapy, but in rare instances the outcome has been fatal."

The sponsor proposes to retain the statement under LOSS OF VISION: "A causal relationship to the drug has not been clearly established." The Division has asked that statement be removed. The sponsor might submit an expert report containing the estimated background rate for non-drug-related loss of vision from optic neuritis and alternative explanations or pertinent confounding factors in each of the reported cases on amiodarone. The Division's current position is to have the label be mute on the relationship between these events and amiodarone, but a more detailed analysis could support a more definitive statement.

The medical officer has no comment on proposed changes in the sections on NEONATAL HYPO- OR HYPERTHYROIDISM, CARCINOGENESIS, or PREGNANCY.

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1. Donica SK, et al., 1996. Danger of amiodarone therapy and elevated inspired oxygen concentrations in mice. Am J. Cardiol 77(1): 109-110.
2. Leeder RG, et al. 1996. Evaluation of reactive oxygen species involvement in amiodarone pulmonary toxicity in vivo and in vitro. J. Biochem. Toxicol. 11(3):147-160.
3. Futamura Y. Toxicity of amiodarone on mouse pulmonary endothelial cells cultured with or without alveolar macrophages. J Toxicol. Sci. 21(4):253-267.

/S/

N. Stockbridge, M.D., Ph.D.

cc: NDA 18-972
HFD-110
HFD-110/CSO
HFD-110/Pharmacologist
HFD-110/Stockbridge

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S018

ADMINISTRATIVE DOCUMENTS

SEP 22 1997

RHPM Review of Labeling
NDA 18-972/S-016 and S-017

Sponsor:	Wyeth-Ayerst Laboratories
Product:	Cordarone (amiodarone HCl) Tablets, 200 mg
Submission Dates:	April 16, 1997 (S-016) April 24, 1997 (S-017)
Receipt Dates:	April 21, 1997 (S-016) April 30, 1997 (S-017)
Type of Submission:	Special Supplement - Changes Being Effected (S-016) Draft Labeling (S-017)

Background: Supplement 016, submitted with final printed labeling as a Special Supplement - Changes Being Effected on April 16, 1997, provides for changes to the **Warnings**, **Precautions**, and **Adverse Reactions** sections of the labeling to strengthen the safety information regarding optic disorders. The supplement also provides for revised text pertaining to patient monitoring in the **Precautions**/SURGERY/Adult Respiratory Distress Syndrome (ARDS) subsection. In addition, "angioedema" was added to the **Adverse Reactions** section.

Supplement 017, submitted with draft labeling on April 24, 1997, provides for revised text in the **WARNINGS**/Mortality subsection based on safety finding from the European Infarct Amiodarone Trial (EMIAT) and the Canadian Myocardial Infarct Amiodarone Trial (CAMIAT).

Evaluation: When compared with the most recently approved package insert dated October 18, 1995, the following changes were noted:

1) The **Warnings**, the following changes were noted:

   a) The MORTALITY subsection has been changed from:

to:

In the National Heart, Lung and Bloods 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. The applicability of these results to other populations (e.g., those without recent myocardial infarctions) is uncertain.

Cordarone therapy was evaluated in two definitive, 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 for up to 2 years. The results of both studies demonstrated no excess in all-cause mortality in amiodarone-treated patients (CAMIAT: 57/606 amiodarone-treated patients vs. 68/596 placebo patients; EMIAT: 103/743 amiodarone-treated patients vs. 102/743 placebo patients).

These data confirm the results of a pooled analysis of small, controlled studies involving patients with structural heart disease (including post-myocardial infarction) where there was no excess mortality in the Cordarone-treated population.

b) A LOSS OF VISION subsection has been added between the subsections LIVER INJURY and PREGNANCY: PREGNANCY CATEGORY D. This subsection states:

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 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."**)

2) Under **Precautions**, The following changes were noted:

a) The subsection CORNEAL MICRODEPOSITS/IMPAIRMENT OF VISION has been changed from:

to:

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**").

NOTE: The word "alone" has been added to the last sentence in the IMPAIRMENT OF VISION/*Corneal Microdeposits* subsection.

b) The subsection SURGERY/Adult Respiratory Distress Syndrome (ARDS) has been changed from:

to:

Postoperatively, rare 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 FiO2 and the determinants of oxygen delivery to the tissues (e.g., SaO_2, PaO_2) be closely monitored in patients on Cordarone.

3) Under **Adverse Reactions,** the following changes were noted:

a) The words ' have been deleted from the third sentence of the first paragraph. The sentence has been changed from:

to:

They are often reversible with dose reduction or cessation of Cordarone treatment.

b) The following paragraph has been added after the third paragraph of this section:

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**.")

c) The following paragraph has been added after the sixth paragraph in this section:

Hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudotumor cerebri, thrombocytopenia, and angioedema also have been reported in patients receiving Cordarone.

NOTE: This paragraph was moved from a different place under **Adverse Reactions** and the word "angioedema" has been added.

d) The second paragraph under ' in this section has been deleted.

This paragraph stated:

Rare occurrences of hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia have been reported in patients receiving Cordarone.

Comments/Recommendations: Supplement 014, submitted with draft labeling on April 24, 1995, provided for changes to the **Precautions** section of the labeling relative to the possible mechanism of Adult Respiratory Distress Syndrome coincident with Cordarone therapy and for text regarding specific FiO_2 recommendations. The supplement also provided for revising the **Precautions**/ PEDIATRIC USE subsection to replace the word with the term "pediatric patients." The approval letter for this supplement, issued October 18, 1995, requested final printed labeling (FPL) identical to the draft labeling included with the April 24, 1995 submission. No FPL has been submitted for this supplement.

The cover letter for Supplement 015 states that before FPL is prepared as requested in the October 18, 1995 approval letter for S-014, Wyeth would like to make two revisions to the Cordarone Tablet labeling. S-015 provided for revisions to the **Precautions**/SURGERY subsection of the labeling regarding the monitoring of patients receiving Cordarone Therapy who undergo general anesthesia with volatile anesthetic agents as well as text regarding a lack of substantial data to support specific FiO_2 recommendations. In addition, text was added that referred to volatile anesthetics in the **Precautions**/DRUG INTERACTIONS subsection. The approvable letter that issued for this supplement on April 26, 1996 requested FPL incorporating changes noted in the CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY, PREGNANCY: Pregnancy Category D, and NEONATAL HYPO- OR HYPERTHYROIDISM subsections under **Precautions**. No FPL has been submitted for this supplement.

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 19 1997 MAR 21 1997

FROM: Nancy Chamberlin, Pharm.D., Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Vincent Guinee, M.D., M.P.H., Director
Division of Pharmacovigilance and Epidemiology, HFD-730

TO: Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Consult/Monitored Adverse Reaction Report: Optic Neuropathy/blindness or permanent damage associated with Cordarone® (amiodarone hydrochloride)

In response to your consult request on November 12, 1996 for review of cases of permanent blindness and optic neuropathy associated with amiodarone, we provide the following evaluation from the FDA Spontaneous Reporting System (SRS) of all ophthalmological reports for your information. Preliminary information has been presented to your staff in the safety meeting on February 25, 1997. In summary, amiodarone associated corneal microdeposits and optic neuritis are well known. Symptoms from these labeled disorders are not listed and some SRS reports indicated permanent damage to the vision including blindness which is not necessarily reversible upon discontinuation of the drug or reduction of dose.

INTRODUCTION:

Cordarone® (amiodarone hydrochloride) tablets manufactured by Wyeth-Ayerst was approved for marketing on December 24, 1985 and intravenous formulation on August 3, 1995. It has predominantly class III antiarrhythmic effects. It is indicated for treatment of life-threatening recurrent ventricular fibrillation and recurrent hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

According to the labeling, following oral administration in man amiodarone is slowly and variably absorbed. It has a very large volume of distribution with extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. 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.

Amiodarone is primarily eliminated via hepatic excretion into bile with some enterohepatic

recirculation. There is considerable intersubject variation in elimination of amiodarone. It has a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days of the drug from well-perfused tissue, followed by a terminal phase with extremely slow elimination from poorly perfused tissue compartments such as fat. Half-life of the parent drug in the slower terminal elimination phase has been reported to range from 26 to 107 days, with a mean of 53 days and the metabolite's mean elimination half-life was 61 days.

Dosage suggestions for amiodarone tablets are summarized below:

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

DRUG USE DATA

The following chart shows total projected amiodarone usage over the last 4 years. (This information is not to be used outside of the FDA without prior clearance by IMS AMERICA.)

PROJECTED TOTAL PRESCRIPTIONS DISPENSED BY RETAIL PHARMACIES (INDEPENDENT, CHAIN, FOOD STORE AND MAIL ORDER) IN THE U.S. FOR AMIODARONE ORAL AND INTRAVENOUS, 1992 THROUGH 1996

	1996	1995	1994	1993	1992
TOTAL					
ORAL					
INJECTABLES					

NOTES: * = less than blank = no projection
SOURCE: IMS AMERICA, LTD, NATIONAL PRESCRIPTION AUDIT PLUS, THERAPEUTIC CATEGORY REPORT, ON-LINE

LABELING:

The Precautions section of Cordarone®'s labeling states: *"CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION. 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 are not a reason to reduce dose or discontinue treatment."*

The following is included in the Adverse Reaction section of the labeling: *peripheral*

neuropathy, visual disturbances, and optic neuritis. Also it states that *"Asymptomatic corneal microdeposits are present in virtually all adult patients who have been on drug for more than six months. Some patients develop eye symptoms of halos, photophobia, and dry eyes. Vision is rarely affected and drug discontinuation is rarely needed."*

SELECTION OF CASES:

As of February 24, 1997, the SRS had a total of 1791 reports for amiodarone as the suspect drug. The SRS was searched under the Midlevel COSTART OPH% term on November 12, 1996 for adverse reaction reports associated with amiodarone use and 140 (134 unduplicated) reports were identified. Fifty-four of the 140 were classified as serious: 33 hospitalized, 27 disabled, 2 life-threatening, and 1 death.

The following COSTART terms were reported in decreasing frequency (Underlined term is labeled, a report may have more than 1 COSTART term, and the COSTART term for corneal deposits is corneal opacity, for optic neuropathy is optic neuritis.):

corneal opacity-40,
vision abn-38,
neuritis optic-29,
blind-13,
amblyopia-12, corneal lesion-12,
visual field defect-11,
papilledema-10,
cataract-8,
atrophy optic-7,
diplopia-3,
hem retinal-3,
eye dis-2, glaucoma-2, retinal degenerat-2, retinal dis-2, vitreous dis-2, accommodation abn-1, blind night-1, cataract nos-1, conjunctivitis-1, exophthalmos-1, keratitis-1, occlus retinal art-1, ophthalmoplegia-1, pain eye-1, photophobia-1, thromb retinal vein-1, and chromatopsia-1.

The demographics of the 140 reports consisted of the following:

sex-	20 females, 110 males and 10 gender not supplied;
age-	10-19 yrs. (1), 20-29 yrs(1), 30-39 yrs(2), 40-49 yrs(4), 50-59 yrs (26), 60-69 yrs(45), 70-79 yrs(28), 80-120 yrs (1), and unknown (32).
outcome-	54 serious: 33 hospitalized, 27 disabled, 2 life-threatening, and 1 death.
report year-	1982-1, 1983-1, 1984-2, 1986-13, 1987-11, 1988-6, 1989-7, 1990-5, 1991-7, 1992-5, 1993-15, 1994-20, 1995-27, 1996-20
source-	19 foreign (Argentina-2, Belgium-1, Canada-2, France-6, Israel-1, Italy-

1, Sweden-1, Switzerland-3, United Kingdom-2) and the rest were domestic.

The following ophthalmological term definitions found in Dorlands Medical Dictionary, 28th Edition are provided for your information:

Optic neuritis = inflammation of the optic nerve.
Optic nerve atrophy = atrophy of the optic disk resulting from degeneration of the nerve fibers of the optic nerve and optic tract.
Papilledema = chocked disc; edema of the optic disc (papilla), most commonly due to increased intracranial pressure, malignant hypertension, or thrombosis of the central retinal vein; called also chocked disc.
Papillitis= 1. Inflammation of a papilla; 2. A form of optic neuritis involving the optic papilla (disk).
Keratopathy= a noninflammatory disease of the cornea
Cataract = an opacity, partial or complete, of one or both eyes, on or in the lens or capsule, especially an opacity impairing vision or causing blindness.
Glaucoma= of a group of eye diseases characterized by an increase intraocular pressure which causes pathological changes in the optic disk and typically defects in the field of vision.
Amblyopia = impairment of vision without detectable organic lesion of the eye.
Diplopia = the perception of 2 images of a single office; called also ambiopia, double vision, and binocular polyopia.
Scotoma = an area of lost depressed vision within the visual field, surrounded by an area of less depressed or of normal vision.

SUMMARY OF CASES:

The majority of events consisted of one or a combination of the following optic neuropathy in one or both eyes; optic nerve (optic neuritis, optic atrophy), corneal microdeposits (corneal opacity, corneal lesion), lens opacities and cataracts, optic disk (papilledema) or retina changes (retina hemorrhage, retinal degeneration). The signs and symptoms from these neuropathies might be manifested as abnormal vision, blindness, amblyopia, visual field defect, or diplopia which are not labeled. A number of the abnormal vision symptoms developed into irreversible visual field defects and blindness.

The following summary including description of symptoms is categorized based on the reported area of the optic neuropathy and emphasized on unlabeled events.

I. Optic Nerve- optic neuritis is labeled.

Optic Atrophy

Seven cases of optic atrophy were identified in the SRS. One case with blindness was excluded as the reporter thought the cause of blindness was secondary to radiation for pituitary tumor or the tumor compression itself (#1750284). Of the six remaining cases, three resulted in blindness (#519933, 436340, and 1697608) and three had visual impairment (#1562974, 1525335, and 410815). One case of optic atrophy which progressed from optic neuritis is summarized below and another is summarized as #3 in the blindness case summaries.

A 75 year old male with history of malignant ventricular arrhythmias, automatic implantable cardioverter/ defibrillator was started on amiodarone 400 mg PO daily on January 7, 1994. Three months later he developed *optic neuritis which progressed to optic atrophy*. Amiodarone was discontinued and he *continued to have visual impairment*. Concomitant meds: Lasix, aspirin, Prinivil, and K-dur. Tests: Neurologic work-up negative, Syphilis and Lyme tests negative, normal thyroid and liver function tests. (1562974, 1995, periodic, CT)

Blindness

In the SRS there were 13 cases of blindness and 1 night blindness. Three cases were excluded due to: one was secondary to radiation for pituitary tumor or tumor compression itself (#1750284), another the reporter in follow-up stated that the patient did not have blindness (#1717633), and the other case had no details (#426340). All of the remaining 11 cases became disabled and did not recover their sight. Nine were noted as having optic neuritis or neuropathy prior to blindness, 2 were not noted. The dose was within the recommended guidelines. The events occurred within 12 days to 2 years. The patients were elderly and the majority were male. Only 2 were noted to have a medical history of diabetes which may be a risk factor for blindness. There were 2 foreign reports which occurred in September 1992 in a female from Canada and it might be a duplicate.

DEMOGRAPHICS:

SOURCE:	Domestic- 9, Foreign-2
AGE:	Range 63-75 yr (mean 69.3 yr), unknown-3
SEX:	Male-9, Female-2,
ONSET TIME:	12 days to 2 years (mean 7.1 months)
DAILY DOSE:	600 mg-1, 400 mg-5, 300 mg-1, 200 mg-1, unknown-3
DECHALLENGE:	Not recovered-11
RECHALLENGE:	1
OUTCOME:	Hospitalized-5 , Disabled-11
REPORT TYPE:	15-day-6, Direct-2, Periodic-3
REPORT YEAR:	1986-1, 1987-1, 1988-2, 1989-1, 1992-1,1993-1, 1995-4

Representative cases of blindness:

1. A 65 year old with history of myocardial infarctions, cardiac surgery, and paroxysmal atrial fibrillation started taking amiodarone in November 1984. On July 2, 1985 he developed visual disturbances

characterized by smear/smudge in the lower visual field of the right eye with 20/20 vision in the affected eye. He was diagnosed with *ischemic optic neuropathy* and amiodarone was discontinued on August 27, 1985. It was restarted in January 86. In April 1986 there were no complaints of visual problems. In September 1986, *optic neuritis* recurred. Amiodarone was discontinued in November 1986 and the patient claims severe visual problems with *90% blindness in the left eye, ½ visual field blindness in the right eye*. (#441563, 1986, 15 day, NY)

2. A 66 year old male with history of arrhythmias started on amiodarone tablets on April 9, 1985. Concomitant meds: digoxin, Isordil, Lasix, potassium supplements. In July 1985 he experienced ongoing loss of vision in the right eye. By September 1985, he had completely lost vision in the right eye and also suffered blurred vision of the left eye. Condition was due to *bilateral optic neuritis*. On April 1986 MRI, VER, EMG showed permanent vision impairment. He was *declared legally blind*. He later developed *peripheral neuropathy* as evident by the April 1986 nerve biopsy of the left ankle which showed degeneration and traces of drug. Medical history was negative for diabetes and multiple sclerosis. (#638744/567294/547170, 1988, periodic, CO)

3. A 70 year old male with history of cardiac arrhythmias was started on amiodarone 400 mg PO daily. Three months later he developed *papilledema with resultant optic atrophy and visual loss (blindness)*. His neurological exam was normal except for papilledema and optic atrophy. His vision somewhat improved immediately after stopping drug; however, this resulted in a permanent disability. Concomitant meds: Persantine, aspirin. (#519933, 1988, direct, MI)

4. A 70 year old male with history of atrial fibrillation, diabetes mellitus, hypertension, and congestive heart failure started on amiodarone 400 mg PO daily on December 27, 1993. On January 7, 1994, he developed *sudden loss of vision in his right eye*. He received unspecified treatment. On February 23, 1994, he developed *sudden loss of vision in the left eye*. He was hospitalized and was treated with intravenous steroids. The loss of vision is partial. On follow-up, the physician noted that the patient had *ischemic optic neuropathy with resultant loss of vision in the lower visual field of his right eye*. Concomitant meds: enalapril, isradipine, digoxin, Lasix, warfarin, kcl, insulin. He continued on amiodarone. (#1569605, 1995, periodic, IN)

5. A 75 year old male developed optic *nerve damage and blindness* (described as a gradual loss of vision, the right eye is more severely affected than the left) while being treated with amiodarone 600 mg PO daily for 14 months. Concomitant meds: Lasix, Slow-K. He was treated with prednisone. Amiodarone was discontinued. Nine months later the exam showed VER abnormal OD>OS, ERA nl, color vision abnormal, octopus visual field abnormal. This event resulted in hospitalization and disability. (#488026/445142/425634, 1986, periodic, CA)

II. Corneal-corneal opacity (microdeposits) is labeled.

Corneal lesions

There were 12 cases COSTARTed as corneal lesions in the SRS. However, 7 appeared to be coded wrong as corneal lesions and were actually the following: corneal microdeposits (4) (#1577730, #1697157, #1563987/1739080, and #1720886); corneal changes like a "Technicolor show" (#934442); and keratopathy (#386657, and #494045). Two old reports of corneal lesion were missing in the retrieval system (#312630, and #312631). In two of the three remaining cases, it was unknown whether corneal lesion was the result of corneal

deposits from amiodarone. The other case was found to have corneal abrasions with deposits. These cases are summarized below.

1. A 50 year old male with history of ventricular tachycardia, anterior infarct received amiodarone orally for 1 year. Concomitant meds: Captopril, nitroglycerin, and Persantine. He was found to have sub-epithelial deposits in both eyes. The right eye developed corneal abrasions with a 1.5 mm diameter area where deposits were confluent. The eye was patched for 48 hours and abrasions healed, but deposits remained. Amiodarone therapy was not discontinued. (#636154, 1989, periodic, MS)

2. A 63 year old male with history of cardiac arrhythmias developed corneal lesion after taking amiodarone for 1 year. Concomitant meds: Coumadin, Inderal, Isordil, nitroglycerin, quinidine, Procardia, and Lanoxin. (#426973, 1986, direct, unknown)

3. A male patient with history of cardiomyopathy following repeated bouts of dyspnea on exertion, fatigue, and arrhythmias was stabilized on Lanoxin, Persantine, Coumadin, Lasix and Micro-K. In 1985 treatment with Quinaglute and Tonocard failed and he was started on amiodarone PO. One week later his rhythm became very unstable and amiodarone was increased. He was subsequently diagnosed with corneal lesions, congestive heart failure, multiple pulmonary lesions, and chest x-ray showed metastatic lesions. No primary site of malignancy was found. Amiodarone therapy was decreased to 200 mg daily. (#564272, 1988, periodic, LA)

III. Lens opacities-Cataracts

By definition cataracts is an opacity in the lens or capsule. The drug is already labeled for corneal deposits/corneal opacity. There were 8 cases COSTARTed as cataracts; however, two were confounded with prior history of cataracts of which one was in a 62 year old male that had worsening of cataracts coincident with the use of Cordarone (#1563600). In the six remaining cases onset varied from 7 weeks to 7 years (2 unknown). Three became disabled and 1 required surgery. Not much details were provided in the cases. However, cataracts normally occur in the elderly population and it is often difficult to determine if it was associated with amiodarone use or if it was due to aging.

The two best cases are summarized below. In the second case the patient received Pravastatin which is labeled for worsening of cataracts, it was not the suspected agent reported by the physician, nor was it mentioned how long the patient had been on that drug, but we could not exclude the possibility that amiodarone was associated with the cataract.

1. A male patient received amiodarone for 10 months. He was referred to an ophthalmologist for an examination at which time an asymptomatic cataract was discovered and stated that it was drug-induced. Concomitant meds: Isordil, Carafate, Coumadin, Diltiazem, digoxin, K-Lor, and Lasix. Patient remained on amiodarone. (#478177, 1987, periodic, NJ) A

2. A 44 year old male with a history of left ventricular aneurysm and sustained ventricular performance took amiodarone 200 mg PO daily for 2 years. He presented with complaints of "Dazzling sensation and sensation of visual fog". Ophthalmologic examination revealed a posterior subcapsular cataract requiring surgery. Concomitant meds: Captopril, Pravastatin, and Fluindione. One year prior to this adverse event he was noted to have corneal deposits. (#1570366, 1995, 15 day, France)

Additionally, we received a recent MEDWATCH report from a physician who reported that 2 patients developed cataracts after 1½ years on amiodarone. Both had marked bilateral cornea staining and haze and they developed the cataracts rapidly this past year. The only other common medication was Coumadin.

> First patient was a 58 year old female on amiodarone, Coumadin, Norvasc, atenolol, Prinivil, baby aspirin, Zoloft, tenazepam, Nitrostat, K-Dur, furosemide and Serevent. Second patient was a 75 year old male on amiodarone, Coumadin, Micronase, Synthroid, Lanoxin, Zestrol, and Bumex. (New, 1997, direct, MO)

IV. Optic disk-

Papilledema

Sixteen (15 unduplicated) cases associated with amiodarone use were identified from the SRS including reports COSTARTed as papilledema and other reports mentioning papilledema but not COSTARTed as such. The reported papilledema was associated with impairment of vision as blindness (summarized above under BLINDNESS, #519933), decreased visual acuity or visual field defect. Eight of the cases did not recover full eyesight, of which 5 were noted as becoming disabled, 4 recovered, and the outcome was unknown in 2. The reaction occurred within a mean onset of 10.3 months and was generally associated with higher dosages (mean 540 mg and range 200-1200 mg). The mean age was 57.8 years. A large number of the reports were from foreign sources. Relevant concurrent events described in the 15 cases included optic neuritis (6), intracranial hypertension/pseudotumor cerebri (4), and retinal hemorrhage (2).

It is unknown whether amiodarone caused papilledema. Given that amiodarone is associated with optic neuritis and corneal deposits, further pathophysiological changes to optic disc edema should be expected. Of note, intracranial hypertension/pseudotumor cerebri is a labeled event. There were 4 cases (one did not have details) that described intracranial hypertension/ pseudotumor cerebri after amiodarone use and then developed either acute blurred vision or gradual loss of eyesight that had papilledema diagnosed. Three also had corneal deposits but one did not recover from the events. Therefore, papilledema with or without corneal deposits might be a result of increased intracranial pressure from amiodarone in these cases.

The demographics of the 15 cases of papilledema are provided below.

DEMOGRAPHICS:	
SOURCE:	Domestic-7, Foreign-8 (Argentina-2, Belgium-1, Switzerland-1, France-2, Sweden-1, UK-1)
AGE:	Range 42-73 yr (mean 57.8 years)
SEX:	Male-15
ONSET TIME:	3-24 months (mean 10.3 months), unknown-2
DAILY DOSE:	200-1200 mg (mean 540 mg, median 400 mg), unknown-1
DECHALLENGE:	Positive (recovered)-4, Not recovered full eyesight-9, Unk-2

RECHALLENGE: NONE
OUTCOME: Serious-7, Hospitalized-3, Disabled-5, Died-1
REPORT TYPE: 15-day-10, Direct-3 , Periodic-2
REPORT YEAR: 1986-2, 1987-4, 1988-1, 1991-2, 1995-4, 1996-2

Representative cases of papilledema including 4 literature cases which had more details are summarized below.

1. A 52 year old male with history of paroxysmal tachycardia received amiodarone 400 mg PO daily for 1 year. He experienced pseudotumor cerebri manifested by gradual loss of vision in the left eye and was hospitalized. He had no headache, nausea or vomiting. General examination was unremarkable. Blood pressure 140/85, EKG sinus rhythm, blood and urine normal, CSF pressure 175 mm. Neurological exam showed *bilateral papilledema. Ocular examination revealed corneal deposits, partial field defect in the nasal inferior quadrant of the left eye;* however, visual acuity and color vision were normal. CT scan of brain and orbitae was normal. Amiodarone was discontinued and patient started on Verapamil. During the following weeks the patient's symptoms gradually resolved. (#496748/454939, 1987, 15 day, Belgium)

2. A 70 year old male with history of atrial fibrillation and hypercholesterolemia received amiodarone 400 mg PO daily for 22 months. Concomitant meds: aspirin and gemfibrozil. He developed *optic neuritis, abnormal vision, visual field defect, and papilledema.* Brain MRI was normal. Amiodarone was discontinued and patient was treated with corticosteroids. One month later he has shown slight improvement. (#1657335, 1995, 15 day, France)

3. A 73 year old male with history of heart disease, heart failure, temporal arteritis and atrial fibrillation received amiodarone 200 mg PO daily for 12 ½ months. Concomitant meds: furosemide, aspirin, isosorbide mononitrate, and prednisone. He presented *with papilledema accompanied by blurred vision (right > left).* CT scan of the brain was normal. ESR was elevated (74 mm/hr). Amiodarone was discontinued 2 months after the onset of blurred vision. Papilledema resolved; however, the patient *sustained permanent loss of vision in the right lower visual field.* (#1580367, 1995, 15 day, UK)

Two cases of papillopathy associated with disc swelling and hemorrhages were submitted under #467998 (1987, 15 day, MA) and published in the Archives of Ophthalmology 1987;105:349-351.

A 61 year old male with history of accelerated hypertension, MI, cardiac arrhythmias was placed on amiodarone 1200 mg PO daily. Concomitant meds: aspirin, clonidine, nifedipine. Baseline ophthalmologic examination revealed visual acuity of 20/20 OD and 20/25 OS and mild lens changes. After arrhythmias stabilized amiodarone dose was reduced to 400 mg daily. About 2 ½ months later he developed *hazy vision* in the right eye. Eye examination revealed *visual acuity of 20/25 OU; a relative afferent pupillary defect present in the right eye. Amiodarone keratopathy had developed. The right disc was swollen with a few flame-shaped hemorrhages at the nasal margins.* With *similar changes in the left eye, but its visual function was unchanged.* An erythrocyte sedimentation rate was 11 mm/h, and the *diagnosis of nonarteritic anterior ischemic optic neuropathy* was made. Neurological exam was normal, temporal artery biopsy normal. No changes in therapy except he was given prednisone. Doppler of the carotid arteries, CT of head and orbits, and results of routine blood studies were unremarkable. Over the next two months his discs remained swollen and new hemorrhages appeared. In addition, he had developed an *inferior defect to the right eye visual field.* Then amiodarone dose was decreased to 200 mg daily to control the papillopathy and 1½ months later the hemorrhages around the right disc had resolved, and his visual field showed only mild constriction.

A 45 year old male with history of MI and ventricular arrhythmias was placed on amiodarone 1200 mg daily. Five days after beginning therapy he has a baseline ophthalmologic exam with normal results. (Patient provided information that he had double vision several years previously which was diagnosed as myasthenia gravis and had responded to pyridostigmine.) Concomitant meds: Isordil, and NTG. Five months later he was given bifocals. Then 2 months later his exam showed *visual acuity 20/20 bilaterally, normal color vision, full visual fields* by Goldmann perimetry and amiodarone *keratopathy* had developed. The *left disc was swollen with splinter hemorrhages.* No treatment was prescribed. Upon follow up 2 weeks later exam was unchanged. One month later the images and disc swelling had resolved. He went on to develop a right hypertropia (right superior oblique palsy), CT scan was normal, an edrophonium test was negative, EMG and nerve conduction showed a mild peripheral neuropathy. These resolved over the next six months and eye exam showed no disc abnormalities.

Two cases of anterior ischemic optical neuropathy associated with scotoma, papilledema and reduction in visual field were submitted under #758304/758427 (1991, 15 day, Argentina) and published in the Neurologia 1990; 5(5):160-163.

A 50 year old patient with history of mild hypertension, ischemic coronaropathy with ventricular extrasystole, and sinus tachycardia received amiodarone 800 mg for 3 months and the dose was decreased to 600 mg. Then at the end of 10 months the dose was decreased to 300 mg. Concomitant meds: low sodium diet and chlorthalidone. Five months later he complained of tremors, *reduced visual acuity of the left eye (5/10 in left and right was 9/10) and had papilledema.* The visual field of the left eye displayed a lower altitudinal relative *scotoma* and the visual evoked potentials displayed an alteration in the shape of the waves, with an increased in their latencies with left predominance indicating bilateral pre-chiasmic disease. Rest of neurological exam was normal. CT and x-ray were normal. Amiodarone was discontinued and 8 months later the papilledema disappeared. The left papilla remained a little pale, with visual acuity of 7/10 in the left eye and 9/10 for the right; the posterior tremor was totally extinguished.

A 61 year old male with history of ventricular tachycardia, extrasystoles, MI received amiodarone 400 mg daily for 20 months. The dose was then decreased to 200 mg. Twenty-four months after starting amiodarone patient had a *reduction in the visual acuity of the left eye (6/10 and right eye was 8/10); and a blurring of both papillae. Campimetry showed the blind spots increased and a contraction of the left peripheral isopters.* The visual evoked potentials showed deflections of acceptable reproducibility, with a delay in their latencies indicating bilateral pre-chiasmic disease. Rest of neurological exam was normal. CT and x-ray were normal. Patient had attenuation of reflexes and nocturnal cramps for last 6 months. Died 38 days later of a MI.

V. Retinal Changes-Hemorrhage and degeneration

Most of the 9 reports that had retinal changes (hem retinal, retinal degenerat, retinal dis, occlu retinal art, thromb retinal vein) appeared to be resulted from underlying conditions or did not have enough details provided to determine if there was a causal relationship with amiodarone use. The 2 literature cases of papillopathy associated with disc swelling and hemorrhages submitted to the SRS under #467998 were presented above with papilledema. The other cases are summarized below.

A female had *retinal degeneration* after 18 months of amiodarone 200 mg PO daily for 540 days.(#1801890, 1996, UK). No details provided.

A 76 year old female developed *macular degeneration* coincident with amiodarone. (#814117, 1991, TX). No details provided.

A 65 year old male developed *blurred vision, increased prothrombin time, posterior vitreous detachment with old hemorrhage and underwent eye surgery*. It appeared to be due to a drug interaction with Coumadin and amiodarone. (#1763473/1723337/1720885, 1995, NY)

V. Other Visual Changes-abnormal vision, photophobia, dry eyes, and halos are labeled.

Visual Field Defects

Eleven cases had visual field defects in the SRS associated with amiodarone (cases under blindness with visual field defects are not included in these counts). One case was due to a CVA (#578188).

In the 10 remaining cases of visual field defects, there were 4 that had hypertension, vascular disease and/or history of cataracts. Some of the cases presented with one or more symptoms of optic neuritis-5, papilledema-3, optic atrophy-1, and intracranial hypertension-1. The time to onset for visual field defects occurred with chronic use of amiodarone from 4 months to 4 years (mean 13.8 months) and 2 were unknown. The doses were within the normal dosage range of 200 to 600 mg (mean 343.7 mg) and 2 were unknown. The visual field defect involved both eyes-4, left eye-2, right eye-1 and not mentioned which eye(s) defect in-3. Three were left with a visual disability, 3 patients recovered, and the outcome was unknown in 4.

There was a new MEDWATCH report of visual field defect with corneal microdeposits but not in the SRS and it is summarized below.

A 72 year old male with history of atrial fibrillation, gastroesophageal reflux, and pulmonary embolism in 1981 was started on amiodarone 200 mg PO daily in October 1995. Ten months later he presented with quadrantanopia *(visual field defect)*. Ophthalmological examination showed: *corneal microdeposits*, vessels Doppler was normal, visual evoked responses found a retrobulbar conduction slowing. Ischemic etiology was evoked. Amiodarone was continued. He was diagnosed with *retrobulbar neuritis*. Concomitant med: fluinidione, domperiodone, ranitidine. Reporter considered the event to be serious. (New MEDWATCH report, 1997, 15 day, France)

Diplopia

Three cases of diplopia were identified in the SRS. One case was excluded because the event was related to Dilantin toxicity (921407/1452468). The 2 remaining cases are summarized below.

1. A female with history of arrhythmias and a pacemaker received amiodarone for six months. She was

admitted to the hospital with ophthalmoplegia manifested by *diplopia* and a non-reactive pupil. The patient's neurologist discontinued amiodarone, and the symptoms resolved. (#1465026, 1994, 15 day, WI)

2. A 71 year old male with history of sudden cardiac death secondary to ventricular tachycardia, non Q Wave MI, DM, CRI, Raynaud's was started on amiodarone 400 mg PO daily in December 1993. He noticed a rash on his ankles on February 7th. This rash spread upwards and he complained of abdominal pain and *intermittent double vision* since February 18 and was admitted. The rash was a macular papular rash with confluent areas and excoriation. Concomitant meds; insulin, Isordil, digoxin, Lasix, heparin, amlodipine, gemfibrozil, and NTG. (#1470246, 1994, direct, FL)

There was a new MEDWATCH report of diplopia not in the SRS.

A 75 year old male with history of hypothyroidism, ischemic heart disease, and chronic open angle glaucoma diagnosed in 1990 was started on amiodarone 600 mg PO daily. Concomitant meds: pilocarpine 4%, and Betoptic 0.5%. Two months after beginning amiodarone therapy he presented with *reduced right visual acuity and pain in both eyes* which was worsened on eye movement and colors were less clear in the right eye. One week later he began to experience *horizontal diplopia* and ophthalmology examination at this time showed visual acuities were unchanged, but the conjunctiva was diffusely inflamed chemosed bilaterally, color vision was reduced on both sides. Normal thyroid and lab results. CT scan showed marked increase in size of all the extraocular muscles, but particularly the medial rectus on both sides with crowding of the orbital apex. A diagnosis of *dysthyroid eye disease* was made and he was treated with acetazolamide and prednisolone. Over the next week there was gradual improvement in both symptoms and clinical sign. After 4 weeks visual acuities had returned to baseline, chemosis had resolved and there was a full range of extraocular movements. (New MEDWATCH, 1997, 15 day, UK-also was published in the Br. J. Ophthalmol., 1996:80(9),851-852).

List of Drugs in the SRS that had the following most frequently reported events (as of 3/7/97):

Optic Neuritis:

isotretinoin (38), ethambutol (33), fluoxetine (33), amiodarone (32), ibuprofen (31)

Papilledema:

isotretinoin (53), levonorgestrel (51), somatrem (20), minocycline (17), danazole (13), ibuprofen (11), amiodarone (10)

Blindness:

norethindrone (69), mestranol (51), cisplatin (40), estradiol (37), diatrizoic acid (33), fluoxetine (33)... amiodarone (13)

DISCUSSION AND CONCLUSION:

In response to your Consult request, we have evaluated all ophthalmological adverse events associated with amiodarone in the SRS. For your information, all were with the oral

formulation of amiodarone. The majority of the events consisted of one or multiple of the optic neuropathy in one or both eyes: optic nerve (optic neuritis, optic atrophy), corneal microdeposits (corneal opacity, corneal lesion), lens opacities and cataracts, optic disk (papilledema) or retina changes (retina hemorrhage, retinal degeneration). The signs and symptoms from these neuropathies might be manifested as abnormal vision, blindness, amblyopia, visual field defect, or diplopia. The labeling has listed corneal deposits, optic neuritis, photophobia and abnormal vision in the Precautions and Adverse Reactions sections. However, symptoms related to these labeled events were not listed. Most importantly our evaluation indicates that further optic neuropathy associated with amiodarone might develop into loss of vision which is disabling and not always reversible as the label claims.

Most of the ophthalmological events occurred in the males and elderly. For blindness reports, most patients had optic neuritis prior to progressing to optic atrophy or loss of vision in one or both eyes. The mean time to onset was 7 months. Additionally, there were 15 reports of diagnosed papilledema occurring within a mean onset of 10 months. It is unknown whether optic neuritis occurred first and progressed into further changes in the optic disc area with edema. Visual field defects with reduction or loss of visual acuity or diplopia could be manifested as symptoms of these optic neuropathy.

Amiodarone is known to cause microdeposits in the corneal region of the eye. Thus corneal lesions or abrasions should not be unexpected. As for reports of cataract and retinal changes, it is difficult to determine based on the available information if other etiology, vascular disease or aging plays any role.

There were several published articles on amiodarone related ophthalmological effects. Four had been included in the above summary. According to the authors in these articles, amiodarone is a benzofuran derivative which can bind to polar lipids and accumulate in the lysosomes leading to lipidosis and may cause harmful ophthalmologic changes in susceptible individuals. And because of its extremely long half-life the drug may stay in the body for a long time and it takes time for a patient to recover once the drug is discontinued. The mechanism of amiodarone related corneal microdeposits is unknown. It was suggested in one article (Drug Safety 9 (3); 1993) that the clinical appearance of the cornea appears to be dose related. The SRS case series did not indicate a pattern of dose related events. However, it is noted that the reports of blindness and papilledema appeared to occur after a mean of 7 to 10 months use of amiodarone. It is also noted that some of these reports stated that amiodarone was not discontinued after the optic neuropathy was diagnosed. There could be a risk/benefit concern on this population by not discontinuing amiodarone due to the long half-life of the drug and patients' underlying disease.

In conclusion, the number of adverse ophthalmologic reports has increased in the last three years, but so has the drug usage increased during this same time. Current labeling does not reflect postmarketing experiences on the potential serious and disabling ophthalmological events which are also irreversible in some cases, such as loss of vision in one or both eyes.

/S/
Nancy Chamberlin, Pharm.D., R.Ph.

Concur:

/S/
Min Chen, R.Ph., M.S.
Group Leader

/S/
David Barash, R.Ph.
Chief, Reports Evaluation Branch

cc:
HF-2 Kennedy/Goldman
HFD-110 Willard/Stockbridge
HFD-730 Guinee
HFD-733 Davis/Graham
HFD-735 Chamberlin/Chen/Barash/Bacsanyi/Chron/MAR
#amioeye

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18972/S018

CORRESPONDENCE

ORIGINAL

WYETH-AYERST RESEARCH

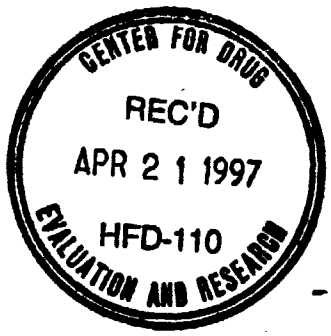
P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

April 16, 1997

NDA No. 18-972
Cordarone® Tablets



Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Attn: Document Control Room, HFD-110
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

NDA NO. 18-972 SUPPL. NO. 016
NDA SUPPL FOR SLR

"SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED"

Dear Dr. Lipicky:

Reference is made to our approved New Drug Application No. 18-972 for Cordarone®, amiodarone hydrochloride, Tablets.

We are submitting herewith a "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c)(2)(i) in order to strengthen the safety information in the labeling that is necessary for the safe and effective use of this drug product.

We have modified or expanded the text on optic disorders in the **Warnings, Precautions,** and **Adverse Reactions** sections of the labeling. Additionally, we have revised the text pertaining to patient monitoring in the **Precautions/SURGERY/Adult Respiratory Distress Syndrome** subsection, and we have added a new adverse drug event term, "angioedema" to the **Adverse Drug Reactions** section. Details of these changes and a description of the information to support them is provided below.

ORIGINAL

Optic Disorders

1. **Warnings Section**:

We have added a "LOSS OF VISION" subheading and paragraph of text relating to optic neuropathy and optic neuritis. This new **Warnings** subsection appears between the current labeling subsections pertaining to "LIVER INJURY" and "PREGNANCY : PREGNANCY CATEGORY D".

2. **Precautions Section/CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION** subsection:
We have modified this subsection to include an additional statement relating to optic neuropathy and optic neuritis.

3. **Adverse Reactions Section**

In the third sentence of the first paragraph of this section we have deleted the words so that the third sentence reads **"They are often reversible with dose reduction or cessation of Cordarone treatment."**

We have also added a paragraph regarding various ophthalmic abnormalities to this section. The new text precedes the current fourth paragraph which discusses corneal microdeposits and other eye symptoms.

The labeling changes pertaining to optic disorders are based on ophthalmic abnormalities reported coincidentally with Cordarone therapy. In support of these changes we are providing the information shown below.

Tab 1. Copy of a Narrative Alert Report for an increased frequency of optic neuritis for Cordarone® Tablets submitted to FDA under 21 CFR 314.80 on February 14, 1997.

Tab 2. Copies of all Adverse Drug Experience Reports (FDA Form 3500) in the Wyeth-Ayerst Data Base pertaining to optic disorders. Please note that all of these Reports were previously submitted to FDA under 21 CFR 314.80.

Tab 3. Full copies of several articles from the medical literature pertaining to ophthalmic events associated with amiodarone administration.

Tab 4. Copies of abstracts of articles pertaining to amiodarone and/or eye diseases, obtained by on-line searches of the Derwent Drug File and EMBASE data bases for the period 1974-1988.

Tab 5. Copies of abstracts of articles pertaining to amiodarone and/or eye diseases, obtained by on-line searches of the Medline and EMBASE data bases. The Medline search was "comprehensive" in that all pertinent articles in the data base were retrieved. The EMBASE search was confined to the period 1988-to the present.

In regard to the copies of abstracts provided in this submission, please note that some abstracts may have been retrieved in more than one search and will therefore appear more than once.

Revised Patient Monitoring Text in the Precaution/SURGERY/Adult Respiratory Distress Syndrome Subsection

Precautions Section/SURGERY/Adult Respiratory Distress Syndrome (ARDS) subsection:

We have deleted the last sentence of this subsection and added the sentence "**Until further studies have been performed, it is recommended that FiO_2 and determinants of oxygen delivery to the tissues (e.g., SaO_2, PaO_2) be closely monitored in patients on Cordarone.**"

This labeling change is based on text pertaining to ARDS which was submitted to the Division in Supplement 014 on April 24, 1995 and approved on October 18, 1995.

New Adverse Drug Reactions Term: Angioedema

Adverse Reactions Section:

We have relocated the penultimate paragraph of the **Adverse Relations** section in the current labeling so that it immediately precedes the sentence "The following side-effects rates are based on a retrospective study of 241 patients treated for 2 to 1, 515 days (mean 441.3 days).

The relocated sentence has also been slightly modified to delete the term "optic neuritis" and add the term "angioedema". The relocated sentence now reads "**Hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudotumor cerebri, thrombocytopenia, and angioedema also have been reported in patients receiving Cordarone.**"

This labeling change is based on the Division's request in the letter to Wyeth-Ayerst dated February 11, 1997 to add the term "angioedema" to the **Adverse Reactions** section.

Included in this submission are 16 sets of mounted, final printed labeling (FPL) at Tab 6. To facilitate the review of the FPL we have also included two copies of the draft labeling used as a template for preparation of the FPL at Tab 7, and two copies of the current Cordarone Tablets package insert at Tab 8.

Please be advised that we have implemented the use of the FPL included in this submission.

We trust that you will find this FPL satisfactory and that this "Special Supplement" will be approved at your earliest convenience. Should any questions arise, please telephone the undersigned at (610) 902-3770 or Ms. Jean Lassen at (610) 902-3762.

Sincerely,

Mr. Timothy K. Ressler
Manager, Marketed Products
U.S. Regulatory Affairs

JL/TKR/drk.314a.doc

ORIGINAL

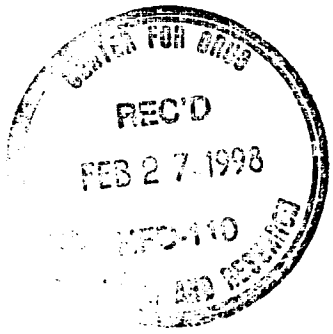
WYETH-AYERST RESEARCH

U.S. REGULATORY AFFAIRS

NDA SUPPL AMEND
SLR-015 (BL) & SLR-016 (BL) & SLR-017 (BL)

February 26, 1998

Cordarone® Tablets
NDA No. 18-972/S-015, S-016, and S-017



Raymond J. Lipicky, M. D. Director
Division of Cardio-Renal Drug Products
Attention: Document Control Room HFD-110
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lipicky:

Reference is made to our approved New Drug Application No. 18-972 for Cordarone®, amiodarone, Tablets.

Reference is also made to labeling supplements S-015 submitted January 17, 1996, S-016, submitted April 16, 1997, and S-017, submitted April 24, 1997.

In the letters commenting on these supplements (provided in Tab 1), the Division has requested a number of changes in the draft labeling or FPL originally submitted by Wyeth-Ayerst.

Although we agree with some of the Division's recommendations in these letters, and will revise the Cordarone Tablets labeling accordingly, we would like to propose alternate language for some of the text recommendations made by the Division.

On October 16, 1997 Wyeth-Ayerst representative, Ms. Jean Lassen, telephoned Consumer Safety Officer Diana Willard, to ask for administrative guidance regarding the best way to update the Cordarone labeling with important safety data in supplements 015, 016, and 017 on which the Division and Wyeth-Ayerst agreed, but also to resolve the issues in these supplements on which no agreement had been reached. Ms. Willard advised that we should submit draft labeling indicating the areas of agreement with text prescribed by the Division, and areas of disagreement. the Division's recommendations. In the latter case she requested that we provide justification our position.

We are providing herewith four copies of the draft labeling requested by Ms. Willard which reflects the areas of agreement with the Division's recommendations as well as the alternate language that we are proposing. We are also providing information to support the alternate language. This submission is organized as follows:

Tab 1. Copies of the Divisions Letters of Comment for Supplements 015, 016, and 017

Tab 2. Wyeth-Ayerst Comments on the Draft Labeling Included in this Submission

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710 • FAX (610) 964-5973

ORIGINAL

LTH-138 D

Section 1.

List of the specific labeling issues in supplements 015, 016, and 017 indicating issues for which Wyeth -Ayerst is in agreement with the Division's recommendations, and issues for which we are proposing alternate language.

Section 2.

Justification for proposed alternate language for the **Precautions/**SURGERY/*Adult Respiratory Distress Syndrome* Subsection including articles from the medical literature

Tab 3. Draft labeling

Tab 4. Current FPL in use for Cordarone Tablets

If you have any questions regarding this submission, please contact Ms. Jean Lassen at (610) 902-3762.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products I
U. S. Regulatory Affairs

DCM/IL/drk.510.doc