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March 13, 2001

**BY HAND DELIVERY**

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852



Re: ANDA Suitability Petition for Amiodarone Hydrochloride 100 mg Tablets

Dear Sir or Madam:

Olsson, Frank and Weeda, P.C. (OFW) respectfully submits this suitability petition pursuant to 21 U.S.C. §355(j)(2)(C) and 21 C.F.R. §§ 10.30 and 314.93. OFW requests that the Food and Drug Administration (FDA) determine that 100 mg tablets of amiodarone hydrochloride are suitable for an Abbreviated New Drug Application (ANDA) based on the listed drug Cordarone® Tablets, **200** mg.

## ACTION REQUESTED

OFW seeks a determination that a 100 mg amiodarone hydrochloride tablet drug product is suitable for an ANDA, based on the listed drug Cordarone Tablets, 200 mg.

## STATEMENT OF GROUNDS

The reference listed drug for the proposed generic drug product will be Cordarone Tablets (amiodarone hydrochloride), 200 mg. Cordarone is approved for use at daily doses up to 1600 mg per day, with a usual maintenance dose of 400 mg per day.

The approved Cordarone labeling, however, states, in boldface type, **"The lowest effective dose should be used to prevent the occurrence of side effects."** For many patients, 100 mg is a sufficient dose and, in fact, 9.1% of patients receiving amiodarone take the drug at a dose below 200

mg. See IMS NDTI Audit (February 9, 2001), copy attached (Tab 1). Another 0.7% take a 1-1/2 tablet dose. Id. In fact, the 200 mg version of the Cordarone is scored, to make it possible for patients to cut the tablet in half. The availability of 100 mg amiodarone hydrochloride tablets will make it easier and more convenient for patients prescribed smaller daily doses of amiodarone hydrochloride tablets to take their medication. Therefore, OFW seeks a determination that amiodarone hydrochloride tablets, 100 mg, is suitable for an ANDA, with Cordarone Tablets 200 mg as the reference listed drug.

The active ingredient of the proposed drug product will be the same as that in Cordarone Tablets. (The sponsor of the ANDA for the proposed 100 mg product, Eon Labs Manufacturing, Inc., has already received approval for a 200 mg and a 400 mg product.)

Because the active ingredient is the same, and because the proposed drug product will be bioequivalent to Cordarone Tablets, the proposed drug product can be expected to have the same therapeutic effect as Cordarone Tablets when administered to patients under the same conditions of use. In accordance with FDA regulations and policies, the company will either obtain a bioequivalency waiver or will demonstrate bioequivalence in its ANDA submission.

Pursuant to 21 C.F.R. § 3 14.93(d), a copy of the approved labeling for Cordarone Tablets is attached (Tab 2). A copy of the proposed labeling for a generic 100 mg strength of that drug product is also attached, both with the changes from the approved labeling indicated in a "red-lined" version (Tab 3), and as the proposed labeling will actually be printed (Tab 4). No changes to the labeling are necessary other than those necessitated by the different strength and manufacturer. The brand name Cordarone Tablets will be deleted, and descriptions of the strength and tablet and references to the manufacturer of Cordarone Tablets will be modified.

## ENVIRONMENTAL IMPACT

Pursuant to 21 C.F.R. § 25.3 l(a), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

## ECONOMIC IMPACT

According to 2 1 C.F.R. §10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of this petition.

**CERTIFICATION**

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition,

Respectfully submitted,

Naomi J. Halpern

Arthur Y. Tsien
Naomi Joy Levan Halpern

NJLH:lac
Attachments

| CORDARONE 200mg - Product Dosage | | |
|---|---|---|
| (#'s in thousands) | P-Drug Appearances 1999 | % Share |
| CORDARONE - 200MG | | |
| 1 PER DAY | 263 | 54.2 |
| 2 PER DAY | 110 | 22.8 |
| LESS THAN 1 ONCE DAILY | 36 | 7.4 |
| 2 TWO TIMES DAILY | 22 | 4.6 |
| 3 PER DAY | 11 | 2.3 |
| UNKNOWN OR UNSPECIFIED | 11 | 2.2 |
| 2 THREE TIMES DAILY | 6 | 1.3 |
| LESS THAN 1 EVERY OTHER DAY | 4 | 0.9 |
| 4 PER DAY | 4 | 0.8 |
| 1 EVERY OTHER DAY | 4 | 0.8 |
| 1 1/2 DAILY | 4 | 0.7 |
| 1 TIME ONLY | 3 | 0.6 |
| 3 PER WEEK | 3 | 0.6 |
| 2 FOUR TIMES DAILY | 3 | 0.6 |
| TOTAL | 484 | 99.8 |

Source: IMS NDTI Audit (National Disease and Therapeutic Index)

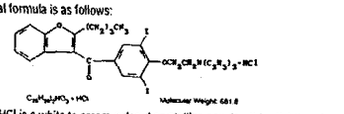
2/9/01

DUCTS

# Cordarone®
(amiodarone HCl)
## TABLETS

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

The structural formula is as follows:



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

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

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

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

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

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

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

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

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

Following single dose administration in 12 healthy subjects, Cordarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA). In patients, following discontinuation of chronic oral therapy, Cordarone has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26 to 107 days, with a mean of approximately 53 days and most patients in the 40- to 55-day range. In the absence of a loading-dose period, steady-state plasma concentrations, at constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat. The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of Cordarone should be based on individual patient requirements (see "**DOSAGE AND ADMINISTRATION**").

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

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

Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of Cordarone, effects on abnormal rhythms are not seen before 2 to 3 days and usually require 1 to 3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods with chronic administration. 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 more aggressive treatment.

Several predictors of success not based on PES have also been suggested including complete elimination of all nonsustained ventricular tachycardia on ambulatory monitor 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 capable of preventing bradycardia).

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

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

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

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

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

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

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

| | Placebo | | Amiodarone | | Relative Risk | |
|---|---|---|---|---|---|---|
| | N | Deaths | N | Deaths | | 95%CI |
| EMIAT | 743 | 102 | 743 | 103 | 0.99 | 0.76-1.31 |
| CAMIAT | 596 | 68 | 608 | 57 | 0.88 | 0.58-1.16 |

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

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

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

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

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

*Interstitial/alveolar pneumonitis* may result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), due to inhibition of phospholipase, will be present in most cases of Cordarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on Cordarone therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of Cordarone-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the Cordarone to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone-induced pulmonary toxicity was usually noted within the first week, and a clinical improvement was greatest in the first two to three weeks.

Chest X ray changes usually resolve within two to four months. According to some experts, steroids may prove beneficial. Prednisone in doses of 40 to 60 mg/day or equivalent doses of other steroids have been given and tapered over the course of several weeks depending upon the condition of the patient. In some cases rechallenge with Cordarone at a lower dose has not resulted in return of toxicity. Recent reports suggest that the use of lower loading and maintenance doses of Cordarone are associated with a decreased incidence of Cordarone-induced pulmonary toxicity.

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

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

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

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

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

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

**Cordarone®**
(amiodarone HCl)
Tablets
CI 6036-Z

**Cordarone®**
(amiodarone HCl)
Tablets
CI 6036-2

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

**Neonatal Hypo- or Hyperthyroidism**

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

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

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

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

## PRECAUTIONS

**Impairment of Vision**

*Optic Neuropathy and/or Neuritis*

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

*Corneal Microdeposits*

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

**Neurologic**

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

**Photosensitivity**

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

**Thyroid Abnormalities**

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

Hypothyroidism has been reported in 2 to 4% of patients in most series, but in 8 to 10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal.

Hypothyroidism is best managed by Cordarone dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue Cordarone in some patients.

Hyperthyroidism occurs in about 2% of patients receiving Cordarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Hyperthyroidism is best identified by relevant clinical symptoms and signs, accompanied usually by abnormally elevated levels of serum $T_3$ RIA, and further elevations of serum $T_4$, and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of Cordarone. The institution of antithyroid drugs, ß-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism. Experience with thyroid surgery in this setting is extremely limited, and this form of therapy runs the theoretical risk of inducing thyroid storm. Cordarone-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

**Surgery**

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

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

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

**Laboratory Tests**

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

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

**Drug Interactions**

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

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

*Cyclosporine*

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

*Digitalis*

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

*Anticoagulants*

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

*Antiarrhythmic Agents*

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

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

In general, combination of Cordarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to Cordarone.

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

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

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

SUMMARY OF DRUG INTERACTIONS WITH CORDARONE

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

*NAPA = n-acetyl procainamide.

**Electrolyte Disturbances**

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

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Amiodarone HCl was associated with a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control even at the lowest dose level tested, i.e., 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).

Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with Cordarone were negative.

In a study in which amiodarone HCl was administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*).

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

**Pregnancy: Pregnancy Category D**

See "**WARNINGS, Neonatal Hypo- or Hyperthyroidism.**"

**Labor and Delivery**

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

**Nursing Mothers**

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

**Pediatric Use**

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

**Geriatric Use**

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

## ADVERSE REACTIONS

Adverse reactions have been very common in virtually all series of patients treated with Cordarone for ventricular arrhythmias with relatively large doses of drug (400 mg/day and above), occurring in about three-fourths of all patients and causing discontinuation in 7 to 18%. The most serious reactions are pulmonary toxicity, exacerbation of arrhythmia, and rare serious liver injury (see "**WARNINGS**"), but other adverse effects constitute important problems. They are often reversible with dose reduction or cessation of Cordarone treatment. Most of the adverse effects appear to become more frequent with continued treatment beyond six months, although rates appear to remain relatively constant beyond one year. The time and dose relationships of adverse effects are under continued study.

Neurologic problems are extremely common, occurring in 20 to 40% of patients and including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy; they are rarely a reason to stop therapy and may respond to dose reductions or discontinuation (see "**PRECAUTIONS**").

Gastrointestinal complaints, most commonly nausea, vomiting, constipation, and anorexia, occur in about 25% of patients but rarely require discontinuation of drug. These commonly occur during high-dose administration (i.e., loading dose) and usually respond to dose reduction or divided doses.

Ophthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness, papilledema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities, and macular degeneration have been reported. (See "**WARNINGS.**")

Asymptomatic corneal microdeposits are present in virtually all adult patients who have been on drug for more than 6 months. Some patients develop eye symptoms of halos, photophobia, and dry eyes. Vision is rarely affected and drug discontinuation is rarely needed.

Dermatological adverse reactions occur in about 15% of patients, with photosensitivity being most common (about 10%). Sunscreen and protection from sun exposure may be helpful, and drug discontinuation is not usually necessary. Prolonged exposure to Cordarone occasionally results in a blue-gray pigmentation. This is slowly and occasionally incompletely reversible on discontinuation of drug but is of cosmetic importance only.

Cardiovascular adverse reactions, other than exacerbation of the arrhythmias, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dosage reduction but may require a pacemaker for control. CHF rarely requires drug discontinuation. Cardiac conduction abnormalities occur infrequently and are reversible on discontinuation of drug.

In postmarketing surveillance, hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudotumor cerebri, thrombocytopenia, angioedema, bronchiolitis obliterans organizing pneumonia (possibly fatal), pleuritis, pancreatitis, toxic epidermal necrolysis, myopathy, hemolytic anemia, aplastic anemia, pancytopenia, and neutropenia also have been reported in patients receiving Cordarone.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

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

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

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

**The following side effects were each reported in less than 1% of patients:**
Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities.

In surveys of almost 5,000 patients treated in open U.S. studies and in published reports of treatment with Cordarone, the adverse reactions most frequently requiring discontinuation of Cordarone included pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, congestive heart failure, and elevation of liver enzymes. Other symptoms causing discontinuations less often included visual disturbances, solar dermatitis, blue skin discoloration, hyperthyroidism, and hypothyroidism.

## OVERDOSAGE

There have been a few reported cases of Cordarone overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. The acute oral $LD_{50}$ of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.

In addition to general supportive measures, the patient's cardiac rhythm and blood pressure should be monitored, and if bradycardia ensues, a ß-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither Cordarone nor its metabolite is dialyzable.

## DOSAGE AND ADMINISTRATION

BECAUSE OF THE UNIQUE PHARMACOKINETIC PROPERTIES, DIFFICULT DOSING SCHEDULE, AND SEVERITY OF THE SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, CORDARONE SHOULD BE ADMINISTERED ONLY BY PHYSICIANS WHO ARE EXPERIENCED IN THE TREATMENT OF LIFE-THREATENING ARRHYTHMIAS WHO ARE THOROUGHLY FAMILIAR WITH THE RISKS AND BENEFITS OF CORDARONE THERAPY, AND WHO HAVE ACCESS TO LABORATORY FACILITIES CAPABLE OF ADEQUATELY MONITORING THE EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT.

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

*For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia:* Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1,600 mg/day are required for 1 to 3 weeks (occasionally longer) until initial therapeutic response occurs. (Administration of Cordarone in divided doses with meals is suggested for total daily doses of 1,000 mg or higher, or when gastrointestinal intolerance occurs.) If side effects become excessive, the dose should be reduced. Elimination of recurrence of ventricular fibrillation and tachycardia usually occurs within 1 to 3 weeks, along with reduction in complex and total ventricular ectopic beats.

Upon starting Cordarone therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs (see section on "**Drug Interactions**"). When adequate arrhythmia control is achieved, or if side effects become prominent, Cordarone dose should be reduced to 600 to 800 mg/day for one month and then to the maintenance dose, usually 400 mg/day (see "**CLINICAL PHARMACOLOGY–Monitoring Effectiveness**"). Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses. Cordarone may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a b.i.d. dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation and by patient tolerance. Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity (see "**CLINICAL PHARMACOLOGY**").

**The lowest effective dose should be used to prevent the occurrence of side effects. In all instances, the physician must be guided by the severity of the individual patient's arrhythmia and response to therapy.**

When dosage adjustments are necessary, the patient should be closely monitored for an extended period of time because of the long and variable half-life of Cordarone and the difficulty in predicting the time required to attain a new steady-state level of drug. Dosage suggestions are summarized below:

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

## HOW SUPPLIED

Cordarone® (amiodarone HCl) Tablets are available in bottles of 60 tablets and in Redipak® cartons containing 100 tablets (10 blister strips of 10) as follows:

200 mg, NDC 0008-4188, round, convex-faced, pink tablets with a raised "C" and marked "200" on one side, with reverse side scored and marked "WYETH" and "4188."

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

℞ only

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

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

CI 6036-2 Revised August 1, 2000

~~Cordarone~~AMIODARONE Hydrochloride
Tablets

**DESCRIPTION:**

~~Cordarone~~Amiodarone hydrochloride is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects, available for oral administration as yellow, scored tablets. Each tablet for oral administration contains ~~200~~100 mg of amiodarone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, povidone, and D&C Yellow #10 Aluminum Lake.

~~Cordarone~~Amiodarone hydrochloride 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:

$C_{25}H_{29}I_2NO_3 \cdot HCl$ M.W.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~~amiodarone hydrochloride is effective in the prevention or suppression of experimentally induced arrhythmias. The antiarrhythmic effect of ~~Cordarone~~amiodarone 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 $\alpha$- and $\beta$-adrenergic inhibition.

~~Cordarone~~Amiodarone 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~~Amiodarone 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~~amiodarone as they are evidence of its pharmacological action, although ~~Cordarone~~amiodarone 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~~amiodarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. After oral dosing, however, ~~Cordarone~~amiodarone produces no significant change in left ventricular ejection fraction (LVEF),, even in patients with depressed LVEF. After acute intravenous dosing in man, ~~Cordarone~~amiodarone may have a mild negative inotropic effect.

**Pharmacokinetics**

Following oral administration in man, ~~Cordarone~~amiodarone is slowly and variably absorbed. The bioavailability of ~~Cordaron~~amiodarone is approximately 50%, but has varied between 3 5 and 65% in various studies. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100 to 600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day . These means, however, include considerable individual variability. Food increases the rate and extent of absorption of ~~Cordarone~~amiodarone. The effects of food upon the bioavailability of ~~Cordarone~~amiodarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration ($C_{max}$) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration ($T_{max}$) by 37%. The mean AUC and mean $C_{max}$ of desethylamiodarone increased by 55% (range 58 to 101%) and 32% (range 4 to 84%) respectively, but there was not change in the $T_{max}$ in the presence of food.

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

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither arniodarone nor DEA is dialyzable. In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 ml/hr/kg. Age, sex, renal disease and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of intravenous amiodarone in cirrhotic patients, significantly lower $C_{max}$ and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower clearances (about 100 ml/hr/kg) than younger subjects (about 150 ml/hr/kg) and an increase in $T_{1/2}$ from about 20 to 47 days. In patients with severe left ventricular dysfunction, the

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

Following single dose administration in 12 healthy subjects, ~~Cordarone~~amiodarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA). In patients, following discontinuation of chronic oral therapy, ~~Cordarone~~Amiodarone hydrochloride 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 m&n plasma-elimination half-life was approximately 6 1 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 1 O-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~~amiodarone should be based on individual patient requirements **(see "DOSAGE AND ADMINISTRATION").**

Amiodarone 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.

Amiodarone 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~~amiodarone hydrochloride, 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, ant&rhythmic effects persist for weeks or months after ~~Cordarone~~amiodarone hydrochloride 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~~amiodarone 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~~amiodarone (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~~amiodarone 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~~amiodarone. 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~~amiodarone, as for other agents, the prescriber of ~~Cordarone~~amiodarone 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~~amiodarone, 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~~amiodarone, the duration of follow- up, the dose of ~~Cordarone~~amiodarone, the use of additional antiarrhythmic agents, and many other factors. As ~~Cordarone~~amiodarone 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~~amiodarone hydrochloride 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 fi-om controlled trials that the use of ~~Cordarone~~amiodaone favorably affects survival.

~~Cordarone~~Amiodarone 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~~amiodarone should be carried out in the hospital.

**CONTRAINDICATIONS:**

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

**WARNINGS:**

**~~Cordarone~~Amiodarone hydrochloride is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity. ~~Cordarone~~Amiodarone hydrochloride 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~~amiodarone hydrochloride, 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~~amiodarone hydrochloride 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~~amiodarone hydrochloride 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~~amiodarone hydrochloride is an acceptable risk, ~~Cordarone~~amiodarone hydrochloride 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~~amiodarone hydrochloride effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of ~~Cordarone~~amiodarone hydrochloride 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~~amiodarone hydrochloride must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone hydrochloride body burden. A similar problem exists when ~~Cordarone~~ amiodarone hydrochloride 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 (561730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months. ~~Cordarone~~Amiodarone therapy was evaluated in two multi-centered, randomized double-blind, placebo-controlled trials involving 1202 (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CAMIAT) and 1486 (European Myocardial Infarction Arrhythmia Trial;

**EMIAT) post-MI patients followed for up to 2 years. Patients in CAMIAT qualified with ventricular arrhythmias, and those randomized to amiodarone received weight- and response-adjusted doses of 200 to 400 mg/day. Patients in EMIAT qualified with ejection fraction <40%, and those randomized to amiodarone received fixed doses of 200 mg/day. Both studies had weeks-long loading dose schedules. Intent-to-treat all-cause mortality results were as follows:**

| | Placebo | | Amiodarone | | Relative Risk | |
|---|---|---|---|---|---|---|
| | N | Deaths | N | Deaths | | 95% Cl |
| EMIAT | 743 | 102 | 743 | 103 | 0.99 | 0.76-1.31 |
| CAMIAT | 596 | 68 | 606 | 57 | 0.88 | 0.58-1.16 |

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

**Pulmonary Toxicity**

~~Cordarone~~Amiodarone 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~~amiodarone 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~~amiodarone hydrochloride seems to result from either indirect or direct toxicity as represented by hypersensitivity pneumonitis or interstitial/alveolar pneumonitis, respectively.

*Hypersensitivitypneumonitis* usually appears earlier in the course of therapy, and rechallenging these patients with ~~Cordarone~~amiodarone 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 (CDS-positive) lymphocytosis is noted. Steroid therapy should be instituted and ~~Cordarone~~amiodarone therapy discontinued in these patients.

***Interstitial/alveolar pneumonifis*** 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 ofphospholipase, will be present in most cases of ~~Cordarone-induced~~amiodarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on ~~Cordarone~~amiodarone hydrochloride therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of ~~Cordarone-induced~~amiodarone-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to

withdrawal of the ~~Cordarone~~amiodarone 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~~ amiodarone 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~~ amiodarone are associated with a decreased incidence of ~~Cordarone-induced~~amiodarone-induced pulmonary toxicity. In a patient receiving ~~Cordarone~~amiodarone, 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~~amiodarone 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~~ amiodarone 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~~amiodarone-induced hypersensitivity pneumonitis is made, ~~Cordarone~~amiodarone should be discontinued, and treatment with steroids should be instituted. If a diagnosis o f ~~amiodarone-induced~~ interstitial/alveolar pneumonitis is made, steroid therapy should be instituted and, preferably, ~~Cordarone~~amiodarone discontinued or, at a minimum, reduced in dosage. Some cases of ~~Cordarone-induced~~amiodarone-induced interstitial/alveolar pneumonitis may resolve following a reduction in ~~Cordarone~~amiodarone 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~~ Amiodarone, 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~~ amiodarone 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~~ amiodarone 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~~ amiodarone 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~~ amiodarone.

**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~~ amiodarone therapy. The risks and complications of antiarrhythmic therapy with ~~Cordarone~~ amiodarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including funduscopy and slit-lamp examination, is recommended during administration of ~~Cordarone~~. (See "**ADVERSE REACTIONS**.")

~~**Neonatal Hypo- Or Hyperthyroidism**~~

~~Cordarone can cause fetal harm when administered to a pregnant woman~~amiodarone. ~~Although Cordarone use during pregnancy is uncommon, there have been~~(See "**ADVERSE REACTIONS.**")

**Neonatal Hypo- Or Hyperthyroidism**

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

In general, amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus. In pregnant rats and rabbits, amiodarone HCl in doses of 25 mg/kg/day (approximately 0.4 and 0.9 times, respectively, the maximum recommended human maintenance dose*) had no adverse effects in the fetus. In the rabbit, 75 mg/kg/day (approximately 2-7 times the maximum recommended human maintenance dose*) caused abortions in greater than 90% of the animals. In the rat, doses of 50 mg/kg/day or more were associated with slight displacement of the testes and an increased incidence of incomplete ossification of some skull and digital bones; at 100 mg/kg/day or more, fetal body weights were reduced; at 200 mg/kg/day there was an increased incidence of fetal resorption. (These doses in the rat are approximately 0.8, 1.6 and 3.2 times the maximum recommended human maintenance dose.*) Adverse effects on fetal growth and survival also were noted in one of two strains of mice at a dose of 5 mg/kg/day (approximately 0.04 times the maximum recommended human maintenance dose*).

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

**PRECAUTIONS**

**Impairment of Vision**

*Optic Neuropathy And/Or Neuritis*

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

*Cornea1 Microdeposits*

Cornea1 microdeposits appear in the majority of adults treated with ~~Cordarone~~ amiodarone. 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. Cornea1 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~~Amiodarone 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~~Amiodarone 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 $T_3$ (r $T_3$) 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~~amiodarone 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~~amiodarone 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~~amiodarone 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~~amiodarone hydrochloride dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue ~~Cordarone~~amiodarone in some patients.

Hyperthyroidism occurs in about 2% of patients receiving ~~Cordarone~~amiodarone hydrochloride, but the incidence may be higher among patients with prior inadequate dietary iodine intake. ~~Cordarone-induced~~Amiodarone hydrochloride-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 ~~induced~~amiodarone hydrochloride-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of ~~Cordarone~~amiodarone hydrochloride. 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~~Amiodarone hydrochloride-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

**Surgery**

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

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

*Adult Respiratory Distress Syndrome (ARDS):* Postoperatively, occurrences of ARDS have been reported in patients receiving ~~Cordarone~~amiodarone hydrochloride 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~~amiodarone hydrochloride.

**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~~amiodarone hydrochloride or discontinuing therapy.

~~Cordarone~~Amiodarone hydrochloride 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~~amiodarone hydrochloride 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~~amiodarone hydrochloride, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of ~~Cordarone~~amiodarone hydrochloride.

*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~~amiodarone hydrochloride 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~~amiodarone hydrochloride, 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~~amiodarone hydrochloride 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~~amiodarone hydrochloride.

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

In general, combination of ~~Cordarone~~amiodarone 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~~amiodarone hydrochloride. During transfer to ~~Cordarone~~amiodarone the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of ~~Cordarone~~amiodarone hydrochloride, when arrhythmia suppression should be beginning. The continued need for the other ant&rhythmic agent should be reviewed after the effects of ~~Cordarone~~amiodarone 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~~amiodarone is continued. In ~~Cordarone-treated~~amiodarone hydrochloride-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

~~Cordarone~~Amiodarone should be used with caution in patients receiving P-blocking agents or calcium antagonists because of the possible potentiation of bradycardia, sinus arrest, and AV block;

if necessary, ~~Cordarone~~amiodarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

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

SUMMARY OF DRUG INTERACTIONS WITH ~~CORDARONE~~AMIODARONE HYDROCHLORIDE

| Concomitant Drug | Interaction Onset (days) | Interaction Magnitude | Recommended Dose Reduction of Concomitant Drug |
|---|---|---|---|
| Warfarin | 3 to 4 | Increases prothrombin time by 100% | ↓ ⅓ to ½ |
| Digoxin | 1 | Increases serum concentration by 70% | ↓ ½ |
| Quinidine | 2 | Increases serum concentration by 33% | ⅓ to ½ (or discontinue) |
| Procainamide | <7 | Increases plasma concentration by 55%; NAPA* concentration by 33% | ⅓ (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~~amiodarone therapy.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Amiodarone HCl was associated with a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control even at the lowest dose level tested, *i.e., 5* mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).

Mutagenicity studies (Ames, micronucleus, and lysogenic tes~~amiodarone~~ were negative.

In a study in which ~~Cordarone~~amiodarone hydrochloride was administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*).

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

**Pregnancy: Pregnancy Category D**
**See "WARNINGS, Neonatal Hypo- or Hyperthyroidism."**
**Labor and Delivery**
It is not known whether the use of ~~Cordarone~~amiodarone during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect of ~~Cordarone~~amiodarone on the duration of gestation or on parturition.
**Nursing Mothers**
~~Cordarone~~Amiodarone 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~~amiodarone have been shown to be less viable and have reduced body-weight gains. Therefore, when ~~Cordarone~~amiodarone therapy is indicated, the mother should be advised to discontinue nursing.
**Pediatric Use**
The safety and effectiveness of ~~Cordarone~~amiodarone hydrochloride in pediatric patients have not been established.
**Geriatric Use**
Clinical studies of ~~Cordarone Tablets~~amiodarone hydrochloride tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or drug therapy.

**ADVERSE REACTIONS:**
Adverse reactions have been very common in virtually all series of patients treated with ~~Cordarone~~amiodarone hydrochloride 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~~amiodarone 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, cornea1 degeneration, photosensitivity, eye

discomfort, scotoma, lens opacities, and macular degeneration have been reported. (See "**WARNINGS.**")

Asymptomatic cornea1 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~~amiodarone 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. Bradycardiausually 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.

In postmarketing surveillance, 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~~amiodarone.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,5 15 days (mean 441.3 days).

**The following side effects were 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 US. studies and in published reports of treatment with ~~Cordarone~~amiodarone hydrochloride, the adverse reactions most frequently requiring discontinuation of ~~Cordarone~~amiodarone 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~~amiodarone hydrochloride overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. The acute oral LD,, of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.

In addition to general supportive measures, the patient's cardiac rhythm and blood pressure should be monitored, and if bradycardia ensues, a β-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither ~~Cordarone~~amiodarone 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~~AMIODARONE HYDROCHLORIDE 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~~AMIODARONE 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 an&rhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of ~~Cordarone~~amiodarone has not been determined. Because of the food effect on absorption, ~~Cordarone~~amiodarone should be administered consistently with regard to meals (see **"CLINICAL PHARMACOLOGY").** Individual patient titration is suggested according to the following guidelines.

*For Life-threatening Ventricular Arrhythmias, Such As Ventricular Fibrillation Or Hemodynamically Unstable Ventricular Tachycardia:* Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1,600 mg/day are required for 1 to 3 weeks (occasionally longer),, until initial therapeutic response occurs. (Administration of ~~Cordarone~~amiodarone hydrochloride 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~~amiodarone hydrochloride 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~~amiodarone hydrochloride 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~~Amiodarone 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~~amiodarone 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~~Amiodarone hydrochloride 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~~flat-faced, ~~pink tablets with a raised "C" and marked "200~~beveled edge, yellow tablets debossed "E" over bisect, and "144" below the bisect, and plain on ~~one side, with reverse side scored and marked "WYETH" and "4188~~the other side, available in bottles of 60, 90, 100, and 500."

**Keep tightly closed.**
**Store at room temperature, approximately 15-30° C (59-86° F). Protect from light.**
**Dispense in a light-resistant, tight container as defined in the USP, with a child-resistant closure as required.**

~~Use carton to protect contents from light~~Manufactured by:
Eon Labs Manufacturing Inc.
Laurelton, New York 11413

~~Rx only.~~

~~Manufactured for:~~
~~Wyeth Laboratories~~

~~A Wyeth-Ayerst Company~~
~~Philadelphia, PA 19101~~

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

AMIODARONE Hydrochloride
Tablets

**DESCRIPTION:**

Amiodarone hydrochloride is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects, available for oral administration as yellow, scored tablets. Each tablet for oral administration contains 100 mg of amiodarone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, povidone, and D&C Yellow # 10 Aluminum Lake.

Amiodarone hydrochloride is a benzofuranderivative: 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:

$C_{25}H_{29}I_2NO_3 \cdot HCl$ M.W.681.8

Amiodarone HCI 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, amiodarone hydrochloride is effective in the prevention or suppression of experimentally induced arrhythmias. The antiarrhythmic effect of amiodarone 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 $\alpha$- and $\beta$-adrenergic inhibition.

Amiodarone 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. Amiodarone 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 amiodarone as they are evidence of its pharmacological action, although amiodarone 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, amiodarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. After oral dosing, however, amiodarone produces no significant change in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF. After acute intravenous dosing in man, amiodarone may have a mild negative inotropic effect.

**Pharmacokinetics**

Following oral administration in man, amiodarone is slowly and variably absorbed. The bioavailability of amiodarone is approximately 50%, but has varied between 35 and 65% in various studies. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100 to 600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day. These means, however, include considerable individual variability. Food increases the rate and extent of absorption of amiodarone. The effects of food upon the bioavailability of amiodarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration ($C_{max}$) of amiodarone increased by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration ($T_{max}$) by 37%. The mean AUC and mean $C_{max}$ of desethylamiodarone increased by 55% (range 58 to 101%) and 32% (range 4 to 84%) respectively, but there was not change in the $T_{max}$ in the presence of food.

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

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable. In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 ml/hr/kg. Age, sex, renal disease and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of intravenous amiodarone in cirrhotic patients, significantly lower $C_{max}$ and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower clearances (about 100 ml/hr/kg) than younger subjects (about 150 ml/hr/kg) and an increase in $T_{1/2}$ from about 20 to 47 days. In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition T,,, of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac

abnormalities has been defined during chronic treatment with amiodarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

Following single dose administration in 12 healthy subjects, amiodarone exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA). In patients, following discontinuation of chronic oral therapy, Amiodarone hydrochloride has been shown to have a biphasic elimination with an initial one-halfreduction 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 53 5 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 amiodarone should be based on individual patient requirements **(see "DOSAGE AND ADMINISTRATION").**

Amiodarone 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.

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

Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of amiodarone hydrochloride, 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 amiodarone hydrochloride 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, cornea1 deposits and facial pigmentation, peripheral neuropathy, gastrointestinal and central nervous system effects.

**Monitoring Effectiveness**

Predicting me 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 amiodarone 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 amiodarone (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 amiodarone 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 amiodarone. 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 arniodarone, as for other agents, the prescriber of amiodarone should have access to (direct or through referral), and familiarity with, the full range of evaluator-y procedures used in the care of patients with life-threatening arrhythmias.

It is difficult to describe the effectiveness rates of amiodarone, 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 amiodarone, the duration of follow- up, the dose of amiodarone, the use of additional antiarrhythmic agents, and many other factors. As amiodarone 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), amiodarone hydrochloride 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 amiodarone favorably affects survival.

Amiodarone 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 amiodarone should be carried out in the hospital.

**CONTRAINDICATIONS:**

Amiodarone 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).

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

**WARNINGS:**

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

**Amiodarone hydrochloride 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 amiodarone hydrochloride, 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, amiodarone hydrochloride 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 amiodarone hydrochloride 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 amiodarone hydrochloride is an acceptable risk, amiodarone hydrochloride 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 amiodarone hydrochloride effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone hydrochloride 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 amiodarone hydrochloride must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone hydrochloride body burden. A similar problem exists when amiodarone hydrochloride 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.**

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

| | Placebo | | Amiodarone | | Relative Risk | |
|---|---|---|---|---|---|---|
| | N | Deaths | N | Deaths | | 95% Cl |
| EMIAT | 743 | 102 | 743 | 103 | 0.99 | 0.76-1.31 |
| CAMIAT | 596 | 68 | 606 | 57 | 0.88 | 0.58-1.16 |

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

**Pulmonary Toxicity**

Amiodarone 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 amiodarone 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 amiodarone hydrochloride 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 amiodarone 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 (CDS-positive) lymphocytosis is noted. Steroid therapy should be instituted and amiodarone 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 amiodarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on amiodarone hydrochloride therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of amiodarone-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the amiodarone 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 amiodarone at a lower dose has not resulted

in return of toxicity. Recent reports suggest that the use of lower loading and maintenance doses of amiodarone are associated with a decreased incidence of amiodarone-induced pulmonary toxicity. In a patient receiving amiodarone, 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, inpatients with life-threatening arrhythmias, discontinuation of amiodarone 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 ofrespiratory impairment (i.e., congestive heart failure with Swan-Ganz catheterization if necessary, respiratory infection, pulmonary embolism, malignancy, etc.) before discontinuing amiodarone 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 amiodarone-induced hypersensitivity pneumonitis is made, amiodarone should be discontinued, and treatment with steroids should be instituted. If a diagnosis of amiodarone-induced interstitial/alveolar pneumonitis is made, steroid therapy should be instituted and, preferably, amiodarone discontinued or, at a minimum, reduced in dosage. Some cases of amiodarone-induced interstitial/alveolar pneumonitis may resolve following a reduction in amiodarone 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**

Arniodarone, 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, arniodarone 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 amiodarone and in most cases are asymptomatic. If the increase exceeds three times normal, or doubles in a patient with an elevated baseline, discontinuation of amiodarone 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 amiodarone.

**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 amiodarone therapy. The risks and complications of antiarrhythmic therapy with amiodarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including funduscopy and slit-lamp examination, is recommended during administration of amiodarone. **(See "ADVERSE REACTIONS.")**

**Neonatal Hypo- Or Hyperthyroidism**

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

In general, amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus. In pregnant rats and rabbits, amiodarone HCl in doses of 25 mg/kg/day (approximately 0.4 and 0.9 times, respectively, the maximum recommended human maintenance dose*) had no adverse effects in the fetus. In the rabbit, 75 mg/kg/day (approximately 2-7 times the maximum recommended human maintenance dose*) caused abortions in greater than 90% of the animals. In the rat, doses of 50 mg/kg/day or more were associated with slight displacement of the testes and an increased incidence of incomplete ossification of some skull and digital bones; at 100 mg/kg/day or more, fetal body weights were reduced; at 200 mg/kg/day there was an increased incidence of fetal resorption. (These doses in the rat are approximately 0.8, 1.6 and 3.2 times the maximum recommended human maintenance dose. *) Adverse effects on fetal growth and survival also were noted in one of two strains of mice at a dose of 5 mg/kg/day (approximately 0.04 times the maximum recommended human maintenance dose*).

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

**PRECAUTIONS**

**Impairment of Vision**

*Optic Neuropathy And/Or Neuritis*

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

*Corneal Microdeposits*

Cornea1 microdeposits appear in the majority of adults treated with amiodarone.

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. Cornea1 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**

Amiodarone 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**

Amiodarone 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 $T_3$ (r T,) 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, amiodarone 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 amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for several weeks or even months following amiodarone 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 amiodarone hydrochloride dose reduction and/or thyroid horrnone supplement. However, therapy must be individualized, and it may be necessary to discontinue amiodarone in some patients.

Hyperthyroidism occurs in about 2% of patients receiving amiodarone hydrochloride, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Amiodarone hydrochloride-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 arniodarone hydrochloride-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of amiodarone hydrochloride. 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. Amiodarone hydrochloride-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

**Surgery**

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

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

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

**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 amiodarone hydrochloride or discontinuing therapy.

Amiodarone hydrochloride 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 amiodarone hydrochloride 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 amiodarone hydrochloride, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone hydrochloride.

*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 amiodarone hydrochloride 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 amiodarone hydrochloride, 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 amiodarone hydrochloride 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 amiodarone hydrochloride.

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

In general, combination of amiodarone 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 amiodarone hydrochloride. During transfer to amiodarone the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of amiodarone hydrochloride, when arrhythmia suppression should be beginning. The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone 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 amiodarone is continued. In amiodarone hydrochloride-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

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

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

SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE HYDROCHLORIDE

| Concomitant Drug | Interaction | | Recommended Dose Reduction of Concomitant Drug |
|---|---|---|---|
| | Onset (days) | Magnitude | |
| Warfarin | 3 to 4 | Increases prothrombin time by 100% | 1 ⅓ to ½ |
| Digoxin | 1 | Increases serum concentration by 70% | ↓ ½ |
| Quinidine | 2 | Increases serum concentration by 33% | ↓ ⅓ to ½ (or discontinue) |
| Procainamide | <7 | Increases plasma | ↓ ⅓ |

| | | |
|---|---|---|
| | concentration by 55%; NAPA* concentration by 33% | (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 amiodarone therapy.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Amiodarone HCl was associated with a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control even at the lowest dose level tested, *i.e.*, 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).

Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with amiodarone were negative.

In a study in which amiodarone hydrochloride was administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*).

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

**Pregnancy: Pregnancy Category D**

**See "WARNINGS, Neonatal Hypo- or Hyperthyroidism."**

**Labor and Delivery**

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

**Nursing Mothers**

Amiodarone 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 amiodarone have been shown to be less viable and have reduced body-weight gains. Therefore, when amiodarone therapy is indicated, the mother should be advised to discontinue nursing.

**Pediatric Use**

The safety and effectiveness of amiodarone hydrochloride in pediatric patients have not been established.

**Geriatric Use**

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

**ADVERSE REACTIONS:**

Adverse reactions have been very common in virtually all series of patients treated with amiodarone hydrochloride 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 amiodarone 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% ofpatients 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, cornea1 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 amiodarone 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.

In postmarketing surveillance, 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 amiodarone.

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 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 amiodarone hydrochloride, the adverse reactions most frequently requiring discontinuation of amiodarone 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 amiodarone hydrochloride overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. The acute oral LD,, of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.

In addition to general supportive measures, the patient's cardiac rhythm and blood pressure should be monitored, and if bradycardia ensues, a β-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither amiodarone 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, AMIODARONE HYDROCHLORIDE 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 AMIODARONE 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 amiodarone has not been determined. Because of the food effect on absorption, amiodarone should be

administered consistently with regard to meals (see **"CLINICAL PHARMACOLOGY').** Individual patient titration is suggested according to the following guidelines.

*For Life-threatening Ventricular Arrhythmias, Such As Ventricular Fibrillation Or Hemodynamically Unstable Ventricular Tachycardia:* Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1,600 mg/day are required for 1 to 3 weeks (occasionally longer) until initial therapeutic response occurs. (Administration of amiodarone hydrochloride 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 amiodarone hydrochloride 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, amiodarone hydrochloride 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. Amiodarone 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 amiodarone 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:**

Amiodarone hydrochloride tablets are round, flat-faced, beveled edge, yellow tablets debossed "E" over bisect, and "144" below the bisect, and plain on the other side, available in bottles of 60, 90, 100, and 500.

**Keep tightly closed.**
**Store at room temperature, approximately 15-30° C (59-86° F). Protect from light.**
**Dispense in a light-resistant, tight container as defined in the USP, with a child-resistant closure as required.**

Manufactured by:
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