



Taro Pharmaceuticals U.S.A., Inc.

September 26, 2001

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

3917 '01 SEP 28 AM 10:05

CITIZEN PETITION

The undersigned submits this petition pursuant to section 505 (j) (2) (c) of the Federal Food, Drug and Cosmetic Act and 21 CFR Parts 314.55 (d) (2) and 10.30 of the Food and Drug Administration's regulations, to request the Commissioner of Food and Drugs to make a determination of ANDA suitability for Amiodarone Hydrochloride Tablets, 100 mg based on the reference-listed drug, Wyeth-Ayerst's Cordarone Tablets, 200 mg [Exhibit 1].

A. Action Requested

The petitioner requests the Commissioner of the Food and Drug Administration for a change to a listed drug to allow the undersigned to submit an Abbreviated New Drug Application for Amiodarone HCl Tablets, 100 mg. The reference-listed drug is Cordarone Tablets, 200 mg manufactured by Wyeth-Ayerst. The safety of the proposed strengths is supported by the bioequivalence study conducted on our approved Amiodarone HCl Tablets, 200 mg, Abbreviated New Drug Application (ANDA) # 75-424. In that study, 1 x 200-mg tablet was dosed on healthy adult male subjects. Furthermore, safety is supported by the fact that tablets of 200 mg are the routine oral dosage strengths of this product.

B. Statement of Grounds

Amiodarone HCl Tablet dosage should be adjusted to the needs of the individual patients. Amiodarone HCl Tablets are approved for use at daily doses up to 1600 mg per day, with a usual maintenance dose of 400 mg per day. Because of the unique pharmacokinetic properties and potential severity of the side effects if patients are improperly monitored, Amiodarone HCl tablets should be administered at the lowest effective dosage and should be closely monitored by the physicians. The availability of 100 mg tablets will provide the physicians with greater flexibility in prescribing the drug, as well as enabling the patients to take dose appropriate tablets, which will improve patient compliance. It should be noted that Amiodarone HCl Tablets, 100 mg are also available as a prescription in UK [Exhibit 2].

01P-0445

CP

The proposed Amiodarone HCl tablets; 100 mg will be the same as the reference-listed product in respect of:

- Active ingredient, Amiodarone Hydrochloride
- Indications
- Dosing regimen
- Bioequivalence: the proposed strength, 100 mg will be dose proportional to Taro's approved 200 mg strength. A bioequivalence study was conducted comparing Taro's 200 mg tablets to the reference-listed product, Cordarone Tablets, 200 mg. Bioequivalence studies under both fast and fed conditions were conducted on Taro's Amiodarone HCl tablets, 200 mg approved on 03/03/2001, ANDA # 75-424. *In-Vitro* dissolution profiles and assay will also be conducted on the 100 mg tablets by comparing them to 200 mg tablets.

Copies of the approved labeling for Wyeth-Ayerst's Cordarone Tablets, 200 mg and the proposed labeling for Taro's Amiodarone HCl Tablets 100 mg with highlighting of the changes [Exhibit 1,3] are attached.

C. Environmental Impact

The undersigned, hereby requests a categorical exclusion under 21 CFR 25.24 (c) (1). The proposed drug product will not be administered at higher dosage levels, for longer duration, or for different indications than for the reference-listed product.

D. Economic Impact

This information will be submitted on request of the Commissioner.

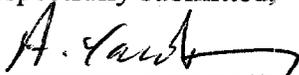
E. Advantages

The proposed Amiodarone HCl Tablets, 100 mg will provide the physicians a greater flexibility in prescribing the drug.

F. 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,



Avraham Yacobi, Ph.D.
President, Taro Research Institute

Exhibit 1

Cordarone Tablets, 200 mg
Approved Packaged Insert

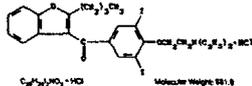


Cordarone®
(amiodarone HCl)
TABLETS

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-benzofuran-4-yl-(diethylamino)-ethoxy-3,5-dimethyl ketone hydrochloride. It is not chemically related to any other available antiarrhythmic drug.

The structural formula is as follows:



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 the peripheral vascular fraction (LVF), even in patients with depressed LVF. 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 3.5) 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 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 38 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 530 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat. The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of Cordarone should be based on individual patient requirements (see "DOSAGE AND ADMINISTRATION").

Cordarone and its metabolite have a limited transplacental transfer of approximately 10 to 50%. The parent drug and its metabolite have been detected in breast milk. Cordarone is highly protein-bound (approximately 96%). Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of Cordarone, effects on abnormal rhythms are not seen before 2 to 3 days and usually require 1 to 3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods still. There is evidence that the time to effect is shorter when a loading-dose regimen is used.

Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after 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 observed side effects include 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.

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 observed side effects include 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 a 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 studies have found greater recurrence rates in patients who remain inducible to test. 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 low recurrence rates. While these criteria require confirmation and further study in general, easier inducibility or *poor* 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 non-sustained ventricular tachycardia on ambulatory monitoring and very low premature ventricular-beat rates (less than 1 WPB/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 evaluation 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 or very 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 5% to 50%, 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% 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 fully 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 any episodes of bradycardia have caused syncope (except when used in conjunction with a pacemaker).

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

WARNINGS

Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity. Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifested 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 not considered to be a significant cause of mortality. Over a 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 15% of patients in various series, and significant heart block is usually not considered to be a significant cause of mortality. The frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, but 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 a major management problem because of its life-threatening side effects and the 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 dosing is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 102 patients with ventricular tachyarrhythmias, 64 required dose reduction and 16 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 prompt 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, patients who had had myocardial infarction more 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 (22/752). The average duration of treatment with encainide or flecainide in this study was 1.6 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 1485 (European Myocardial Infarction Amiodarone Trial; EMIAAT) 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 208 to 400 mg/day. Patients in EMIAAT 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 | N | 95%CI | | | |
| EMIAAT | 743 | 102 | 743 | 103 | 0.99 | 0.76-1.31 |
| CAMIAT | 596 | 88 | 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 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 diffusing 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 results 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 rechallenge 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 suppressor/cytotoxic (CD8-positive) lymphocytosis is noted. Steroid therapy should be instituted and Cordarone discontinued in these patients.

Interstitial/alveolar pneumonitis may result from the release of oxygen radicals and/or phospholipids and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung

biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), 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, 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 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.

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
Cl 6036-2

Cordarone®
(amiodarone HCl)
Tablets
Cl 6036-2

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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 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. 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 effect on the maximum recommended human maintenance dose*) caused abortions in greater than 50% 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 250 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").

Concomitant Use
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").

Neuroleptic
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-burner 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 (T₄) to triiodothyronine (T₃) and may cause increased thyroxine levels, decreased T₃ levels, and increased levels of inactive reverse T₃ (rT₃) 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.

Hyperthyroidism 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 T₃RIA, and further elevations of serum T₃ and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of Cordarone. The institution of antithyroid drugs, β-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of pre-formed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radiiodine 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 Possibility: 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 FIO₂ and the determinants of oxygen delivery to the tissues (e.g., SaO₂, PaO₂) 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 T₄ and serum reverse T₃, and a decline in serum T₃ 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 amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

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

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

SUMMARY OF DRUG INTERACTIONS WITH CORDARONE

| Concomitant Drug | 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 93% | 1/3 to 1/2 (or discontinue) |
| Procainamide | <7 | Increases plasma concentration by 53%; 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, low 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 of 1 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 8 weeks prior to mating, reduced fertility was observed at a dose level of 100 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: 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"). Other adverse effects include constipation 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, photophobia, eye discoloration, 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 the most common (about 4%). 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 (5%) and bradycardia. Bradycardia usually responds to dose 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, testicular pain, pseudotumor cerebri, thrombocytopenia, angiodema, bronchiolitis obliterans organizing pneumonia (presumably 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).

Gastrointestinal: Constipation, anorexia.
Ophthalmic: 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, proximal 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 LD₅₀ of amiodarone HCl in mice and rats is greater than 3,000 mg/kg. In addition to general supportive measures, the patient's cardiac rhythm and blood pressure should be monitored, and if bradycardia ensues, a β-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither Cordarone nor its metabolite is dialyzable.

DOSE 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 patient 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, 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 nonresponse 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. Dose suggestions are summarized below:

| Ventricular Arrhythmias | Loading Dose (Daily) | Adjustment and Maintenance Dose (Daily) |
|-------------------------|----------------------|---|
| | 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 0008-4189, 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, light container.
Use caution to protect contents from light.

By only
Manufactured for
Wyeth Laboratories
A Wyeth-Ayerst Company
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CI 6036-2 Revised August 1, 2000

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Cordarone X 100, Cordarone X 200

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- 10. Date of (Partial) Revision of the Text**

1. Trade Name of the Medicinal Product

Cordarone X 100

Cordarone X 200

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2. Qualitative and Quantitative Composition

Cordarone X 100 contain 100mg of amiodarone hydrochloride FP.

Cordarone X 200 contain 200mg of amiodarone hydrochloride FP.

3. Pharmaceutical Form

Tablet.

Clinical Particulars

Treatment should be initiated and normally monitored only under hospital or specialist supervision. Oral Cordarone X is indicated only for the treatment of severe rhythm disorders not responding to other therapies or when other treatments cannot be used.

4.1 Therapeutic Indications

Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.

Atrial flutter and fibrillation when other drugs cannot be used.

All types of tachyarrhythmias of paroxysmal nature including: supraventricular, nodal and ventricular tachycardias, ventricular fibrillation; when other drugs cannot be used.

Tablets are used for stabilisation and long term treatment.

4.2 Posology and Method of Administration

Adults

It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual response and well being. The following dosage regimen is generally effective.

Initial Stabilisation

Treatment should be started with 200mg, three times a day and may be continued for 1 week. The dosage should then be reduced to 200mg, twice daily for a further week.

Maintenance

After the initial period the dosage should be reduced to 200mg daily, or less if appropriate. Rarely, the patient may require a higher maintenance dose. The scored 100mg tablet should be used to titrate the minimum dosage required to maintain control of the arrhythmia. The maintenance dose should be regularly reviewed, especially where this exceeds 200mg daily.

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Changeover from Intravenous to Oral Therapy

As soon as an adequate response has been obtained, oral therapy should be initiated concomitantly at the usual loading dose (200mg three times a day). Cordarone X Intravenous should then be phased out gradually.

General Considerations

Initial dosing

A high dose is needed in order to achieve adequate tissue levels rapidly.

Maintenance

Too high a dose during maintenance therapy can cause side effects which are believed to be related to high tissue levels of amiodarone and its metabolites.

Amiodarone is strongly protein bound and has an average plasma half life of 50 days (reported range 20-100 days). It follows that sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dosage.

It is particularly important that the minimum effective dosage is used and the patient is monitored regularly to detect the clinical features of excess amiodarone dosage. Therapy may then be adjusted accordingly.

Dosage reduction/withdrawal

Side effects slowly disappear as tissue levels fall. Following drug withdrawal, residual tissue bound amiodarone may protect the patient for up to a month. However, the likelihood of recurrence of arrhythmia during this period should be considered. In patients with potentially lethal arrhythmias the long half life is a valuable safeguard as omission of occasional doses does not significantly influence the overall therapeutic effect.

Elderly

As with all patients it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function. See *Contra-indications, Warnings etc.*

Cordarone X is for oral administration.

4.3 Contra-indications

Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, Cordarone X should be used only in conjunction with a pacemaker.

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Evidence or history of thyroid dysfunction. Thyroid function tests should be performed prior to therapy in all patients.

Known hypersensitivity to iodine or to amiodarone. (One 100mg tablet contains approximately 37.5mg iodine; one 200mg tablet contains approximately 75mg iodine).

The combination of Cordarone X with drugs which may induce Torsades de Pointes is contra-indicated (see *Drug Interactions* section).

4.4 Special Warnings and Special Precautions for Use

Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances, Cordarone X treatment should be withdrawn. If necessary beta-adrenostimulants or glucagon may be given.

Oral Cordarone X is not contra-indicated in patients with latent or manifest heart failure but caution should be exercised as, occasionally, existing heart failure may be worsened. In such cases, Cordarone X may be used with other appropriate therapies.

Amiodarone induces ECG changes: QT interval lengthening corresponding to prolonged repolarisation with the possible development of U and deformed T waves; these changes are evidence of its pharmacological action and do not reflect toxicity.

Although there have been no literature reports on the potentiation of hepatic adverse effects of alcohol, patients should be advised to moderate their alcohol intake while taking Cordarone X.

4.5 Interaction with Other Medicaments and Other Forms of Interaction

Some of the more important drugs that interact with amiodarone include warfarin, digoxin, phenytoin and any drug which prolongs the QT interval.

Amiodarone raises the plasma concentrations of highly protein bound drugs, for example oral anticoagulants and phenytoin. The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended. Phenytoin dosage should be reduced if signs of overdose appear, and plasma levels may be measured.

Administration of Cordarone X to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Monitoring is recommended and digoxin dosage usually has to be reduced. A synergistic effect on heart rate and atrioventricular conduction is also possible.

Combined therapy with the following drugs which prolong the QT interval is contra-indicated (see *Contra-Indications* section) due to the increased risk of

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Torsades de Pointes; for example:

- Class Ia anti-arrhythmic drugs eg quinidine, procainamide, disopyramide
- Class III anti-arrhythmic drugs eg sotalol, bretylium
- intravenous erythromycin, co-trimoxazole or pentamidine injection
- anti-psychotics eg chlorpromazine, thioridazine, pimozide, haloperidol
- lithium and tricyclic anti-depressants eg doxepin, maprotiline, amitriptyline
- certain antihistamines eg terfenadine, astemizole
- anti-malarials eg quinine, mefloquine, chloroquine, halofantrine.

Combined therapy with the following drugs is not recommended:

- beta blockers and certain calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur.

Caution should be exercised over combined therapy with the following drugs which may cause hypokalaemia and/or hypomagnesaemia: diuretics, systemic corticosteroids, tetracosactrin, intravenous amphotericin.

In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case of Torsades de Pointes antiarrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.

Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy.

Potentially severe complications have been reported in patients taking amiodarone undergoing general anaesthesia: bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output.

A few cases of adult respiratory distress syndrome, most often in the period immediately after surgery, have been observed. A possible interaction with a high oxygen concentration may be implicated. The anaesthetist should be informed that the patient is taking Cordarone X.

Amiodarone may increase the plasma levels of cyclosporin when used in combination, due to a decrease in the clearance of this drug.

4.6 Pregnancy and Lactation

Pregnancy

Although no teratogenic effects have been observed in animals, there are insufficient data on the use of amiodarone during pregnancy in humans to judge

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any possible toxicity. However, in view of the pharmacological properties of the drug on the foetus and its effect on the foetal thyroid gland, its administration in pregnancy should be avoided.

Lactation

Amiodarone is excreted into the breast milk in significant quantities and breast-feeding is contra-indicated.

4.7 Effects on Ability to Drive and Use Machines

None stated.

4.8 Undesirable Effects

Amiodarone can cause serious adverse reactions affecting the lung, liver, thyroid gland, skin and peripheral nervous system (see below). Because these reactions can be delayed, patients on long-term treatment should be carefully supervised.

Pulmonary: Cordarone X can cause pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia). Sometimes this toxicity can be fatal.

Presenting features can include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough and deterioration in general health (fatigue, weight loss and fever). The onset is usually slow but may be rapidly progressive. Whilst the majority of cases have been reported with long term therapy, a few have occurred soon after starting treatment.

Patients should be carefully evaluated clinically and consideration given to chest X-ray before starting therapy. During treatment, if pulmonary toxicity is suspected, this should be repeated and associated with lung function testing including where possible measurement of transfer factor. Initial radiological changes may be difficult to distinguish from pulmonary venous congestion. Pulmonary toxicity has usually been reversible following early withdrawal of amiodarone therapy, with or without corticosteroid therapy. Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing Cordarone X.

A few cases of adult respiratory distress syndrome, most often in the period after surgery, have been observed, resulting sometimes in fatalities (see *Interactions*).

Cardiac: Bradycardia which is generally moderate and dose dependent has been reported. In some cases (sinus node disease, elderly patients) marked bradycardia or more exceptionally sinus arrest has occurred. There have been rare instances of conduction disturbances (sino-atrial block, various degrees of AV block). Because of the long half life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.

Amiodarone has a low proarrhythmic effect. However arrhythmia (new

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occurrence or aggravation), followed in some cases by cardiac arrest has been reported; with current knowledge, it is not possible to differentiate a drug effect from the underlying cardiac condition or lack of therapeutic efficacy. This has usually occurred in combination with other precipitating factors particularly other antiarrhythmic agents, hypokalaemia and digoxin.

Hepatic: Amiodarone may be associated with a variety of hepatic effects, including cirrhosis, hepatitis and jaundice. Some fatalities have been reported, mainly following long-term therapy, although rarely they have occurred soon after starting treatment particularly after Cordarone X intravenous. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter.

At the beginning of therapy, elevation of serum transaminases which can be in isolation (1.5 to 3 times normal) may occur. These may return to normal with dose reduction, or sometimes spontaneously.

Isolated cases of acute liver disorders with elevated serum transaminases and/or jaundice may occur; in such cases treatment should be discontinued.

There have been reports of chronic liver disease. Alteration of laboratory tests which may be minimal (transaminases elevated 1.5 to 5 times normal) or clinical signs (possible hepatomegaly) during treatment for longer than 6 months should suggest this diagnosis. Routine monitoring of liver function tests is therefore advised. Abnormal clinical and laboratory test results usually regress upon cessation of treatment. Histological findings may resemble pseudo-alcoholic hepatitis, but they can be variable and include cirrhosis.

Thyroid: Both hyper and hypothyroidism have occurred during, or soon after, amiodarone treatment. Simple monitoring of the usual biochemical tests is confusing because some tests such as free T_4 and free T_3 may be altered where the patient is euthyroid. Clinical monitoring is therefore recommended before start of treatment, then six monthly and should be continued for some months after discontinuation of treatment. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular assessment is recommended.

Hyperthyroidism: Clinical features such as weight loss, asthenia, restlessness, increase in heart rate, recurrence of the cardiac dysrhythmia, angina or congestive heart failure, should alert the clinician. The diagnosis may be supported by an elevated serum tri-iodothyronine (T_3), a low level of thyroid stimulating hormone (TSH) as measured by high sensitivity methods, and a reduced TSH response to thyrotrophin releasing hormone (TRH). Elevation of reverse T_3 (rT_3) may also be found.

In the case of hyperthyroidism, therapy should be withdrawn. Clinical recovery usually occurs within a few weeks, although severe cases, sometimes resulting in fatalities, have been reported.

Courses of anti-thyroid drugs have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. These may not always be

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effective and concomitant high dose corticosteroid therapy (eg 1mg/kg prednisolone) may be required for several weeks.

Hypothyroidism: Clinical features such as weight gain, reduced activity or excessive bradycardia should suggest the diagnosis. This may be supported by an elevated serum TSH level and an exaggerated TSH response to TRH. T₄ and T₃ levels may be low.

Thyroid hypofunction usually resolves within 3 months of cessation of therapy; it may be treated cautiously with L-thyroxine. Concomitant use of Cordarone X should be continued only in life threatening situations, when TSH levels may provide a guide to L-thyroxine dosage.

Ophthalmological: Patients on continuous therapy almost always develop microdeposits in the cornea. The deposits are usually only discernible by slit-lamp examinations and may rarely cause subjective symptoms such as visual haloes and blurring of vision. The deposits are considered essentially benign, do not require discontinuation of amiodarone and regress following termination of treatment. Rare cases of impaired visual acuity due to optic neuritis have been reported, although at present, the relationship with amiodarone has not been established. Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually.

Dermatological: Patients taking Cordarone X can become unduly sensitive to sunlight and should be warned of this possibility. In most cases, symptoms are limited to tingling, burning and erythema of sun exposed skin but severe phototoxic reactions with blistering may be seen. Photosensitivity may persist for several months after discontinuation of Cordarone X. Photosensitivity can be minimised by limiting exposure to UV light, wearing suitable protective hats and clothing and by using a broad spectrum sun screening preparation. Rarely, a slate grey or bluish discoloration of light exposed skin, particularly on the face, may occur. Resolution of this pigmentation may be very slow once the drug is discontinued. Other types of skin rashes including isolated cases of exfoliative dermatitis have also been reported. Cases of erythema have been reported during radiotherapy.

Neurological: Peripheral neuropathy can be caused by Cordarone X. Myopathy has occasionally been reported. Both these conditions may be severe although they are usually reversible on drug withdrawal. Nightmares, vertigo, headaches, sleeplessness and paraesthesia may also occur. Tremor and ataxia have also infrequently been reported usually with complete regression after reduction of dose or withdrawal of the drug. Benign intracranial hypertension (pseudo-tumour cerebri) has been reported.

Other: Other unwanted effects occasionally reported include nausea, vomiting, metallic taste (which usually occur with loading dosage and which regress on dose reduction), fatigue, impotence, epididymo-orchitis and alopecia. Isolated cases suggesting a hypersensitivity reaction involving vasculitis, renal involvement with moderate elevation of creatinine levels or thrombocytopenia have been observed. Haemolytic or aplastic anaemia have rarely been reported.

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4.9 Overdose

Animal studies indicate that amiodarone has a high LD₅₀, hence it is most unlikely that a patient will ingest an acute toxic dose. In such an event gastric lavage may be employed to reduce absorption in addition to general supportive measures. The patient should be monitored; if bradycardia occurs beta-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended. Neither amiodarone nor its metabolites are dialysable.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Amiodarone hydrochloride is an antiarrhythmic.

5.2 Pharmacokinetic Properties

Amiodarone is strongly protein bound and the plasma half life is usually of the order of 50 days. However there may be considerable inter-patient variation; in individual patients a half life of less than 20 days and a half life of more than 100 days has been reported. High doses of Cordarone X, for example 600mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half life of the drug, a maintenance dose of only 200mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by Cordarone X.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Pharmaceutical Particulars

6.1 List of Excipients

Lactose, Maize starch, Polyvidone, Colloidal silicon dioxide, Magnesium stearate.

6.2 Incompatibilities

None stated.

6.3 Shelf Life

60 months.

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6.4 Special Precautions for Storage 

The tablets should be protected from light.

6.5 Nature and Contents of Container 

Cordarone X 100 and 200 tablets are supplied in blister packs of 28 tablets packed in cardboard cartons.

6.6 Instructions for Use/Handling 

Not applicable.

Administration Details

7. Marketing Authorisation Holder 

Sanofi-Synthelabo

PO Box 597

Guildford

Surrey

8. Marketing Authorisation Number 

Cordarone X 100: PL 11723/0012.

Cordarone X 200: PL 11723/0013.

9. Date of First Authorisation/Renewal of Authorisation 

Cordarone X 100: 15th January 2001

Cordarone X 200: 12 December 1995

10. Date of (Partial) Revision of the Text 

Cordarone X 100: January 2000

Cordarone X 200: January 2000

Legal classification: POM

<http://emc.vhn.net/emc/assets/c/html/DisplayDoc.asp?DocumentID=7124>

0015

Exhibit 3

Taro's Amiodarone Hydrochloride Tablets
100 mg and 200 mg
Proposed Packaged Insert

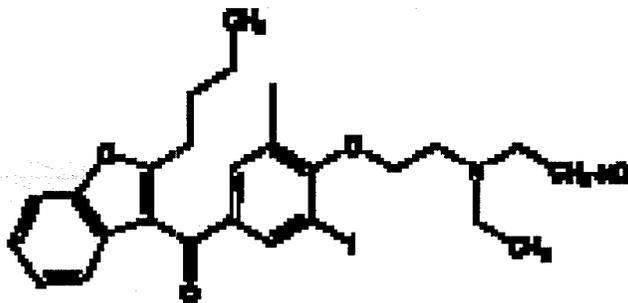
Cordarone[®]
(Amiodarone HCl)
Amiodarone HCl Tablets

Rx only

Description

Cordarone Amiodarone HCl is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects, available for oral administration as **light orange, scored tablets containing 200 mg of Amiodarone hydrochloride and white scored tablets containing 100 mg of Amiodarone hydrochloride**. The inactive ingredients present are colloidal silicone dioxide, corn starch, **FD&C yellow #6 lake (200 mg only), FD&C yellow #10 lake (200 mg only)**, anhydrous lactose, magnesium stearate and povidone. **Cordarone Amiodarone HCl** 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 amiodarone HCl** is effective in the prevention or suppression of experimentally induced arrhythmias. The antiarrhythmic effect of **Cordarone amiodarone HCl** 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 HCl 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 HCl** 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 HCl** 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, **Cordarone amiodarone HCl** 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, **Cordarone amiodarone HCl** may have a mild negative inotropic effect.

PHARMACOKINETICS

Following oral administration in man, **Cordarone amiodarone HCl** is slowly and variably absorbed. The bioavailability of **Cordarone amiodarone HCl** 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 amiodarone HCl**. The effects of food upon the bioavailability of **Cordarone amiodarone HCl** 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 Amiodarone HCl 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 HCl**, 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 HCl** 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~~ **amiodarone HCl**, 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 HCl** 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 HCl** 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~~ **amiodarone HCl** should be based on individual patient requirements (see "Dosage and Administration").

~~Cordarone~~ **Amiodarone HCl** 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~~ **Amiodarone HCl** 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 HCl**, effects on abnormal rhythms are not seen before 2 to 3 days and usually require 1 to 3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods still. There is evidence that the time to effect is shorter when a loading-dose regimen is used.

Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after ~~Cordarone~~ **amiodarone HCl** 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 HCl** 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 HCl** (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 HCl** 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 HCl**. 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 HCl**, as for other agents, the prescriber of ~~Cordarone~~ **amiodarone HCl** 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 HCl**, 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 HCl**, the duration of follow-up, the dose of ~~Cordarone~~ **amiodarone HCl**, the use of additional antiarrhythmic agents, and many other factors. As ~~Cordarone~~ **amiodarone HCl** 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 HCl** 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.

~~Cordarone~~ **Amiodarone HCl** 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 HCl** should be carried out in the hospital.

Contraindications

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

Warnings

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

Cordarone amiodarone HCl 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 HCl**, 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 HCl** 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 HCl** 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 HCl** is an acceptable risk, **Cordarone amiodarone HCl** 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 HCl** 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 HCl** 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 HCl** must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone HCl body burden. A similar problem exists when **Cordarone amiodarone HCl** 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~~ **Amiodarone HCl** therapy was evaluated in two multi-centered, randomized double-blind, placebo-controlled trials involving 1202 (Canadian ~~Cordarone~~ **Amiodarone HCl** 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 | 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 HCl** 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 HCl** 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 a 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 HCl** 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~~ **amiodarone HCl** 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~~ **amiodarone HCl** 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 amiodarone HCl**-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on **Cordarone amiodarone HCl** therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of **Cordarone amiodarone HCl**-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the **Cordarone amiodarone HCl** 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 HCl** 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 HCl** are associated with a decreased incidence of **Cordarone Amiodarone HCl**-induced pulmonary toxicity.

In a patient receiving **Cordarone amiodarone HCl**, 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 HCl** 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 HCl** 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 amiodarone HCl**-induced hypersensitivity pneumonitis is made, **Cordarone amiodarone HCl** should be discontinued, and treatment with steroids should be instituted. If a diagnosis of **Cordarone amiodarone HCl**-induced interstitial/alveolar pneumonitis is made, steroid therapy should be instituted and, preferably, **Cordarone amiodarone HCl** discontinued or, at a minimum, reduced in dosage. Some cases of **Cordarone amiodarone HCl**-induced interstitial/alveolar pneumonitis may resolve following a reduction in **Cordarone amiodarone HCl** 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.

WORSENER ARRHYTHMIA

~~Cordarone~~ **Amiodarone HCl**, 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 HCl** 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 HCl** 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 HCl** 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 HCl**.

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 HCl** therapy. The risks and complications of antiarrhythmic therapy with ~~Cordarone~~ **amiodarone HCl** 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~~ **amiodarone HCl**. (See "Adverse Reactions".)

NEONATAL HYPO- OR HYPERTHYROIDISM

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

In general, ~~Cordarone~~ **amiodarone HCl** 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 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. 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~~ **Amiodarone HCl** 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 HCl** inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and may cause increased thyroxine levels, decreased T3 levels, and increased levels of inactive reverse T3 (rT3) 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 HCl** 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 HCl** 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 HCl** 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 HCl** dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue ~~Cordarone~~ **amiodarone HCl** in some patients.

Hyperthyroidism occurs in about 2% of patients receiving ~~Cordarone~~ **amiodarone HCl**, but the incidence may be higher among patients with prior inadequate dietary iodine intake. ~~Cordarone~~ **amiodarone HCl**-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 T3 RIA, and further elevations of serum T4, 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~~ **amiodarone HCl**-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of ~~Cordarone~~ **amiodarone HCl**. The institution of antithyroid drugs, beta-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~~ **amiodarone HCl**-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 HCl** have been reported. The relationship of this event to ~~Cordarone~~ **amiodarone HCl** therapy is unknown.

Adult Respiratory Distress Syndrome (ARDS): Postoperatively, occurrences of ARDS have been reported in patients receiving ~~Cordarone~~ **amiodarone HCl** therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FiO₂ and the determinants of oxygen delivery to the tissues (e.g., SaO₂, PaO₂) be closely monitored in patients on ~~Cordarone~~ **amiodarone HCl**.

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 HCl** or discontinuing therapy.

Cordarone Amiodarone HCl alters the results of thyroid-function tests, causing an increase in serum T4 and serum reverse T3, and a decline in serum T3 levels. Despite these biochemical changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS

Although only a small number of drug-drug interactions with **Cordarone amiodarone HCl** 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 HCl**, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of **Cordarone amiodarone HCl**.

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 HCl** 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 HCl**, 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

Potential of warfarin-type anticoagulant response is almost always seen in patients receiving **Cordarone amiodarone HCl** 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 HCl**.

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

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

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

| Concomitant Drug | Interaction | | Recommended Dose Reduction of Concomitant Drug |
|------------------|--------------|--|--|
| | Onset (days) | Magnitude | |
| 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~~ **amiodarone HCl** therapy.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Amiodarone 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 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 HCl** during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not

shown any effect of ~~Cordarone~~ **amiodarone HCl** on the duration of gestation or on parturition.

NURSING MOTHERS

~~Cordarone~~ **Amiodarone HCl** 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 HCl** 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 ~~Cordarone~~ **amiodarone HCl** in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of amiodarone 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~~ **amiodarone HCl** 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 HCl** 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 the 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 HCl** 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~~ **amiodarone HCl**.

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 amiodarone, the adverse reactions most frequently requiring discontinuation of ~~Cordarone~~ **amiodarone HCl** 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 HCl** overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. The acute oral LD₅₀ of amiodarone hydrochloride 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 b-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 HCl** 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 HCL 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 HCL 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~~ **amiodarone HCl** has not been determined. Because of the food effect on absorption, ~~Cordarone~~ **amiodarone HCl** 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 HCl** 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 HCl** 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 HCl** 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 HCl** 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 HCl** 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 800 to 1,600 mg | ~1 month 600 to 800 mg usual maintenance 400 mg |

How Supplied

Amiodarone HCl Tablets, 200 mg are available in bottles of 60 tablets as follows: 200 mg, light orange, round flat beveled edge, tablets; one side plain, the second side scored and engraved "TARO" above the score line and "56" below the score line.

Amiodarone HCl Tablets, 100 mg are available in bottles of 30, 100 and 100 tablets and in cartons containing 100 tablets (10 blister strips of 10) as follows: 100 mg, white, round flat beveled scored tablets, debossed with "Taro over 55" on the scored side, plain on the other side.

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

Manufactured by:

**Taro Pharmaceutical Industries Ltd.
Haifa Bay, Israel 26110**

Made in Israel

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