CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-972

Approved Labeling

WYETH

CORDARONE® (amiodarone hydrochloride) Tablets

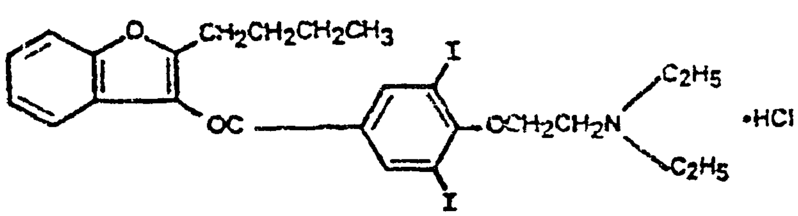
PACKAGE INSERT

CAUTION   Federal law prohibits dispensing without prescription

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 white scored tablets containing 200 mg of amiodarone hydrochloride The inactive ingredients present are colloidal silicone dioxide, lactose, magnesium stearate, povidone and starch CORDARONE is a benzofuran derivative 2-butyl-3 benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone, hydrochloride It is not chemically related to any other available antiarrhythmic drug

The structural formula is as follows



[illegible]   Molecular Weight 681.8

Amiodarone HCl is a white to cream-colored crystalline powder It is slightly soluble in water, soluble in alcohol and freely soluble in chloroform It contains 37 3% iodine by weight

CLINICAL PHARMACOLOGY

Electrophysiology/Mechanisms of Action

In animals, CORDARONE is effective in the prevention or suppression of experimentally induced arrhythmias The antiarrhythmic effect of CORDARONE may be due to at least two major properties 1) a prolongation of the myocardial cell action potential duration and refractory period, and 2) noncompetitive alpha- and beta-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 15-20% 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 there 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 WARNING)

Hemodynamics

In animal studies and after intravenous administ ation in man CORDARONE relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), ar slightly increases cardiac ndex After oral dosing, however, CORDARONE produces no significant change in left ventr cular ejection fraction (LVEF), even in patients wi.h depressed LVEF After acute intravenous dosing in man, CORDARONE may have a mild negative irotropic 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 n 2-3 days, but more commonly ta es 1-3 weeks, even with loading doses Plasma concentrations with chronic dosing at 100-600 mg day ar approximately dose proportional with a mean 0 5 mg L increase for each 100 mg/day These means however, include considerable individual variability

CORDARONE has a very large, but var able volume of distribution, averaging about 30 L/kg, because of extensive accumulation in various sites, especially ad pose tissue and highly perfused organs such as the liver lung and spleen One major metabolite of CORDARONE, desethyl-amiodarone has been dentified in man it accumulates to an even greater ex en in almost all t sues The pharmacological activity of this metabolite however is not know n During chron treatment the plasma rat o of metabol te to parent compound s app oximat ly or

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

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

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

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

CORDARONE is highly protein-bound (approximately 96%)

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

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

Pharmacodynamics

There is no well-established relationship of plasma concentration to effectiveness, but it does appear that concentrations much below 1 mg/L are often ineffective and that levels above 2.5 mg/L are generally not needed Within individuals dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control Plasma concentration measurements can be used to identify patients whose levels are unusually low and who might benefit from a dose increase or unusually high and who might have dosage reduction in the hope of minimizing side effects Some observations have suggested a plasm

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 anti-arrhythmic 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 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 require 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 non-inducible by CORDARONE (a fraction that has varied widely in various series from less than 10% to almost 40%, perhaps due to different stimulation criteria) the prognosis has been almost uniformly excellent, with very low recurrence (ventricular tachycardia or sudden

death) rates More controversial is the meaning of continued inducibility There has been an impression that continued inducibility in CORDARONE patients may not foretell a poor prognosis, but, in fact, many observers have found greater recurrence rates in patients who remain inducible than in those who do not A number of criteria have been proposed, however, for identifying patients who remain inducible but who seem likely nonetheless to do well on CORDARONE These criteria include increased difficulty of induction (more stimuli or more rapid stimuli), which has been reported to predict a lower rate of recurrence, and ability to tolerate the induced ventricular tachycardia without severe symptoms, a finding that has been reported to correlate with better survival but not with lower recurrence rates While these criteria require confirmation and further study in general, easier inducibility or poorer tolerance of the induced arrhythmia should suggest consideration of a need to revise treatment

Several predictors of success not based on PES have also been suggested, including complete elimination of all non-sustained ventricular tachycardia on ambulatory monitoring and very low premature ventricular beat rates (less than 1 VPB/1000 normal beats)

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

It is difficult to describe the effectiveness rates of CORDARONE as these depend on the specific arrhythmia treated the success criteria

used, the underlying cardiac disease of the patient, the number of drugs tried before resorting to CORDARONE, the duration of follow-up, the dose of CORDARONE, the use of additional anti-arrhythmic agents, and many other factors. As CORDARONE has been studied principally in patients with refractory life-threatening ventricular arrhythmias, in whom drug therapy must be selected on the basis of response and cannot be assigned arbitrarily, randomized comparisons with other agents or placebo have not been possible. Reports of series of treated patients with a history of cardiac arrest and mean follow-up of one year or more have given mortality (due to arrhythmia) rates that were highly variable, ranging from less than 5% to over 30%, with most series in the range of 10-15%. Overall arrhythmia recurrence rates (fatal and non-fatal) 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 20-40% in series with a mean follow-up of a year or more.

INDICATIONS AND USAGE

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

1 Recurrent ventricular fibrillation

2 Recurrent hemodynamically unstable ventricular tachycardia

As is the case for other anti-arrhythmic agents, there is no evidence from controlled trials that the use of CORDARONE favorably affects survival

CORDARONE should be used only by physicians familiar with and with access to (directly or through referral) the use of all available modalities for treating recurrent life-threatening ventricular arrhythmias, and who have access to appropriate monitoring facilities including in hospital and ambulatory continuous electrocardiographic monitoring and electrophysiologic techniques Because of 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 hospital

CONTRAINDICATIONS

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

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 (interstitial pneumonitis/alveolitis) that has resulted in clinically manifest disease at rates as high as 10-15% in some series of patients with ventricular arrhythmias given doses around 400 mg/day and as abnormal diffusion capacity without symptoms in a much higher percentage of patients Pulmonary toxicity has been fatal about 10% of the time Liver injury is common with CORDARONE, but is usually mild and evidenced only by abnormal liver enzymes Overt liver disease can occur, however, and has been fatal in a few cases Like other antiarrhythmics, CORDARONE can exacerbate the arrhythmia e g , by making the arrhythmia less well tolerated or more difficult to reverse This has occurred in 2-5% of patients in various series and significant heart block or sinus bradycardia has been seen in 2-5% All of these events should be manageable in the proper clinical setting in most cases Although the frequency of such proarrhythmic events does not appear greater with CORDARONE than with many other agents used in this population the effects are prolonged when they occur

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

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

Pulmonary Toxicity

CORDARONE causes a clinical syndrome of progressive dyspnea and cough accompanied by functional, radiographic gallium scan, and pathological data showing a pulmonary interstitial process, sometimes called alveolitis The frequency of pulmonary toxicity has generally been low varying from 2 7% in most published reports but recent preliminary reports have found rates of 11 to 15% in patients treated for

more than a year on average and there is evidence of increasing frequency with time and/or daily or cumulative dose Although the syndrome is usually reversible when CORDARONE is discontinued, with or without steroid therapy, fatalities have occurred in about 10% of cases

Any new respiratory symptom in a patient receiving CORDARONE should suggest the possibility of pulmonary toxicity and lead to clinical and radiographic evaluation, with gallium scan and pulmonary functional evaluation if needed Particular care should be taken not to presume that such symptoms are related to cardiac failure Again, diffusion capacity appears to be the pulmonary function test most likely to show abnormality Evidence of toxicity should lead at a minimum, to dose reduction, and preferably to withdrawal of the drug to establish reversibility In some cases rechallenge at a lower dose has not resulted in return of toxicity

Periodic chest x-rays and clinical evaluation (every 3-6 months) are recommended and baseline pulmonary function tests, including diffusion capacity should be obtained

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 2-5% in most series and has included new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion and polymorphic ventricular tachycardia associated with QT prolongation (Torsade de Pointes)

In addition, CORDARONE has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients

Liver Injury

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

PRECAUTIONS

Corneal Microdeposits, Impairment of Vision

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

Photosensitivity

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

Thyroid Abnormalities

CORDARONE inhibits peripheral conversion of thyroxine (T_4) to tri-iodothyronine (T_3) tending to cause somewhat increased thyroxine levels and increased levels of inactive reverse T_3, and somewhat decreased levels of T_3 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 both hypothyroidism or hyperthyroidism Thyroid function should be monitored at baseline and periodically, particularly in any patient with a history of thyroid nodules, goiter or other dysfunction

Hypothyroidism has been reported in 2-4% of patients in most series but in 8-10% in others and is probably best identified by a finding of elevated TSH Careful supplementation with thyroid hormone can eliminate this problem

A more difficult problem is hyperthyroidism, best identified by a serum T_3 of more than 200 mg/dl, presumably resulting from an increased supply of iodine to an autonomous nodule or gland, occurring in 1-3% of patients and potentially a reason for discontinuing drug

Hypotension Post-Bypass

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

Laboratory Tests

Elevations in liver enzymes (SGOT and SGPT) can occur Liver enzymes in patients on relatively high maintenance doses should be

monitored on a regular basis Persistent significant elevations in the liver enzymes or hepatomegaly should alert the physician to consider reducing the maintenance dose of CORDARONE or discontinuing therapy

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

Drug Interactions

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

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

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

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

Summary of Drug Interactions with CORDARONE

Concomitant Drug	Interaction		Recommended Dose Reduction of Concomitant Drug
	Onset (days)	Magnitude	
Warfarin	3-4	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%	↓ 1/2 (or discontinue)

*NAPA = n-acetyl procainamide

Electrolyte Disturbances

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Pregnancy. Pregnancy Category C.

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

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

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 children have not been established

ADVERSE REACTIONS

Adverse reactions have been very common in virtually all series of patients treated with CORDARONE for ventricular arrhythmias with relatively large doses of drug (400 mg/day and above) occurring in about three fourths of all patients and causing discontinuation in 7-18% 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 and virtually always reversible with cessation of CORDARONE treatment Most of the adverse effects appear to become more frequent with continued treatment beyond six months although rates appear to remain relatively constant beyond one year The time and dose relationships of adverse effects are under continued study

Neurologic problems are extremely common occurring in 20-40% 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

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

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

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

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

The following side effect rates are based on a retrospective study of 241 patients treated for 2 to 1515 days (mean 4[illegible] days)

The following side effects were each reported in 10-33% of patients

Gastrointestinal	Nausea and vomiting

The following side effects were each reported in 4-9% 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 1-3% 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

Rare occurrences of hepatitis and cirrhosis have been reported in patients receiving CORDARONE The relationship of these events to CORDARONE therapy has not been definitively established

In surveys of almost 5000 patients treated in open U S studies and in published reports of treatment with CORDARONE, the adverse reactions most frequently requiring discontinuation of CORDARONE included pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, congestive heart failure, and elevation of liver enzymes Other symptoms causing discontinuations less often included visual disturbances, solar dermatitis, blue skin discoloration, hyperthyroidism and hypothyroidism

OVERDOSAGE

There have been 3 reported cases of CORDARONE overdose in which 3-8 grams were taken There were no deaths or permanent sequelae Animal studies indicate that CORDARONE has a high oral LD_{50} (>3000 mg/kg)

In addition to general supportive measures the patient's cardiac rhythm and blood pressure should be monitored and if bradycardia ensues a β-adrenergic agonist or a pacemaker may be used Hypotension

with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents Neither CORDARONE nor its metabolite is dialyzable

DOSAGE AND ADMINISTRATION

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

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required A uniform, optimal dosage schedule for administration of CORDARONE has not been determined Individual patient titration is suggested according to the following guidelines

For life-threatening ventricular arrhythmias such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia

Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated Because of the serious nature of the arrhythmia, and the lack of predictable time course of effect, loading should be performed in a hospital setting Loading doses of 800-1600 mg/day are required for 1-3 weeks (occasionally longer)

until initial therapeutic response occurs (Administration of CORDARONE in divided doses with meals is suggested for total daily doses of 1000 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 1-3 weeks, along with reduction in complex and total ventricular ectopic beats

Upon starting CORDARONE therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs (see section on Drug Interactions) When adequate arrhythmia control is achieved, or if side effects become prominent, CORDARONE dose should be reduced to 600-800 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 BID 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 non-responsiveness or unexpectedly severe toxicity (See Clinical Pharmacology)

The lowest effective dose should be used to prevent the occurrence of side effects In all instances, the physician must be guided by the severity of the individual patient's arrhythmia and response to therapy When dosage adjustments are necessary the patient should be closely monitored for an extended period of time because of the

long and variable half-life of CORDARONE and the difficulty in predicting the time required to attain a new steady state level of drug. Dosage suggestions are summarized below:

	Loading Dose (Daily)	Adjustment and Maintenance Dose (Daily)	
Ventricular Arrhythmias	1-3 weeks	~1 month	usual maintenance
	800-1600 mg	600-800 mg	400 mg ~~(some 600 mg)~~

HOW SUPPLIED

CORDARONE® (amiodarone HCl) Tablets are supplied in the following dosage strength in bottles of 60 tablets and in Redipak® Strip Pack cartons (6 strips of 10)

200 mg, NDC 0008-4188, round, convex, white to slightly cream-colored tablets, scored on one side and marked "Ives" and "4188" on the reverse side

Protect from light

Manufactured for Wyeth Laboratories Inc , Philadelphia, PA , 19101

By Sanofi, S A , Paris, France, by arrangement with Sanofi Pharmaceuticals, Inc

CODE NO

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December 23, 1985

Cordarone
NDA 18-972

Center for Drugs & Biologics
Office of Drug Research & Review
Division of Cardio-Renal Drug Products
HFN-110, Rm 168-30
5600 Fishers Lane
Rockville, Maryland 20857

Attention Raymond J Lipicky M D , Acting Director

Dear Dr Lipicky

Reference is made to our pending new drug application for Cordarone (amiodarone hydrochloride) tablets and to the meeting of December 19, 1985 between Ives Laboratories and the Agency at which time the package insert for Cordarone was discussed

Submitted herewith, in triplicate, is a package insert revised in accordance with the agreements made at that meeting This document is considered final labeling and final printed labeling will be identical in content

Thank you for your cooperation

Sincerely yours,

Robert H Harris, Ph D
Director, Regulatory Affairs

PHH tca