LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

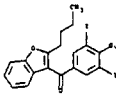
ATTACHMENT 2

Cordarone® Intravenous
(amiodarone hydrochloride)

℞ only

DESCRIPTION

Cordarone Intravenous (Cordarone I V) contains amiodarone HCl ($C_{25}H_{29}I_2NO_3$ • HCl), a class III antiarrhythmic drug Amiodarone HCl is (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride Amiodarone HCl has the following structural formula



Amiodarone HCl is a white to slightly yellow crystalline powder, and is very slightly soluble in water It has a molecular weight of 681 78 and contains 37.3% iodine by weight Cordarone I V is a sterile clear, pale-yellow solution visually free from particulates Each milliliter of the Cordarone I V formulation contains 50 mg of amiodarone HCl, 20.2 mg of benzyl alcohol, 100 mg of polysorbate 80, and water for injection

CLINICAL PHARMACOLOGY

Mechanisms of Action

Amiodarone is generally considered a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes Like class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like class II drugs, it exerts a noncompetitive antisympathetic action One of its main effects, with prolonged administration, is to lengthen the cardiac action potential, a class III effect The negative chronotropic effect of amiodarone in nodal tissues is similar to the effect of class IV drugs In addition to blocking sodium channels, amiodarone blocks myocardial potassium channels, which contributes to slowing of conduction and prolongation of refractoriness. The antisympathetic action and the block of calcium and potassium channels are responsible for the negative dromotropic effects on the sinus node and for the slowing of conduction and prolongation of refractoriness in the atrioventricular (AV) node Its vasodilatory action can decrease cardiac workload and consequently myocardial oxygen consumption

Cordarone I.V administration prolongs intranodal conduction (Atrial-His, AH) and refractoriness of the atrioventricular node (ERP AVN), but has little or no effect on sinus cycle length (SCL), refractoriness of the right atrium and right ventricle (ERP RA and ERP RV), repolarization (QTc), intraventricular conduction (QRS), and infranodal conduction (His-ventricular, HV) A comparison of the electrophysiologic effects of Cordarone I V and oral Cordarone is shown in the table below

EFFECTS OF INTRAVENOUS AND ORAL CORDARONE ON ELECTROPHYSIOLOGIC PARAMETERS

Formulation	SCL	QRS	QTc	AH	HV	ERP RA	ERP RV	ERP AVN
I V	--	--	--	↑	--	--	--	↑
Oral	↑	--	↑	↑	--	↑	↑	↑

-- No change

At higher doses (>10 mg/kg) of Cordarone I V , prolongation of the ERP RV and modest prolongation of the QRS have been seen These differences between oral and intravenous administration suggest that the initial acute effects of Cordarone I V may be predominantly focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel blockade (class IV activity) and noncompetitive adrenergic antagonism (class II activity)

Pharmacokinetics and Metabolism

Amiodarone exhibits complex disposition characteristics after intravenous administration. Peak serum concentrations after single 5 mg/kg 15-minute intravenous infusions in healthy subjects range between 5 and 41 mg/L. Peak concentrations after 10-minute infusions of 150 mg Cordarone I.V. in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) range between 7 and 26 mg/L. Due to rapid distribution, serum concentrations decline to 10% of peak values within 30 to 45 minutes after the end of the infusion In clinical trials, after 48 hours of continued infusions (125, 500, or 1000 mg/day) plus supplemental (150 mg) infusions (for recurrent arrhythmias), amiodarone mean serum concentrations between 0 7 to 1.4 mg/L were observed (n = 250)

N-desethylamiodarone (DEA) is the major active metabolite of amiodarone in humans. DEA serum concentrations above 0.05 mg/L are not usually seen until after several days of continuous infusion but with prolonged therapy reach approximately the same concentration as amiodarone The enzymes responsible for the N-deethylation are believed to be the cytochrome P-450 3A (CYP3A) subfamily, *principally CYP3A4 This isozyme is present in both the liver and intestines The highly variable systemic availability of oral amiodarone may be attributed potentially to large interindividual variability in CYP3A4 activity*

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 Amiodarone and DEA cross the placenta and both appear in breast milk.

No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain The development of maximal ventricular class III effects after oral Cordarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation. On the other hand (see Clinical Trials), after Cordarone I V administration, there is evidence of activity well before significant concentrations of DEA are attained

The following table summarizes the mean ranges of pharmacokinetic parameters of amiodarone reported in single dose i v (5 mg/kg over 15 min) studies of healthy subjects

PHARMACOKINETIC PROFILE AFTER I.V. AMIODARONE ADMINISTRATION

Drug	Clearance (mL/hr/kg)	V_C (L/kg)	V_{SS} (L/kg)	$t_{1/2}$ (days)
Amiodarone	90-158	0.2	40-84	20-47
Desethylamiodarone	197-290	—	68-166	≥ AMI $t_{1/2}$

Notes: V_C and V_{SS} denote the central and steady-state volumes of distribution from I.v studies
" — " denotes not available

Desethylamiodarone clearance and volume involve an unknown biotransformation factor.

The systemic availability of *oral* amiodarone in healthy subjects ranges between 33% and 65% From *in vitro* studies, the protein binding of amiodarone is >96%

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/h/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 Cordarone I.V. 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 oral Cordarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction

There is no established relationship between drug concentration and therapeutic response for short-term intravenous use Steady-state amiodarone concentrations of 1 to 2 5 mg/L have been associated with antiarrhythmic effects and acceptable toxicity following chronic *oral* Cordarone therapy.

Pharmacodynamics

Cordarone I V. has been reported to produce negative inotropic and vasodilatory effects in animals and humans. In clinical studies of patients with refractory VF or hemodynamically unstable VT, treatment-emergent, drug-related hypotension occurred in 286 of 1836 patients (16%) treated with Cordarone I.V No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of Cordarone I V.

Clinical Trials

Apart from studies in patients with VT or VF, described below, there are two other studies of amiodarone showing an antiarrhythmic effect before significant levels of DEA could have accumulated A placebo-controlled study of i v. amiodarone (300 mg over 2 hours followed by 1200 mg/day) in post-coronary artery bypass graft patients with supraventricular and 2- to 3-consecutive-beat ventricular arrhythmias showed a reduction in arrhythmias from 12 hours on. A baseline-controlled study using a similar i v regimen in patients with recurrent, refractory VT/VF also showed rapid onset of antiarrhythmic activity; amiodarone therapy reduced episodes of VT by 85% compared to baseline

The acute effectiveness of Cordarone I.V. in suppressing recurrent VF or hemodynamically unstable VT is supported by two randomized, parallel, dose-response studies of approximately 300 patients each. In these studies, patients with at least two episodes of VF or hemodynamically unstable VT in the preceding 24 hours were randomly assigned to receive doses of approximately 125 or 1000 mg over the first 24 hours, an 8-fold difference In one study, a middle dose of approximately 500 mg was evaluated The dose regimen consisted of an initial rapid loading infusion, followed by a slower 6-hour loading infusion, and then an 18-hour maintenance infusion The maintenance infusion was continued up to hour 48 Additional 10-minute infusions of 150 mg Cordarone I.V were given for "breakthrough" VT/VF more frequently to the 125-mg dose group, thereby considerably reducing the planned 8-fold differences in total dose to 1 8- and 2.6- fold, respectively, in the two studies.

The prospectively defined primary efficacy end point was the rate of VT/VF episodes per hour For both studies, the median rate was 0.02 episodes per hour in patients receiving the high dose and 0.07 episodes per hour in patients receiving the low dose, or approximately 0.5 versus 1 7 episodes per day (p = 0 07, 2-sided, in both studies). In one study, the time to first episode of VT/VF was significantly prolonged (approximately 10 hours in patients receiving the low dose and 14 hours in patients receiving the high dose) In both studies, significantly fewer supplemental infusions were given to patients in the high-dose group Mortality was not affected in these studies, at the end of double-blind therapy or after 48 hours, all patients were given open access to whatever treatment (including Cordarone I.V.) was deemed necessary

INDICATIONS AND USAGE

Cordarone I V. is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy

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Cordarone I V also can be used to treat patients with VT/VF for whom oral Cordarone is indicated, but who are unable to take oral medication During or after treatment with Cordarone I V , patients may be transferred to oral Cordarone therapy (see DOSAGE AND ADMINISTRATION)

Cordarone I V should be used for acute treatment until the patient's ventricular arrhythmias are stabilized Most patients will require this therapy for 48 to 96 hours, but Cordarone I V may be safely administered for longer periods if necessary

CONTRAINDICATIONS

Cordarone I V is contraindicated in patients with known hypersensitivity to any of the components of Cordarone I V , or in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block unless a functioning pacemaker is available

WARNINGS

Hypotension

Hypotension is the most common adverse effect seen with Cordarone I V In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with Cordarone I V Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and was not dose related, but appeared to be related to the rate of infusion Hypotension necessitating alterations in Cordarone I V therapy was reported in 3% of patients, with permanent discontinuation required in less than 2% of patients Hypotension should be treated initially by slowing the infusion; additional standard therapy may be needed, including the following vasopressor drugs, positive inotropic agents, and volume expansion *The initial rate of infusion should be monitored closely and should not exceed that prescribed in* DOSAGE AND ADMINISTRATION

Bradycardia and AV Block

Drug-related bradycardia occurred in 90 (4 9%) of 1836 patients in clinical trials while they were receiving Cordarone I.V. for life-threatening VT/VF; it was not dose-related Bradycardia should be treated by slowing the infusion rate or discontinuing Cordarone I.V In some patients, inserting a pacemaker is required Despite such measures, bradycardia was progressive and terminal in 1 patient during the controlled trials. Patients with a known predisposition to bradycardia or AV block should be treated with Cordarone I V in a setting where a temporary pacemaker is available.

Long-Term Use

See labeling for oral Cordarone There has been limited experience in patients receiving Cordarone I V for longer than 3 weeks.

Neonatal Hypo- or Hyperthyroidism

Although Cordarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with its oral administration If Cordarone I V is administered during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

Cordarone I.V 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 facilities adequate for monitoring the effectiveness and side effects of treatment

Liver Enzyme Elevations

Elevations of blood hepatic enzyme values—alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)—are seen commonly in patients with immediately life-threatening VT/VF Interpreting elevated AST activity can be difficult because the values may be elevated in patients who have had recent myocardial infarction, congestive heart failure, or multiple electrical defibrillations. Approximately 54% of patients receiving Cordarone I.V in clinical studies had baseline liver enzyme elevations, and 13% had clinically significant elevations. In 61% of patients with both baseline and on-therapy data available, the liver enzyme elevations either improved during therapy or remained at baseline levels Baseline abnormalities in hepatic enzymes are not a contraindication to treatment

Rare cases of fatal hepatocellular necrosis after treatment with Cordarone I V. have been reported Two patients, one 26 years of age and the other 60 years of age, were treated for atrial arrhythmias with an initial infusion of 1500 mg over 5 hours, a rate much higher than recommended Both patients developed hepatic and renal failure within 24 hours after the start of Cordarone I.V. treatment and died on day 14 and day 4, respectively Because these episodes of hepatic necrosis may have been due to the rapid rate of infusion with possible rate-related hypotension, *the initial rate of infusion should be monitored closely and should not exceed that prescribed in* DOSAGE AND ADMINISTRATION

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of Cordarone I V therapy, but patients receiving Cordarone I V should be *monitored carefully for evidence of progressive hepatic injury Consideration should be given to reducing* the rate of administration or withdrawing Cordarone I.V In such cases.

Proarrhythmia

Like all antiarrhythmic agents, Cordarone I.V may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsades de pointes, has been associated with prolongation by Cordarone I.V. of the QTc interval to 500 ms or greater Although QTc prolongation occurred frequently in patients receiving Cordarone I V , torsades de pointes or new-onset VF occurred infrequently (less than 2%) Patients should be monitored for QTc prolongation during infusion with Cordarone I V Combination of amiodarone with other antiarrhythmic therapy that prolongs the QTc should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely *responsive to a single agent.*

The need to co-administer amiodarone with any other drug known to prolong the QTc interval must be based on a careful assessment of the potential risks and benefits of doing so for each patient.

A careful assessment of the potential risks and benefits of administering Cordarone I.V. must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia, which may result in death, in these patients.

Pulmonary Disorders

ARDS

Two percent (2%) of patients were reported to have adult respiratory distress syndrome (ARDS) during clinical studies. ARDS is a disorder characterized by bilateral, diffuse pulmonary infiltrates with pul*monary edema and varying degrees of respiratory insufficiency* The clinical and radiographic picture can arise after a variety of lung injuries, such as those resulting from trauma, shock, prolonged cardiopulmonary resuscitation, and aspiration pneumonia, conditions present in many of the patients enrolled in the clinical studies It is not possible to determine what role, if any, Cordarone I.V. played in causing or exacerbating the pulmonary disorder in those patients.

Postoperatively, occurrences of ARDS have been reported in patients receiving *oral* Cordarone therapy who have undergone either cardiac or noncardiac surgery Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FIO_2 and the determinants of oxygen delivery to the tissues (e g , SaO_2, PaO_2) be closely monitored in patients on Cordarone

Pulmonary fibrosis

Only 1 of more than 1000 patients treated with Cordarone I V In clinical studies developed pulmonary fibrosis In that patient, the condition was diagnosed 3 months after treatment with Cordarone I V , during which time she received *oral* Cordarone Pulmonary toxicity is a well-recognized complication of long-term Cordarone use (see labeling for oral Cordarone).

Surgery

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 defects of halogenated inhalational anesthetics.

Drug Interactions

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) This isoenzyme is present in both the liver and intestines (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism) Amiodarone is also known to be an inhibitor of CYP3A4. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4 While only a limited number of *in vivo* drug-drug interactions with amiodarone have been reported, chiefly with the oral formulation, the potential for other interactions should be anticipated This is especially important for drugs associated with serious toxicity, such as other antiarrhythmics If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured. In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone

Since amiodarone is a substrate for CYP3A4, drugs/substances that inhibit CYP3A4 may decrease the metabolism and increase serum concentrations of amiodarone, with the potential for toxic effects. Reported examples of this interaction include the following:

Protease inhibitors:

Protease inhibitors are known to inhibit CYP3A4 to varying degrees. Inhibition of CYP3A4 by **indinavir** has been reported to result in increased serum concentrations of amiodarone Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy should be considered

Histamine H_2 antagonists:

Cimetidine inhibits CYP3A4 and can increase serum amiodarone levels.

Other substances:

Grapefruit juice inhibits CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone, therefore, grapefruit juice should not be taken during treatment with oral amiodarone. This information should be considered when changing from intravenous amiodarone to oral amiodarone (see DOSAGE AND ADMINISTRATION, Intravenous to Oral Transition).

Amiodarone may suppress certain CYP450 enzymes (enzyme inhibition). This can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes and may lead to toxic effects. Reported examples of this interaction include the following:

Immunosuppressives:

Cyclosporine (CYP3A4 substrate) administered in combination with oral amiodarone has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine

Cardiovascular:

Cardiac glycosides: In patients receiving **digoxin** therapy, administration of oral amiodarone regularly results in an increase in serum digoxin concentration that may reach toxic levels with resultant clinical

toxicity Amiodarone taken concomitantly with digoxin increases the serum digoxin concentration by 70% after one day **On administration of oral amiodarone, 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

Antiarrhythmics. Other antiarrhythmic drugs, such as **quinidine, procainamide, disopyramide,** and **phenytoin**, have been used concurrently with amiodarone There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone Phenytoin decreases serum amiodarone levels. Amiodarone taken concomitantly with quinidine increases quinidine serum concentration by 33% after two days Amiodarone taken concomitantly with procainamide for less than seven days increases plasma concentrations of procainamide and n-acetyl procainamide by 55% and 33%, respectively Quinidine and procainamide doses should be reduced by one-third when either is administered with amiodarone. Plasma levels of **flecainide** have been reported to increase in the presence of oral amiodarone, because of this, the dosage of flecainide *should be adjusted when these drugs are administered concomitantly* In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring Combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone During transfer to oral amiodarone, the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of oral amiodarone (see **DOSAGE AND ADMINISTRATION, Intravenous to Oral Transition**) The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted If the treatment is continued, these patients *should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias,* as amiodarone is continued In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose

Antihypertensives. Amiodarone should be used with caution in patients receiving **β-receptor blocking agents** (e g , propanolol, a CYP3A4 inhibitor) or **calcium channel antagonists** (e g., verapamil, a *CYP3A4 substrate, and diltiazem, a CYP3A4 inhibitor) because of the possible potentiation* of bradycardia, sinus arrest, and AV block, If necessary, amiodarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

Anticoagulants. Potentiation of **warfarin-type** (CYP2C9 and CYP3A4 substrate) anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding Since the concomitant administration of warfarin with amiodarone increases the prothrombin time by 100% after 3 to 4 days, **the dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A4 (enzyme induction) This may lead to low amiodarone serum levels and potential decrease in efficacy. Reported examples of this interaction include the following:

Antibiotics:
Rifampin is a potent inducer of CYP3A4 Administration of rifampin concomitantly with oral amiodarone has been shown to result in decreases in serum concentrations of amiodarone and desethylamiodarone

Other substances, including herbal preparations:
St. John's Wort (Hypericum perforatum) induces CYP3A4 Since amiodarone is a substrate for CYP3A4, there is the potential that the use of St John's Wort in patients receiving amiodarone could result in reduced amiodarone levels

Other reported interactions with amiodarone:
Fentanyl (CYP3A4 substrate) in combination with amiodarone may cause hypotension, bradycardia, decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with **lidocaine** *(CYP3A4* substrate) given for local anesthesia Seizure, associated with increased lidocaine concentrations, has been reported with concomitant administration of intravenous amiodarone.

Dextromethorphan is a substrate for both CYP2D6 and CYP3A4 Amiodarone inhibits CYP2D6

Cholestyramine increases enterohepatic elimination of amiodarone and may reduce serum levels and $t_{1/2}$

Disopyramide increases QT prolongation which could cause arrhythmia.

Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with **propranolol, diltiazem,** and **verapamil**

Volatile Anesthetic Agents (see **PRECAUTIONS, Surgery**)

In addition to the interactions noted above, chronic (> 2 weeks) *oral* Cordarone administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.

Electrolyte Disturbances
Patients with hypokalemia or hypomagnesemia should have the condition corrected whenever possible before being treated with Cordarone I.V , as these disorders can exaggerate the degree of QTc prolongation and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity studies were conducted with Cordarone I V However, *oral* 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 in rats was greater than the incidence in controls *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 conducted with amiodarone HCl (Ames, micronucleus, and lysogenic induction tests) were negative

No fertility studies were conducted with Cordarone I.V. However, in a study in which amiodarone HCl was orally 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
Category D. See **WARNINGS, Neonatal Hypo- or Hyperthyroidism.** In addition to causing infrequent congenital goiter/hypothyroidism and hyperthyroidism, amiodarone has caused a variety of adverse effects in animals

In a reproductive study in which amiodarone was given intravenously to rabbits at dosages of 5, 10, or *25 mg/kg per day (about 0.1, 0.3, and 0 7 times the maximum recommended human dose [MRHD]* on a body surface area basis), maternal deaths occurred in all groups, including controls. Embryotoxicity (as manifested by fewer full-term fetuses and increased resorptions with concomitantly lower litter weights) occurred at dosages of 10 mg/kg and above No evidence of embryotoxicity was observed at 5 mg/kg and no teratogenicity was observed at any dosages

In a teratology study in which amiodarone was administered by continuous i v. infusion to rats at dosages of 25, 50, or 100 mg/kg per day (about 0.4, 0.7, and 1 4 times the MRHD when compared on a body surface area basis), maternal toxicity (as evidenced by reduced weight gain and food consumption) and embryotoxicity (as evidenced by increased resorptions, decreased live litter size, reduced body weights, and retarded sternum and metacarpal ossification) were observed in the 100 mg/kg group

Cordarone® I.V (amiodarone HCl) should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

Nursing Mothers
Amiodarone is excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug Nursing offspring of lactating rats administered amiodarone have demonstrated reduced viability and reduced body weight gains. The risk of exposing the infant to amiodarone should be weighed against the potential benefit of arrhythmia suppression in the mother. The mother should be advised to discontinue nursing

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 on the duration of gestation or on parturition

Pediatric Use
The safety and efficacy of Cordarone in the pediatric population have not been established, therefore, its use in pediatric patients is not recommended

Cordarone I V contains the preservative benzyl alcohol (see **DESCRIPTION**). There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse

Geriatric Use
Clinical studies of Cordarone I V, 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
In a total of 1836 patients in controlled and uncontrolled clinical trials, 14% of patients received Cordarone I V for at least 1 week, 5% received it for at least 2 weeks, 2% received it for at least 3 weeks, and 1% received it for more than 3 weeks, without an increased incidence of severe adverse reactions The mean duration of therapy in these studies was 5.6 days; median exposure was 3 7 days.

The most important treatment-emergent adverse effects were hypotension, asystole/cardiac arrest/electromechanical dissociation (EMD), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. Overall, treatment was discontinued for about 9% of the patients because of adverse effects The most common adverse effects leading to discontinuation of Cordarone I.V therapy were hypotension (1.6%), asystole/cardiac arrest/EMD (1.2%), VT (1 1%), and cardiogenic shock (1%)

The following table lists the most common (incidence ≥ 2%) treatment-emergent adverse events during Cordarone I V therapy considered at least possibly drug-related These data were collected from the Wyeth-Ayerst clinical trials involving 1836 patients with life-threatening VT/VF. Data from all assigned treatment groups are pooled because none of the adverse events appeared to be dose-related

SUMMARY TABULATION OF TREATMENT-EMERGENT DRUG-RELATED STUDY EVENTS IN PATIENTS RECEIVING CORDARONE I.V. IN CONTROLLED AND OPEN-LABEL STUDIES (≥ 2% INCIDENCE)

Study Event	Controlled Studies (n=814)	Open-Label Studies (n=1022)	Total (n=1836)
Body as a Whole			
Fever	24 (2 9%)	13 (1.2%)	37 (2 0%)
Cardiovascular System			
Bradycardia	49 (6 0%)	41 (4 0%)	90 (4 9%)
Congestive heart failure	18 (2.2%)	21 (2 0%)	39 (2 1%)
Heart arrest	29 (3 5%)	26 (2.5%)	55 (2 9%)
Hypotension	165 (20 2%)	123 (12.0%)	288 (15 6%)
Ventricular tachycardia	15 (1.8%)	30 (2 9%)	45 (2 4%)
Digestive System			
Liver function tests abnormal	35 (4 2%)	29 (2 8%)	64 (3 4%)
Nausea	29 (3 5%)	43 (4.2%)	72 (3 9%)

Other treatment-emergent possibly drug-related adverse events reported in less than 2% of patients receiving Cordarone I V in Wyeth-Ayerst controlled and uncontrolled studies included the following abnormal kidney function, atrial fibrillation, diarrhea, increased ALT, increased AST, lung edema, nodal *arrhythmia, prolonged QT interval,* respiratory disorder, shock sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting

Postmarketing Reports
In postmarketing surveillance, sinus arrest, pseudotumor cerebri, toxic epidermal necrolysis, exfoliative dermatitis, pancytopenia, neutropenia, erythema multiforme, angioedema, bronchospasm, and anaphylactic shock also have been reported with amiodarone therapy

OVERDOSAGE
There have been cases, some fatal, of amiodarone overdose Effects of an inadvertent overdose of Cordarone I.V Include hypotension, cardiogenic shock, bradycardia, AV block, and hepatotoxicity Hypotension and cardiogenic shock should be treated by slowing the infusion rate or with standard therapy vasopressor drugs, positive inotropic agents, and volume expansion Bradycardia and AV block may require temporary pacing Hepatic enzyme concentrations should be monitored closely Amiodarone is not dialyzable

DOSAGE AND ADMINISTRATION
Amiodarone shows considerable interindividual variation in response Thus, although a starting dose adequate to suppress life-threatening arrhythmias is needed, close monitoring with adjustment of dose as needed is essential The recommended starting dose of Cordarone I V is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen

CORDARONE I.V. DOSE RECOMMENDATIONS — FIRST 24 HOURS —

Loading infusions	***First Rapid:***	**150 mg over the FIRST 10 minutes (15 mg/min).** Add 3 mL of Cordarone I V (150 mg) to 100 mL D_5W (concentration = 1.5 mg/mL) Infuse 100 mL over 10 minutes
	Followed by Slow:	**360 mg over the NEXT 6 hours (1 mg/min).** Add 18 mL of Cordarone I V (900 mg) to 500 mL D_5W (concentration = 1.8 mg/mL)
Maintenance infusion		***540 mg over the REMAINING 18 hours (0.5 mg/min).*** Decrease the rate of the slow loading infusion to 0 5 mg/min

After the first 24 hours, the maintenance infusion rate of 0 5 mg/min (720 mg/24 hours) should be continued utilizing a concentration of 1 to 6 mg/mL (Cordarone I.V concentrations greater than 2 mg/mL should be administered via a central venous catheter) In the event of breakthrough episodes of VF or hemodynamically unstable VT, 150-mg supplemental infusions of Cordarone I V. mixed in 100 mL of D_5W may be administered Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2100 mg were associated with an increased risk of hypotension. The initial infusion rate should not exceed 30 mg/min

Based on the experience from clinical studies of Cordarone I V , a maintenance infusion of up to *0 5 mg/min can be cautiously continued for 2 to 3 weeks regardless of the patient's age, renal function,* or left ventricular function There has been limited experience in patients receiving Cordarone I V. for longer than 3 weeks

The surface properties of solutions containing injectable amiodarone are altered such that the drop size may be reduced. This reduction may lead to underdosage of the patient by up to 30% if drop counter infusion sets are used. Cordarone I.V. must be delivered by a volumetric infusion pump.

Cordarone I V should, whenever possible, be administered through a central venous catheter dedicated to that purpose. An in-line filter should be used during administration.

Cordarone I.V concentrations greater than 3 mg/mL in D_5W have been associated with a high incidence of peripheral vein phlebitis, however, concentrations of 2.5 mg/mL or less appear to be less irritating Therefore, for infusions longer than 1 hour, Cordarone I V concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

Cordarone I.V infusions exceeding 2 hours must be administered in glass or polyolefin bottles containing D_5W **Use of evacuated glass containers for admixing Cordarone I V is not recommended as incompatibility with a buffer in the container may cause precipitation.**

It is well known that amiodarone adsorbs to polyvinyl chloride (PVC) tubing and the clinical trial dose administration schedule was designed to account for this adsorption All of the clinical trials were conducted using PVC tubing and its use is therefore recommended. The concentrations and rates of infusion provided in **DOSAGE AND ADMINISTRATION** reflect doses identified in these studies It is important that the recommended infusion regimen be followed closely

Cordarone I V has been found to leach out plasticizers, including DEHP [di-(2-ethylhexyl)phthalate] from *intravenous tubing (including PVC tubing). The degree of leaching increases when infusing* Cordarone I V at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION.**

Cordarone I.V does not need to be protected from light during administration

AMIODARONE HCl SOLUTION STABILITY

Solution	Concentration (mg/mL)	Container	Comments
5% Dextrose in Water (D_5W)	1 0 - 6 0	PVC	Physically compatible, with amiodarone loss <10% at 2 hours.
5% Dextrose In Water (D_5W)	1.0 - 6 0	Polyolefin, Glass	Physically compatible, with no amiodarone loss at 24 hours.

Admixture Incompatibility
Cordarone I V in D_5W is incompatible with the drugs shown below

Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Amiodarone Concentration	Comments
Aminophylline	D_5W	4 mg/mL	Precipitate
Cefamandole Nafate	D_5W	4 mg/mL	Precipitate
Cefazolin Sodium	D_5W	4 mg/mL	Precipitate
Mezlocillin Sodium	D_5W	4 mg/mL	Precipitate
Heparin Sodium	D_5W	----	Precipitate
Sodium Bicarbonate	D_5W	3 mg/mL	Precipitate

Intravenous to Oral Transition
Patients whose arrhythmias have been suppressed by Cordarone I.V may be switched to oral Cordarone The optimal dose for changing from intravenous to oral administration of Cordarone will depend on the dose of Cordarone I V already administered, as well as the bioavailability of oral Cordarone. When changing to oral Cordarone therapy, clinical monitoring is recommended, particularly for elderly patients.

Since there are some differences between the safety and efficacy profiles of the intravenous and oral formulations, the prescriber is advised to review the package insert for oral amiodarone when switching from intravenous to oral amiodarone therapy.

Since grapefruit juice is known to inhibit CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone, grapefruit juice should not be taken during treatment with oral amiodarone (see **PRECAUTIONS, Drug Interactions**)

The following table provides suggested doses of oral Cordarone to be initiated after varying durations of Cordarone I V. administration These recommendations are made on the basis of a comparable total body amount of amiodarone delivered by the intravenous and oral routes, based on 50% bioavailability of oral amiodarone.

RECOMMENDATIONS FOR ORAL DOSAGE AFTER I.V. INFUSION

Duration of Cordarone I.V. Infusion#	Initial Daily Dose of Oral Cordarone
<1 week	800-1600 mg
1-3 weeks	600-800 mg
>3 weeks*	400 mg

Assuming a 720 mg/day infusion (0 5 mg/min)
* Cordarone I.V is not intended for maintenance treatment

HOW SUPPLIED
Cordarone® I.V. (amiodarone HCl) is available in packages of 10 ampuls (2 cartons each containing 5 ampuls), 3 mL each, as follows
50 mg per mL, NDC 0008-0814-01.

Store at controlled room temperature 20° to 25°C (68° to 77°F).

Protect from light and excessive heat.

Use carton to protect contents from light until used.

Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101

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