GensiaSicor™
PHARMACEUTICALS
A sicor Company

June 19, 2000

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

RE: ANDA Suitability Petition
Camiodarone Hydrochloride Injection

ANDA Suitability Petition

The undersigned submits this Suitability Petition (the "Petition") under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505(j)(2)(c) and 21 CFR 314.93 to request the Commissioner of Food and Drugs to allow submission of an abbreviated new drug application (ANDA) for Camiodarone Hydrochloride Injection in a strength of 900 mg/18 mL, single use vial.

A. Action Requested

The Petitioner requests that the Commissioner of Food and Drugs permits a change in the total drug content (strength) to allow for submission of an abbreviated new drug application (ANDA) for Camiodarone Hydrochloride Injection in a strength of 900 mg/18 mL (50 mg/mL), single use vial. The basis of the Petition is the reference listed drug product, Cordarone® I.V., marketed by the innovator, Wyeth Ayerst, which is available in one presentation; a single use ampule containing 150 mg/3 mL of camiodarone hydrochloride. Wyeth Ayerst received approval for the 150 mg/3 mL ampule product under **NDA 20-377** on August 3, 1995.

B. Statement of Grounds

The subject of the Petition for Camiodarone Hydrochloride Injection is to permit a change in the total drug content (strength). The reference listed drug product, Cordarone® I.V., marketed by the innovator, Wyeth Ayerst, is available as a single use ampule containing 150 mg/3 mL.

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OOP-1352 CP1

Gensia Sicor's proposed drug product will be packaged in a single use vial at the same concentration, 50 mg/mL, as the reference listed drug product, but in a different strength of 900 mg/18 mL.

Product	Dosage Form	Route of Administration	Strength
WYETH AYERST'S Cordarone®	Liquid	Intravenous	150 mg Camiodarone/3 mL Single Use Ampule
GENSIA SICOR'S PROPOSED Camiodarone	Liquid	Intravenous	900 mg Camiodarone/18 mL Single Use Vial

The proposed presentation contains the drug amount prescribed in the package insert for dilution with 500 mL D_5W to make a Camiodarone infusion. Since the need to open multiple ampules will be reduced, the proposed drug product will reduce the potential for contamination resulting from the handling of the product, such as blood borne pathogens from cut fingers and glass particulates. The proposed presentation will also provide a reduction in hazardous waste disposal and cost for the course of therapy.

The subject drug is intended for use only as described in the **Indications** and **Dosage and Administration** sections of the draft package insert appended in **Attachment 1**. To support this petition, a Medical Rationale for the proposed product strength is provided in **Attachment 2**.

Appended in **Attachment 3** is the package insert for Cordarone® I.V., marketed by Wyeth Ayerst. The labeling for the proposed drug is essentially identical to that of Wyeth Ayerst's Cordarone, but differs only with respect to the description of the product, product name, dilution volume, the how-supplied statement, and the specific manufacturer's information.

C. Environmental Impact

In accord with 21 CFR 25.24(c)(1), an Environmental Impact Analysis Statement is not required if there is a determination that Camiodarone Hydrochloride Injection is suitable for ANDA status.

D. 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.

We trust you will find the information in the Petition to be satisfactory for your review and approval. If there are any questions or require further clarification, please do not hesitate in contacting me at (949) 455-4724. I can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Associate Director, Regulatory Affairs

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Attachment 1

Proposed Package Insert for

Gensia Sicor's

Camiodarone Hydrochloride Injection

Y36-001-301
Package Insert

R_{x} only 1

GensiaSicor® PHARMACEUTICALS

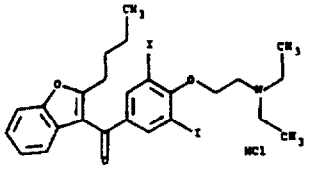
Camiodarone Hydrochloride Injection 2

1. Gensia Sicor is utilizing the "Rx only" symbol located in the title section in compliance with the FDA Modernization Act of 1997.
2. All references to Cordarone (innovator's brand name) have been replaced by the generic nomenclature of the drug.

* A "C" has been added to the name of the active drug substance, amiodarone, to conform to the in-process revision in the *Pharmacopeial Forum*; Volume 25, Number 5 (Sept.-Oct. 1999), p. 8795

DESCRIPTION

Camiodarone* Hydrochloride Injection contains camiodarone HCl ($C_{25}H_{29}I_2NO_3$•HCl), a class III antiarrhythmic drug. Camiodarone HCl is (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride. Camiodarone HCl has the following structural formula:



Camiodarone 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. Camiodarone is a sterile clear, pale-yellow solution visually free from particulates. Each milliliter of the Camiodarone formulation contains 50 mg of camiodarone HCl, 20.2 mg of benzyl alcohol, 100 mg of polysorbate 80, and water for injection.

CLINICAL PHARMACOLOGY
MECHANISMS OF ACTION

Camiodarone Hydrochloride Injection is generally considered a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes. Like class I drugs, camiodarone 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 camiodarone in nodal tissues is similar to the effect of class IV drugs. In addition to blocking sodium channels, camiodarone 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.

Camiodarone 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 Camiodarone Hydrochloride Injection and oral camiodarone is shown in the table below.

EFFECTS OF INTRAVENOUS AND ORAL CAMIODARONE 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 Camiodarone, 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 Camiodarone 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

Camiodarone 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 Camiodarone 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), camiodarone mean serum concentrations between 0.7 to 1.4 mg/L were observed (n=260).

N-desethylcamiodarone (DEA) is the major active metabolite of camiodarone 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 camiodarone. 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 camiodarone may be attributed potentially to large interindividual variability in CYP3A4 activity.

Camiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of camiodarone or DEA in urine. Neither camiodarone nor DEA is dialyzable. Camiodarone 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 camiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral camiodarone are not certain. The development of maximal ventricular class [illegible] administration in humans correlates more closely with DEA accumulation [illegible] camiodarone accumulation. On the other hand (see **Clinical Trials**), after Camiodarone 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 camiodarone reported in single dose i.v. (5 mg/kg over 15 min) studies of healthy subjects.

PHARMACOKINETIC PROFILE AFTER I.V. CAMIODARONE ADMINISTRATION

Drug	Clearance (mL/h/kg)	V c (L/kg)	V ss (L/kg)	$t_{1/2}$ (days)
Camiodarone	90-158	0.2	40-84	20-47
Desethylcamiodarone	197-290	—	68-168	≥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.

Desethylcamiodarone clearance and volume involve an unknown biotransformation factor.

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

In clinical studies of 2 to 7 days, clearance of camiodarone 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 camiodarone or DEA. Renal impairment does not influence the pharmacokinetics of camiodarone. After a single dose of Camiodarone in cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean camiodarone 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 camiodarone 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* camiodarone, 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 camiodarone concentrations of 1 to 2.5 mg/L have been associated with antiarrhythmic effects and acceptable toxicity following chronic *oral* camiodarone therapy.

Pharmacodynamics

Camiodarone 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 288 of 1836 patients (16%) treated with Camiodarone No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of Camiodarone

Clinical Trials

Apart from studies in patients with VT or VF, described below, there are two other studies of camiodarone showing an antiarrhythmic effect before significant levels of DEA could have accumulated. A placebo-controlled study of i.v. camiodarone (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; camiodarone therapy reduced episodes of VT by 85% compared to baseline.

The acute effectiveness of Camiodarone 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 Camiodarone 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 Camiodarone) was deemed necessary.

INDICATIONS AND USAGE

Camiodarone is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy. Camiodarone also can be used to treat patients with VT/VF for whom oral Camiodarone is indicated, but who are unable to take oral medication. During or after treatment with Camiodarone, patients may be transferred to oral camiodarone therapy (see **DOSAGE AND ADMINISTRATION**).

Camiodarone HCl Injection 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 Camiodarone may be safely administered for longer periods if necessary.

CONTRAINDICATIONS

Camiodarone HCl Injection is contraindicated in patients with known hypersensitivity to any of the components of Camiodarone, or in patients with cardiogenic shock, marked sinus bradycardia, and [illegible] AV block unless a functioning pacemaker is available.

WARNING

Hypotension

Hypotension is the most common adverse effect seen with Camiodarone in clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with Camiodarone 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 Camiodarone 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 Camiodarone for life-threatening VT/VF; it was not dose-related. Bradycardia should be treated* by slowing the infusion rate or discontinuing Camiodarone 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 Camiodarone in a setting where a temporary pacemaker is available.

Long-Term Use

See labeling for oral camiodarone. There has been limited experience in patients receiving Camiodarone for longer than 3 weeks.

Neonatal Hypo- or Hyperthyroidism

Although ***oral*** *camiodarone use during pregnancy is uncommon, there have been a small number of* published reports of congenital goiter/hypothyroidism and hyperthyroidism. If Camiodarone is administered during pregnancy, the patient should be apprised of the potential hazard to the fetus.

In pregnant rats and rabbits, ***oral*** amiodarone HCl in doses of 25 mg/kg/day (approximately 0.4 and 0.9 times, respectively, the maximum recommended human maitenance 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

Camiodarone HCl Injection 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 camiodarone therapy, and who have access to facilities adequate for monitoring the effectiveness and side effects of treatment.

Liver Enzyme Elevation

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 Camiodarone in clinical studies had baseline liver enzyme elevations, and 13% had clinically significant elevations. In 81% 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.

Two (2) cases of fatal hepatocellular necrosis after treatment with Camiodarone have been reported. The patients, one 28 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 Camiodarone 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 Camiodarone therapy, but patients receiving Camiodarone should be monitored carefully for evidence of progressive hepatic injury. Consideration should be given to *reducing the rate of administration or withdrawing Camiodarone in such cases.*

Proarrhythmia

Like all antiarrhythmic agents, Camiodarone may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsades de pointes, has been associated with prolongation by Camiodarone of the QTc interval to 500 ms or greater. Although QTc prolongation occurred frequently in patients receiving Camiodarone, torsades de pointes or new-onset VF occurred infrequently (less than 2%). Patients should be monitored for QTc prolongation during infusion with Camiodarone

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 pulmonary 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, Camiodarone played in causing or exacerbating the pulmonary disorder in those patients.

Pulmonary fibrosis

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

Surgery

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

Drug Interactions

Camiodarone can inhibit metabolism mediated by cytochrome P-450 enzymes, probably accounting for the significant effects of oral camiodarone (and presumably Camiodarone HCl Injection) on the pharmacokinetics of various therapeutic agents including digoxin, quinidine, procainamide, warfarin (CYP2C9), dextromethorphan (CYP2D6), and cyclosporine (CYP3A4). Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with propranolol, diltiazem, and verapamil. Conversely, agents producing a significant effect on camiodarone pharmacokinetics include phenytoin, cimetidine, and cholestyramine. Because of the long half-life of camiodarone, drug interactions may persist long after discontinuation of drug administration. Few data are available on drug interactions with Camiodarone Except as noted, the following tables summarize the important interactions between ***oral*** camiodarone and other therapeutic agents.

SUMMARY OF DRUG INTERACTIONS WITH CAMIODARONE

Drugs Whose Effects May Be Increased by Camiodarone

Concomitant Drug	Interaction
Warfarin	Increases prothrombin time.
Digoxin	Increases serum concentration.
Quinidine	Increases serum concentration.
Procainamide	Increases serum concentration, NAPA concentration.
Disopyramide	Increases QT prolongation which could cause arrhythmia.
Fentanyl	May cause hypotension, bradycardia, decreased cardiac output.
Flecainide	Reduces the dose of flecainide needed to maintain therapeutic plasma concentrations.
Lidocaine	**Oral**: Sinus bradycardia was observed in a patient receiving oral camiodarone who was given lidocaine for local anesthesia.
	I.V.: Seizure associated with increased lidocaine concentrations was observed in one patient.
Cyclosporine	Produces persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

SUMMARY OF DRUG INTERACTIONS WITH CAMIODARONE

Drugs that May Interfere with the Actions of Camiodarone

Concomitant Drug	Interaction
Cholestyramine	Increases enterohepatic elimination of camiodarone and may reduce serum levels and $t_{1/2}$.
Cimetidine	Increases serum camiodarone levels.
Phenytoin	Decreases serum camiodarone levels.

Potential drug class interactions with camiordarone

Beta Blockers: Since camiodarone has weak beta blocking activity, use with beta blocking agents could increase risk of hypotension and bradycardia.

Calcium Channel Blockers: camiodarone inhibits atrioventricular conduction and decreases myocardial contractility, increasing the risk of AV block with verapamil or diltiazem or of hypotension with any calcium channel blocker.

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

In addition to the interactions noted above, chronic (>2 weeks) ***oral*** *camiodarone 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 Camiodarone, 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 camiodarone I.V. However, oral camiodarone 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 camiodarone HCl (Ames, micronucleus, and lysogenic induction tests) were negative.

No fertility studies were conducted with camiodarone I.V.. However, in a study in which oral camiodarone HCl was administered to male and female rates, 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)

Mutagenicity studies conducted with camiodarone HCl (Ames, micronucleus, and lysogenic induction tests) were negative.

No fertility studies were conducted with Camiodarone However, oral Camiodarone administration resulted in reduced fertility of rats at a dose of 90 mg/kg/day (about 1.3 times the maximum recommended oral human maintenance dose in mg/m 2). No significant effects on fertility occurred at 30 mg/kg/day.

Pregnancy

Category D. See **WARNINGS, Neonatal Hypo- or Hyperthyroidism**.

In addition to causing infrequent congenital goiter/hypothyroidism and hyperthyroidism, camiodarone has caused a variety of adverse effects in animals.

In a reproductive study in which camiodarone 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 camiodarone 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.

Camiodarone should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

Nursing Mothers

Camiodarone 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 camiodarone have demonstrated reduced viability and reduced body weight gains. The risk of exposing the infant to camiodarone 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 camiodarone 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 Usage

The safety and efficacy of camiodarone in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended.

ADVERSE REACTIONS

In a total of 1836 patients in controlled and uncontrolled clinical trials, 14% of patients received Camiodarone 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 Camiodarone 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 Camiodarone 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 CAMIODARONE 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 Camiodarone 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.

In postmarketing surveillance, toxic epidermal necrolysis also has been reported with camiodarone therapy.

OVERDOSAGE

The most likely effects of an inadvertent overdose of Camiodarone are 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. Camiodarone is not dialyzable. The acute ***oral*** LD_{50} of camiodarone HCl in mice and rats is greater than 3,000 mg/kg.

DOSAGE AND ADMINISTRATION

Camiodarone 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 Camiodarone is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

CAMIODARONE DOSE RECOMMENDATIONS

— FIRST 24 HOURS —

Loading Infusions

***First* Rapid:** **150 mg over the FIRST 10 minutes (15 mg/min).** Add 3 mL of Camiodarone (150 mg) to 100 mL D_5W (concentration = 1.5mg/mL). Infuse 100 mL over 10 minutes.

***Followed by* Slow:** **360 mg over the NEXT 6 hours (1 mg/min).** Add 18 mL of Camiodarone (900 mg) to 500 mLD_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 (Camiodarone 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 Camiodarone 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 Camiodarone, 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 Camiodarone for longer than 3 weeks.

The surface properties of solutions containing injectable camiodarone 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. Camiodarone must be delivered by a volumetric infusion pump.

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

Camiodarone concentrations greater than 3 mg/mL in D5W 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, Camiodarone concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

Camiodarone infusions exceeding 2 hours must be administered in glass or polyolefin bottles containing D_5W. Use of **evacuated glass containers** for admixing Camiodarone is not recommended as

incompatibility with a buffer in the container may cause precipitation.

It is well known that camiodarone 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 **DOSAGE AND ADMINISTRATION** reflect doses identified in these studies. It is important that the recommended infusion regimen be followed closely. Camiodarone does not need to be protected from light during administration.

CAMIODARONE HCl SOLUTION STABILITY

Solution	Concentration (mg/mL)	Container	Comments
5% Dextrose in Water (D_5W)	1.0-6.0	PVC	Physically compatible, with camiodarone loss <10% at 2 hours.
5% Dextrose in Water (D_5W)	1.0-6.0	Polyolefin, Glass	Physically compatible, with no camiodarone loss at 24 hours.

Admixture Incompatibility

Camiodarone in D_5W is incompatible with the drugs shown below.

Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Camiodarone 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 camiodarone may be switched to oral camiodarone. The optimal dose for changing from intravenous to oral administration of camiodarone will depend on the dose of camiodarone already administered, as well as the bioavailability of oral camiodarone. When changing to oral Camiodarone therapy, clinical monitoring is recommended, particularly for elderly patients.

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

RECOMMENDATIONS FOR ORAL DOSAGE AFTER I.V. INFUSION

Duration of Camiodarone Infusion#	Initial Daily Dose of Oral Camiodarone
<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).

* Camiodarone HCl Injection is not intended for maintenance treatment.

HOW SUPPLIED

Camiodarone HCl Injection is supplied as follows:

NDC Number	Contents	Vial Size
N0703-1332-03	150 mg/3 mL	3 mL (Packaged 10 per shelfpack)
★ N0703-1336	900 mg/18 mL	20 mL (Individually packaged.)

Store at room temperature, 15° to 25°C (59° to 77°F).

Protect from light and excessive heat.

Use carton to protect contents from light until used.

★ Gensia Sicor is proposing a product package configuration which the innovator does not carry.

Attachment 2

Medical Rationale for the Proposed Product Included as Statement of Grounds

Medical Rationale

Camiodarone Hydrochloride Injection, 900 mg/18 mL

PHARMACOLOGY:

Camiodarone is generally considered a class III antiarrhythmic drug, with electrophysiologic characteristics to block sodium channels at rapid pacing frequencies and to exert a noncompetitive antisympathetic action. With prolonged administration, the cardiac action potential is lengthened. In addition to blocking sodium channels, camiodarone 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.

INDICATIONS FOR USE:

Camiodarone is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy. Camiodarone also can be used to treat patients with VT/VF who are unable to take oral medication. During or after treatment with Camiodarone, patients may be transferred to oral therapy.

DOSAGE:

Camiodarone is administered intravenously. The recommended starting dose of Camiodarone is 1050 mg over the first 24 hours of therapy using the following loading infusions:

150 mg over the first 10 minutes (15 mg/min), using a concentration of 1.5 mg/mL in D_5W.

360 mg over the next 6 hours (1 mg/min), using a concentration of 1.8 mg/mL in D_5W (900 mg Camiodarone in 500 mL D_5W).

540 mg over the remaining 18 hours (0.5 mg/min), using a concentration of 1.8 mg/mL in D_5W (900 mg Camiodarone in 500 mL D_5W).

After the initial dosing, 720 mg of Camiodarone is normally administered over a 24-hour period, using an infusion rate of 0.5 mg/min.

Concentrations greater than 2 mg/mL should be administered using a central venous catheter, and concentrations of 3 mg/mL and higher in D_5W, have been associated with high incidence of peripheral vein phlebitis.

Most patients will require this therapy for 48 to 96 hours, but Camiodarone may be safely administered for longer periods if necessary.

RATIONALE:

The currently marketed product, Cordarone I.V., is available in one size - 150 mg single use ampule. As indicated above in the DOSAGE section of this Petition, infusions prepared at 1.8 mg/mL by using 900 mg of Camiodarone in 500 mL of D_5W is prescribed in the package insert.

The proposed strength is intended to assist in compounding the 1.8 mg/mL concentration of Camiodarone. Specifically, when using the proposed Gensia Sicor product of 900 mg/18 mL, one would require only 1 (one) vial of product instead of 6 (six) ampules (150 mg/3 mL) of Cordarone®.

The proposed product size, 900 mg, does not pose a question of safety or effectiveness because the uses, doses, and route of administration of the proposed product are the same as those of the listed drug. The sole difference is the total amount of drug in the container.

Market research indicates that the proposed 900mg product would be advantageous for practitioners as the 900 mg size conforms to the directions in the package insert for preparation of the 1.8 mg/mL infusion. Additionally, the 900 mg strength would reduce the number of drug containers to be opened, reduce the potential for contamination resulting from the handling of the product, such as blood borne pathogens from cut fingers and glass particulates, and increase safety (i.e., prevention of cuts caused by opening ampules).

The availability of Camiodarone in a single use vial of containing 900 mg will offer a reduction in waste disposal compared to Cordarone® I.V., because fewer drug containers are required to dose in the range set forth in the approved labeling.

SUMMARY:

In summary, the availability of Camiodarone Hydrochloride Injection in a 900 mg single dose vial will offer safety, convenience and cost savings advantages over Cordarone I.V. in 150 mg ampules. Specifically, since dose concentrations at approximately 1.8 mg/mL prepared by using 900 mg Camiodarone are common when using an

approved regimen, the proposed 900 mg size offers the advantage of convenience (saves time and money), reduces the possibility of a dosing error (because the number of vials required is less), and reduces the number of vial contact by medical personnel that could introduce microbial and/or particulate contamination to the sterile product.

The proposed drug product size is intended for use only as described in the *Indications and Usage* and *Dosage and Administration* sections of Gensia Sicor's draft package insert, provided in **Attachment 1**.

We believe that the information presented in this correspondence for Camiodarone Hydrochloride Injection supports our claim that the product size is suitable for an abbreviated new drug application.

REFERENCES:

1. Package insert for Cordarone® I.V., Wyeth Ayerst. Revised May 7, 1999.

Attachment 3

Wyeth Ayerst

Cordarone

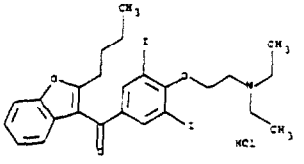
Package Insert

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 tachycar[illegible] VT) range between 7 and [illegible] Due to [illegible] stribution, serum concentrations decline to 10% of peak values within 30 to 45 minute[illegible] er 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 [illegible] an serum concentrations between 0.7 to 1.4 mg/L were observed (n = 260).

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/h/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	—	68-168	≥ 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 288 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

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Cordarone®
Intravenous
(amiodarone hydrochloride)

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

In pregnant rats and rabbits, ***oral*** 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 [illegible] 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
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 amino - transferase (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 81% 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.*
Two (2) cases of fatal hepatocellular necrosis after treatment with Cordarone I.V. have been reported. The patients, one 28 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.

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 pulmonary 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 can inhibit metabolism mediated by cytochrome P-450 enzymes, probably accounting for the significant effects of oral Cordarone (and presumably Cordarone I.V.) on the pharmacokinetics of various therapeutic agents including digoxin, quinidine, procainamide, warfarin (CYP2C9), dextromethorphan (CYP2D6), and cyclosporine (CYP3A4). Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with propranolol, diltiazem, and verapamil. Conversely, agents producing a significant effect on amiodarone pharmacokinetics include phenytoin, cimetidine, and cholestyramine. Because of the long half-life of amiodarone, drug interactions may persist long after discontinuation of drug administration. Few data are available on drug interactions with Cordarone I.V. Except as noted, the following tables summarize the important interactions between ***oral*** Cordarone and other therapeutic agents.

SUMMARY OF DRUG INTERACTIONS WITH CORDARONE
Drugs Whose Effects May Be Increased by Cordarone

Concomitant Drug	Interaction
Warfarin	Increases prothrombin time.
Digoxin	Increases serum concentration.
Quinidine	Increases serum concentration.
Procainamide	Increases serum concentration, NAPA concentration.
Disopyramide	Increases QT prolongation which could cause arrhythmia.
Fentanyl	May cause hypotension, bradycardia, decreased cardiac output.
Flecainide	Reduces the dose of flecainide needed to maintain therapeutic plasma concentrations.
Lidocaine	**Oral:** Sinus bradycardia was observed in a patient receiving oral Cordarone who was given lidocaine for local anesthesia. **I.V.:** Seizure associated with increased lidocaine concentrations was observed in one patient.
Cyclosporine	Produces persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

SUMMARY OF DRUG INTERACTIONS WITH CORDARONE
Drugs that May Interfere with the Actions of Cordarone

Concomitant Drug	Interaction
Cholestyramine	Increases enterohepatic elimination of amiodarone and may reduce serum levels and $t_{1/2}$.
Cimetidine	Increases serum amiodarone levels.
Phenytoin	Decreases serum amiodarone levels.

Potential drug class interactions with Cordarone

Beta Blockers: Since Cordarone has weak beta-blocking activity, use with beta-blocking agents could increase risk of hypotension and bradycardia.

Calcium Channel Blockers: Cordarone inhibits atrioventricular conduction and decreases myocardial contractility, increasing the risk of AV block with verapamil or diltiazem or of hypotension with any calcium channel blocker.

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

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

Pregnancy

Category D. See **WARNINGS and 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. 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 Usage
The safety and efficacy of Cordarone in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended.

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.

In postmarketing surveillance, toxic epidermal necrolysis, pancytopenia, neutropenia, angioedema, and anaphylactic shock also have been reported with amiodarone therapy.

OVERDOSAGE
The most likely effects of an inadvertent overdose of Cordarone I.V. are 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. The acute ***oral*** LD_{50} of amiodarone HCl in mice and rats is greater than 3,000 mg/kg.

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. 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.

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 room temperature, 15° to 25°C (59° to 77°F).
Protect from light and excessive heat.
Use carton to protect contents from light until used.

Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

by arrangement with Sanofi S.A.
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From: Regulatory Affairs (949)455-4794
GENSIA SICOR PHARMACEUTICALS
19 HUGHES ST

IRVINE, CA, 92618

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SHIP DATE: 19JUN00
WEIGHT 1 LBS

Ref: 4830 - ANDA Camiodarone

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