

September 18, 2002

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1 – 23, 12420 Parklawn Drive
Rockville MD USA
20857

ANDA Suitability Petition

Dear Sir or Madame:

Bioniche Pharma (Canada) Ltd. submits this ANDA suitability petition under 21 CFR section 314.93.

Action Requested:

Bioniche Pharma (Canada) Ltd. requests that the Commissioner of Food and Drugs permit us to file an ANDA/ Supplemental ANDA (tentatively approved ANDA 76-217 for the 3 mL vial) for our product Amiodarone Hydrochloride Injection, 50 mg/mL, 18 mL vial, total content in vial is 900 mg/mL, which differs from the reference listed drug, Cordarone I.V. (Amiodarone Hydrochloride Injection) 50 mg/mL, Wyeth Ayerst, Application #NDA 20-377, by the following:

Amiodarone Hydrochloride Injection, 50 mg/mL

50 mg/mL of Amiodarone hydrochloride, polysorbate 80 NF, 100 mg/mL and Benzyl Alcohol NF, 20.2 mg/mL in a **18 mL vial**.

Cordarone® I.V. 50 mg/mL

50 mg/mL of Amiodarone hydrochloride, polysorbate 80 NF, 100 mg/mL and Benzyl Alcohol NF, 20.2 mg/mL in a **3 mL ampule**.

Statement of Grounds:

The proposed presentation contains the same amount per mL of active and inactive ingredients as shown above. It also contains the total drug amount prescribed in the package insert for dilution with 500 mL D₅W to make an Amiodarone hydrochloride Injection 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. The proposed presentation will also provide a reduction in hazardous waste disposal and cost for the course of therapy.

02 P-0419

CPI

Amiodarone Hydrochloride Injection, 50 mg/mL, 18 mL vial, is intended for use only as described in the **Indications** and **Dosage and Administration** sections of the draft package insert Attached.

Environmental Impact:

Bioniche Pharma (Canada) Ltd. is also requesting, under 21 CFR 25.31, categorical exclusion from filing an Environmental Impact Assessment.

Certification:

Bioniche Pharma (Canada) Ltd. certifies, that, to the best of our knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes all information that is known to us to be unfavorable to the petition.

Sincerely,



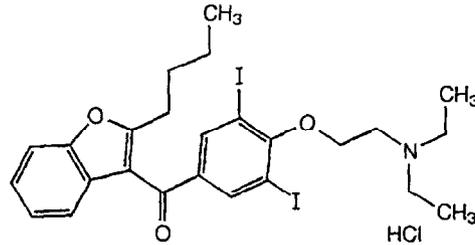
Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma Group

Enclosed

AMIODARONE HYDROCHLORIDE INJECTION

DESCRIPTION

Amiodarone Hydrochloride Injection contains amiodarone HCl ($C_{25}H_{29}I_2NO_3 \cdot HCl$), 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. Amiodarone Hydrochloride Injection is a sterile clear, pale-yellow solution visually free from particulates. Each milliliter of the Amiodarone Hydrochloride Injection 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 antisymphathetic 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 antisymphathetic 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.

Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection and oral amiodarone HCl is shown in the table below.

**EFFECTS OF INTRAVENOUS AND ORAL
AMIODARONE HYDROCHLORIDE 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 Amiodarone Hydrochloride Injection, 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 Amiodarone Hydrochloride Injection 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 15-minute infusions of 150 mg Amiodarone Hydrochloride Injection 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=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 amiodarone HCl administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation. On the other hand (see CLINICAL TRIALS), after Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection 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* amiodarone HCl, 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* amiodarone HCl therapy.

Pharmacodynamics

Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection. No correlations were seen between the baseline injection fraction and the occurrence of clinically significant hypotension during infusion of Amiodarone Hydrochloride Injection.

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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection) was deemed necessary.

INDICATIONS AND USAGE

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

Amiodarone Hydrochloride 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 Amiodarone Hydrochloride Injection may be safely administered for longer periods if necessary.

CONTRAINDICATIONS

Amiodarone Hydrochloride Injection is contraindicated in patients with known hypersensitivity to any of the components of Amiodarone Hydrochloride Injection, 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 Amiodarone Hydrochloride Injection. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with Amiodarone Hydrochloride Injection. 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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection for life-threatening VT/VF; it was not dose-related. Bradycardia should be treated by slowing the infusion rate or discontinuing Amiodarone Hydrochloride Injection. 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 Amiodarone Hydrochloride Injection in a setting where a temporary pacemaker is available.

Long-Term Use

See labeling for oral amiodarone HCl. There has been limited experience in patients receiving Amiodarone Hydrochloride Injection for longer than 3 weeks.

Neonatal Hypo- or Hyperthyroidism

Although amiodarone 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 Amiodarone Hydrochloride Injection is administered during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

Amiodarone Hydrochloride 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 amiodarone HCl 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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection therapy, but patients receiving Amiodarone Hydrochloride Injection should be monitored carefully for evidence of progressive hepatic injury. Consideration should be given to reducing the rate of administration or withdrawing Amiodarone Hydrochloride Injection in such cases.

Proarrhythmia

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

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, Amiodarone Hydrochloride Injection played in causing or exacerbating the pulmonary disorder in those patients.

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

Pulmonary fibrosis

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

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 amiodarone HCl (and presumably Amiodarone Hydrochloride 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 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 Amiodarone Hydrochloride Injection. Except as noted, the following tables summarize the important interactions between **oral** amiodarone HCl and other therapeutic agents.

SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE HCL
Drug Whose Effects May Be Increased by Amiodarone HCl

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 amiodarone HCl 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 cyclosporin.

SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE HCL
Drugs that May Interfere with Actions of Amiodarone HCl

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 Amiodarone HCl

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

Calcium Channel Blockers: Amiodarone HCl 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** amiodarone HCl 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 Amiodarone Hydrochloride Injection, 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 Amiodarone Hydrochloride Injection. However, **oral** amiodarone HCl 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 Amiodarone Hydrochloride Injection. 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** 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.

Amiodarone Hydrochloride Injection 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 amiodarone HCl 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 amiodarone HCl in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended.

Amiodarone Hydrochloride Injection contains the preservative benzyl alcohol (see DESCRIPTION). There have been reports of fatal "gaspings 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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection 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 $\geq 2\%$) treatment-emergent adverse events during Amiodarone Hydrochloride Injection therapy considered at least possibly drug-related. These data were collected from the 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 AMIODARONE HYDROCHLORIDE INJECTION IN CONTROLLED AND OPEN-LABEL STUDIES ($\geq 2\%$ 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 Amiodarone Hydrochloride Injection in 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 Amiodarone Hydrochloride Injection 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.

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 Amiodarone Hydrochloride Injection is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen.

AMIODARONE HYDROCHLORIDE INJECTION DOSE RECOMMENDATIONS - FIRST 24 HOURS -

Loading infusions	First Rapid:	150 mg over the FIRST 10 minutes (15 mg/min). Add 3mL of Amiodarone Hydrochloride Injection (150 mg) to 100 mL D ₅ W (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 Amiodarone Hydrochloride Injection (900 mg) to 500 mL D ₅ W (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 (Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection mixed in 100 mL of D₅W 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 Amiodarone Hydrochloride Injection, 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 Amiodarone Hydrochloride Injection 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. Amiodarone Hydrochloride Injection must be delivered by a volumetric infusion pump.

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

Amiodarone Hydrochloride Injection 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, Amiodarone Hydrochloride Injection concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

Amiodarone Hydrochloride Injection infusions exceeding 2 hours must be administered in glass or polyolefin bottles containing D₅W. Use of **evacuated glass containers** for admixing Amiodarone Hydrochloride Injection 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.

Amiodarone Hydrochloride Injection 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 Amiodarone Hydrochloride Injection at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION**.

Amiodarone Hydrochloride Injection 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 ₅ W)	1.0 - 6.0	PVC	Physically compatible, with amiodarone loss <10% at 2 hours
5% Dextrose in Water (D ₅ W)	1.0 - 6.0	Polyolefin, Glass	Physically compatible, with no amiodarone loss at 24 hours

Admixture Incompatibility

Amiodarone Hydrochloride Injection in D₅W is incompatible with the drugs shown below.

Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Amiodarone Concentration	Comments
Aminophylline	D ₅ W	4 mg/mL	Precipitate
Cefamandole Nafate	D ₅ W	4 mg/mL	Precipitate
Cefazolin Sodium	D ₅ W	4 mg/mL	Precipitate
Mezlocillin Sodium	D ₅ W	4 mg/mL	Precipitate
Heparin Sodium	D ₅ W	----	Precipitate
Sodium Bicarbonate	D ₅ W	3 mg/mL	Precipitate

Intravenous to Oral Transition

Patients whose arrhythmias have been suppressed by Amiodarone Hydrochloride Injection may be switched to oral amiodarone HCl. The optimal dose for changing from intravenous to oral administration of amiodarone HCl will depend on the dose of Amiodarone Hydrochloride Injection already administered, as well as the bioavailability of oral amiodarone HCl. When changing to oral amiodarone HCl therapy, clinical monitoring is recommended, particularly for elderly patients.

The following table provides suggested doses of oral amiodarone HCl to be initiated after varying durations of Amiodarone Hydrochloride Injection 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 Amiodarone I.V. Infusion#	Initial Daily Dose of Oral Amiodarone HCl
<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).

* Amiodarone Hydrochloride Injection is not intended for maintenance treatment.

HOW SUPPLIED

Amiodarone Hydrochloride Injection is available in packages of 10 vials, 3 mL each, as follows: 50 mg per mL, NDC 62086-153-03. *and 18 mL vials, 50 mg per mL, NDC 62086-153-18.*

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.

Manufactured by:
Bioniche Teo
Co. Galway, Ireland

Manufactured for:
Bioniche Pharma (Canada) Ltd
London, ON N6A 5R7
Canada

Rev. 00; July 2001

0456L100

Reference Listed Drug Package Insert

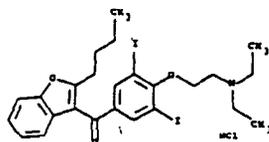
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Cordarone® Intravenous (amiodarone hydrochloride)

Description

Cordarone Intravenous (Cordarone I.V.) contains amiodarone HCl ($C_{25}H_{29}I_2NO_3 \cdot HCl$), a class III antiarrhythmic drug. Amiodarone HCl is (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diodophenyl]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 antisymphathetic 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 antisymphathetic 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.

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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 = 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.

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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. 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.*

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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 HYPOTHYROIDISM 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.

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 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.

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 effects 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.

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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 adenomas in rats. The incidence of thyroid adenomas in rats was greater than the incidence in controls even at the lowest tested dose of 5 mg/kg/day (about 0.1 times the maximum recommended oral human maintenance dose in mg/m²).

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

No fertility studies were conducted with Cordarone I.V. However, *oral* Cordarone administration resulted in reduced fertility of rats at a dose of 90 mg/kg/day (about 1.3 times the maximum rec-

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ommended oral human maintenance dose in mg/m²). No significant effects on fertility occurred at 30 mg/kg/day.

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 \geq 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 (\geq 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 also has been reported with amiodarone therapy.

REFERENCE LISTED DRUG PACKAGE INSERT

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.

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 ₅ W (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 ₅ W (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 D₅W 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 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, 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 D₅W. 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.

REFERENCE LISTED DRUG PACKAGE INSERT

AMIODARONE HCl SOLUTION STABILITY

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

ADMIXTURE INCOMPATIBILITY

Cordarone I.V. in D₅W is incompatible with the drugs shown below.

Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Amlodarone Concentration	Comments
Aminophylline	D ₅ W	4 mg/mL	Precipitate
Cefamandole Nafate	D ₅ W	4 mg/mL	Precipitate
Cefazolin Sodium	D ₅ W	4 mg/mL	Precipitate
Mezlocillin Sodium	D ₅ W	4 mg/mL	Precipitate
Heparin Sodium	D ₅ W	---	Precipitate
Sodium Bicarbonate	D ₅ W	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.
Cl 4351-2 Revised August 6, 1997

Printed in USA

FedEx Express International Air Waybill

Origin Copy

1 From

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Company Wm/Khonda Noll

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Address 1211 WINDYBROOK DR

City LONDON Province ON CANADA Postal Code N6A 1K1

2 Your Internal Reference

3 To

Recipient's Name Dept. Management Council Phone _____

Company Department of Health and Human Services

Address Room 1-23, 1200 Parklawn Drive Dept./Floor _____

Address _____

City Rockville State MD Province _____

Country USA ZIP 20850 Postal Code _____

Sender's Tax ID number required for Customs purposes (FC/NAT/NEIN, or as locally required)

4 Shipment Information

Total Packages 1 Total Weight 0.5 lb kg DIM 1/1 in cm

Commodity Description REQUIRED	Harmonized Code	Country of Manufacture	Value for Customs REQUIRED
<u>10000000</u>		<u>Canada</u>	<u>0</u>

Export Declaration / B13A

No B-3A required Manual B13A attached B13A filed electronically

Total Declared Value for Carriage _____ Total Declared Value for Customs 0

B-3A Summary Reporting B-3A Summary Reporting

Auth ID / Form ID# _____

5 Express Package Service

FedEx International Priority FedEx International First
Available to select locations Higher rates apply

_____ _____ FedEx International Economy
FedEx Envelope and FedEx Pak rate not available

Packages up to 150 lb / 68 kg
For packages over 150 lb (68 kg), use the FedEx Expanded Service International Air Waybill

Not all services and options are available to all destinations.

6 Packaging

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FedEx Acct No _____ Credit Card No _____

Credit Card Exp. Date _____ Credit Card Auth _____

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ALL shipments can be subject to Customs charges, which FedEx does not estimate prior to clearance

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Use of this Air Waybill constitutes your agreement to the Conditions of Contract on the back of this Air Waybill, and you represent that this shipment does not contain Dangerous Goods. Certain international treaties, including the Warsaw Convention, may apply to this shipment and limit our liability for damage, loss, or delay, as described in the Conditions of Contract.

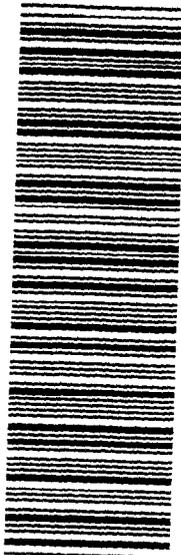
Sender's Signature Khonda Noll Date Executed 09-14-02

This is not authorization to deliver this shipment without a recipient signature. Received above shipment in good order and condition. We agree to pay all charges, including Customs duties and taxes as applicable, and we agree to the Conditions of Contract as stated on the reverse side of the Recipient's Copy.

Recipient's Signature _____

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Origin Station I.D.	Destination Station I.D.	URSA Routing	Handling Units
<u>JFK</u>	<u>GAI</u>	<u>ENGA</u>	Total Volume _____
Received At	Reg Stop <input type="checkbox"/> On-Call Stop <input type="checkbox"/> Drop Box <input type="checkbox"/> World Service Center <input type="checkbox"/> Station <input type="checkbox"/>	Forms Attached: <input type="checkbox"/> CI <input type="checkbox"/> SED <input type="checkbox"/> CD	
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Freight _____	Other _____	Total _____	



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