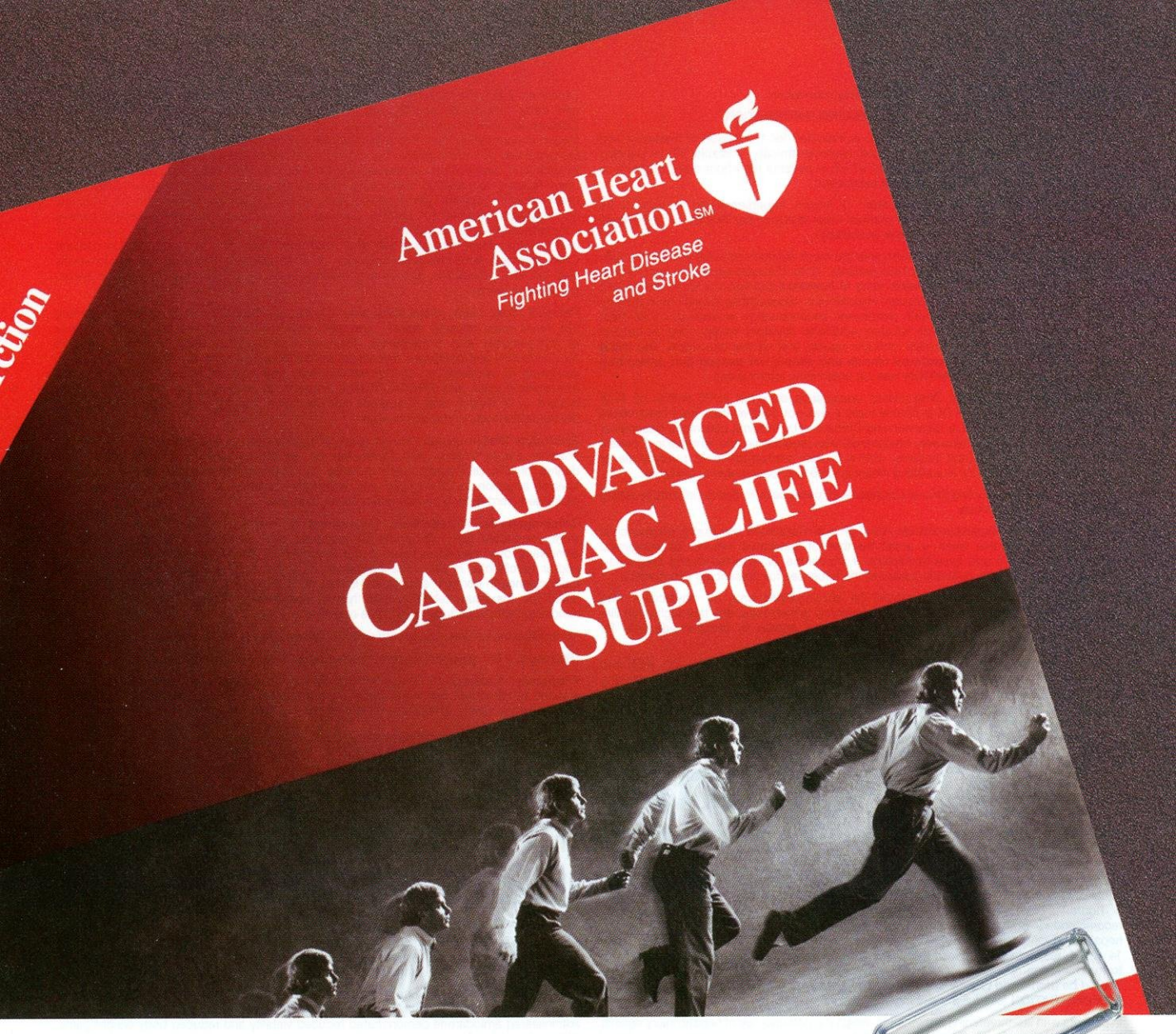
Cordarone I.V. advertisement.

[s.l.]: [s.n.], 2000



Now before lidocaine

Cordarone I.V.—Now first-choice antiarrhythmic for persistent VF/pulseless VT in the ACLS guidelines[1]

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. is contraindicated in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block in the absence of a functioning pacemaker. Hypotension is the most common adverse effect seen with Cordarone I.V. and may be related to the rate of infusion. The most important treatment-emergent adverse effects are hypotension (16%), bradycardia (4.9%), liver function test abnormalities (3.4%), cardiac arrest (2.9%), VT (2.4%), congestive heart failure (2.1%), cardiogenic shock (1.3%), and AV block (0.5%).

Please see adjacent brief summary of Prescribing Information.

Cordarone® I.V.
(amiodarone HCl) 150 mg/3 mL

Before lidocaine.

CORDARONE I.V. - Brief summary of prescribing information

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: Cordarone I.V. is indicated for 1) initiation of treatment and prophylaxis of frequently recurring VF and hemodynamically unstable VT in patients refractory to other therapy; 2) treatment of VT/VF in patients for whom oral Cordarone is indicated, but who are unable to take oral medication.

CONTRAINDICATIONS: In patients with: 1) known hypersensitivity to any of its components; 2) cardiogenic shock; 3) marked sinus bradycardia; 4) 2nd- or 3rd-degree AV block unless a functioning pacemaker is available.

WARNINGS: Hypotension: Hypotension was the most common adverse effect seen with Cordarone I.V. in clinical trials (288 of 1836 patients; 16%). Clinically significant hypotension was most often seen in the first several hours of treatment and was not dose related, but appeared to be related to rate of infusion. Hypotension necessitating alterations in therapy was reported in 3% of patients, with permanent discontinuation required in < 2%. Treat hypotension initially by slowing the infusion; additional standard therapy may be needed including 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** (see full prescribing information).

Bradycardia and AV Block: Drug-related bradycardia occurred in 90 (4.9%) of 1836 patients receiving Cordarone I.V. in clinical trials; it was not dose related. Treat bradycardia by slowing the infusion rate or discontinuing Cordarone I.V. In some patients, a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 patient during controlled trials. Treat patients with a known predisposition to bradycardia or AV block with Cordarone I.V. in a setting where a temporary pacemaker is available.

Long-term Use: See labeling for oral Cordarone. Experience is limited in patients receiving Cordarone I.V. for > 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 given during pregnancy, apprise the patient of the potential hazard to the fetus (see full prescribing information).

PRECAUTIONS: Cordarone I.V. should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, are thoroughly familiar with the risks and benefits of Cordarone, and have access to facilities adequate for monitoring the effectiveness and side effects of treatment.

Liver Enzyme Elevations: Elevations of blood hepatic enzyme values—ALT, AST, and GGT—are seen commonly in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because values may be elevated in patients who have had recent myocardial infarction, CHF, or multiple electrical defibrillations. In clinical studies, approximately 54% of patients had baseline liver enzyme elevations; 13% had clinically significant elevations. Liver enzyme elevations may improve during therapy or remain at baseline levels. Baseline abnormalities in hepatic enzymes are not a contraindication to treatment.

Two cases of fatal hepatocellular necrosis have been reported after Cordarone I.V. treatment of atrial arrhythmias with an initial infusion rate 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. and died on day 14 and 4, respectively. Because these episodes of hepatic necrosis may have been due to rapid infusion rate with possible rate-related hypotension, ***the initial rate of infusion should be monitored closely and should not exceed that prescribed in*** **DOSAGE AND ADMINISTRATION** (see full prescribing information).

In patients with life-threatening arrhythmias, weigh the potential risk of hepatic injury against the potential benefit of Cordarone I.V., but carefully monitor patients for evidence of progressive hepatic injury. Give consideration to reducing administration rate or withdrawing Cordarone I.V. in such cases.

Proarrhythmia: Like all antiarrhythmics, 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. Although QTc prolongation occurred frequently in Cordarone I.V. patients, torsades de pointes or new-onset VF occurred infrequently (< 2%). Monitor patients for QTc prolongation during Cordarone I.V. infusion.

Pulmonary Disorders: *ARDS:* Two percent of patients were reported to have adult respiratory distress syndrome (ARDS) during clinical studies. ARDS 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, ARDS has been reported in patients receiving ***oral*** Cordarone 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 are performed, FiO_2 and the determinants of oxygen delivery to the tissues (e.g., SaO_2, PaO_2) should be closely monitored in Cordarone 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 Cordarone I.V. treatment, 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 amiodarone-treated patients undergoing general anesthesia 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, dextromethorphan, and cyclosporine. Hemodynamic and electrophysiologic interactions also have been observed after concomitant propranolol, diltiazem, and verapamil therapy. 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 its discontinuation. Few data are available on drug interactions with Cordarone I.V.

Except as noted, the following summarizes important interactions between ***oral*** Cordarone and other therapeutic agents. **Drugs Whose Effects May Be Increased (inc.) By Cordarone:** Warfarin (prothrombin time inc.), Digoxin (serum concentration inc.), Quinidine (serum concentration inc.), Procainamide (serum concentration, NAPA concentration inc.), Disopyramide (QT prolongation inc., which could cause arrhythmia), Fentanyl (may cause hypotension, bradycardia, decreased cardiac output), Flecainide (reduces the flecainide dose needed to maintain therapeutic plasma concentrations), Lidocaine (**Oral:** sinus bradycardia in 1 patient during local anesthesia; **I.V.:** seizure associated with inc. lidocaine concentration observed in 1 patient), Cyclosporine (produces persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in cyclosporine dose). **Drugs That May Interfere With The Actions Of Cordarone:** Cholestyramine (enterohepatic elimination of amiodarone inc.; may reduce serum levels and half-life), Cimetidine (serum amiodarone levels inc.), 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 AV 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 above, chronic (> 2 weeks) ***oral*** Cordarone administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.

Electrolyte Disturbances: Correct cases of hypokalemia or hypomagnesemia whenever possible before treating with Cordarone I.V., as these disorders can exaggerate the degree of QTc prolongation and increase the potential for torsades de pointes. Give special attention to electrolyte and acid-base balance in patients with severe or prolonged diarrhea or 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 tested, i.e., 5 mg/kg/day (approx. 0.08 times the maximum recommended human maintenance dose*). Mutagenicity studies conducted with amiodarone HCl were negative.

No fertility studies were conducted with Cordarone I.V. (see full prescribing information).

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

Pregnancy: *Category D.* See **WARNINGS, Neonatal Hypo- or Hyperthyroidism.** In addition to infrequent congenital goiter/hypothyroidism and hyperthyroidism, amiodarone has caused a variety of adverse effects in animals (see full prescribing information). In a reproductive study in which amiodarone was given intravenously to rabbits at dosages 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 occurred at dosages of 0.3 x MRHD and above. No evidence of embryotoxicity was observed at 0.1 x MRHD 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 about 0.4, 0.7, and 1.4 times the MRHD when compared on a body surface area basis, maternal toxicity and embryotoxicity were observed in the 1.4 x MRHD 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; breast-feeding could expose the nursing infant to a significant dose of drug. Nursing offspring of lactating rats administered amiodarone demonstrated reduced viability and reduced body weight gains. Weigh the risk of exposing the infant to amiodarone against the potential benefit of arrhythmia suppression in the mother. Advise the mother to discontinue nursing.

Labor and Delivery: It is not known whether use of Cordarone during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect on duration of gestation or parturition.

Pediatric Usage: Safety and efficacy of Cordarone in the pediatric population have not been established; such use is not recommended.

ADVERSE REACTIONS: In a total of 1836 patients in clinical trials, 14% received Cordarone I.V. for ≥ 1 week, 5% received it for ≥ 2 weeks, 2% received it for 3 weeks, and 1% received it for > 3 weeks, without an increased incidence of severe adverse reactions. The mean duration of therapy was 5.6 days; median exposure was 3.7 days. The most important treatment-emergent adverse effects were hypotension, asystole/cardiac arrest/EMD, cardiogenic shock, CHF, bradycardia, LFT abnormalities, VT, and AV block. Treatment was discontinued for about 9% of patients because of adverse effects, most commonly hypotension (1.6%), asystole/cardiac arrest/EMD (1.2%), VT (1.1%), and cardiogenic shock (1%).

The following are the most common (incidence ≥ 2%) and possibly drug-related adverse events during Cordarone I.V. 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: Fever, 2.0%; Bradycardia, 4.9%; CHF, 2.1%; Heart arrest, 2.9%; Hypotension, 15.6%; VT, 2.4%; LFTs abnormal, 3.4%; Nausea, 3.9%. Other possibly drug-related adverse events reported in < 2% of patients receiving Cordarone I.V. in clinical studies included abnormal kidney function, atrial fibrillation, diarrhea, inc. ALT, inc. 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.

This Brief Summary text is based on Direction Circular CI 5032-3, Revised 5/7/99.

Reference: 1. American Heart Association. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2000;102(suppl): I-86–I-166.

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WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

Cordarone® (amiodarone HCl) I.V. 150 mg/3 mL

Before lidocaine.