Cordarone advertisement.

[s.l.]: [s.n.], 1991

In life-threatening recurrent VT or VF refractory to conventional antiarrhythmic agents

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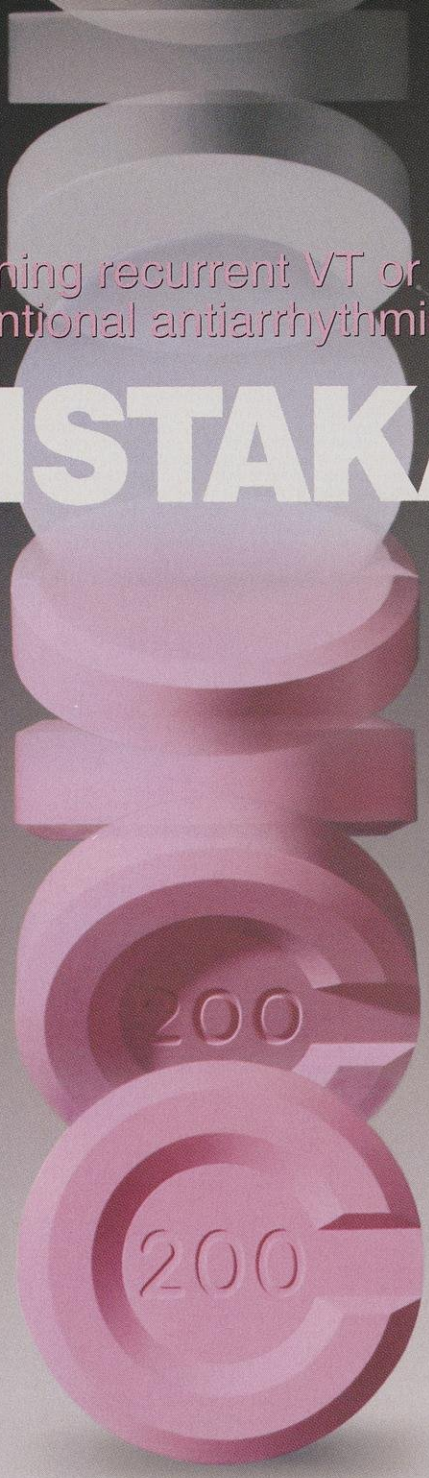

NEW TABLET **SAME PRODUCT**

Cordarone®

(amiodarone HCl) 200 mg tablets

The most effective antiarrhythmic you can prescribe.

The "C design" of the Cordarone® tablet is a registered trademark of Wyeth-Ayerst Laboratories.

Cordarone® is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by serious adverse reactions.

See adjacent page for brief summary of prescribing information.

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

Cordarone® (amiodarone HCl) Tablets

BRIEF SUMMARY
(See Package Circular for full prescribing information.)

Indications and Usage: Because of life-threatening side effects and substantial management difficulties (See "Warnings" below) use only for treating documented, life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia that are unresponsive to documented adequate doses of other antiarrhythmics or when alternative agents are not tolerated.

Controlled trials show no evidence that Cordarone favorably affects survival.

For use only by physicians familiar with and with access to (directly or via referral) all available modalities for treating recurrent life-threatening ventricular arrhythmias, including access to appropriate monitoring facilities and continuous electrocardiographic monitoring and electrophysiologic techniques. Due to the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential arrhythmia exacerbation, start Cordarone in a hospital setting.

Contraindications: Severe sinus-node dysfunction, with marked sinus bradycardia; 2nd- and 3rd-degree atrioventricular (AV) block; episodes of bradycardia which cause syncope (except when used with a pacemaker); known hypersensitivity to the drug.

Warnings: Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/ alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.

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

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

PULMONARY TOXICITY: Cordarone may cause a syndrome of cough and progressive dyspnea with functional, radiographic, gallium-scan and pathological data consistent with pulmonary toxicity; frequency usually varies from 2-7%, but can be as high as 10-17%. Thus, at start of therapy, perform baseline chest x-ray and pulmonary-function tests, including diffusion capacity. Repeat history, physical exam (PE), and chest x-ray every 3-6 months.

Preexisting pulmonary disease does not appear to increase risk of toxicity; however, prognosis is poorer if pulmonary toxicity develops.

Cordarone-induced pulmonary toxicity seems to result from indirect (hypersensitivity pneumonitis) or direct (interstitial/alveolar pneumonitis) toxicity.

Hypersensitivity pneumonitis usually appears early in therapy; rechallenge results in a more rapid and severe recurrence. Bronchoalveolar lavage is procedure of choice to confirm diagnosis, made when a T suppressor/cytotoxic (CD8 - positive) lymphocytosis noted. Treat with steroids and stop Cordarone.

Interstitial/alveolar pneumonitis, characterized by diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsies. Phospholipidosis (foamy cells, foamy macrophages) is present in most cases of Cordarone-induced pulmonary toxicity; however, this also occurs in approximately 50% of all Cordarone patients. Use these cells as therapy markers, not evidence of toxicity. If interstitial/alveolar pneumonitis is diagnosed, reduce dose or, preferably, withdraw Cordarone, especially if other acceptable antiarrhythmics are available. Where these measures were instituted, symptoms usually decreased in the first week; most clinical improvement was in first 2-3 weeks. Chest X-ray changes usually resolve in 2-4 months. Some experts feel steroids may be helpful. Prednisone (40-60 mg/day) or equivalent doses of other steroids have been used and tapered over several weeks. At times rechallenge at a lower dose will not result in return of toxicity. Reports suggest lower loading and maintenance doses are associated with a lower incidence of pulmonary toxicity.

In Cordarone patients, any new respiratory symptoms suggest a possibility of pulmonary toxicity; repeat and evaluate history, PE, chest X-ray, and pulmonary-function tests (with diffusion capacity). A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as decreases in diffusion capacity approach 30%, sensitivity decreases but specificity increases. A diagnostic gallium scan may also be performed.

Fatalities from pulmonary toxicity occur in about 10% of cases. However, when life-threatening arrhythmias exist, stop Cordarone (amiodarone HCl) cautiously if drug-induced pulmonary toxicity is suspected. As the most common cause of death in these patients is sudden cardiac death, first rule out other causes of respiratory impairment. Bronchoalveolar lavage or lung biopsy may be necessary to confirm the diagnosis, especially when there is no acceptable alternative therapy.

If hypersensitivity pneumonitis is diagnosed, stop Cordarone and treat with steroids. If Cordarone-induced interstitial/alveolar pneumonitis is diagnosed, start steroids and, preferably, stop Cordarone or, minimally, reduce the dose. Some cases may resolve after dose reduction and steroid use. Sometimes, rechallenge at lower doses did not result in return of interstitial/alveolar pneumonitis; however, pulmonary lesions are irreversible in some.

WORSENED ARRHYTHMIA: Cordarone may cause serious exacerbation of a presenting arrhythmia, possibly enhanced by concomitant antiarrhythmic therapy. Exacerbation (about 2-5% in most series), includes new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and Torsade de Pointes. Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients.

LIVER INJURY: Increased hepatic enzymes, mostly asymptomatic, are seen frequently. Consider discontinuation or dose reduction if increase exceeds 3 times normal, or doubles in patient with elevated baseline. Rarely, hepatic failure has been fatal.

PREGNANCY — PREGNANCY CATEGORY D: Cordarone is embryotoxic (increased fetal resorption and growth retardation) in rats at 18 times the maximum recommended oral maintenance dose. Similar results are seen in one mice strain at about 1/2 the maximum recommended maintenance dose or higher, but not in a second strain nor rabbits at doses up to 9 times the maximum recommended maintenance dose.

Neonatal hypo- or hyperthyroidism: In utero exposure can cause fetal harm. There are some reports of congenital goiter/ hypothyroidism and hyperthyroidism. If used anytime during pregnancy apprise patient of potential fetal hazard. In general, use during pregnancy only if potential benefit to the mother justifies unknown fetal risk.

Precautions

CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION: Corneal microdeposits appear in a majority of adults on Cordarone. Usually discernible only by slit-lamp, up to 10% of patients have symptoms like visual halos or blurred vision. Microdeposits are reversible if dose reduced or treatment stopped; if asymptomatic, no need to reduce dose or stop drug.

PHOTOSENSITIVITY: Seen in about 10% of patients; sun-barrier creams or protective clothing may afford some protection. On long-term therapy, may have a blue-gray skin discoloration of exposed skin. Fair complexion or excess sun exposure may increase risk; also may be related to cumulative dose and therapy duration.

THYROID ABNORMALITIES: Cordarone inhibits conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine, decreased T_3, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. Due to its release of inorganic iodine, or perhaps other reasons, Cordarone can cause either hypo- or hyperthyroidism. Monitor thyroid function before treatment and periodically thereafter, particularly in the elderly and those with history of thyroid nodules, goiter, or other thyroid dysfunction. Due to slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for weeks or months after withdrawal.

Hypothyroidism occurred in 2-4% of patients in most series, but in 8-10% in some. To treat, reduce Cordarone dose and/or give thyroid hormone supplement. Individualize therapy; may need to stop Cordarone.

Hyperthyroidism occurs in about 2% of patients; incidence may be higher with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism is usually a greater hazard than hypothyroidism due to possible arrhythmia breakthrough or aggravation. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Flat TSH response to TRH is confirmatory. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or Cordarone withdrawal. Antithyroid drugs, β-blockers and/or temporary steroid therapy may be needed. (See full prescribing information for additional information regarding treatment).

SURGERY: *Hypotension Postbypass:* Rarely, hypotension is seen on cessation of cardiopulmonary bypass during open-heart surgery in Cordarone patients; relationship to Cordarone is unknown.

Adult Respiratory Distress Syndrome (ARDS): Rarely, ARDS occurs in Cordarone patients after surgery. Patients usually respond to vigorous respiratory therapy; rarely, the outcome is fatal. The mechanism may be generation of superoxide radicals during oxygenation; therefore, keep operative FiO_2 as close to room air as possible.

LABORATORY TESTS: Elevated liver enzymes (SGOT and SGPT) can occur; monitor closely if high maintenance doses used. Consider dose reduction or stopping therapy if significant elevations persist or hepatomegaly occurs.

Thyroid-function tests (increased T_4 and reverse T_3, and decreased T_3) may be altered; despite these changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS: Few drug-drug interactions have been explored formally but most have shown an interaction. Thus, anticipate other interactions, especially drugs with potentially serious toxicity, like other antiarrhythmics. With its long, variable half-life, a potential for interaction also exists with drugs given after stopping Cordarone.

Digitalis: Serum digoxin increases (by up to 70%) and may reach toxic levels; onset is about 1 day. **On initiation of Cordarone, review need for digitalis and reduce its dose by about 50% or stop it.** If digitalis continued, monitor serum levels closely and observe for toxicity. Precautions probably also apply to digitoxin.

Anticoagulants: Potentiation of warfarin-type anticoagulant response is almost always seen and can result in serious or fatal bleeding. Prothrombin time may increase by 100%; onset is 3 to 4 days. **Reduce anticoagulant dose by 1/3 to 1/2, and monitor prothrombin times closely.**

Antiarrhythmic Agents: Although they have been used concurrently with Cordarone, steady-state levels of quinidine, procainamide, and phenytoin may increase during such combined therapy. Quinidine serum concentrations may increase by 33% within 2 days. Procainamide serum concentrations may increase by 55% (n-acetyl procainamide by 33%) in < 7 days. In general, reserve such combinations for patients with life-threatening ventricular arrhythmias incompletely responsive to a single agent, or incompletely responsive to Cordarone (amiodarone HCl), and start any added antiarrhythmic at a lower than usual dose with careful monitoring. During transfer to Cordarone, reduce dose of previous agents 30-50% several days after adding Cordarone, when arrhythmia suppression should be starting. After Cordarone effects are established, discontinue other antiarrhythmics if possible. If treatment is maintained, continue monitoring carefully for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. In Cordarone patients requiring additional antiarrhythmic therapy, initial dose of such agents should be approximately 1/2 of the usual dose.

Use Cordarone cautiously with β-blockers or calcium antagonists as bradycardia, sinus arrest, and AV block may be potentiated; if necessary, Cordarone can continue after pacemaker insertion in patients with severe bradycardia or sinus arrest.

ELECTROLYTE DISTURBANCES: May be ineffective or arrhythmogenic if hypokalemia is present; correct any potassium or magnesium deficiency before starting drug.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Fertility reduced in male and female rats at 8 x the highest recommended human maintenance dose. Cordarone caused a statistically significant, dose-related increase in thyroid tumors in rats. Incidence greater than control even at lowest dose tested, i.e., about 1/2 the highest recommended human maintenance dose. Mutagenicity studies were negative.

PREGNANCY: PREGNANCY CATEGORY D — See **Warnings.**

LABOR AND DELIVERY: Occurrence of adverse effects during labor or delivery is unknown. Preclinical studies in rodents have shown no effect on gestation duration or parturition.

NURSING MOTHERS: Cordarone is excreted in human milk; breast-feeding may expose nursing infants to a significant drug dose. Nursing offspring of lactating rats given Cordarone were less viable and had reduced body-weight gains. Advise mothers to discontinue nursing before taking.

PEDIATRIC USE: Safety and effectiveness have not been established.

Adverse Reactions: Adverse effects are very common (about 3/4 of all patients) with doses of 400 mg/day or more, and cause 7-18% to discontinue. The most serious are pulmonary toxicity, arrhythmia exacerbation, and rare serious liver injury (see "**Warnings**"), but other adverse effects constitute important problems. They are often reversible by reducing dose and virtually always reversible by stopping Cordarone. Most adverse effects appear more frequent with continued treatment beyond 6 months; rates appear relatively constant beyond one year. Neurologic problems, including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy are common (20-40% of patients); these may respond to dose reduction, rarely need to stop therapy.

Gastrointestinal (GI) complaints, commonly seen with high doses (i.e., loading dose), usually respond to dose reduction or divided doses; rarely need to stop drug.

Asymptomatic corneal microdeposits. See **Precautions** and full prescribing information.

Photosensitivity. See **Precautions** and full prescribing information.

Cardiovascular adverse reactions, other than arrhythmia exacerbation, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dose reduction but may require a pacemaker. CHF rarely requires stopping drug. Cardiac conduction abnormalities occur infrequently and are reversible upon stopping drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

Each reported in 10-33% of patients: GI–Nausea and vomiting.

Each reported in 4-9% of patients: Dermatologic–Solar dermatitis/photosensitivity; Neurologic–Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias; GI–Constipation, anorexia; Ophthalmologic–Visual disturbances; Hepatic–Abnormal liver-function tests; Respiratory–Pulmonary inflammation or fibrosis.

Each reported in 1-3% of patients: Thyroid–Hypo- or hyperthyroidism; Neurologic–Decreased libido, insomnia, headache, sleep disturbances; Cardiovascular–CHF, cardiac arrhythmias, SA node dysfunction; GI–Abdominal pain; Hepatic–Nonspecific hepatic disorders; Other–Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

Each reported in < 1% of patients: Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities. Rarely hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia.

Adverse reactions most frequently requiring Cordarone discontinuation include pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, CHF, and elevated liver enzymes. Symptoms causing discontinuation less often include visual disturbances, solar dermatitis, blue skin discoloration, hyper- or hypothyroidism.

Overdosage: The few reports of Cordarone overdose, in which 3 to 8 grams were taken, resulted in no deaths or permanent sequelae. Animal studies indicate that Cordarone has a high oral LD_{50} (>3,000 mg/kg).

Along with general supportive measures, monitor patient's cardiac rhythm and blood pressure; if bradycardia ensues, may use a β-adrenergic agonist or pacemaker. Use positive inotropic and/or vasopressor agents to treat hypotension with inadequate tissue perfusion. Neither Cordarone nor its metabolite is dialyzable.

Dosage and Administration: See full prescribing information.

Manufactured for
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WYETH-AYERST LABORATORIES
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