CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75315

DRAFT FINAL PRINTED LABELING

Final Printed Insert Labeling

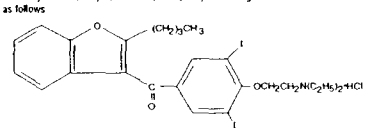
AMIODARONE HYDROCHLORIDE TABLETS, 200 MG
Rx only

DESCRIPTION

Amiodarone hydrochloride is a member of a new class of antiarrhythmic drugs with predominant Class III (Vaughan Williams' classification) effects, available for oral administration as yellow, scored tablets. Each tablet for oral administration contains 200 mg of amiodarone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, povidone, and D&C Yellow #10 Aluminum Lake.

Amiodarone hydrochloride is a benzofuran derivative: 2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone, hydrochloride. It is not chemically related to any other available antiarrhythmic drug.

The structural formula is as follows:



$C_{25}H_{29}I_2NO_3 \cdot HCl$ M.W. 681.8

Amiodarone hydrochloride is a white to cream-colored crystalline powder. It is slightly soluble in water; soluble in alcohol; and freely soluble in chloroform. It contains 37.3% iodine by weight.

CLINICAL PHARMACOLOGY

Electrophysiology/Mechanisms of Action

In animals, amiodarone hydrochloride is effective in the prevention or suppression of experimentally induced arrhythmias. The antiarrhythmic effect of amiodarone may be due to at least two major properties: 1) a prolongation of the myocardial cell-action potential duration and refractory period and 2) noncompetitive α- and β-adrenergic inhibition.

Amiodarone prolongs the duration of the action potential of all cardiac fibers while causing minimal reduction of dV/dt (maximal upstroke velocity of the action potential). The refractory period is prolonged in all cardiac tissues. Amiodarone increases the cardiac refractory period without influencing resting membrane potential, except in automatic cells where the slope of the prepotential is reduced, generally reducing automaticity. These electrophysiologic effects are reflected in a decreased sinus rate of 15 to 20%, increased PR and QT intervals of about 10%, the development of U-waves, and changes in T-wave contour. These changes should not require discontinuation of amiodarone as they are evidence of its pharmacological action, although amiodarone can cause marked sinus bradycardia or sinus arrest and heart block. On rare occasions, QT prolongation has been associated with worsening of arrhythmia (see "**WARNINGS**").

Hemodynamics

In animal studies and after intravenous administration in man, amiodarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. After oral dosing, however, amiodarone produces no significant change in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF. After acute intravenous dosing in man, amiodarone may have a mild negative inotropic effect.

Pharmacokinetics

Following oral administration in man, amiodarone is slowly and variably absorbed. The bioavailability of amiodarone is approximately 50%, but has varied between 35 and 65% in various studies. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100 to 600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day. These means, however, include considerable individual variability.

Amiodarone has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of amiodarone, desethylamiodarone, has been identified in man; it accumulates to an even greater extent in almost all tissues. The pharmacological activity of this metabolite, however, is not known. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one.

The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. However, its kinetics in patients with hepatic insufficiency have not been elucidated. Amiodarone has a very low plasma clearance with negligible renal excretion, so that it does not appear necessary to modify the dose in patients with renal failure. In patients with renal impairment, the plasma concentration of amiodarone is not elevated. Neither amiodarone nor its metabolites is dialyzable.

In patients, following discontinuation of chronic oral therapy, amiodarone has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26 to 107 days, with a mean of approximately 53 days and most patients in the 40- to 55-day range. In the absence of a loading-dose period, steady-state plasma concentrations, at constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat.

The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of amiodarone should be based on individual patient requirements (see "**DOSAGE AND ADMINISTRATION**").

Amiodarone and its metabolite have a limited transplacental transfer of approximately 10 to 50%. The parent drug and its metabolite have been detected in breast milk.

Amiodarone is highly protein-bound (approximately 96%).

Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of amiodarone hydrochloride, effects on abnormal rhythms are not seen before 2 to 3 days and usually require 1 to 3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods still. There is evidence that the time to effect is shorter when a loading-dose regimen is used.

Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after amiodarone hydrochloride is discontinued, but the time of recurrence is variable and unpredictable. In general, when the drug is resumed after recurrence of the arrhythmia, control is established relatively rapidly compared to the initial response, presumable because tissue stores were not wholly depleted at the time of recurrence.

Pharmacodynamics

There is no well-established relationship of plasma concentration to effectiveness; but it does appear that concentrations much below 1 mg/L are often ineffective and that levels above 2.5 mg/L are generally not needed. Within individuals dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control. Plasma-concentration measurements can be used to identify patients whose levels are unusually low, and who might benefit from a dose increase, or unusually high, and who might have dosage reduction in the hope of minimizing side effects. Some observations have suggested a plasma concentration, dose, or dose/duration relationship for side effects such as pulmonary fibrosis, liver-enzyme elevations, corneal deposits and facial pigmentation, peripheral neuropathy, gastrointestinal and central nervous system effects.

Monitoring Effectiveness

Predicting the effectiveness of any antiarrhythmic agent in long-term prevention of recurrent ventricular tachycardia and ventricular fibrillation is difficult and controversial, with highly qualified investigators recommending use of ambulatory monitoring, programmed electrical stimulation with various stimulation regimens, or a combination of these, to assess response. There is no present consensus on many aspects of how best to assess effectiveness, but there is a reasonable consensus on some aspects:

1. If a patient with a history of cardiac arrest does not manifest a hemodynamically unstable arrhythmia during electrocardiographic monitoring prior to treatment, assessment of the effectiveness of amiodarone requires some provocative approach, either exercise or programmed electrical stimulation (PES).

2. Whether provocation is attempted in patients who do manifest their life-threatening arrhythmia spontaneously is not settled, but there are reasons to consider PES or other provocation in such patients. In the fraction of patients whose PES-inducible arrhythmia can be made noninducible by amiodarone (a fraction that has varied widely in various series from less than 10% to almost 40%, perhaps due to different stimulation criteria), the prognosis has been almost uniformly excellent, with very low recurrence (ventricular tachycardia or sudden death) rates. More controversial is the meaning of continued inducibility. There has been an impression that continued inducibility in amiodarone patients may not foretell a poor prognosis but, in fact, many observers have found greater recurrence rates in patients who remain inducible than in those who do not. A number of criteria have been proposed, however, for identifying patients who remain inducible but who seem likely nonetheless to do well on amiodarone. These criteria include increased difficulty of induction (more stimuli or more rapid stimuli), which has been reported to predict a lower rate of recurrence, and ability to tolerate the induced ventricular tachycardia without severe symptoms, a finding that has been reported to correlate with better survival but not with lower recurrence rates. While these criteria require confirmation and further study in general, *easier* inducibility or *poorer* tolerance of the induced arrhythmia should suggest consideration of a need to revise treatment.

Several predictors of success not based on PES have also been suggested, including complete elimination of all non-sustained ventricular tachycardia on ambulatory monitoring and very low premature ventricular-beat rates (less than 1 VPB/1,000 normal beats).

While these issues remain unsettled for amiodarone, as for other agents, the prescriber of amiodarone should have access to (direct or through referral), and familiarity with, the full range of evaluatory procedures used in the care of patients with life-threatening arrhythmias.

It is difficult to describe the effectiveness rates of amiodarone, as these depend on the specific arrhythmia treated, the success criteria used, the underlying cardiac disease of the patient, the number of drugs tried before resorting to amiodarone hydrochloride, the duration of follow-up, the dose of amiodarone hydrochloride, the use of additional antiarrhythmic agents, and many other factors. As amiodarone has been studied principally in patients with refractory life-threatening ventricular arrhythmias, in whom drug therapy must be selected on the basis of response and cannot be assigned arbitrarily, randomized comparisons with other agents or placebo have not been possible. Reports of series of treated patients with a history of cardiac arrest and mean follow-up of one year or more have given mortality (due to arrhythmia) rates that were highly variable, ranging from less than 5% to over 30%, with most series in the range of 10 to 15%. Over all arrhythmia-recurrence rates (fatal and non-fatal) also were highly variable (and, as noted above, depended on response to PES and other measures), and depend on whether patients who do not seem to respond initially are included. In most cases, considering only patients who seemed to respond well enough to be placed on long-term treatment, recurrence rates have ranged from 20 to 40% in series with a mean follow-up of a year or more.

INDICATIONS AND USAGE

Because of its life-threatening side effects and the substantial management difficulties associated with its use (see "**WARNINGS**" below), amiodarone hydrochloride is indicated only for the treatment of the following documented, life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated.

1. Recurrent ventricular fibrillation
2. Recurrent hemodynamically unstable ventricular tachycardia

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of amiodarone favorably affects survival.

Amiodarone should be used only by physicians familiar with and with access to (directly or through referral) the use of all available modalities for treating recurrent life-threatening ventricular arrhythmias, and who have access to appropriate monitoring facilities, including in-hospital and ambulatory continuous electrocardiographic monitoring and electrophysiologic techniques. Because of the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of the arrhythmia, initiation of therapy with amiodarone should be carried out in the hospital.

CONTRAINDICATIONS

Amiodarone hydrochloride is contraindicated in severe sinus-node dysfunction, causing marked sinus bradycardia; second- and third-degree atrioventricular block; and when episodes of bradycardia have caused syncope (except when used in conjunction with a pacemaker).

Amiodarone hydrochloride is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

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

Amiodarone 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 amiodarone, 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, amiodarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2 to 5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2 to 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 amiodarone 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 amiodarone is an acceptable risk, amiodarone 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 amiodarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone 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 of treatment 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 amiodarone must be stopped will be made difficult by the gradually, but unpredictably changing amiodarone body burden. A similar problem exists when amiodarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

Mortality

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of these results to other populations (e.g., those without recent myocardial infarctions) or to amiodarone hydrochloride-treated patients is uncertain. While definitive controlled trials with amiodarone are in progress, pooled analysis of small controlled studies in patients with structural heart disease (including post-myocardial infarction) have not shown excess mortality in the amiodarone-treated population.

Pulmonary Toxicity

Amiodarone may cause a clinical syndrome of cough and progressive dyspnea accompanied by functional, radiographic, gallium-scan, and pathological data consistent with pulmonary toxicity, the frequency of which varies from 2 to 7% in most published reports, but is as high as 10 to 17% in some reports. Therefore, when amiodarone therapy is initiated, a baseline chest X-ray and pulmonary-function tests, including diffusion capacity, should be performed. The patient should return for a history, physical exam, and chest X-ray every 3 to 6 months.

Preexisting pulmonary disease does not appear to increase the risk of developing pulmonary toxicity; however, these patients have a poorer prognosis if pulmonary toxicity does develop.

Pulmonary toxicity secondary to amiodarone seems to result from either indirect or direct toxicity as represented by hypersensitivity pneumonitis or interstitial/alveolar pneumonitis, respectively.

Hypersensitivity Pneumonitis usually appears earlier in the course of therapy, and rechallenging these patients with amiodarone results in a more rapid recurrence of greater severity. Bronchoalveolar lavage is the procedure of choice to confirm this diagnosis, which can be made when a T suppressor/cytotoxic (CD8-positive) lymphocytosis is noted. Steroid therapy should be instituted and amiodarone therapy discontinued in these patients.

Interstitial/Alveolar pneumonitis may result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis, or fibrosis on lung biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), due to inhibition of phospholipase, will be present in most cases of amiodarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on amiodarone therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of amiodarone -induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the amiodarone hydrochloride to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone-induced pulmonary toxicity was usually noted within the first week, and a clinical improvement was greatest in the first two to three weeks. Chest X-ray changes usually resolve within two to four months. According to some experts, steroids may prove beneficial. Prednisone in doses of 40 to 60 mg/day or equivalent doses of other steroids have been given and tapered over the course of several weeks depending upon the condition of the patient. In some cases rechallenge with amiodarone at a lower dose has not resulted in return of toxicity. Recent reports suggest that the use of lower loading and maintenance doses of amiodarone are associated with a decreased incidence of amiodarone-induced pulmonary toxicity.

In a patient receiving amiodarone, any new respiratory symptoms should suggest the possibility of pulmonary toxicity, and the history, physical exam, chest X-ray, and pulmonary-function tests (with diffusion capacity) should be repeated and evaluated. A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as the decrease in diffusion capacity approaches 30%, the sensitivity decreases but the specificity increases. A gallium-scan also may be performed as part of the diagnostic workup.

Fatalities, secondary to pulmonary toxicity, have occurred in approximately 10% of cases. However, in patients with life-threatening arrhythmias, discontinuation of amiodarone therapy due to suspected drug-induced pulmonary toxicity should be undertaken with caution, as the most common cause of death in these patients is sudden cardiac death. Therefore, every effort should be made to rule out other causes of respiratory impairment (i.e., congestive heart failure with Swan-Ganz catheterization if necessary, respiratory infection, pulmonary embolism, malignancy, etc.) before discontinuing amiodarone in these patients. In addition, bronchoalveolar lavage, transbronchial lung biopsy and/or open lung biopsy may be necessary to confirm the diagnosis, especially in those cases where no acceptable alternative therapy is available.

If a diagnosis of amiodarone-induced hypersensitivity pneumonitis is made, amiodarone should be discontinued, and treatment with steroids should be instituted. If a diagnosis of amiodarone-induced interstitial/alveolar pneumonitis is made, steroid therapy should be instituted and, preferably, amiodarone discontinued or, at a minimum, reduced in dosage. Some cases of amiodarone-induced interstitial/alveolar pneumonitis may resolve following a reduction in amiodarone dosage in conjunction with the administration of steroids. In some patients, rechallenge at a lower dose has not resulted in return of interstitial/alveolar pneumonitis; however, in some patients (perhaps because of severe alveolar damage) the pulmonary lesions have not been reversible.

Worsened Arrhythmia

Amiodarone, like other antiarrhythmics, can cause serious exacerbation of the presenting arrhythmia, a risk that may be enhanced by the presence of concomitant antiarrhythmics. Exacerbation has been reported in about 2 to 5% in most series, and has included new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia associated with QT prolongation (Torsade de Pointes). In addition, amiodarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2 to 4% of patients.

Liver Injury

Elevations of hepatic enzyme levels are seen frequently in patients exposed to amiodarone and in most cases are asymptomatic. If the increase exceeds three times normal, or doubles in a patient with an elevated baseline, discontinuation of amiodarone or dosage reduction should be considered. In a few cases in which biopsy has been done, the histology has resembled that of alcoholic hepatitis or cirrhosis. Hepatic failure has been a rare cause of death in patients treated with amiodarone.

Loss of Vision

Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and/or neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. If symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral vision, prompt ophthalmic examination is recommended. Appearance of optic neuropathy and/or neuritis calls for re-evaluation of amiodarone therapy. The risks and complications of antiarrhythmic therapy with amiodarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including fundoscopy and slit-lamp examination, is recommended during administration of amiodarone (see "**ADVERSE REACTIONS**").

Pregnancy: Pregnancy Category D

Amiodarone has been shown to be embryotoxic (increased fetal resorption and growth retardation) in the rat when given orally at a dose of 200 mg/kg/day (18 times the maximum recommended maintenance dose). Similar findings have been noted in one strain of mice at a dose of 5 mg/kg/day (approximately $^1/_2$ the maximum recommended maintenance dose) and higher, but not in a second strain nor in the rabbit at doses up to 100 mg/kg/day (9 times the maximum recommended maintenance dose).

Neonatal Hypo- or hyperthyroidism

Amiodarone can cause fetal harm when administered to a pregnant woman. Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If amiodarone is used during pregnancy, or if the patient becomes pregnant while taking amiodarone, the patient should be apprised of the potential hazard to

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the fetus.
In general, amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus.

PRECAUTIONS

Impairment of Vision

Optic Neuropathy and/or Neuritis

Cases of optic neuropathy and optic neuritis have been reported (see "**WARNINGS**").

Corneal Microdeposits

Corneal microdeposits appear in the majority of adults treated with amiodarone. They are usually discernible only by slit-lamp examination but give rise to symptoms such as visual halos or blurred vision in as many as 10% of patients. Corneal microdeposits are reversible upon reduction of dose or termination of treatment. Asymptomatic microdeposits are not a reason to reduce dose or discontinue treatment (see "**ADVERSE REACTIONS**").

Neurologic

Chronic administration of oral amiodarone in rare instances may lead to the development of peripheral neuropathy that may resolve when amiodarone is discontinued but this resolution has been slow and incomplete.

Photosensitivity

Amiodarone has induced photosensitization in about 10% of patients; some protection may be afforded by the use of sun-barrier creams or protective clothing. During long-term treatment, a blue-gray discoloration of the exposed skin may occur. The risk may be increased in patients of fair complexion or those with excessive sun exposure, and may be related to cumulative dose and duration of therapy.

Thyroid Abnormalities

Amiodarone inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine levels, decreased T_3 levels, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. It is also a potential source of large amounts of inorganic iodine. Because of its release of inorganic iodine, or perhaps for other reasons, amiodarone can cause either hypothyroidism or hyperthyroidism. Thyroid function should be monitored prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of the slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for several weeks or even months following amiodarone withdrawal. Hypothyroidism has been reported in 2 to 4% of patients in most series, but in 8 to 10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Hypothyroidism is best managed by amiodarone hydrochloride dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue amiodarone in some patients.

Hyperthyroidism occurs in about 2% of patients receiving amiodarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Amiodarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Hyperthyroidism is best identified by relevant clinical symptoms and signs, accompanied usually by abnormally elevated levels of serum T_3 RIA, and further elevations of serum T_4, and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany amiodarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of amiodarone. The institution of antithyroid drugs, β-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism. Experience with thyroid surgery in this setting is extremely limited, and thus form of therapy runs the theoretical risk of inducing thyroid storm. Amiodarone induced hyperthyroidism may be followed by a transient period of hypothyroidism.

Surgery

Hypotension Postbypass: Rare occurrences of hypotension upon discontinuation of cardiopulmonary bypass during open-heart surgery in patients receiving amiodarone have been reported. The relationship of this event to amiodarone therapy is unknown.

Adult Respiratory Distress Syndrome (ARDS): Postoperatively, rare occurrences of ARDS have been reported in patients receiving amiodarone 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.

Laboratory Tests

Elevations in liver enzymes (SGOT and SGPT) can occur. Liver enzymes in patients on relatively high maintenance doses should be monitored on a regular basis. Persistent significant elevations in the liver enzymes or hepatomegaly should alert the physician to consider reducing the maintenance dose of amiodarone hydrochloride or discontinuing therapy.

Amiodarone hydrochloride alters the results of thyroid-function tests, causing an increase in serum T_4 and serum reverse T_3, and a decline in serum T_3 levels. Despite these biochemical changes, most patients remain clinically euthyroid.

Drug Interactions

Although only a small number of drug-drug interactions with amiodarone hydrochloride have been explored formally, most of these have shown such an interaction. The potential for other interactions should be anticipated, particularly for drugs with potentially serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured.

In view of the long and variable half-life of amiodarone hydrochloride, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone hydrochloride.

Cyclosporine

Concomitant use of amiodarone and cyclosporine has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

Digitalis

Administration of amiodarone hydrochloride to patients receiving digoxin therapy regularly results in an increase in the serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. **On initiation of amiodarone hydrochloride, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.

Anticoagulants

Potentiation of warfarin-type anticoagulant response is almost always seen in patients receiving amiodarone hydrochloride and can result in serious or fatal bleeding. The dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.

Antiarrhythmic Agents

Other antiarrhythmic drugs, such as quinidine, procainamide, disopyramide, and phenytoin, have been used concurrently with amiodarone hydrochloride.

There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring.

In general, combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to amiodarone the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of amiodarone, when arrhythmia suppression should be beginning. The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as amiodarone is continued. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Amiodarone should be used with caution in patients receiving β-blocking agents or calcium antagonists because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, amiodarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE HYDROCHLORIDE

Concomitant Drug	Interaction		Recommended Dose Reduction of Concomitant Drug
	Onset (days)	Magnitude	
Warfarin	3 to 4	Increases prothrombin time by 100%	↓ 1/3 to 1/2
Digoxin	1	Increases serum concentration by 70%	↓ 1/2
Quinidine	2	Increases serum concentration by 33%	↓ 1/3 to 1/2 (or discontinue)
Procainamide	<7	Increases plasma concentration by 55%; "**NAPA**" concentration by 33%	↓ 1/3 (or discontinue)

"**NAPA** = n-acetyl procainamide

Electrolyte Disturbances

Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting amiodarone therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Amiodarone hydrochloride reduced fertility of male and female rats at a dose level of 90 mg/kg/day (8 x highest recommended human maintenance dose).

Amiodarone 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 was greater than control even at the lowest dose level of amiodarone hydrochloride tested, i.e., 5 mg/kg/day or approximately equal to $1/2$ the highest recommended human maintenance dose. Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with amiodarone were negative.

Pregnancy: Pregnancy Category D

See "**WARNINGS**."

Labor and Delivery

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

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 been shown to be less viable and have reduced body-weight gains. Therefore, when amiodarone therapy is indicated, the mother should be advised to discontinue nursing.

Pediatric Use

The safety and effectiveness of amiodarone hydrochloride in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions have been very common in virtually all series of patients treated with amiodarone hydrochloride for ventricular arrhythmias with relatively large doses of drug (400 mg/day and above), occurring in about three-fourths of all patients and causing discontinuation in 7 to 18%. The most serious reactions are pulmonary toxicity, exacerbation of arrhythmia, and rare serious liver injury (see "**WARNINGS**"), but other adverse effects constitute important problems. They are often reversible with dose reduction and virtually always reversible with cessation of amiodarone treatment. Most of the adverse effects appear to become more frequent with continued treatment beyond six months, although rates appear to remain relatively constant beyond one year. The time and dose relationships of adverse effects are under continued study.

Neurologic problems are extremely common, occurring in 20 to 40% of patients and including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy; they are rarely a reason to stop therapy and may respond to dose reductions or discontinuation (see "**PRECAUTIONS**").

Gastrointestinal complaints, most commonly nausea, vomiting, constipation, and anorexia, occur in about 25% of patients but rarely require discontinuation of drug. These commonly occur during high-dose administration (i.e., loading dose) and usually respond to dose reduction or divided doses.

Opthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness; papilledema; corneal degeneration; photosensitivity; eye discomfort; scotoma; lens opacities; and macular degeneration have been reported (see "**WARNINGS**").

Asymptomatic corneal microdeposits are present in virtually all adult patients who have been on drug for more than 6 months. Some patients develop eye symptoms of halos, photophobia, and dry eyes. Vision is rarely affected and drug discontinuation is rarely needed.

Dermatological adverse reactions occur in about 15% of patients, with photosensitivity being most common (about 10%). Sunscreen and protection from sun exposure may be helpful, and drug discontinuation is not usually necessary. Prolonged exposure to amiodarone occasionally results in a blue-gray pigmentation. This is slowly and occasionally incompletely reversible on discontinuation of drug but is of cosmetic importance only.

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

Hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudomotor cerebri, thrombocytopenia, angioedema, bronchiolitis obliterans organizing pneumonia (possibly fatal), pleuritis, pancreatitis, toxic epidermal necrolysis, pancytopenia, and neutropenia also have been reported in patients receiving amiodarone.

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).

The following side effects were each reported in 10 to 33% of patients:

Gastrointestinal: Nausea and vomiting.

The following side effects were each reported in 4 to 9% of patients:

Dermatologic: Solar dermatitis/photosensitivity.

Neurologic: Malaise and fatigue; tremor/abnormal involuntary movements; lack of coordination; abnormal gait/ataxia; dizziness; paresthesias.

Gastrointestinal: Constipation, anorexia.

Ophthalmologic: Visual disturbances.

Hepatic: Abnormal liver-function tests.

Respiratory: Pulmonary inflammation or fibrosis.

The following side effects were each reported in 1 to 3% of patients:

Thyroid: Hypothyroidism, hyperthyroidism.

Neurologic: Decreased libido, insomnia, headache, sleep disturbances.

Cardiovascular: Congestive heart failure, cardiac arrhythmias, SA node dysfunction.

Gastrointestinal: Abdominal pain.

Hepatic: Nonspecific hepatic disorders.

Other: Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

The following side effects were each reported in less than 1% of patients:

Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities.

In surveys of almost 5,000 patients treated in open U.S. studies and in published reports of treatment with amiodarone hydrochloride, the adverse reactions most frequently requiring discontinuation of amiodarone included pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, congestive heart failure, and elevation of liver enzymes. Other symptoms causing discontinuations less often included visual disturbances, solar dermatitis, blue skin discoloration, hyperthyroidism, and hypothyroidism.

OVERDOSAGE

There have been a few reported cases of amiodarone hydrochloride overdose in which 3 to 8 grams were taken. There were no deaths or permanent sequelae. Animal studies indicate that amiodarone hydrochloride has a high oral LD_{50} (>3,000 mg/kg). In addition to general supportive measures, the patient's cardiac rhythm and blood pressure should be monitored, and if bradycardia ensues, a β-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither amiodarone nor its metabolite is dialyzable.

DOSAGE AND ADMINISTRATION

BECAUSE OF THE UNIQUE PHARMACOKENETIC PROPERTIES, DIFFICULT DOSING SCHEDULE, AND SEVERITY OF THE SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, AMIODONE HYDROCHLORIDE 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 THERAPY, AND WHO HAVE ACCESS TO LABORATORY FACILITIES CAPABLE OF ADEQUATELY MONITORING THE EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT.

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of amiodarone hydrochloride has not been determined. Individual patient titration is suggested according to the following guidelines:

For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia: Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800 to 1,600 mg/day are required for 1 to 3 weeks (occasionally longer) until initial therapeutic response occurs. (Administration of amiodarone hydrochloride in divided doses with meals is suggested for total daily doses of 1,000 mg or higher, or when gastrointestinal intolerance occurs.) If side effects become excessive, the dose should be reduced. Elimination of recurrence of ventricular fibrillation and tachycardia usually occurs within 1 to 3 weeks, along with reduction in complex and total ventricular ectopic beats.

Upon starting amiodarone therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs (see **PRECAUTIONS-"Drug Interactions"**). When adequate arrhythmia control is achieved, or if side effects become prominent, amiodarone hydrochloride dose should be reduced to 600 to 800 mg/day for one month and then to the maintenance dose, usually 400 mg/day (see "**CLINICAL PHARMACOLOGY—Monitoring Effectiveness:**"). Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses. Amiodarone may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a b.i.d. dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation and by patient tolerance. Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity (see "**CLINICAL PHARMACOLOGY**").

The lowest effective dose should be used to prevent the occurrence of side effects. In all instances, the physician must be guided by the severity of the individual patient's arrhythmia and response to therapy.

When dosage adjustments are necessary, the patient should be closely monitored for an extended period of time because of the long and variable half-life of amiodarone and the difficulty in predicting the time required to attain a new steady-state level of drug. Dosage suggestions are summarized below:

	Loading Dose (Daily)	Adjustment and Maintenance Dose (Daily)	
Ventricular Arrhythmias	1 to 3 weeks	~1 month	usual maintenance
	800 to 1,600 mg	600 to 800 mg	400 mg

HOW SUPPLIED

Amiodarone hydrochloride tablets are available in bottles of 60, 100, and 500 as follows:
200 mg, round, flat-faced, bevelled edge, yellow tablets debossed "$\mathcal{E}$" over bisect, and "144" below the bisect, and plain on the other side.

Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light.

Dispense in a tight, light-resistant container as defined in the USP, with a child resistant closure as required.

Rx only

Manufactured by
Eon Labs Manufacturing, Inc
Laurelton, New York 11413

Issued 12/97
MF0144ISS12/97

Final Printed Labels

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Protect from light.

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 12/97

NDC 0185-0144-60

Amiodarone Hydrochloride Tablets

200 mg

Rx only

60 Tablets

Eon Labs

Each tablet contains:
Amiodarone
Hydrochloride ..... 200 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 23

N 3 0185-0144-60 0

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Protect from light.

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 12/97

NDC 0185-0144-01

Amiodarone Hydrochloride Tablets

200 mg

Rx only

100 Tablets

Eon Labs

Each tablet contains:
Amiodarone
Hydrochloride ..... 200 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0144-01 3

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Protect from light.

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 12/97

NDC 0185-0144-05

Amiodarone Hydrochloride Tablets

200 mg

Rx only

500 Tablets

Eon Labs

Each tablet contains:
Amiodarone
Hydrochloride ..... 200 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

DEC 23

N 3 0185-0144-05 1

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