For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

XXXXXX-8883

RITEBEAT

(Amiodarone Hydrochloride Tablets 100 mg & 200 mg)

COMPOSITION

RITEBEAT 100

Each uncoated tablet contains :

Amiodarone Hydrochloride 100 mg

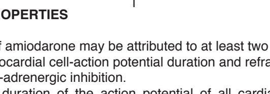
RITEBEAT 200

Each uncoated tablet contains :

Amiodarone Hydrochloride 200 mg

PROPERTIES

Amiodarone HCl is a member of a class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects. It has the chemical formula 2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride. The molecular formula is $C_{25}H_{29}I_2NO_3$ •HCl and the molecular weight is 681.8. The structural formula is :



PHARMACOLOGICAL PROPERTIES

Mechanism of action

The antiarrhythmic effect of amiodarone may be attributed to at least two major properties:

1) a prolongation of the myocardial cell-action potential duration and refractory period

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. 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, 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

Absorption

Following oral administration, amiodarone is slowly and variably absorbed. The bioavailability of amiodarone is approximately 50%, but in various studies it has been reported to vary between 35 and 65%. Peak plasma concentration is 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. Food increases the rate and extent of absorption of amiodarone. The effects of food upon the bioavailability of amiodarone have been studied in 30 healthy subjects who received a single 600-mg dose immediately after consuming a high-fat meal and following an overnight fast. The areas under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of amiodarone have been reported to increase by 2.3 (range 1.7 to 3.6) and 3.8 (range 2.7 to 4.4) times, respectively, in the presence of food (high fat meal). Food also increases the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (T_{max}) by 37%. The mean AUC and mean C_{max} of desethylamiodarone increased by 55% (range 58 to 101%) and 32% (range 4 to 84%), respectively, but there was no change in the T_{max} in the presence of food.

Distribution

Amiodarone is approximately 96% protein bound. It accumulates extensively in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. Therefore it has a very large but variable volume of distribution, averaging about 60 L/kg. One major metabolite of amiodarone, desethylamiodarone (DEA), accumulates to an even greater extent in almost all tissues.

Metabolism and Elimination

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines. 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 administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation. 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. Following single dose administration, amiodarone exhibits multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15 to 142 days) for amiodarone and 36 days (range 14 to 75 days) for the active metabolite (DEA). 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 days 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.

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 intravenous amiodarone 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 amiodarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction. Antiarrhythmic effects persist for weeks or months after amiodarone 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, presumably 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. 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, the duration of follow-up, the dose of amiodarone, 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.

INDICATIONS

Ritebeat 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.

Ritebeat 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

Ritebeat is contraindicated in severe sinus-node dysfunction, causing marked sinus bradycardia; second- or third-degree atrioventricular block; and when episodes of bradycardia have caused syncope (except when used in conjunction with a pacemaker). Ritebeat is contraindicated in patients with a known hypersensitivity to the drug or to any of its components, including iodine.

- Evidence or history of thyroid dysfunction
- Pregnancy (Except in special circumstances)
- Lactation
- The combination of amiodarone with other drugs which may induce TdP.

WARNINGS

Amiodarone HCl Tablets are intended for use only in patients with the indicated life-threatening arrhythmias because amiodarone 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 tablets pose 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 tablets effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone tablets 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 amiodarone tablets 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

Amiodarone therapy was evaluated in two multi-centered, randomized, double-blind, placebo-controlled trials involving 1202 (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CAMIAT) and 1486 (European Myocardial Infarction Amiodarone Trial; EMIAT) post-MI patients followed for up to 2 years. Patients in CAMIAT with ventricular arrhythmias, and those randomized to amiodarone received weight- and response-adjusted doses of 200 to 400 mg/day. Patients in EMIAT with ejection fraction < 40%, and those randomized to amiodarone received fixed doses of 200 mg/day. Both studies had weeks-long loading dose schedules. Intent-to-treat all-cause mortality results reported were as follows:

	Placebo		Amiodarone		Relative Risk	
	N	Deaths	N	Deaths	95% CI	
EMIAT	743	102	743	103	0.99	0.76 -1.31
CAMIAT	596	68	606	57	0.88	0.58 -1.16

These reported data are consistent with the results of a pooled analysis of smaller, controlled studies involving patients with structural heart disease (including myocardial infarction).

Implantable Cardiac Devices

In patients with implanted defibrillators or pacemakers, chronic administration of antiarrhythmic drugs may affect pacing or defibrillating thresholds. Therefore, at the inception of and during amiodarone treatment, pacing and defibrillation thresholds should be assessed.

Corneal Refractive Laser Surgery

Patients should be advised that most manufacturers of corneal refractive laser surgery devices contraindicate that procedure in patients taking amiodarone.

Pulmonary Toxicity

There have been reports of acute-onset (days to weeks) pulmonary injury in patients treated with oral amiodarone with or without initial I.V. therapy. Findings have included pulmonary infiltrates on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure and/or death. 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. When amiodarone therapy is initiated, a baseline chest X-ray and pulmonary-function tests, including diffusion capacity, should be performed. The patient should be followed up for a history, physical examination and chest X-ray evaluation every 3 to 6 months.

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

Patients with preexisting pulmonary disease have a poorer prognosis if pulmonary toxicity develops.

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.

This diagnosis can be confirmed by performing a bronchoalveolar lavage where by T suppressor/cytotoxic (CD8-positive) lymphocytosis will be observed. 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 in 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 amiodarone 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. 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 should be discontinued or the dose needs to be reduced. 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 QTc prolongation (torsades de pointes [TdP]). In addition, amiodarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2 to 4% of patients. Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly. The need to co-administer amiodarone with any other drug known to prolong the QTc interval must be based on a careful assessment of the potential risks and benefits of doing so for each patient. A careful assessment of the potential risks and benefits of administering amiodarone must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia in these 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 reduction in dosage 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 would require 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 funduscopy and slit-lamp examination, is recommended during administration of amiodarone.

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 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.

Corneal Microdeposits

Corneal microdeposits appear in the majority of adults treated with amiodarone. They are usually evident 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 alone are not a reason to reduce dose or discontinue treatment.

Neurologic

Chronic administration of oral amiodarone may lead to the development of peripheral neuropathy in rare instances 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 dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue amiodarone. Tablets 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, which may result in death. 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 this form of therapy runs the theoretical risk of inducing thyroid storm. Amiodarone-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

Surgery

Volatile Anesthetic Agents: 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.

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, 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 or discontinuing therapy.

Amiodarone 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.

ADVERSE EFFECTS

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: very common (≥10%), common (≥ 1% and < 10%); uncommon (≥ 0.1% and < 1%); rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

• Very rare:
- haemolytic anemia
- aplastic anaemia
- thrombocytopenia.

In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.

Cardiac disorders:

• Common: bradycardia, generally moderate and dose-related.

• Uncommon:
- onset or worsening of arrhythmia, sometimes followed by cardiac arrest
- conduction disturbances (sinoatrial block, AV block of various degrees)

• Very rare: marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients.

Endocrine disorders:

• Common:
- hypothyroidism
- hyperthyroidism, sometimes fatal

• Very rare
- syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye disorders:

• Very common: corneal microdeposits usually limited to the area under the pupil, which are usually only discernable by slit-lamp examinations. They may be associated with colored halos in dazzling light or blurred vision. Corneal micro-deposits consist of complex lipid deposits and are reversible following discontinuation of treatment. The deposits are considered essentially benign and do not require discontinuation of amiodarone. Also papilledema, corneal degeneration, eye discomfort, scotoma, lens opacities, dry eyes, macular degeneration.

• Very rare: optic neuropathy/neuritis that may progress to blindness.

Gastrointestinal disorders:

• Very common: benign gastrointestinal disorders (nausea, vomiting, dysgeusia, anorexia) usually occurring with loading dosage and resolving with dose reduction.

Hepato-biliary disorders:

• Very common: isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times normal range), occurring at the beginning of therapy. It may return to normal with dose reduction or even spontaneously.

• Common: acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, which are sometimes fatal

• Very rare: chronic liver disease (pseudo alcoholic hepatitis, cirrhosis), sometimes fatal.

Immune system disorders:

Angioedema (there have been some reports of angioedema, although exact frequencies are not known)

Investigations:

• Very rare: increase in blood creatinine.

Nervous system disorders:

• Common:
- extrapyramidal tremor, for which regression usually occurs after reduction of dose or withdrawal, malaise, fatigue
- nightmares
- sleep disorders.

• Uncommon: peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug.

• Very rare:
- cerebellar ataxia, for which regression usually occurs after reduction of dose or withdrawal
- benign intracranial hypertension (pseudo- tumor cerebri)
- headache
- vertigo
- Peripheral neuropathy
- Paraesthesia

Reproductive system and breast disorders:

• Very rare:
- epididymo-orchitis
- impotence.

Respiratory, thoracic and mediastinal disorders:

• Common: pulmonary toxicity [hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia (BOOP)], sometimes fatal.

• Very rare:
- bronchospasm in patients with severe respiratory failure and especially in asthmatic patients
- surgery (possible interaction with a high oxygen concentration).

Pulmonary haemorrhage (there have been some reports of pulmonary haemorrhage, although exact frequencies are not known)

Skin and subcutaneous tissue disorders:

• Very common: photosensitivity/solar dermatitis.

• Common: slate grey or bluish pigmentations of light-exposed skin, particularly the face, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation.

• Very rare:
- erythema during the course of radiotherapy
- skin rashes, usually non- specific
- exfoliative dermatitis
- alopecia.

Not known: urticaria

Vascular disorders:

Very rare: vasculitis.

Other

Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities

Post Marketing Experience

In postmarketing surveillance, hypotension (sometimes fatal), sinus arrest, anaphylactic/anaphylactoid reaction (including shock), angioedema, urticaria, eosinophilic pneumonia, hepatitis, cholestatic hepatitis, cirrhosis, pancreatitis, renal impairment, renal insufficiency, acute renal failure, bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest, and ARDS), bronchiolitis obliterans organizing pneumonia (possibly fatal), fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates and/or mass, pulmonary alveolar hemorrhage, pleural effusion, pleuritis, pseudotumor cerebri, parkinsonian symptoms such as akinesia and bradykinesia (sometimes reversible with discontinuation of therapy), syndrome of inappropriate antidiuretic hormone secretion (SIADH), thyroid nodules/thyroid cancer, toxic epidermal necrolysis (sometimes fatal), erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, drug rash with eosinophilia and systemic symptoms (DRESS), eczema, skin cancer, vasculitis, pruritus, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, thrombocytopenia, agranulocytosis, granuloma, myopathy, muscle weakness, rhabdomyolysis, demyelinating polyneuropathy, hallucination, confusional state, disorientation, delirium, epididymitis, and impotence, also have been reported with amiodarone therapy.

DRUG INTERACTIONS

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines. Amiodarone is an inhibitor of CYP3A4 and p-glycoprotein. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4 and substrates of p-glycoprotein. While only a limited number of *in vivo* drug-drug interactions with amiodarone have been reported, the potential for other interactions should be anticipated. This is especially important for drugs associated with 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, potential for drug interactions exists, not only with concomitant medication, but also with drugs administered after discontinuation of amiodarone. Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit CYP3A4 may decrease the metabolism and increase serum concentrations of amiodarone. Reported examples include the following:

Protease inhibitors:

Protease inhibitors are known to inhibit CYP3A4 to varying degrees. Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy should be considered.

Histamine H_1 antagonists

Loratadine, a non-sedating antihistaminic, is metabolized primarily by CYP3A4. QT interval prolongation and Torsade de Pointes have been reported with the co-administration of loratadine and amiodarone.

Histamine H_2 antagonists:

Cimetidine inhibits CYP3A4 and can increase serum amiodarone levels.

Antidepressants

Trazodone, an antidepressant, is metabolized primarily by CYP3A4. QT interval prolongation and Torsade de Pointes have been reported with the co-administration of trazodone and amiodarone.

Other substances:

Grapefruit juice inhibits CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone; therefore, grapefruit juice should not be taken during treatment with oral amiodarone. It was reported that when grapefruit juice given to healthy volunteers increased amiodarone AUC by 50% and Cmax by 84%, and decreased DEA to unquantifiable concentrations. This information should be considered when changing from intravenous amiodarone to oral amiodarone. Class Ia (e.g. quinidine, procainamide, disopyramide), Class III anti-arrhythmic agents (e.g. sotalol, bretylium), moxifloxacine, antimalarials (quinidine, mefloquine, chloroquine, halofantrine), IV erythromycine, co-trimoxazole, pentamidine with amiodarone are contraindicated due to increased risk of TdP. Stimulant laxatives also increase the risk of TdP, hence alternative laxative is recommended.

Caution should be exercised over combined therapy with the following drugs which may also cause hypokalaemia and/or hypomagnesaemia, e.g. diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin.

Immunosuppressives:

Cyclosporine (CYP3A4 substrate) administered in combination with oral amiodarone has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

HMG-CoA reductase inhibitors:

Simvastatin (CYP3A4 substrate) in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis. When co-administered with amiodarone, lower starting and maintenance doses of these agents should be considered.

Cardiovasculars:

Cardiac glycosides: In patients receiving digoxin therapy, administration of oral amiodarone regularly results in an increase in the serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. Amiodarone taken concomitantly with digoxin increases the serum digoxin concentration by 70% after one day. On initiation of oral amiodarone, 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.

Antiarrhythmics:

Other antiarrhythmic drugs, such as quinidine, procainamide, disopyramide, and phenytoin, have been used concurrently with oral amiodarone. There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. Phenytoin decreases serum amiodarone levels. Amiodarone taken concomitantly with quinidine increases quinidine serum concentration by 33% after two days. Amiodarone taken concomitantly with procainamide for less than seven days increases plasma concentrations of procainamide and n-acetyl procainamide by 55% and 33%, respectively. Quinidine and procainamide doses should be reduced by one-third when either is administered with amiodarone. Plasma levels of flecainide have been reported to increase in the presence of oral amiodarone; because of this, the dosage of flecainide should be adjusted when these drugs are administered concomitantly. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring.

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.

Antihypertensives:

Amiodarone should be used with caution in patients receiving β-receptor blocking agents (e.g., propranolol, a CYP3A4 inhibitor) or calcium channel antagonists (e.g., verapamil, a CYP3A4 substrate, and diltiazem, a CYP3A4 inhibitor) 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.

Anticoagulants:

Potentiation of warfarin-type (CYP2C9 and CYP3A4 substrate) anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone increases the prothrombin time by 100% after 3 to 4 days, the dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely. Clopidogrel, an inactive thienopyridine prodrug, is metabolized in the liver by CYP3A4 to an active metabolite. A potential interaction between clopidogrel and amiodarone resulting in ineffective inhibition of platelet aggregation has been reported. Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A4 (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy. Reported examples of this interaction include the following:

Antibiotics:

Rifampin is a potent inducer of CYP3A4. Administration of rifampin concomitantly with oral amiodarone has been shown to result in decreases in serum concentrations of amiodarone and desethylamiodarone.

Other substances, including herbal preparations:

St. John's Wort (Hypericum perforatum) induces CYP3A4. Since amiodarone is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving amiodarone could result in reduced amiodarone levels.

Other reported interactions with amiodarone:

Fentanyl (CYP3A4 substrate) in combination with amiodarone may cause hypotension, bradycardia, and decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with lidocaine (CYP3A4 substrate) given for local anesthesia. Seizure, associated with increased lidocaine concentrations, has been reported with concomitant administration of intravenous amiodarone.

Dextromethorphan is a substrate for both CYP2D6 and CYP3A4. Amiodarone inhibits CYP2D6.

Cholestyramine increases enterohepatic elimination of amiodarone and may reduce its serum levels and t½.

Disopyramide increases QT prolongation which could cause arrhythmia.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation.

There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly.

Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with propranolol, diltiazem, and verapamil.

Volatile Anesthetic Agents.

In addition to the interactions noted above, chronic (> 2 weeks) oral amiodarone administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.

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 and during amiodarone therapy. Caution must be used when coadministering amiodarone with drugs, which may induce hypokalemia and/or hypomagnesemia.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Amiodarone was associated with 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 tested, i.e., 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*). *600 mg in a 50 kg patient (dose compared on a body surface area basis)

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

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

PREGNANCY: Pregnancy Category D

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

LABOUR AND DELIVERY

It is not known whether the use of amiodarone during labour 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 and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk. Therefore, when amiodarone therapy is indicated, the mother should be advised to discontinue nursing.

PAEDIATRIC USE

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

GERIATRIC USE

Clinical studies of amiodarone 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.

DOSAGE AND ADMINISTRATION

Because of the unique pharmacokinetic properties, difficult dosing schedule, and severity of the side effects if patients are improperly monitored, amiodarone 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 has not been determined. Because of the food effect on absorption, amiodarone should be administered consistently with regard to meals. Individual patient titration is suggested according to the following guidelines:

For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamicallyunstable 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 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.

Since grapefruit juice is known to inhibit CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone, grapefruit juice should not be taken during treatment with oral amiodarone.

Upon starting amiodarone therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs. When adequate arrhythmia control is achieved, or if side effects become prominent, amiodarone dose should be reduced to 600 to 800 mg/day for one month and then to the maintenance dose, usually 400 mg/day. 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.

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:

Ventricular Arrhythmias:

Loading dose (Daily):

• for 1 to 3 weeks - 800 to 1600 mg

Adjustment and maintenance dose (Daily):

• for approximately one month - 600 to 800 mg

• Usual maintenance - 400 mg

OVERDOSAGE

There have been reports of some fatal cases of amiodarone overdose.

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.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 30°C, protected from light

PRESENTATION

Ritebeat 100 & 200 mg are available in blister pack of 10 tablets.

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Manufactured by :

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