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

RITEBEAT I.V

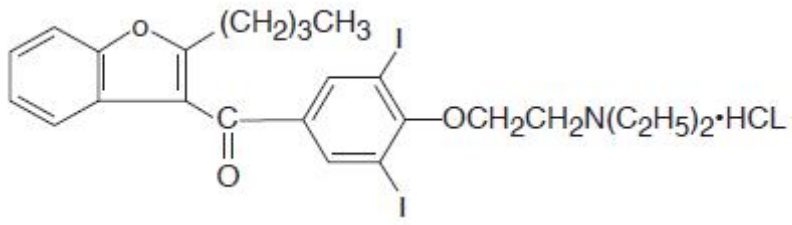
(Amiodarone Sterile Concentrate I.P. 3 ml)

COMPOSITION

Each ml contains:
Amiodarone Hydrochloride I.P. 50 mg
Benzyl Alcohol I.P. 2% w/v (As preservative)
Water for injection I.P. q.s.

DESCRIPTION

Amiodarone hydrochloride ($C_{25}H_{29}I_2NO_3$ .HCl) is a class III antiarrhythmic drug. Amiodarone hydrochloride is (2-butyl-benzofuran-3yl-4-(2-diethyl aminoethoxy)-3,5-diiodophenyl ketone hydrochloride.



Amiodarone hydrochloride is a white or almost white, fine crystalline powder. It has a molecular weight of 681.8 and contains 37.3% iodine by weight. Ritebeat I.V. is a sterile clear, pale-yellow micellar solution visually free from particulates. Each milliliter of the Ritebeat I.V. formulation contains 50 mg of amiodarone hydrochloride, 20 mg of benzyl alcohol, 100 mg of polysorbate 80, and water for injection.

CLINICAL PHARMACOLOGY

Mechanism of action

Amiodarone is generally considered a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes. Like class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like class II drugs, it exerts a noncompetitive antisympathetic action. One of its main effects, with prolonged administration, is to lengthen the cardiac action potential, a class III effect. The negative chronotropic effect of amiodarone in nodal tissues is similar to the effect of class IV drugs. In addition to blocking sodium channels, amiodarone blocks myocardial potassium channels, which contributes to slowing of conduction and prolongation of refractoriness. The antisympathetic action and the block of calcium and potassium channels are responsible for the negative dromotropic effects on the sinus node and for the slowing of conduction and prolongation of refractoriness in the atrioventricular (AV) node. Its vasodilatory action can decrease cardiac workload and consequently myocardial oxygen consumption.

Amiodarone I.V. administration prolongs intranodal conduction (Atrial-His, AH) and refractoriness of the atrioventricular node (ERP AVN), but has little or no effect on sinus cycle

length (SCL), refractoriness of the right atrium and right ventricle (ERP RA and ERP RV), repolarization (QTc), intraventricular conduction (QRS), and infranodal conduction (His-ventricular, HV). The initial acute effect of Amiodarone I.V. may be predominantly focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel blockade (class IV activity) and noncompetitive adrenergic antagonism (class II activity)

Pharmacodynamics
Amiodarone I.V. has been reported to produce negative inotropic and vasodilatory effects in animals and humans. In clinical studies of patients with refractory VF or hemodynamically unstable VT, treatment-emergent, drug-related hypotension occurred in 16% of patients treated with Amiodarone I.V. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of
Amiodarone I.V.

Pharmacokinetic
Amiodarone exhibits complex disposition characteristics after intravenous administration. After single 5mg/kg, 15-minute intravenous infusions in healthy subjects, peak serum concentrations ranged between 5 and 41 mg/L. Peak concentrations after 10-minute infusions of 150mg Amiodarone I.V. in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) ranged between 7 and 26 mg/L. In clinical trials, after 48 hours of continued infusions (125, 500, or 1000 mg/day) plus supplemental (150 mg) infusions (for recurrent arrhythmias), amiodarone mean serum concentrations have been reported to range from 0.7 to 1.4 mg/L.

N-desethylamiodarone (DEA) concentrations above 0.05 mg/L are not usually seen until after several days of continuous infusion but with prolonged therapy reach approximately the same concentration as amiodarone.

Distribution:
Intravenous amiodarone is rapidly distributed. Tissue distribution accounts for most of the decline in plasma concentration. Concentrations can decline to 10% of peak values within 30 to 45 minutes after completion of infusion. These distribution characteristics explain why plasma concentrations of the drug donot correlate well with observable clinical effect.

Amiodarone's calculated volume of distribution exceeds 5000 L. This large volume occurs because amiodarone and its major metabolite, Ndesethylamiodarone, are taken up from plasma and concentrated (as much as 1000-fold) in erythrocyte membranes and peripheral tissue, especially tissues with a high fat content. In fact, it has been hypothesized that amiodarone exerts at least some of its pharmacologic effects by concentrating in lipid-rich cell membranes and perturbing the milieu around ion channels rather than by modulating ion flow through channels.

From in vitro studies, the protein binding of amiodarone is reported to be>96%.

Metabolism
Amiodarone is metabolized to desethylamiodarone (DEA) 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. The highly variable systemic availability of oral amiodarone may be attributed potentially to large interindividual variability in CYP3A4 activity.

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.

Elimination
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. The elimination half-life of intravenous amiodarone is 3.2-80 hours.

Special Populations
Patients with VT and VF
In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 to 440 mL/h/kg.

Renal impairment
Renal impairment does not influence the pharmacokinetics of amiodarone.

Hepatic insufficiency
After a single dose of Amiodarone I.V. in cirrhotic patients, mean amiodarone levels are unchanged; however, significantly lower C_{max} and average concentration values are seen for DEA.

Elderly patients
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.

Patients with severe left ventricular dysfunction
In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone is not significantly altered but the terminal disposition $t_{1/2}$ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with oral amiodarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

INDICATIONS AND USAGE
Ritebeat I.V. is indicated for:

- Initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

- Ritebeat I.V. also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication. During or after treatment with Ritebeat I.V., patients may be transferred to oral amiodarone therapy.

Ritebeat I.V. should be used for acute treatment until the patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but Ritebeat I.V. may be safely administered for longer periods if necessary.

CONTRAINDICATIONS

Ritebeat I.V. is contraindicated in patients with known hypersensitivity to any of the components of Ritebeat I.V., including iodine, or in patients with cardiogenic shock, marked sinus bradycardia, and second-or third-degree AV block unless a functioning pacemaker is available.

DRUG INTERACTIONS

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 pglycoprotein.

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 H1 antagonists:

Loratadine: QT interval prolongation and torsade de pointes have been reported with the co-administration of loratadine and amiodarone.

Histamine H2 antagonists:

Cimetidine inhibits CYP3A4 and can increase serum amiodarone levels.

Antidepressants:

Trazodone:

QT interval prolongation and torsade de pointes have been reported with the co-administration of trazodone and amiodarone.

Other substances:

Grapefruit juice given to healthy volunteers increased amiodarone AUC by 50% and Cmax by 84%, resulting in increased plasma levels of amiodarone. Grapefruit juice should not be taken during treatment with oral amiodarone. This information should be considered when changing from intravenous amiodarone to oral amiodarone.

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.

Cardiovasculars:
Cardiac glycosides: In patients receiving **digoxin** therapy, administration of oral amiodarone regularly results in an increase in 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 administration 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 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 oral amiodarone, the dose levels of

previously administered agents should be reduced by 30 to 50% several days after the addition of oral amiodarone.

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 α-**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.**

A similar effect has been reported with **fluindione**, an oral vitamin K antagonist, when administered concomitantly with Amiodarone.

Clopidogrel: A potential interaction between clopidogrel and amiodarone resulting in ineffective inhibition of platelet aggregation has been reported.

Antibiotics:
Rifampin: 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: 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.

Fentanyl in combination with amiodarone may cause hypotension, bradycardia, and decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with lidocaine 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 $t_{1/2}$.

Disopyramide increases QT prolongation which could cause arrhythmia.
There have been reports of QTc prolongation, with or without torsades de pointe (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:

Oral Amiodarone administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.

Electrolyte Disturbances
Patients with hypokalemia or hypomagnesemia should have the condition corrected whenever possible before being treated with Ritebeat I.V., as these disorders can exaggerate the degree of QTc prolongation and increase the potential for TdP. Special attention should be given to electrolyte and acidbase balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics.

HMG-CoA reductase inhibitors:
Limit the dose of simvastatin in patients on amiodarone to 20 mg daily. Limit the daily dose of lovastatin to 40 mg. lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required as amiodarone may increase the plasma concentration of these drugs.

WARNINGS
Hypotension
Hypotension is the most common adverse effect seen with Amiodarone I.V. Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and was not dose related, but appeared to be related to the rate of infusion. Hypotension should be treated initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. In some cases, hypotension may be refractory resulting in fatal outcome.

Bradycardia and AV Block
Drug-related bradycardia occurred in 4.9% patients in clinical trials and was not dose-related. Bradycardia should be treated by slowing the infusion rate or discontinuing Amiodarone I.V. In some patients, inserting a pacemaker is required. Patients with a known predisposition to bradycardia or AV block should be treated with Amiodarone I.V. in a setting where a temporary pacemaker is available.

Liver Enzyme Elevations
Elevations of blood hepatic enzyme values-alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)-are seen commonly in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because the values may be elevated in patients who have had recent myocardial infarction, congestive heart failure, or multiple electrical defibrillations. Patients receiving Amiodarone I.V. in clinical studies had baseline liver enzyme elevations, and clinically significant elevations. In most patients with both baseline and on-therapy data available, the liver enzyme elevations have been reported to have either improved during therapy or remained at baseline levels. Baseline abnormalities in hepatic enzymes are not a contraindication to treatment.

Acute, centrolobular confluent hepatocellular necrosis leading to hepatic coma, acute renal failure, and death has been associated with the administration of Amiodarone I.V. at a much higher loading dose concentration and much faster rate of infusion than recommended. Therefore, ***the initial concentration and rate of infusion should be monitored closely.***

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of Amiodarone I.V. therapy, but patients receiving Amiodarone I.V. should be monitored carefully for evidence of progressive hepatic injury. Consideration should be given to reducing the rate of administration or withdrawing Amiodarone I.V. in such cases.

Proarrhythmia
Like all antiarrhythmic agents, Amiodarone I.V. may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsade de pointes (TdP), has been associated with prolongation by Amiodarone I.V. of the QTc interval to 500 ms or greater. Patients should be monitored for QTc prolongation during infusion with Amiodarone I.V. Combination of amiodarone with other antiarrhythmic therapy that prolongs the QTc should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent.

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 I.V. must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia, which may result in death, in these patients.

Pulmonary Disorders
Early-onset pulmonary toxicity
There have been postmarketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with Amiodarone I.V. Findings have included pulmonary infiltrates and/or mass on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some

cases have progressed to respiratory failure and/or death. Adult Respiratory Distress Syndrome *(ARDS)* There have been postmarketing reports of ARDS in Amiodarone I.V. patients. Amiodarone I.V. may play a role in causing or exacerbating pulmonary disorders in those patients.

Postoperatively, occurrences of ARDS have been reported in patients receiving oral 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. It is recommended that FiO2 and the determinants of oxygen delivery to the tissues (e.g., SaO2, PaO2) be closely monitored in patients on amiodarone.

Pulmonary fibrosis
Patient may develop developed pulmonary fibrosis, however, the incidence is about 1 in 1000 patients. Pulmonary toxicity is a well-recognized complication of long-term amiodarone use.

Loss of Vision
Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with oral 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 administrations of amiodarone.

Long-Term Use
There has been limited experience in patients receiving Amiodarone I.V. for longer than 3 weeks.

Neonatal Hypo- or Hyperthyroidism
Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with its oral administration. If Amiodarone I.V. is administered during pregnancy, the patient should be apprised of the potential hazard to the fetus.

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

Surgery
Close perioperative monitoring is recommended in patients undergoing general anesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction defects of halogenated inhalational anesthetics.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity studies were conducted with Amiodarone I.V. However, oral 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 in rats was greater than the incidence in controls even at the lowest dose level tested, i.e., 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose).

Mutagenicity studies conducted with amiodarone HCl were negative.
No fertility studies were conducted with Amiodarone I.V. However, in a study in which amiodarone HCl was orally administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose). In a reproductive study in which amiodarone was given intravenously to rabbits at dosages of 5, 10, or 25 mg/kg per day (about 0.1, 0.3, and 0.7 times the maximum recommended human dose [MRHD] on a body surface area basis), maternal deaths occurred in all groups, including controls. Embryotoxicity (as manifested by fewer full-term fetuses and increased resorptions with concomitantly lower litter weights) occurred at dosages of 10 mg/kg and above. No evidence of embryotoxicity was observed at 5 mg/kg and no teratogenicity was observed at any dosages. In a teratology study in which amiodarone was administered by continuous I.V. infusion to rats at dosages of 25, 50, or 100 mg/kg per day (about 0.4, 0.7, and 1.4 times the MRHD when compared on a body surface area basis), maternal toxicity (as evidenced by reduced weight gain and food consumption) and embryotoxicity (as evidenced by increased resorptions, decreased live litter size, reduced body weights, and retarded sternum and metacarpal ossification)were observed in the 100 mg/kg group.

Pregnant women
Amiodarone I.V. should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

Nursing Mothers
Amiodarone and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered amiodarone have demonstrated reduced viability and reduced body weight gains. The risk of exposing the infant to amiodarone should be

weighed against the potential benefit of arrhythmia suppression in the mother. The mother should be advised to discontinue nursing.

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

Pediatric Use
The safety and efficacy of amiodarone in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended.

Geriatric Use
Clinical studies of Amiodarone I.V. 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.

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 10% of patients receiving amiodarone and may be primary or subsequent to resolution of preceding amiodarone-induced hyperthyroidism. This condition may be identified by clinical symptoms and elevated serum TSH levels. Cases of severe hypothyroidism and myxedema coma, sometimes fatal, have been reported in association with amiodarone therapy. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Manage hypothyroidism by reducing the dose of or discontinuing Amiodarone and considering the need for thyroid hormone supplement.

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 thyrotoxicosis and/or arrhythmia breakthrough or aggravation, all of which may result in death. There have been reports of death associated with amiodarone-induced thyrotoxicosis. 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. amiodarone-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

When aggressive treatment of amiodarone-induced thyrotoxicosis has failed or amiodarone cannot be discontinued because it is the only drug effective against the resistant arrhythmia, surgical management may be an option. Experience with thyroidectomy as a treatment for amiodarone-induced thyrotoxicosis is limited, and this form of therapy could induce thyroid storm. Therefore, surgical and anesthetic management require careful planning.

There have been postmarketing reports of thyroid nodules/thyroid cancer in patients treated with Amiodarone. In some instances hyperthyroidism was also present.

ADVERSE REACTIONS

In patients who received Amiodarone I.V for a mean duration of 5.6 days (median exposure of 3.7 days), the most important treatment-emergent adverse effects were hypotension, asystole/cardiac arrest/electromechanical dissociation (EMD), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. Overall, treatment was discontinued for about 9% of the patients because of adverse effects. The most common adverse effects leading to discontinuation of Amiodarone I.V. therapy were hypotension (1.6%), asystole/cardiac arrest/EMD (1.2%), VT (1.1%), and cardiogenic shock (1%). The following table lists the most common (incidence-2%) treatmentemergent adverse events during Amiodarone I.V. therapy considered at least possibly drug-related. These data were collected in clinical trials involving patients with life-threatening VT/VF. Data from all assigned treatment groups are pooled because none of the adverse events appeared to be dose-related.

Adverse Event Body as a Whole	**% of patients**
Fever	2.0
Cardiovascular System	
Bradycardia	4.9
Congestive heart failure	2.1
Heart arrest	2.9
Hypotension	15.6
Ventricular tachycardia	2.4
Digestive System	

Liver function tests abnormal	3.4
Nausea	3.9

Other treatment-emergent possibly drug-related adverse events reported in less than 2% of patients receiving Amiodarone I.V. in controlled and uncontrolled studies included the following: abnormal kidney function, atrial fibrillation, diarrhea, increased ALT, increased AST, lung edema, nodal arrhythmia, prolonged QT interval, respiratory disorder, shock, sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting.

Postmarketing Reports
In postmarketing surveillance, hypotension (sometimes fatal), sinus arrest, anaphylactic/anaphylactoid reaction (including shock), angioedema, hepatitis, cholestatic hepatitis, cirrhosis, pancreatitis, acute 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, pleuritis, pseudotumor cerebri, syndrome of inappropriate antidiuretic hormone secretion (SIADH), thyroid nodules/thyroid cancer, toxic epidermal necrolysis (sometimes fatal), erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, bullous dermatitis, skin cancer, vasculitis, pruritus, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, thrombocytopenia, agranulocytosis, granuloma, myopathy, muscle weakness, rhabdomyolysis, hallucination, confusional state, disorientation, delirium, epididymitis, impotence and dry mouth also have been reported with amiodarone therapy. Acute respiratory distress syndrome in the post-operative setting and drug rash with eosinophilia and systemic symptoms (DRESS).

Also, in patients receiving recommended dosages of Amiodarone I.V., there have been postmarketing reports of the following injection site reactions: pain, erythema, edema, pigment changes, venous thrombosis, phlebitis, thrombophlebitis, cellulitis, necrosis, and skin sloughing.

Incompatibilities
Amiodarone injection has been reported to be incompatible with aminophylline, flucloxacillin, heparin, sodium bicarbonate & sodium chloride solutions. It is also incompatible with ampicillin/sulbactam sodium, ceftazidime sodium, digoxin, furosemide, imipenem/cilastatin sodium, magnesium sulfate, piperacillin solution, piperacillin/tazobactam sodium, potassium phosphate & sodium phosphate.

DOSAGE AND ADMINISTRATION
Amiodarone shows considerable interindividual variation in response. Thus, although a starting dose adequate to suppress life-threatening arrhythmias is needed, close monitoring with adjustment of dose as needed is essential. The recommended starting dose of Ritebeat I.V. is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

Ritebeat I.V. dose recommendations for first 24 hours are as follows:

Loading infusions
First Rapid: **150 mg over the FIRST 10 minutes (15 mg/min)**

Add 3 mL of Ritebeat I.V. (150 mg) to 100 mL D5W (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes.

Followed by Slow: **360 mg over the NEXT 6 hours (1 mg/min)**
Add 18 mL of Ritebeat I.V. (900 mg) to 500 mL D5W (concentration = 1.8 mg/mL).

Maintenance infusion
540 mg over the REMAINING 18 hours (0.5 mg/min)
Decrease the rate of the slow loading infusion to 0.5 mg/min.

After the first 24 hours, the maintenance infusion rate of 0.5 mg/min (720 mg/24 hours) should be continued utilizing a concentration of 1 to 6 mg/mL (Ritebeat I.V. concentrations greater than 2 mg/mL should be administered via a central venous catheter). In the event of breakthrough episodes of VF or hemodynamically unstable VT, 150-mg supplemental infusions of Ritebeat I.V. mixed in 100 mL of D5W may be administered. Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2100 mg were associated with an increased risk of hypotension.The initial infusion rate should not exceed 30 mg/min.

Based on the experience from clinical studies of Ritebeat I.V., a maintenance infusion of up to 0.5 mg/min can be cautiously continued for 2 to 3 weeks regardless of the patient's age, renal function, or left ventricular function. There has been limited experience in patients receiving Ritebeat I.V. for longer than 3 weeks.

The surface properties of solutions containing injectable amiodarone are altered such that the drop size may be reduced. This reduction may lead to underdosage of the patient by up to 30% if drop counter infusion sets are used. Ritebeat I.V. must be delivered by a volumetric infusion pump.

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

Ritebeat I.V. loading infusions at much higher concentrations and rates of infusion much faster than recommended have resulted in hepatocellular necrosis and acute renal failure, leading to death.

Ritebeat I.V. concentrations greater than 3 mg/mL in D5W have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/mL or less appear to be less irritating. Therefore, for infusions longer than 1 hour, Ritebeat I.V. concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

Ritebeat I.V. infusions exceeding 2 hours must be administered in glass or polyolefin bottles containing D5W. Use of **evacuated glass containers** for admixing Ritebeat I.V. is not recommended as incompatibility with a buffer in the container may cause precipitation.

It is well known that amiodarone adsorbs to polyvinyl chloride (PVC) tubing and the clinical trial dose administration schedule was designed to account for this adsorption. All of the clinical trials were conducted using PVC tubing and its use is therefore recommended.

Ritebeat I.V. has been found to leach out plasticizers, including DEHP [di-(2-ethylhexyl) phthalate] from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing Ritebeat I.V. at higher concentrations and lower flow rates than recommended. In addition, polysorbate 80, a component of Ritebeat I.V., is also known to leach DEHP from PVC. Therefore, it is important that Ritebeat I.V. be administered as per recommendations in Dosage and Administration.

Ritebeat I.V. does not need to be protected from light during administration.

Admixture Incompatibility
Ritebeat I.V. in D5W is incompatible with the drugs shown below.

Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Amiodarone Concentration	Comments
Aminophylline	D5W	4 mg/mL	Precipitate
Cefamandole Nafate	D5W	4 mg/mL	Precipitate
Cefazolin Sodium	D5W	4 mg/mL	Precipitate
Mezlocillin Sodium	D5W	4 mg/mL	Precipitate
Heparin Sodium	D5W	----	Precipitate
Sodium Bicarbonate	D5W	3 mg/mL	Precipitate

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

RECOMMENDATIONS FOR ORAL DOSAGE AFTER I.V. INFUSION

Duration of Ritebeat I.V. Infusion#	Initial Daily Dose of Oral Amiodarone
< 1 week	800-1600 mg
1-3 weeks	600- 800 mg
> 3 weeks*	400 mg

Assuming a 720 mg/day infusion (0.5 mg/min).
* Ritebeat I.V. is not intended for maintenance treatment.

DIRECTION
Must be used as an I.V. infusion after dilution with I.V. fluid i.e. glucose intravenous infusion (50 g per litre)

STORAGE
Store at a temperature not exceeding 25^{o}C, Do not freeze, protected from light.

EXPIRY DATE
Do not use later than the date of expiry.

PRESENTATION
Ritebeat I.V. is available as 3 ml ampoule.

MARKETED BY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IN/RITEBEAT I.V./50mg/Feb-15/03/PI