PRODUCT MONOGRAPH

[Pr]AMIODARONE OMEGA

Amiodarone hydrochloride for injection

House Standard

Vials: 50 mg/mL

Antiarrhythmic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous (IV)	Amiodarone hydrochloride for injection, vials, 50 mg/mL	Benzyl alcohol, polysorbate-80, sodium hydroxide and/or hydrochloric acid and water for injection.

INDICATIONS AND CLINICAL USE

No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

Amiodarone HCl therapy should be initiated in hospital and continued in a monitored environment until adequate control of the arrhythmia has occurred.

Patients treated with amiodarone HCl should be under the supervision of a cardiologist or a physician with equivalent experience in cardiology.

Amiodarone Hydrochloride for Injection is indicated for initiation of treatment of documented, life-threatening, frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to all other treatment. Additionally, Amiodarone Hydrochloride for Injection can be used to treat patients with VT/VF for whom ***oral*** amiodarone HCl is indicated, but who are unable to take ***oral*** medication. During or after treatment with Amiodarone Hydrochloride for Injection, patients may be transferred to ***oral*** amiodarone HCl therapy (see **DOSAGE AND ADMINISTRATION**).

Amiodarone Hydrochloride for Injection should be used for acute treatment until the patients ventricular arrhythmias are stabilized. Most patients will require this therapy 48 to 96 hours, but Amiodarone Hydrochloride for Injection may be administered for longer periods if necessary.

CONTRAINDICATIONS

Amiodarone hydrochloride is contraindicated in patients with known hypersensitivity to any of the components of Amiodarone Omega, and in patients with cardiogenic shock. It is contraindicated in severe sinus-node dysfunction, causing bradycardia; second- or third-degree V block, and when episodes of bradycardia have caused syncope (except when used in conjunction with a pacemaker).

WARNINGS AND PRECAUTIONS

The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when amiodarone hydrochloride must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when amiodarone hydrochloride is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

General

Patients with life-threatening arrhythmias may experience serious adverse events during their treatment and therefore should be properly monitored. Amiodarone Omega 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 hydrochloride therapy, and who have access to facilities adequate for monitoring the effectiveness and adverse events of treatment (see INDICATIONS AND CLINICAL USE).

Carcinogenesis and Mutagenesis

No carcinogenicity studies were conducted with intravenous amiodarone. However, oral amiodarone hydrochloride caused a statistically significant, dose-related increase in the incidence of thyroid tumours (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumours 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 hydrochloride (Ames, micronucleus, and lysogenic induction tests) were negative.

No fertility studies were conducted with intravenous amiodarone. However, in a study which amiodarone hydrochloride 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*).

Cardiovascular

Proarrhythmia/QT Interval Prolongation

Amiodarone may cause a worsening of the existing arrhythmias or precipitate a new arrhythmia. Amiodarone causes prolongation of the QT interval. Proarrhythmia, primarily torsades de pointes, has been associated with prolongation of the QTc interval to 500 ms or greater. Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity. Although QTc prolongation occurred frequently in patients receiving IV amiodarone, torsades de pointes or new-onset VF occurred infrequently (less than 2% of all patients treated with IV amiodarone in controlled clinical trials). Patients should be monitored carefully for QTc prolongation during amiodarone therapy. 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.

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.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without torsades de pointes, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly.

A careful assessment of the potential risks and benefits of administering amiodarone hydrochloride must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia in these patients. For patients receiving IV amiodarone, death may result.

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

The difficulty of using amiodarone effectively and safely poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone is given, and a response generally requires at least one week, usually two or more. Because elimination is 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 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.

Bradycardia and AV Block

Bradycardia was reported as an adverse drug reaction in 4.9% of patients receiving IV amiodarone for life-threatening VT/VF in clinical trials. AV block was reported as an adverse drug reaction in 1.4% of patients receiving IV amiodarone. There was no dose-related increase in bradycardia or AV block in these studies.

During intravenous amiodarone therapy, bradycardia should be treated by slowing the infusion rate or discontinuing therapy. In some patients, inserting a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 (<1%) patient during controlled clinical trials. Patients with a known predisposition to bradycardia or AV block should be treated with intravenous amiodarone in a setting where a temporary pacemaker is available.

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

Severe Bradycardia
Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofosbuvir alone or in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir, or ledipasvir. Therefore, coadministration of these agents with amiodarone is not recommended.

If concomitant use with amiodarone cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir alone or in combination with other DAAs. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for at least 48 hours in an appropriate clinical setting after initiation of the concomitant treatment with sofosbuvir.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir alone or in combination with other direct DAAs.

Patients receiving these hepatitis C medicines with amiodarone, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them.

Hypotension
Hypotension is the most common adverse event seen with IV amiodarone therapy: it is uncommon (<1%) during oral amiodarone hydrochloride therapy. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with IV amiodarone. 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 necessitating temporary discontinuation of IV amiodarone therapy was reported in 3% of the 814 patients, with permanent discontinuation required in an additional 2% of the 814 patients. In some cases, hypotension may be refractory resulting in fatal outcome.

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

Endocrine and Metabolism
Neonatal Hypo- or Hyperthyroidism
Amiodarone Omega 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 associated with its oral administration. If Amiodarone Omega is used during pregnancy, or if the patient becomes pregnant while taking amiodarone hydrochloride, the patient should be apprised of the potential hazard to the fetus.

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

In pregnant rats and rabbits, amiodarone hydrochloride in dose of 25 mg/kg/day (approximately 0.4 and 0.9 times, respectively, the maximum recommended human maintenance dose*) had no adverse effects on the fetus. In the rabbit, 75 mg/kg/day (approximately 2.7 times the maximum recommended human maintenance dose*) caused abortions in greater than 90% of the animals. In the rat, doses of 50 mg/kg/day or more were associated with slight displacement of the testes and an increased incidence of incomplete ossification of some skull and digital bones; at 100 mg/kg/day or more, fetal body weights were reduced; at 200 mg/kg/day, there was an increased incidence of fetal resorption. (These doses in the rat are approximately 0.8, 1.6 and 3.2 times the maximum recommended human maintenance dose.*) Adverse effects on fetal growth and survival also were noted in one of two strains of mice at a dose of 5 mg/kg/day (approximately 0.04 times the maximum recommended human maintenance dose*).

Hepatic/Biliary/Pancreatic

Liver Enzyme Elevations

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of amiodarone therapy. However, patients receiving oral amiodarone hydrochloride should be monitored carefully for evidence of progressive hepatic injury.

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 with recent myocardial infarction, congestive heart failure, and in those who have received multiple electrical defibrillations.

If the increase in hepatic enzyme levels exceeds three times normal or double in a patient with elevated baseline, discontinuation of Amiodarone Omegashould be considered.

Approximately 54% of patients receiving IV amiodarone in clinical studies had baseline elevations in liver enzyme values, and 13% had clinically significant elevations. In 81% of patients with baseline and on-therapy data available, the liver enzyme elevations either improved during therapy or remained at baseline levels. Baseline abnormalities in hepatic enzymes are not a contraindication to treatment.

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

Rare cases of fatal hepatocellular necrosis after treatment with IV amiodarone have been reported. Two patients, one 28 and the other 60 years of age, received an initial infusion of 1500 mg over 5 hours, a rate much higher than recommended. Both patients developed hepatic and renal failure within 24 hours after the start of IV amiodarone treatment and died on day 14 and day 4, respectively. Because these episodes of hepatic necrosis may have been due to the rapid rate of infusion and hypotension is related to the rate of infusion, **the initial rate of infusion should be monitored closely and should not exceed that recommended.**

Respiratory

Intravenous and Oral Amiodarone

Pulmonary Toxicity

There have been post-marketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with oral amiodarone hydrochloride with or without initial IV therapy. Findings have included pulmonary infiltrates and/or mass on X-ray, pulmonary alveolar hemorrhage, pleural effusion, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure and/or death.

One of the most serious complications resulting from oral amiodarone hydrochloride therapy is pulmonary toxicity, characterized by pneumonitis. Clinical symptoms include cough, progressive dyspnea, accompanied by functional, radiographic, gallium-scan, weight loss, weakness, and pathological data consistent with pulmonary toxicity. On chest x-ray, there is a diffuse interstitial pattern lung involvement frequently with patchy alveolar infiltrates, particularly in the upper lobe. Predicting which patient will develop pulmonary toxicity has been difficult (see CONTRAINDICATIONS). Pulmonary toxicity can appear abruptly either early or late during therapy and it commonly mimics viral or bacterial infection or worsening congestive heart failure. The relationship of pulmonary toxicity to duration of therapy, maintenance dose, and total dose is unclear. The majority of patients have recovered with this management, although some fatalities have occurred. Therefore, when amiodarone hydrochloride therapy is initiated, a baseline chest X ray and pulmonary-function tests, including diffusion capacity, should beperformed. The patient should return for a history, physical exam, and chest X-ray every 3 to 6 months.

Pulmonary toxicity secondary to amiodarone seems to result from either indirect or direct toxicity as represented by hypersensitivity pneumonitis (including eosinophilic pneumonia) or interstitial/alveolar pneumonitis, respectively at rates as high as 10-17% in patients with ventricular arrhythmias given doses around 400 mg/day. Pulmonary toxicity has been fatal about 10% of the time.

Recent reports suggest that the use of lower loading and maintenance doses of amiodarone are associated with a decreased incidence of amiodarone-induced pulmonary toxicity.

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

Interstitial/alveolar pneumonitis may result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis 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 the 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.

In a patient receiving Amiodarone Omega, 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 hydrochloride 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 Omega 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 hydrochloride 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 hydrochloride discontinued or, at a minimum, reduced in dosage. Some cases of amiodarone-induced interstitial/alveolar pneumonitis may resolve following a reduction in amiodarone hydrochloride 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.

Only 1 of more than 1000 patients treated with IV amiodarone in clinical studies developed pulmonary fibrosis. For that patient, the condition was diagnosed 3 months after treatment with IV amiodarone, during which time she had received oral amiodarone. IV amiodarone therapy

should be discontinued if a diagnosis of pulmonary fibrosis is made.

During clinical studies of IV amiodarone, 2% of patients were reported to have adult respiratory distress syndrome (ARDS). ARDS is a disorder characterized by bilateral, diffuse pulmonary infiltrates with pulmonary edema and varying degrees of respiratory insufficiency. The clinical and radiographic picture can arise after a variety of lung injuries, such as those resulting from trauma, shock, prolonged cardiopulmonary resuscitation, and aspiration pneumonia, conditions present in many of the patients enrolled in the clinical studies. It is not possible to determine what role, if any, IV amiodarone played in causing or exacerbating the pulmonary disorder in those patients.

Severe Bullous reactions
Intravenous and Oral Amiodarone
Life-threatening or even fatal cutaneous reactions: Steven-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) have been reported (See ADVERSE REACTIONS). If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present amiodarone treatment should be discontinued immediately.

Special Populations
Pregnant Women: Amiodarone has been shown to be embryotoxic in some animal species. In three different human case reports, both the parent drug and its DEA metabolite have been shown to pass through the placenta, quantitatively ranging between 10% and 50% of human maternal serum concentrations. Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. Therefore, amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

In addition to causing infrequent congenital goiter/hypothyroidism and hyperthyroidism (See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Neonatal Hypo- or Hyperthyroidism), amiodarone has caused a variety of adverse effects in animals.

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 IV 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. Intravenous amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

Use During 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 on the duration of gestation or on parturition.

Nursing Women: Amiodarone and its DEA metabolite 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.

Pediatrics (<18 years of age): The safety and efficacy of amiodarone in children have not been established; therefore, its use in children is not recommended.

Rare cases of cardiac arrest, life-threatening arrhythmias and hypotension have been reported in neonates and infants who have received amiodarone post-natally.

The following information is provided in order to help the physician who considers that critical and treatment-resistant disease in a pediatric patient makes the use of Amiodarone Omega necessary. In a study of 26 patients aged 6 weeks to 29 years (mean 13 years), an amiodarone hydrochloride dose of 5 mg/kg/day, b.i.d. (10 mg/kg/day) was administered for 10 days; the subsequent mean maintenance dose of oral amiodarone hydrochloride was 7.5 mg/kg/day (range 2.5 to 21.5 mg/kg/day).

Amiodarone Omega contain the preservative benzyl alcohol. There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol.

Manifestations of the disease included: metabolic acidosis, respiratory distress, gasping respirations, central-nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, cardiovascular collapse and death.

Amiodarone has been found to leach out plasticizers, such as DEHP [di-(2-ethylhexyl)phthalate], from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing intravenous amiodarone at higher concentrations and at lower flow rates than provided in DOSAGE AND ADMINISTRATION. DEHP is used in various plastic medical devices, generally to increase flexibility.

Based on data from animal studies, there was concern that exposure to DEHP may adversely affect male reproductive tract development during fetal, infant and toddler stages of development if the exposure in these immature stages is several-fold higher than in adults, a situation that might be associated with intensive medical procedures such as those used in critically ill infants. Although a no-observable-adverse-effect level (NOAEL) by the oral route was identified for sexually mature rats (3.7 to 14 mg/kg per day), a NOAEL was not identified for rats in the post-natal stage. The maximum anticipated exposure to DEHP following intravenous amiodarone administration under conditions of pediatric administration was calculated to be about 1.9 mg/kg per day for a 3 kg infant, which produces a safety margin of between two-fold and seven-fold.

Geriatrics (>65 years of age): Clinical studies of amiodarone hydrochloride tablets did not include sufficient number of subjects aged 65 years 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.

Monitoring and Laboratory Tests

Amiodarone hydrochloride should be used only by physicians familiar with and with access to (directly or 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 technique.

In addition, the following should be considered and/or monitored for patient on amiodarone:

Electrolyte Disturbances

Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in any patient with potassium or magnesium deficiency, patients with hypokalemia or hypomagnesemia should hathe condition corrected whenever possible before instituting amiodarone hydrochloride tablets therapy, since these disorders can exaggerate the degree of QTc prolongation and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics. Use caution when co-administering amiodarone hydrochloride with drugs which may induce hypokalemia and/or hypomagnesemia.

Liver Enzyme Elevations

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of amiodarone therapy. However, patients receiving oral amiodarone hydrochloride should be monitored carefully for evidence of progressive hepatic injury.

QTc Prolongation

Patients should be monitored carefully for QTc prolongation during amiodarone therapy.

Monitoring Effectiveness

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

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

2. Whether provocation is also needed in patients who do manifest their life-threatening

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

Several predictors of success not based on PES have also been suggested, including complete elimination of all nonsustained ventricular tachycardia on ambulatory monitoring and very low premature ventricular-beat rates (less than 1 VPB/1000 normal beats).

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

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates

observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Please see Table 1 (intravenous amiodarone), below.

Commonly Observed Adverse Reactions

Intravenous Amiodarone: In a total of 1836 patients in controlled and uncontrolled clinical trials, 14% of patients received IV amiodarone for up to 1 week, 5% received it for up to 2 weeks, 2% received it for up to 3 weeks, and 1% received it for more than 3 weeks, without an increased incidence of serious adverse events. The mean duration of therapy in these studies was 5.6 days.

Overall, treatment was discontinued in 9% of the patients because of adverse events. The most common serious adverse events leading to discontinuation of IV amiodarone therapy were ventricular tachycardia (2%), hypotension (2%), cardiac arrest (asystole/cardiac arrest/electromechanical dissociation) (1%), and cardiogenic shock (1%).

Table 1 lists the most common (incidence ≥1%) adverse drug reactions during IV amiodarone therapy that were collected from controlled and open-label clinical trials involving 1836 patients with hemodynamically unstable VT or VF.

TABLE 1: SUMMARY TABULATION OF ADVERSE DRUG REACTIONS IN PATIENTS RECEIVING AMIODARONE HYDROCHLORIDE IV. IN CONTROLLED AND OPEN-LABEL STUDIES (≥1% INCIDENCE)

Study Event	Controlled Trials (N=814)	Open-Label Trials (N=1022)	Total Incidence (N=1836)
Any Adverse Reactions	412 (50.6%)	384 (37.5%)	796 (43.3%)
Body as a Whole	54 (6.6%)	32 (3.1%)	86 (4.6%)
Fever	24 (2.9%)	13 (1.2%)	37 (2.0%)
Cardiovascular System	308 (37.8%)	264 (25.8%)	572 (31.1%)
Atrial Fibrillation	15 (1.8%)	9 (<1%)	24 (1.3%)
AV Block	14 (1.5%)	12 (1.2%)	26 (1.4%)
Bradycardia	49 (6.0%)	41 (4.0%)	90 (4.9%)
Congestive Heart Failure	18 (2.2%)	21 (2.0%)	39 (2.1%)
Heart Arrest	29 (3.5%)	26 (2.5%)	55 (2.9%)
Hypotension	165 (20.2%)	123 (12.0%)	288 (15.6%)
Nodal Arrhythmia	15 (1.8%)	15 (1.4%)	30 (1.6%)
QT Interval Prolonged	15 (1.8%)	4 (<1%)	19 (1.0%)
Shock	13 (1.5%)	12 (1.1%)	25 (1.3%)
Ventricular Fibrillation	12 (1.4%)	13 (1.2%)	25 (1.3%)
Ventricular Tachycardia	15 (1.8%)	30 (2.9%)	45 (2.4%)
Digestive System	102 (12.5%)	97 (9.4%)	199 (10.8%)
Diarrhea	8 (<1%)	12 (1.1%)	20 (1.0%)
Liver Function Tests Abnormal	35 (4.2%)	29 (2.8%)	64 (3.4%)

Nausea	29 (3.5%)	43 (4.2%)	72 (3.9%)
Vomiting	16 (1.9%)	17 (1.6%)	33 (1.7%)
Hemic and Lymphatic System	34 (4.1%)	34 (3.3%)	68 (3.7%)
Thrombocytopenia	14 (1.7%)	16 (1.5%)	30 (1.6%)
Metabolic and Nutritional	56 (6.8%)	49 (4.7%)	105 (5.7%)
SGOT Increased (AST)	14 (1.7%)	6 (<1%)	20 (1.0%)
SGPT Increased (ALT)	14 (1.7%)	5 (<1%)	19 (1.0%)
Nervous System	46 (5.6%)	38 (3.7%)	84 (4.5%)
Respiratory System	54 (6.6%)	61 (5.9%)	115 (6.2%)
Lung Edema	6 (<1%)	15 (1.4%)	21 (1.1%)
Respiratory Disorder	11 (1.3%)	8 (<1%)	19 (1.0%)
Study Event	**Controlled Trials (N=814)**	**Open-Label Trials (N=1022)**	**Total Incidence (N=1836)**
Urogenital System	27 (3.3%)	30 (2.9%)	57 (3.1%)
Kidney Function Abnormal	8 (<1%)	16 (1.5%)	24 (1.3%)

Pulmonary Abnormalities: In some studies symptomatic pulmonary disease has been detected at rates as high as 10% to 15%, whereas asymptomatic abnormalities of pulmonary diffusion capacity have been demonstrated at greater than twice that incidence. Pulmonary toxicity has been fatal about 10% of the time (see WARNINGS AND PRECAUTIONS, Respiratory).

Cardiovascular Abnormalities: Exacerbation of arrhythmia has had a reported incidence of about 2% to 5% in most series (new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and paroxysmal polymorphic ventricular tachycardia (torsades de pointes). In addition, symptomatic bradycardia or sinus arrest with suppression of escape foci has occurred in 2% to 4% of patients. Congestive heart failure has occurred in approximately 3% of patients. Second degree AV block and left bundle branch block (LBBB) have occurred in less than 1% of patients, vasculitis and angioedema have also been reported. Hypotension independent of - as well as associated with - discontinuation of cardiopulmonary bypass following open heart surgery has also been reported (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Hepatic Abnormalities: Abnormal elevations of serum levels of enzymes associated with hepatic dysfunction have occurred in approximately 15% of patients. Symptomatic hepatitis has occurred in less than 1% of patients, and cholestatic hepatitis and cirrhosis have been reported (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic). The frequency of rare serious liver injury, abnormal liver-function tests, hepatitis, cholestatic hepatitis and cirrhosis is undetermined. Overt liver disease can occur however, and has been fatal in a few cases.

Post-Market Adverse Drug Reactions

In post-marketing surveillance, hypotension (sometimes fatal), sinus arrest, anaphylactic/anaphylactoid reaction (including shock), angioedema, eosinophilic pneumonia, hepatitis, cholestatic hepatitis, cirrhosis, pancreatitis/acute pancreatitis, dry mouth, constipation, 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, eczema, urticaria, erythema multiforme, exfoliative dermatitis, severe skin reactions sometimes fatal including toxic epidermal necrolysis/Stevens-Johnson syndrome, bullous dermatitis and drug reactions with eosinophilia and systemic symptoms (DRESS), skin cancer, vasculitis, pruritus, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, thrombocytopenia, agranulocytosis, granuloma including bone marrow granuloma, myopathy, muscle weakness, rhabdomyolysis, demyelinating polyneuropathy, hallucination, confusional state, disorientation, delirium, epididymitis, decreased appetite, parosmia, libido decreased and impotence, also have been reported in patients receiving amiodarone.

Women receiving amiodarone have been reported to be at greater risk of experiencing torsade de pointes.

Also, in patients receiving recommended dosages, 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 (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Overview
Drug-Drug Interactions

TABLE 2: SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE
Drugs Whose Effects May Be Increased By Amiodarone

Concomitant Drug	Interaction
Warfarin	Increases prothrombin time.
Digoxin	Oral amiodarone increases digoxin serum concentration by 70% after one day. May reach toxic levels with resultant clinical toxicity.
Digitalis	With 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.
Dabigatran	Caution should be exercised when amiodarone is co-administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran as per its label.
Quinidine	Increases quinidine serum concentration by 33% after two days. Quinidine dose should be reduced by 1/3 when administered with amiodarone.
Procainamide	Increases plasma concentrations of procainamide and n-acetyl procainamide by 55% and 33%, respectively if taken for less than 7 days. Procainamide dose should be reduced by 1/3 when administered with amiodarone.

Flecainide	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.
Lidocaine	Oral: Sinus bradycardia was observed in a patient receiving oral amiodarone who was given lidocaine for local anaesthesia. IV: Seizure associated with increased lidocaine concentrations was observed in one patient.
Phenytoin	Increases phenytoin serum concentration.
Concomitant Drug	**Interaction**
Disopyramide	Increases QT prolongation which could cause arrhythmia.
Fentanyl	May cause hypotension, bradycardia, decreased cardiac output.
Cyclosporine	Administered in combination with oral amiodarone, produces persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.
Fluoroquinolones, Macrolide Anti-biotics, Azoles	Are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without torsades de pointes, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly

TABLE 3: SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE
Drugs That May Interfere With the Actions of Amiodarone

Concomitant Drug	Interaction
Cholestyramine	Increases enterohepatic recirculation of amiodarone and may reduce serum levels and t½.
Cimetidine	Increases serum amiodarone levels.
Phenytoin	Decreases serum amiodarone levels.

Volatile Anaesthetic Agents
Close perioperative monitoring is recommended in patients undergoing general anaesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction effect of halogenated inhalation anaesthetics.

Beta Blockers
Amiodarone should be used with caution in patients receiving ß-receptor blocking agents (e.g., propranolol, 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.

Calcium Channel Antagonists
Amiodarone should be used with caution in patients receiving 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 warfarin should be reduced by one-third to one-half, and prothombin 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.

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.

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

Drugs prolonging QT
Co-administration of amiodarone with drugs known to prolong the QT interval must be based on a careful assessment of the potential risks and benefits for each patient since the risk of torsade de pointes may increase and patients should be monitored for QT prolongation.

Antiarrhythmics
In general, combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to amiodarone the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of amiodarone, when arrhythmia suppression should be beginning.

The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as amiodarone is continued. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Interactions via Cytochrome P450 System
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 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Amiodarone is a substrate and an inhibitor of CYP3A4 and a substrate of 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, chiefly with the oral formulation, 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 ofamiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone.

Examples of drugs that may have serum concentrations increased by amiodarone
Amiodarone inhibits p-glycoprotein and certain CYP450 enzymes (enzyme inhibition: CYP3A4, CYP2C9, CYP2D6). This can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes or are substrates of p-glycoprotein and may lead to toxic effects. Due to the long half-life of amiodarone, interactions may be observed for several months after discontinuation of amiodarone. Reported examples of this interaction include the following:

HMG-CoA Reductase Inhibitors: HMG-CoA reductase inhibitors that are CYP3A4 substrates (including simvastatin and atorvastatin) in combination with amiodarone have been associated with reports of myopathy/rhabdomyolysis.

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

Antihypertensives: Amiodarone should be used with caution in patients receiving ß-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.

Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentrations of amiodarone, with the potential for toxic effects**.** Reported examples include the following:

Protease Inhibitors: Protease inhibitors are known to inhibit CYP3A4 to varying degrees. Inhibition of CYP3A4 by indinavir has been reported to result in increased serum concentrations of amiodarone. Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy should be considered.

Histamine H1 antagonists: Loratadine, a non-sedating antihistaminic, is metabolized primarily by CYP3A4. QT interval prolongation and torsade de pointes have been reported with the coadministration of loratadine and amiodarone.

Antiviral drugs

Coadministration of amiodarone with sofosbuvir alone or in combination with another HCV direct acting antiviral (such as daclatasvir, simeprevir, or ledipasvir) is not recommended as it may lead to serious symptomatic bradycardia. The mechanism for this bradycardia effect is unknown. If coadministration cannot be avoided, cardiac monitoring is recommended.

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

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.

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

Agents which may induce hypokalaemia: Combined therapy with stimulating laxative agents which may cause hypokalaemia thus increasing the risk of torsade de pointes is not recommended. Other types of laxatives should be used.

Drug-Food Interactions

Grapefruit Juice

Grapefruit juice inhibits CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in significant increased plasma levels of amiodarone (C_{max} and AUC increased by 84% and 50%, respectively); therefore, grapefruit juice should not be taken during treatment with oral amiodarone. Therefore, this information should be considered when changing from intravenous amiodarone to **oral** amiodarone (see DOSAGE AND ADMINISTRATION, Intravenous to Oral Transition).

There are no drug-food interactions with amiodarone hydrochloride for injection.

Drug-Herb Interactions

St. John's Wort

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.

DOSAGE AND ADMINISTRATION

AMIODARONE HCl THERAPY SHOULD BE INITIATED IN HOSPITAL AND CONTINUED IN A MONITORED ENVIRONMENT UNTIL ADEQUATE CONTROL OF THE ARRHYTHMIA HAS OCCURRED. PATIENTS TREATED WITH AMIODARONE HCl SHOULD BE UNDER THE SUPERVISION OF A CARDIOLOGIST OR A PHYSICIAN WITH EQUIVALENT EXPERIENCE IN CARDIOLOGY. DOSE ADMINISTRATION MUST BE INDIVIDUALIZED, PARTICULARLY TAKING INTO ACCOUNT CONCOMITANT ANTIARRHYTHMIC THERAPY.

AMIODARONE OMEGA must be delivered by a volumetric infusion pump. 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.

AMIODARONE OMEGA should, whenever possible, be administered through a central venous catheter dedicated to that purpose. An in-line filter (0.22 μ pore size) should be used during administration.

AMIODARONE OMEGA concentrations greater than 3 mg/mL in D_5W 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, **AMIODARONE OMEGA** concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

AMIODARONE OMEGA infusion exceeding 2 hours must be administered in glass or polyolefin bottles containing D_5W. Use of evacuated glass containers for admixing **AMIODARONE OMEGA** 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. The concentrations and rates of infusion provided in **DOSAGE AND ADMINISTRATION** reflect doses identified in these studies. It is important that the recommended infusion regimen be followed closely.
Amiodarone Hydrochloride for Injection has been found to leach out plasticizers, such as DEHP [di-(2-ethylhexyl)phthalate] from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing Amiodarone Hydrochloride for Injection at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION.**
(See PRECAUTIONS - Use in Pediatrics)

AMIODARONE OMEGA does not need to be protected from light during administration.

Table 6- STABILITY OF DILUTED AMIODARONE HCl SOLUTIONS

Solution	Concentration (mg/mL)	Container	Comments
5% Dextrose in Water (D_5W)	1.0 - 6.0	PVC	Physically compatible, with amiodarone loss <10% at 2 hours at room temperature.
5% Dextrose in Water (D_5W)	1.0 - 6.0	Polyolefin, Glass	Physically compatible, with no amiodarone loss at 24 hours at room temperature.

Admixture Incompatibility

Amiodarone Hydrochloride for Injection in D_5W is physically incompatible with the drugs shown blow in Table 7

Table 7- Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Amiodarone Concentration (mg/mL)	Comments
Aminophylline	D_5W	4	Precipitate
Cefamandole Nafate	D_5W	4	Precipitate
Cefazolin Sodium	D_5W	4	Precipitate
Mezlocillin Sodium	D_5W	4	Precipitate
Heparin Sodium	D_5W	-	Precipitate
Sodium Bicarbonate	D_5W	3	Precipitate

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 is essential. The recommended starting dose of Amiodarone Hydrochloride for Injection is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen. It is important that the recommended infusion regimen be followed closely.

Table 8- AMIODARONE HYDROCHLORIDE FOR INJECTION DOSE RECOMMENDATIONS - FIRST 24 HOURS

Loading infusions	**Rapid:**	**150 mg over 10 minutes (15 mg/min).** Add 3 mL of Amiodarone Hydrochloride for Injection (150 mg) to 100 mL D_5W (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes.
	Slow:	**360 mg over 6 hours (1 mg/min).** Add 18 mL of Amiodarone Hydrochloride for Injection (900 mg) to 500 mL D_5W (concentration = 1.8 mg/mL). **540 mg over 18 hours (0.5 mg/min).** Decrease the rate of the slow loading infusion to 0.5 mg/min.
Maintenance infusion		

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 (Amiodarone Hydrochloride for Injection 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 Amiodarone Hydrochloride for Injection mixed in 100 mL of D_5W may be administered. Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of 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 rate of infusion should not exceed 30 mg/min.

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

Intravenous to Oral transition

Patients whose arrhythmias have been suppressed by Amiodarone Hydrochloride for Injection may be switched to ***oral*** amiodarone HCl. The optimal dose for changing from intravenous to oral administration of amiodarone HCl will depend on the dose of Amiodarone Hydrochloride for Injection already administered as well as the bioavailability of ***oral*** amiodarone HCl. When changing to ***oral*** amiodarone HCl therapy, clinical monitoring is recommended, particularly for elderly patients.
Since there are some differences between the safety and efficacy profiles of the intravenous and oral formulations, the prescriber is advised to review the package insert for oral amiodarone when switching from intravenous to oral amiodarone therapy.

The following table provides suggested doses of ***oral*** amiodarone HCl to be initiated after

varying durations of Amiodarone Hydrochloride for Injection administration. These recommendations are made on the basis of a comparable total body amount of amiodarone delivered by the intravenous and oral routes, based on a 50% bioavailability of oral amiodarone.

Table 9- RECOMMENDATIONS FOR ORAL DOSAGE AFTER I.V. INFUSION

Duration of Amiodarone Hydrochloride for Injection Infusion[a]	Initial Daily Dose of Oral Amiodarone HCl (mg)
< 1 week	800 - 1 600
1 to 3 weeks	600 - 800
> 3 weeks [b]	400

a: assuming a 720 mg/day (0.5 mg/min).
b: Amiodarone Hydrochloride for Injection is not intended for maintenance treatment.

OVERDOSAGE

Intravenous Amiodarone

There have been cases, some fatal, of amiodarone overdose. Effects of an inadvertent overdose of IV amiodarone include hypotension, cardiogenic shock, bradycardia, AV block, and hepatotoxicity. Hypotension and cardiogenic shock should be treated by slowing the infusion rate or with standard therapy: vasopressor drugs, positive inotropic agents and volume expansion. Bradycardia and AV block may require temporary pacing. Hepatic enzyme concentrations should be monitored closely. Neither amiodarone nor DEA is dialyzable.

Overdosage Management

The patient's cardiac rhythm and blood pressure should be monitored, and if clinically significant bradycardia ensues, a ß-adrenergic agonist or a temporary pacemaker should be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither amiodarone nor its metabolite is dialyzable.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Amiodarone hydrochloride 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 antisympathetic activity. 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 (Class III effect). The antisympathetic action and 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.

Additionally, amiodarone has vasodilatory action that can decrease cardiac workload and consequently myocardial oxygen consumption.

A comparison of the electrophysiologic effects of oral and intravenous amiodarone is shown in Table 8 below.

TABLE 8: EFFECTS OF ORAL AND INTRAVENOUS AMIODARONE ON ELECTROPHYSIOLOGIC PARAMETERS

	SCL	QRS	QTc	AH	HV	ERP RA	ERP RV	ERP AVN
Oral	↑	↔	↑	↑	↔	↑	↑	↑
Intravenous	↔	↔	↔	↑	↔	↔	↔	↑

— No change

Abbreviations: SCL = sinus cycle length; QRS = a measure of intraventricular conduction; QTc = corrected QT, a measure of repolarization; AH = atrial HIS, a measure of intranodal conduction; HV = HIS ventricular, a measure of intranodal conduction; ERP = effective refractory period; RA = right atrium; RV = right ventricle; AVN = atrioventricular node.

At higher doses (>10 mg/kg) of IV amiodarone, prolongation of the ERP RV and modest prolongation of the QRS have been seen. These differences between oral and intravenous administration suggest that the initial acute effects of intravenous amiodarone may be predominantly focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to calcium channel blockade (Class IV activity) and β-adrenoreceptor antagonism (Class II activity).

Pharmacodynamics

Amiodarone has been reported to produce negative inotropic and vasodilating effects in animals and humans. After long-term treatment with oral amiodarone in a dose range of 200 to 600 mg/day, patients with decreased left ventricular ejection fraction (LVEF) show no

significant change in mean LVEF. Hypotension is uncommon (<1%) during chronic oral amiodarone therapy. In clinical studies of patients with refractory ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT), drug-related hypotension occurred in 15.6% of 1836 patients treated with IV amiodarone. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of IV amiodarone.

Pharmacokinetics

Absorption: The absorption of oral amiodarone is slow and variable, with peak serum amiodarone concentrations being attained at 3 to 12 hours after administration. Absorption may continue for up to 15 hours after oral ingestion. There is extensive intersubject variation: mean oral bioavailability is approximately 50% (mean range, 33% to 65%). First-pass metabolism in the gut wall and liver appears to be an important factor in determining the systemic availability of the drug. The mean terminal half-life after steady-state administration is approximately 53 days and has been found in one study (n=8) to range from 26 to 107 days. Since at least 3 to 4 half-lives are needed to approach steady-state concentrations, loading doses must be administered at the onset of oral amiodarone therapy. 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.

Food increases the rate and extent of absorption of oral amiodarone. The effects of food upon the bioavailability of amiodarone have been studied in thirty healthy subjects who received a single 600 mg dose both immediately after consuming a meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of amiodarone increase by as much as 2.4 and 3.8 times, respectively, in the presence of food. Food also increased the rate of absorption, decreasing the time to peak plasma concentration (T_{max}) by 37%.

Distribution: Amiodarone has a very high apparent volume of distribution (approximately 5000 L) with an extensive accumulation in tissues, especially adipose tissues, and in highly perfused organs such as liver, lung, spleen, heart and kidney. One major metabolite of amiodarone, desethylamiodarone, has been identified, but the pharmacological activity of this metabolite is not known in humans. During chronic treatment, the plasma ratio of metabolite to parent compound approximates 1.

Amiodarone exhibits complex disposition characteristics after intravenous administration. Peak serum concentrations after single 5 mg/kg 15-minute intravenous infusions in healthy subjects range between 5 and 41 mg/L. Peak concentrations after 150 mg supplemental infusions in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) range between 7 and 26 mg/L. Due to rapid disposition, serum concentrations decline to 10% of peak values within 30 to 45 minutes after the end of the infusion. 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 between 0.7 to 1.4 mg/L were observed (n=260).

Metabolism: Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion. Desethylamiodarone (DEA) is the major active metabolite of amiodarone. At the usual amiodarone daily maintenance dose of 400 mg, mean steady-state DEA/amiodarone ratios ranged from 0.61 to 0.93. High-dose oral amiodarone loading in patients yielded 24-hour DEA/amiodarone ratios of 0.083 to 0.19. High-dose intravenous loading yielded a mean 24-hour DEA/amiodarone ratio of 0.041. No data are presently available on the activity of DEA in humans, but animal studies have shown that it has significant electrophysiologic and antiarrhythmic properties. The major enzyme responsible for the N-deethylation to DEA is believed to be cytochrome P450 3A4. Large interindividual variability in CYP-450 3A4 activity may explain the variable systemic availability of amiodarone. DEA is highly lipophilic and has a very large apparent volume of distribution, showing a higher concentration than amiodarone in all tissue except fat at steady-state. Myocardial concentrations of DEA are approximately 3- to 4.5-fold greater than those of amiodarone during long-term oral amiodarone therapy. However, after either acute oral or acute intravenous administration, both mean serum and mean myocardial DEA concentrations are quite low compared to those of amiodarone.

Excretion: Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion. There is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable. Amiodarone and DEA cross the placenta and both appear in breast milk.

Table 9 summarizes the mean ranges of pharmacokinetic parameters of amiodarone reported in single dose IV (5 mg/kg over 15 min) and oral (400 or 600 mg) studies of healthy subjects and in *in vitro* (protein binding) studies. Pharmacokinetics were similar in males and females.

TABLE 9: AMIODARONE PHARMACOKINETIC PROFILE

Drug	Clearance (mL/h/kg)	V_C (L/kg)	V_{SS} (L/kg)	$t_{½}$ (days)	Protein Binding	F_{oral} (%)
Amiodarone	90-158	0.2	40-84	20-47	>0.96	33-65
Desethylamiodarone	197-290	-	68-168	≥AMI $t_{½}$	-	-

Notes: V_C and V_{SS} denote the central and steady-state volumes of distribution from IV studies; F_{oral} is systemic availability of amiodarone. "-" denotes not available. AMI is amiodarone. $t_{½}$ = terminal phase elimination half-life. Desethylamiodarone clearance and volume involve an unknown biotransformation factor.

There is no well-established relationship between drug concentration and therapeutic response for long-term oral use or short-term intravenous use. Steady-state amiodarone concentrations of 1 to 2.5 mg/L, however, have been effective with minimal toxicity following chronic oral amiodarone.

Special Populations and Conditions

Pediatrics: The safety and efficacy of amiodarone in children have not been established; therefore, its use in children is not recommended.

Geriatrics: Clinical studies of amiodarone hydrochloride did not include sufficient number of subjects aged 65 years 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.

Gender: Based on a single-dose clinical trial with the intravenous formulation, no gender-based dosage adjustment is required.

Hepatic Insufficiency: Based on a single-dose clinical trial with the intravenous formulation, no dosage adjustment is required for patients with hepatic impairment, although these patients should be monitored closely. (See WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.)

Renal Insufficiency: Based on a single-dose clinical trial with the intravenous formulation, no dosage adjustment is required for patients with renal dysfunction, end-stage renal disease or dialysis.

Genetic Polymorphism: No data on dosage adjustment available.

Race: No data on dosage adjustment available.

STORAGE AND STABILITY

Amiodarone Omega, 50 mg/mL: Store between 15 and 25°C. Protect from light and excessive heat. Use carton to protect contents from light until use.

SPECIAL HANDLING INSTRUCTIONS

Parenteral Products

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration whenever solution and container permit. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Amiodarone Omega in vials is a clear, pale yellow, sterile aqueous solution. Each mL contains: amiodarone hydrochloride 50 mg, benzyl alcohol 20.2 mg, polysorbate-80 (100 mg), sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.

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Preparation of IV Solution

Amiodarone Omega must be diluted prior to use and are for intravenous infusion only.

Amiodarone Omega should be diluted in Dextrose 5% Injection (in PVC bags, glass or polyolefin bottles), at a concentration ranging from 1 mg/mL to 6 mg/mL. Amiodarone losses of approximately 10-12% were observed after 2 hours when Amiodarone Hydrochloride for Injection was diluted in Dextrose 5% Injection in PVC bags. These losses may be attributed to adsorption of amiodarone to the PVC. However, when diluted in polyolefin or glass container, no apparent losses were observed within 24 hours.

Infusions of Amiodarone Hydrochloride for Injection exceeding 2 hours must be administered in glass or polyolefin bottles containing Dextrose Injection.

Amiodarone Omega, 50 mg/mL, is a clear, pale yellow, sterile aqueous solution available in amber glass vials as follows: 3 mL fill in 5 mL vials, boxes of 10;

PART II: SCIENTIFIC INFORMATION

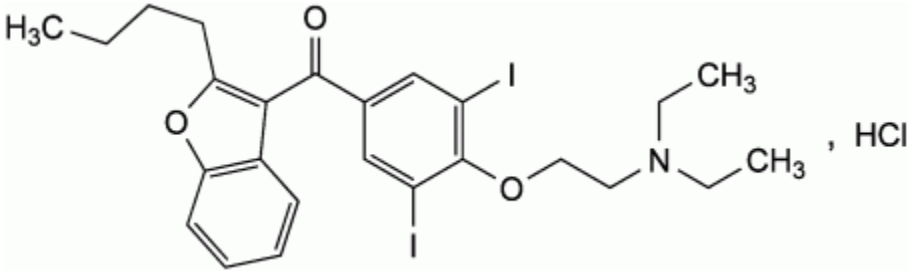
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Amiodarone Hydrochloride

Chemical Name: (2-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxy]-3, 5-diiodophenyl] ketone hydrochloride.

Structural Formula:



Molecular Formula: $C_{25}H_{29}I_2NO_3HCl$

Molecular Mass: 681.8 g/mol

Physical Form: White or almost white, fine crystalline powder.

Solubility: Very slightly soluble in water; freely soluble in dichloromethane; soluble in methanol; sparingly soluble in ethanol (96%); very slightly soluble in hexane.

pH: Between 3.2 and 3.8 (5% Solution in water).

pKa Value: 6.64

Melting Point: 159-163°C

CLINICAL TRIALS

Intravenous Amiodarone

TABLE 10 : CLINICAL TRIALS SUMMARY

Study Drug/ Route of Administration	Study Type	Dose	Patients/ Indication	Results
IV amiodarone	Placebo-controlled	Approximately 1500 mg/day IV amiodarone administered using 2- and 3-stage infusion regimens	Patients with supraventricular arrhythmias and 2- to 3-consecuive-beat ventricular arrhythmias	Rapid onset of antiarrhythmic activity. In patients with complex ventricular arrhythmias, amiodarone therapy reduced episodes of VT by 85%.
IV amiodarone	Pharmacokinetic/ pharmacodynamic study evaluating rapid IV loading	Approximately 1500 mg/day IV amiodarone administered using 2- and 3-stage infusion regimens	Patients with recurrent, refractory VT/VF	Rapid onset of antiarrhythmic activity. In patients with complex ventricular arrhythmias, amiodarone therapy reduced episodes of VT by 85%.
IV amiodarone	Two randomized, parallel, dose-response trials	Approximately 125, 500 (one trial only) or 1000 mg over the first 24 hours; The dose regimen consisted of an initial rapid loading infusion, followed by a slower 6-hour loading infusion, and then an 18-hour maintenance infusion; the maintenance infusion was continued up to hour 48.	Acute effective-ness in suppressing recurrent VF or hemodynamically unstable VT in patients with at least two episodes of VF or hemodynamically unstable VT in the preceding 24 hours	Prospectively defined primary efficacy end point: rate of VT/VF episodes per hour. Median rate was 0.02 episodes per hour in patients receiving the high dose and 0.07 episodes per hour in patients receiving the low dose, or approximately 0.5 versus 1.7 episodes per day (p = 0.07, 2-sided). Significantly fewer supplemental infusions were given to patients in the high-dose group. In one study, the time to first episode of VT/VF was significantly prolonged. Mortality was not affected.

A placebo-controlled study of IV amiodarone in patients with supraventricular arrhythmias and 2- to 3-consecutive-beat ventricular arrhythmias, and a pharmacokinetic/ pharmacodynamic study evaluating rapid IV loading in patients with recurrent, refractory VT/VF have shown rapid onset of antiarrhythmic activity well before significant blood levels of desethylamiodarone (DEA) were present; approximately 1500 mg/day of IV amiodarone were administered using 2- and 3-stage infusion regimens. In the patients with complex ventricular arrhythmias, including sustained and nonsustained VT, amiodarone therapy reduced episodes of VT by 85%.

The acute effectiveness of IV amiodarone in suppressing recurrent VF or hemodynamically unstable VT is supported by two randomized, parallel, dose-response studies of approximately 300 patients each. In these studies, patients with at least two episodes of VF or hemodynamically

unstable VT in the preceding 24 hours were randomly assigned to receive doses of approximately 125 or 1000 mg over the first 24 hours, an 8-fold difference. In one study, a middle dose of approximately 500 mg was evaluated. The dose regimen consisted of an initial rapid loading infusion, followed by a slower 6-hour loading infusion, and then an 18-hour maintenance infusion. The maintenance infusion was continued up to hour 48. Additional supplemental infusions of 150 mg were given for "breakthrough" VT/VF more frequently to the 125-mg dose group, thereby considerably reducing the planned 8-fold differences in total dose to 1.8- and 2.6-fold, respectively, in the two studies.

The prospectively defined primary efficacy end point was the rate of VT/VF episodes per hour. For both studies, the median rate was 0.02 episodes per hour in patients receiving the high dose and 0.07 episodes per hour in patients receiving the low dose, or approximately 0.5 versus 1.7 episodes per day ($p = 0.07$, 2-sided, in both studies). In one study, the time to first episode of VT/VF was significantly prolonged (approximately 10 hours in patients receiving the low dose and 14 hours in patients receiving the high dose). In both studies, significantly fewer supplemental infusions were given to patients in the high-dose group. Mortality was not affected in these studies; at the end of double-blind therapy or after 48 hours, all patients were given open access to whatever treatment (including IV amiodarone) was deemed necessary.

DETAILED PHARMACOLOGY

In anaesthetized dogs, amiodarone, in two separate single-dose studies of 2.5, 5, and 10 (n=7/dose), and 10 (n=10) and 20 (n=5) mg/kg IV, caused a decrease in cardiac contractility (maximal at 10 mg/kg), systemic pressure and heart rate, and an increase in left ventricular end-diastolic pressure.

Direct injection of amiodarone (10 to 1000 mcg) into the anterior descending branch of the left coronary artery of isolated, blood-perfused, dog ventricular muscle (n=8) electrically-paced at 1.5 to 2.0 Hz, produced dose-dependent decreases of left ventricular dp/dt and developed tension to a maximum decrease of 50%.

In anaesthetized dogs, single intravenous doses of 3, 5, or 10 mg/kg increased coronary blood flow and decreased coronary artery resistance, left ventricular work, heart rate, total peripheral vascular resistance, and myocardial oxygen consumption in a dose-dependent manner.

In anaesthetized dogs, single intravenous doses of amiodarone, 10 mg/kg, reduced heart rate an additional 23% after it had been maximally reduced by intravenous propranolol and atropine. Under similar conditions, amiodarone reduced an isoprenaline-mediated increase in heart rate. Further combinations of single doses of intravenous amiodarone with intravenous propranolol, with intravenous glucagon and with intraperitoneal reserpine led the investigators to conclude that the observed antiadrenergic actions of amiodarone were not mediated by competitive blockade of beta-adrenoceptors.

In 19 anaesthetized dogs administered single, rapid, intravenous doses of amiodarone, percutaneously-introduced intracardiac probes measured the monophasic action potentials

(MAP) of right atria and ventricles, bundle of His potentials, and atrial and ventricular stimulation. Under the conditions of the experiment, the peak activity of amiodarone was found between the fifth and the tenth minutes. The rate of discharge of the sinus node was lowered by 36%. At the atrial level, the duration of the MAP was increased by 9% and its dv/dt was lowered slightly, the total refractory period was increased by 22%, the effective refractory period was increased by 27%, the functional refractory period was increased by 19%, the ratio of the length of the effective period/duration of the MAP became slightly greater than unity, conduction facilitation disappeared, and the period of slow conduction increased. In the AV node, the AH interval increased by 44% under normal rhythm, while atrial stimulation at 200/ms resulted in conversion to total AV block in more than half of the cases. The potential of the bundle of His and the HV interval were not altered. At the ventricular level, the duration of the monophasic action potential increased by 25%, its dv/dt decreased slightly, the total refractory period increased by 8%, and the effective refractory period increased by 14%.

Amiodarone, 20 mg/kg, given daily for 6 weeks intraperitoneally to rabbits, had no effect on the resting potential or action potential height and only a small effect on the maximum rate of depolarization of isolated rabbit atrial or ventricular muscle fibres as shown by intracellular recording. It caused a considerable prolongation of the action potential in both tissues.

Using a microelectrode technique, the action of amiodarone (1.5×10^{-5} M) on the sinus node activity of spontaneously-beating, isolated right atria of rabbits was discovered to consist of a significant increase of the action potential duration and a decrease of the slope of diastolic depolarization, both effects leading to a reduction in the sinus rate.

In *in vitro* experiments using voltage clamp conditions by means of the double sucrose gap technique in both frog atrial and ferret ventricular fibres, an aqueous solution of amiodarone (2.10^{-4} to 2.10^{-5} M) decreased outward K+-mediated currents and decreased reactivation of inward currents.

In an experiment involving the simultaneous daily administration by intraperitoneal injection to live rabbits (n=5) for a period of 3 weeks (beginning at week 4) of 5 mcg of thyroxine (assumed normal daily thyroxine requirement for these rabbits: approximately 7 mcg/day) and 20 mg/kg of amiodarone (for a period of 6 weeks), the prolongation by amiodarone of the action potential of isolated rabbit atria and ventricular strips was prevented. Treatment of similar rabbits (n=5) with 10 mg/kg of potassium iodine (equivalent to the iodine content of 20 mg/kg of amiodarone) given daily, intraperitoneally, for 6 weeks had no effect upon cardiac action potential duration. It was concluded by the investigators conducting the rabbit tissue experiments that amiodarone had effects on cardiac action potentials similar to those which occur after thyroidectomy.

Amiodarone has been shown to exhibit antiarrhythmic activity in several experimental animal models. At a single intravenous dose of 5 mg/kg, amiodarone suppressed multifocal ventricular ectopic beats induced by the intravenous injection of epinephrine in an anaesthetized dog: at 10 to 15 mg/kg, intravenous amiodarone suppressed polymorphic ventricular systoles provoked by the intravenous injection of barium chloride in anaesthetized rabbits (n=2) and dogs (n=2). At 10 mg/kg, intravenous amiodarone suppressed ventricular extrasystoles induced by ligature of the anterior descending coronary artery in an anaesthetized dog. At 10 to 20 mg/kg, intravenous

amiodarone suppressed atrial fibrillation induced by acetylcholine in anaesthetized dogs (n=2). At 10 mg/kg, intravenous amiodarone suppressed the ventricular tachycardia induced by aconitine in an anaesthetized dog and the ventricular tachycardia induced by strophanthine in morphinized dogs (n=16).

In the isolated hearts of rats pretreated intravenously with single doses (21 to 42 mcmol/kg: 3.5 to 7.5 mg), amiodarone prevented (in a dose-related fashion) both ventricular tachycardia and ventricular fibrillation during regional myocardial ischemia and during reperfusion of ischemic muscle.

In anaesthetized guinea pigs (n=10/group) amiodarone administered intravenously at single doses of 25 and 50 mg/kg statistically significantly protected against ouabain-induced ventricular flutter-fibrillation although it did not provide significant protection against cardiac arrest.

MICROBIOLOGY

Amiodarone Omega is a sterile solution of amiodarone for intravenous administration.

The products are sterilized by aseptic filtration and are tested for sterility and bacterial endotoxins.

TOXICOLOGY

Acute Toxicity

Amiodarone hydrochloride was evaluated in acute oral studies in mice, rats, and dogs, and in acute intravenous studies in rats and dogs. Multiple-dose toxicity studies were performed by oral administration to mice (20 months), rats (3 to 104 weeks), dogs (4 weeks to 9 months), and pigs (3 or 10 months). Amiodarone was administered intravenously in multiple-dose toxicity studies to rabbits (6 weeks), dogs (4 weeks), and baboons (4 weeks).

TABLE 11: ORAL AMIODARONE: ACUTE TOXICITY STUDIES

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Mouse/NMRI	Oral (gavage)	500 to 3000/Single dose	The oral LD_{50} was greater than 3000 mg/kg. For technical reasons (high viscosity of the solutions at concentrations greater than 10%), the highest dose that could be administered was 3000 mg/kg.
Rat/Wistar	Oral (gavage)	500, 750, 1000, 2000, 3000/Single dose	The oral LD_{50} was greater than 3000 mg/kg. No deaths occurred at the highest dosage.
Dog*	Oral (diet)	0, 1000, 3000, or 5000 in feed	The oral LD_{50} was greater than 5000 mg/kg. No deaths occurred. All dogs vomited within 6 hours of ingestion. One dog given 5000 mg/kg demonstrated tremors 24 hours after ingesting the drug. This lasted for more than 96 hours and was accompanied by hindquarter paralysis.
* Report does not identify strain.			

TABLE 12: INTRAVENOUS AMIODARONE: ACUTE TOXICITY STUDIES

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Rat/Wistar	IV	100, 150, 200/Single dose	The IV LD_{50} was 135 mg/kg. Dyspnea, resulting in cyanosis, was observed premortem.
Rat/Wistar	IV	100, 120, 140, 160, 180, 200/Single dose	The IV LD_{50} was 150 mg/kg.
Rat/SD(BR)	IV	Males 0, 100, 120, 150, 160, 180 Females 0, 160, 170, 180, 220/Single dose	The IV LD_{50} for males and females was 170 and 175 mg/kg, respectively. Clonic convulsions were observed at dosages of 120 mg/kg and above.
Dog/Beagle	IV	5 minute injections of 25-150 5 minute injections of 75-100 20 minute injections of 100-150/Single dose	The IV LD_{50} for a 5-minute infusion was 75 to 100 mg/kg. The LD_{50} for a 20 minute infusion was 150 mg/kg. Injections were followed by excitation with redness of the skin and mucous membranes, sedation, dyspnea, convulsions and electrocardiographic alterations.
Dog*	IV	0.75 mg/kg/min to 110 or 95 mg/kg 0.62 mg/kg/min to 124 mg/kg 0.45 mg/kg/min to 190 mg/kg/Single dose	The IV LD_{50} was 110 to 125 mg/kg for an infusion rate of 0.6 to 0.75 mg/kg/min and was >90 mg/kg for an infusion rate of 0.45 mg/kg/min.
* Report does not identify sex or strain of dogs.			

Long term Toxicity/Carcinogenicity

TABLE 13: INTRAVENOUS AMIODARONE: SUBCHRONIC TOXICITY STUDIES

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Rabbit/Dutch	IV	0, 5, 10, and 25/6 weeks	No drug-related mortality occurred. There was a statistically significant decrease in red blood cell count and hemoglobin values for both males and females at all dose levels. Significant increases in total cholesterol (143% to 200%) were observed at all dose levels. Total lipids were also significantly increased (168%) in males at 25 mg/kg. For females, total lipids were significantly increased at 5 (127%) and 10 (147%) mg/kg, but not at 25 mg/kg. All other blood chemistry parameters showed no difference between treated and control animals. At necropsy, several treated animals exhibited white patches and/or signs of cirrhosis in the liver. Microscopic evaluation revealed hepatocytes and Kupffer cells containing numerous pigments (probably hemosiderines) in several control and treated rabbits. In several treated animals (2, 2 and 1 rabbits at 5, 10 and 25 mg/kg, respectively), part of the hepatic parenchyma degenerated and was replaced by necrotic tissue surrounded by fibrous tissue, giving a cirrhotic appearance. However, these histologic changes were not considered related to drug administration. As a result of the hemotological and biochemical changes, a no toxicologic effect level (NTEL) could not be determined.

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Dog/Beagle	IV	0, 7.5, 15, 30 and 60/4 weeks	Mortality was observed at 60 mg/kg. Adverse physical examination findings were observed in all groups; however, only sedation occurred solely in drug-treated groups at dosages of 30 mg/kg and above. Body weight and food consumption were decreased at 30 and 60 mg/kg. Hematologic (increased fibrinogen and monocyte levels; decreased red blood cell count, hematocrit, and hemoglobin levels), biochemical (increased cholesterol [122% to 216%], triglycerides, alanine aminotransferase, alkaline phosphatase, potassium, and T_4; and decreased protein and T_3/T_4 ratio) changes occurred at all dosage levels, although most frequently at dosages of 30 mg/kg and above. Alterations in cardiac parameters (decreased heart rate, lengthened PR and ST segments, increased T wave amplitude) occurred at 60 mg/kg. Liver weights were increased in all drug-treated groups while adrenal and prostate weights were decreased at 60 mg/kg. Macroscopic changes to the liver, bile, colonic mucosa, and renal cortex occurred in all drug-treated groups. Many of the drug-treated dogs exhibited clots and outgrowths of the valvula tricuspidalis and pulmonary lesions (congestion, crepitation, foamy discharge at sectioning) were observed in the 3 animals that died during the study. Injection site lesions were observed in all groups, including controls. However, the severity in the drug-treated groups followed a dose-response pattern. Microscopic examination revealed foamy macrophages in the lymph nodes, spleen and Peyer's patches at 60 mg/kg and in 1 dog that received 30 mg/kg. Dogs at all dose levels showed islets of clear cells in the adrenal cortex. Marked cholestasis and thymic regression were observed at 60 mg/kg; evidence of increased thyroid activity was observed in all treated animals. As a result of the observed effects, a NTEL could not be determined.

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Baboon/ *Papio papio*	IV	0, 12.5, 25 and 50/4 weeks	One 12.5 mg/kg female and all four 50 mg/kg animals died or were killed *in extremis*. A dosage of 50 mg/kg produced gradual changes in the general condition of the animals (prostration, piloerection) from week 2 onward. Decreased food consumption in all drug-treated groups were associated with body weight loss in the 25 and 50 mg/kg groups. Decreased heart rates (lengthening of the ST segment) were noted in the 25 and 50 mg/kg dosage groups. Changes in hematologic (decreased red blood cell count, hemoglobin, hematocrit, mean cell hemoglobin, and mean cell hemoglobin concentrations; increased reticulocytes, neutrophils and monocytes) and biochemical (increased bilirubin, triglycerides, BUN, creatinine, and T_4 levels) parameters were observed in all drug-treated groups; the majority of effects were observed at 25 and 50 mg/kg. Organ weight changes included a thyroid weight increase at all dose levels. Increased liver and kidney weights occurred at the higher dosage levels and a dose-related thymus weight decrease occurred. Discoloured livers and a cirrhotic appearance was observed in all 4 baboons at 50 mg/kg. All 3 of the animals that died during the study exhibited cardiac lesions, 2 of which had a clot adherent to the endocardium and valvulae in the right side of the heart, while the third showed discolouration of the myocardium and necrotic magma in the muscle. These changes were probably attributable to the irritative properties of amiodarone hydrochloride when the compound is repeatedly administered into the cephalic or saphenous veins. Intravenous treatment with amiodarone hydrochloride caused indurations, edema, abscesses and local necrosis with eschars at the injection sites; the degree of these lesions was dose related. The vehicle alone induced only local indurations that partially regressed when the injection site was changed. Microscopic examination revealed a dose-related increase in incidence and degree of thymic regression at all dose levels, changes in the gall bladder at the higher doses, and colloid retention in the thyroids in all treated groups. As a result of the observed mortality, effects on the thyroid, and injection site lesions, a NTEL could not be determined.

IV=Intravenous administration.

TABLE 14: ORAL AMIODARONE: CHRONIC TOXICITY STUDIES

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Rat/Wistar	Oral (gavage)	100, 200, 300, 450, or 600/3 weeks*	The LD_{50} was 420 mg/kg.
Rat/Wistar	Oral (gavage)	0, 100, 200, 300, 450 or 600/for 3 weeks*	The LD_{50} was greater than 600 mg/kg. A dose related decrease in mean body weights of both males and females occurred.
Rat/Crl BR	Oral (gavage)	10, 19, 37.5, 75, or 150/4 weeks	Drug treatment at 37.5 mg/kg or less did not produce any adverse reactions. At doses of 75 or 150 mg/kg, there was a deterioration in animals' health. Increased mortality occurred at 150 mg/kg. Postmortem examinations showed that those animals' that died on test were cachectic. Body weight gains were decreased in both sexes at 150 mg/kg and in females at 75 mg/kg; food intake was also reduced. Although there were no clinically significant changes in blood pressure among treated animals, heart rate changes did occur at dosages of 37.5 mg/kg and above. Significant increases in the number of neutrophils and a decrease in the number of lymphocytes were observed in the high-dose treatment group. Clinical chemistry values for blood urea nitrogen (BUN), alkaline phosphatase, and total and esterified cholesterol (dose-related in males) were elevated at 75 mg/kg and above. There was an increase in T_4 and a decrease in the T_3/T_4 ratio at 75 mg/kg and 150 mg/kg. At 75 and 150 mg/kg, there was an increase in lung and adrenal weights, and a decrease in thymus, prostate, seminal vesicle, uterine and ovarian weights. At 37.5 mg/kg and higher, the relative weight of the liver in females appeared slightly increased. Macroscopically, the only observation associated with the drug was a yellow colouring of mesenteric lymph nodes in most animals treated at 75 and 150 mg/kg. Histologically, this proved to be a dose-dependent accumulation of foamy macrophages involving the mesenteric lymph nodes with spreading to the liver, spleen and lungs. The adrenal cortex contained lipid-like material. There was a moderate degree of thymic involution observed in high-dose animals and this was possibly associated with stress at this level. The thyroids of treated animals presented a histologic appearance of increased activity.
Rat/Fisher 344	Oral (gavage)	Vehicle-control, 160/7 days*	Treated animals showed signs of toxicity by the fourth day of dosing. This included weakness accompanied by piloerection, epistaxis and softening of the feces. Reversibility of these symptoms did not occur until 8 days after treatment had stopped and often persisted to the 20^{th} day. One death was recorded on day 7 of administration. Initially, body weight gains were depressed in all groups but returned to normal by the end of the treatment schedule.

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			Increases in the weights of the liver and adrenals were also observed, but these too returned to control values 1 to 2 weeks after dosing had stopped. A marked decrease in thymus weight was partially reversible after 2 weeks and completely reversible by 8 weeks. Macroscopic examination revealed a white colouration of the mesenteric lymph nodes in animals sacrificed on days 7 and 14. Histologically, foam cells were present in the mesenteric lymph nodes and lungs. These changes disappeared after a recovery period of about 2 weeks.
Rat/Wistar	Oral (gavage)	Vehicle control, 100, 200, or 300/3 months*	Dose-related increases in mortality were observed (0 at 100 mg/kg, 15% at 200 mg/kg and 25% at 300 mg/kg). Body weights of male rats receiving 200 or 300 mg/kg were depressed 19% and 30%, respectively. Female body weights at 300 mg/kg were depressed by 14% relative to controls. Hemoglobin values slightly depressed at 200 mg/kg and markedly decreased at 300 mg/kg. At 300 mg/kg, the ratio of circulating lymphocytes to polymorphonuclear leukocytes increased during the study; this was more marked in females. Blood urea nitrogen (BUN) was significantly increased in both the 200 and 300 mg/kg groups. Blood glucose levels were not affected by the administration of the drug. At 100 mg/kg, no microscopic lesions were noted except for some hypertrophy of the thyroid gland. With both the 200 and 300 mg/kg, there was centrilobular congestion in the liver, which was more marked at the high dose level. In 2 of 14 rats given 300 mg/kg, lesions of the myocardium were present.
Dog/Beagle	Oral (capsule)	Vehicle control, 100, 200, or 300/3 months*	A 38% decrease in mean body weight was observed in treated animals and this was associated with decreased food intake. One treated animal was moribund sacrificed due to its cachectic state. Autopsy revealed an abnormal increase in bile contained in the gall bladder and intestine. There were no other deaths during the study. Clinically significant increases in SGPT (129%), SGOT (300%), and LDH (363%) were noted in treated animals. All other parameters were similar between dosed and control groups. Increases in the absolute and relative weights of the adrenals and the liver plus the absence of a recognizable thymus were noted in the treated dogs. Macroscopic examinations revealed congestion of the digestive mucosa (primarily in the small intestine), and the presence of an abnormal amount of bile in the gall bladder and/or the intestine in

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			the treated animals. Microscopic examination showed the presence of foamy cells in the mesenteric lymph nodes, spleen and lymphoid tissue of the digestive tract. The foamy cells were characterized by an abundance of polymorphic cytoplasmic inclusions of probable dyslipidic origin. Electron microscopy revealed the dyslipidosis to be widespread although minimal in any one tissue.
Dog/Beagle	Oral (diet at 0 and 30 mg/kg, capsule at 150 mg/kg)	Dietary control, 30 or 150/3 months*	There were no deaths. At 150 mg/kg, gastrointestinal intolerance (vomiting, diarrhea and anorexia) was observed for the first 1½ months and intermittently thereafter. Excessive salivation was noted throughout. Concurrent with the epigastric distress, dogs receiving 150 mg/kg showed a 20% loss in weight during the first 40 days of dosing. Thereafter weight gains were normal. Apart from minor changes in several hematology values, parameters were similar between control and treated groups. A dose-related increase in leukocyte counts was noted at all 3 sampling intervals and decreases on neutrophils during the last month in the high-dose group. Clinical chemistry values were also similar between control and treated animals. SGPT levels rose in animals receiving 150 mg/kg/day during the first month of testing but were normal thereafter. Alkaline phosphatase levels in the high-dose group rose during the study but remained within the normal range for this species. The results of the postmortem macroscopic examination were unremarkable. One dog in the high-dose group exhibited hypertrophy of the thyroid but histopathology was unremarkable. No generalized histopathologic abnormalities were found which were related to drug administration. All findings were slight and occurred either in or were isolated instances or were present in both treated and control animals and could not be attributed to the drug.
Dog†	Oral (diet)	Dietary control, 30 or 60/9 months	One control animal died during the first month of the study and was replaced. There were no abnormal clinical observations or evidence of gastric intolerance in animals receiving amiodarone. Body weights and food intake were unaffected. The only significant laboratory abnormality was a dose-dependent hypercholesteremia. Macroscopic and histological examinations revealed only incidental lesions probably secondary to intercurrent diseases. Organ weights were not markedly different between treated and control animals.

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Pig*	Oral (diet)	Dietary control, 10, 20, 50, or 150/3 months	At 150 mg/kg, clinical signs of toxicity included ataxia, hypotonia and no weight gain; appetite was not affected. At 1½ months, 2 high-dose animals died during blood collecting. An autopsy revealed only gastritis and gastric ulceration. At 2½ months, the remaining 2 high-dose pigs were sacrificed *in extremis*. Autopsy findings were unremarkable. No other mortalities were recorded. Animals in the other treated groups showed no signs of toxicity and weight gains paralleled those of the controls. High-dose animals did not undergo blood tests due to the deaths of 2 animals at the first blood sampling and due to the poor health of the remaining 2 animals. In all other animals, results were within normal limits. Both the treated and control values for a number of the clinical tests were similar between groups. Apart from the gastritis and ulcers noted in animals given 150 mg/kg, no other macroscopic lesions were attributed to drug intake. One control animal also displayed gastritis. Histologically, doses of 10, 20, or 50 mg/kg produced no toxic effects on any organs examined. At the 150 mg/kg dose, there were liver lesions and endocrine (pituitary, thyroid, adrenal) dysfunction in pigs treated for 2½ months. In the liver, this was characterized by a disorganization of the hepatic parenchyma, focal necrosis, sclerosed Kiernan's spaces, and brown pigmented macrophages in the interstitial spaces. In the endocrine system, the adrenal cortex showed clusters of lymphomonocytes and hemorrhagic foci principally in the zona fasciculate. In both the zona glomerulosa and zona fasciculata of the adrenal cortex, there was evidence of hyperfunction. In the thyroid, numerous follicle cells that were larger than normal with vacuolar cytoplasm were suggestive of increased activity. In the pituitary of 1 pig in the 150 mg/kg group, the basophilic cells were more numerous and larger than normal.
Pig*	Oral (diet)	Dietary control, 50/ 10 months	There were no deaths, abnormal behaviour, or clinical signs of toxicity. Increase in body weight was parallel for treated and control animals. No abnormalities were noted for hematology, clinical chemistry, ophthalmic, or macroscopic examinations.

* Animals were dosed 5 days/week.
** Treatment was followed by a sequential sacrifice of 7 animals on days 11, 18, 25, 39, 67 and 121 of study.
† Report does not identify strain.

TABLE 15: ORAL AMIODARONE: CHRONIC TOXICITY/CARCINOGENICITY STUDIES

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Mouse/ BGC3F1	Oral (gavage)	0, 5, 16, 50/20 months	No drug-related effects on mortality occurred. Adverse clinical observations mainly consisted of urogenital trauma, resulting from fighting between male cage mates, and palpable masses. The palpable masses were primarily related to the presence of neoplasms. Weight gain and food intake were slightly increased in treated males during the first months of the study only; the effect was not dose related. A dose-related increase in the thyroid weight in both sexes was observed. Macroscopically, thyroid hypertrophy was observed. Histopathologically, a dose-related increase in incidence and degree of hyperplasia was seen in the thyroids of animals from test groups. However, the only tumours of the thyroid were diagnosed as follicular adenomas. These occurred in 1 control animal and in 4 high-dose animals and were within the normal range for this species at this age. No other non-neoplastic or neoplastic change associated with treatment was observed. The remainder of tumours diagnosed were recognized as those that occur commonly in mice. There was no increase in incidence or change in biological type of these tumours in treated animals when compared to controls. In addition, examination of blood smears taken at autopsy showed no treatment-related effect.
Rat/Sprague-Dawley CD	Oral (gavage)	0, 5, 16, 50/104 weeks	No effect on mortality occurred. Drug treatment at 16 and 50 mg/kg/day to males and females induced minor effects including salivation immediately after dosing, staining of the fur/reduced grooming, paddling of the forefeet, reduced food consumption, reduced body weight gain, decreased erythroid values, and increased alkaline phosphatase activity and cholesterol levels. Liver weight was marginally increased in males treated at 50 mg/kg/day. At terminal examination, an increased incidence of pale foci in the lungs of all treated male groups and females given 16 or 50 mg/kg/day, an increased incidence of thyroid enlargement in all treated male groups, increased incidence of liver masses in males given 50 mg/kg/day, and a slightly higher incidence of pancreatic masses in treated male groups were observed. Liver weight was marginally higher in males given 50 mg/kg/day, and thyroid weight was markedly higher in males given 50 mg/kg/day. An increased incidence of neoplastic changes to the thyroid (follicular tumours) occurred in all treated groups. These changes were statistically significant overall for all male groups, but only at 16 mg/kg/day

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			and above in the females. Non-neoplastic findings included changes to the thyroid at all dosages, and lung lesions in all treated male groups and in females given 16 or 50 mg/kg/day. Lymph node changes occurred in males and females given 16 or 50 mg/kg/day, and systemic and thymic lesions occurred in males given 50 mg/kg/day.

TABLE 16: ORAL AMIODARONE: CHRONIC TOXICITY STUDIES

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Dog/Beagle	Oral (gavage)	0, 12.5, 25, 50, 100/12 months, plus a 3 month recovery period	Mortality and adverse clinical signs (equilibrium and locomotion disorders, vomiting, diarrhea, tremors) occurred at 25 mg/kg/day and above. Electrocardiograms were altered at 50 and 100 mg/kg/day. Dyslipidosis, characterized by the presence of foam cells was observed at 25 mg/kg/day and above in the lymph nodes and lungs. In the lung, these lesions appeared to be totally reversible after 3 months without treatment at 25 mg/kg/day. The dyslipidosis could be related to the increases in total and esterified cholesterol (without any modification of the ratio), together with a moderate but inconsistent increase in triglycerides and phospholipids. A malabsorption syndrome occurred in some animals treated at 100 mg/kg/day. This syndrome was characterized by diarrhea, vomiting, anorexia, weight loss, and partial or subtotal jejunal villi atrophy accompanied by the presence of foam cells observed histologically. Changes in thyroid function were characterized by an increase in T_4 at dose levels of 12.5 mg/kg/day and above, without any variation in T_3 levels or the thyroid weight. There were no pathological changes in this organ attributed to drug treatment. The increase in T_4 was reversible by the end of the recovery phase. Minor adverse effects such as cholestasis and nonspecific changes such as regression or disappearance of the thymus, amyotrophy, and altered spermatogenesis in males were also recorded at dosage levels of 50 and 100 mg/kg/day.

Reproductive Toxicity

Reproductive toxicology studies were performed by both oral and intravenous administration. Amiodarone was administered by oral gavage to mice, rats, and rabbits, and intravenously to rats (continuous infusion) and rabbits (bolus injection). In addition, the mutagenic potential was assessed in studies supporting the oral formulation.

TABLE 17: ORAL AMIODARONE: REPRODUCTIVE STUDIES

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Mouse/NMRI	Oral (gavage)	0 (water control), 5, 50 or 100/ Gestation days 1 to 15.	Drug treatment did not result in any fetal malformations in the mouse. However, there was a clear drug-related reduction in litter size due to an increase in the number of resorptions. It was concluded from this study that amiodarone was embryotoxic to mice. Since signs of maternal toxicity were not recorded in this study, no statement can be made about an association between maternal and fetal toxicity.
Mouse/Charles River	Oral (gavage)	0 (vehicle control), 5, 50, or 100/Gestation days 1 to 16; 50 mg/kg in an additional group/ Gestation days 6 to 16	Drug treatment (50 mg/kg) administered from days 6 to 16 gestation did not appear to be toxic to the fetus. In doses of 5, 50 and 100 mg/kg administered from days 1 to 16 gestation, the drug did not reduce the number of implantations or cause fetal malformations. The study demonstrated no teratogenicity in mice.
Rat/OFA/ Sprague-Dawley	Oral (gavage)	Vehicle control, 10, 30, 60, or 90/**Males** – 64 days prior to mating and throughout the mating period. **Females** - 64 days prior to mating, throughout the mating period, gestation, and until termination on day 21 postpartum.	There were no effects on F_0 survival, clinical observations, or postpartum observations. Body weight gain of females given 60 mg/kg was slightly decreased beginning at week 8, and that of females given 90 mg/kg was decreased throughout the mating and gestation periods. This depression may have resulted from the significantly reduced litter weights and sizes of these groups. Body weight gain of males was marginally reduced only at the highest dose. Food consumption was similar in all groups. There was no effect on estrus cyclicity and pre-coital interval. However, the fecundity index was significantly depressed in the 90 mg/kg group. Drug treatment had no adverse effect on parturition, although 1 female in the 60 mg/kg group died suddenly after delivering 9 live fetuses. During the lactation period, the mean body weight gain of the females was significantly depressed in the highest dose group for the first 10 days; other groups gained weight normally. There were no observed drug-related abnormalities among the offspring. Postnatal viability was reduced in the 90 mg/kg group. Growth and functional development of offspring were similar in all groups, except in the 90 mg/kg group where body weight gain of offspring was markedly depressed from day 1 to day 10 postpartum but not thereafter. Terminal necropsy of adults and of offspring which were not selected for continuation of the study did not reveal any treatment-related abnormalities.

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			The functional development of the special senses (hearing and vision) and reflexes of the offspring was comparable in all treated and control groups as was the body weight gain from 40 days postpartum onwards and of estrus cycles from day 80 to day 100 postpartum.
Rat/Wistar	Oral (gavage)	Water control and 200/ Gestation day 1 to 21	Drug-treated females demonstrated adverse physical examination findings (listless, shaggy and dull fur) and reduced weight gain. Conjunctivitis and a nasal suppuration mixed with blood were observed in several of the treated rats. Six (6) of the 30 treated rats died during the study. These animals were observed to have macerations of the abdominal viscera and severe enteritis. Excluding deaths, the percentage of successful matings was comparable in the treated and control groups. Drug treatment (200 mg/kg) was associated with embryotoxicity. The number of resorptions expressed as a percentage of pregnancies or as a percentage of implantations was significantly increased in the treated group as compared to controls. The percentage of females presenting fetuses with major deformities as well as the percentage of fetuses with major deformities was increased in the treated group. Given the limited number of viable litters from the treated rats, however, no conclusions regarding teratogenicity can be drawn. The mean weight of fetuses from the treated group was also slightly less than the control group.
Rat/Sprague-Dawley	Oral (gavage)	0 (water control), 10, 30, or 90/64 days pre-mating, during mating and from gestation day 1 to 19 (females only)	Prior to mating, treated animals showed no changes in behaviour, food consumption, or estrus cyclicity. Mean body weight gain was slightly depressed in females receiving 90 mg/kg. Although seven deaths occurred during the pre-mating period, none were considered related to amiodarone treatment. The mating period tended to be shorter in the treated groups than controls, though not significantly shorter. There was a significant increase in the number of barren matings in the 90 mg/kg group. The decrease in number of *corpora lutea* and implantation sites among dams of the highest dose treatment group may partially explain the reduced fertility rate. Because total litter loss due to resorption occurred in 1 or 2 of the dams from each treatment group and none occurred in the control group, the percentage of resorbed fetuses was higher in the treated groups than in the control

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			group. Discounting these total litter losses, no significant increase in fetal resorptions occurred in any of the treated groups. No teratogenicity was observed. The number of fetuses which presented minor abnormalities (most commonly incomplete skeletal ossification) was significantly greater in the treated groups compared to controls. However, these minor abnormalities resulted primarily from fetal growth retardation, which is a reversible phenomenon, and are not indicative of a true teratogenic event. Thus, it was concluded that amiodarone was without teratogenic potential in rats.
Rat/Sprague-Dawley	Oral (gavage)	0 (vehicle control), 10, 30, or 90/Gestation day 14 to Postpartum day 21	There were no clinical signs of toxicity and no rats died. A decrease in mean maternal weight gain was observed beginning on gestation day 16 in the 90 mg/kg treatment group. No differences in weight gain were seen during lactation. The duration of gestation was unchanged and parturition was unaffected by amiodarone treatment. The mean live litter size and sex ratio were comparable in treated and control groups. The mean fetal weights were significantly reduced (18% smaller than control) only at 90 mg/kg. This difference was increased on days 4 to 10 of neonatal life (-29% and -31%, respectively), but remained stable thereafter. Although the number of young born to treated females of this group was the same as in the control group, neonatal mortality was higher. Of those terminal offspring, one-third died between birth and day 4, and the remaining two-thirds died between day 5 and weaning. Necropsy revealed no abnormalities related to drug intake in any of the offspring sacrificed on day 21. One offspring from the 10 mg/kg group exhibited agenesis of the right hind limb and a short tail.
Rat/Sprague-Dawley	Oral (gavage)	0 (water control), 5, 50, or 100/Gestation days 1 to 15	Drug treatment did not have any toxic effect on fetuses of rats at administered doses up to 100 mg/kg. The ratio of the number of living fetuses counted at term to the number of implantation sites was not significantly different in treated and untreated groups. None of the fetuses examined showed any external malformations, microscopic or skeletal abnormalities.
Rabbit/Belgian Hare	Oral (gavage)	0 (water control), 5, 50 or 100/Gestation days 1 to 18	Neither the number of implantations or live fetuses observed at sacrifice appeared to vary among treated and control groups. The number of resorptions was higher than control in the low and mid-dose treatment groups, but was lower in the high-dose group. Drug treatment did not affect the

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			fecundity of the animals. Examination of the fetuses revealed no malformations.

TABLE 18: MUTAGENICITY STUDIES

Study	Test System	Concentrations	Conclusions
Ames Test	*S. typhimurium* Tester Strains TA98 TA100 TA1535 TA1537 TA1538	Not identified	No evidence of mutagenicity occurred in the presence or absence of S-9.
Lysogenic Induction Test	Bacterial Strains GY5027 GY4015	Not identified	At concentrations that approached toxic levels (≈100 mcg/dish), no increase in spontaneous lysis occurred.
Micronucleus Test	Mouse/Charles River	50, 100, 225 mg/kg (each animal received 2 intraperitoneal injections administered over a 24 hour period).	No increase in the number of micronuclei per 200 polychromatic erythrocytes was induced by drug treatment.

TABLE 19: INTRAVENOUS AMIODARONE: REPRODUCTIVE STUDIES

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
Rat/CD® BR	IV (infusion)	0 (saline), 0 (stock), 25, 50, 100/Gestation days 8-16	An increased incidence of minor adverse physical examination findings related to the injection procedures and necropsy observations correlated with increased dosage and treatment duration. Body weight gains were decreased in the control-stock group; a dose-related reduction in body weight gains occurred in animals in the 50 and 100 mg/kg dosage group compared to the saline and/or control-stock group. Food consumption was decreased for animals in the 100 mg/kg dosage group compared to either control group. Resorptions were increased, and live litter size and fetal body weights were decreased at a dosage of 100 mg/kg. Delayed ossification of the sternum and metacarpals occurred at the dosage of 100 mg/kg; this delay was reversible and was related to the reduced fetal body weights at this dosage level. Fetal thyroid tissues appeared normal in all groups.

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			Based on reduced body weight gains and food consumption at a dosage of 100 mg/kg, the maternal NTEL was 50 mg/kg. The developmental NTEL was 50 mg/kg, based on resorptions, reductions in live litter size and fetal body weights, and delayed ossification of the sternum and metacarpals.
Rabbit/Dutch	IV	0, 5, 10, and 25/Gestation days 8-16	No drug-related changes in behaviour or maternal body weight were observed during the study. The only evidence of maternal toxicity observed was an increase in mortality that was statistically significant at the high dose. The incidence of deaths was 1, 3, 5, and 8 in the control, low-, middle-, and high-dose groups, respectively. Necropsies revealed degeneration of the liver in the control, bronchopneumonia in the low-dose group, and bronchopneumonia with peritonitis and enteritis in the middle- and high-dose rabbits. Mean fetal weights were significantly decreased at the low- and middle-dose levels. Evidence of embryotoxicity was significant at 10 and 25 mg/kg. However, there was no significant difference in the number of minor abnormalities, and no major abnormalities were observed.

IV=intravenous administration

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PART III: CONSUMER INFORMATION

[Pr]AMIODARONE OMEGA
Amiodarone hydrochloride for injection
House Standard
Vials: 50 mg/mL

This leaflet is part III of a three-part "Product Monograph" published when Amiodarone Omega was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Amiodarone Hydrochloride for. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Treatment of certain abnormal heart rhythms (arrhythmias).

What it does:
Amiodarone Omega has been prescribed to you by your doctor to restore or maintain a normal heart rhythm.

When it should not be used:
- Do not use Amiodarone Omega if you are allergic to it or to any of the components of its formulation (see full list of components below). Contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.
- Do not use Amiodarone Omega if you have hepatitis, thyroid problems, or pulmonary disease (certain lung problems).

What the medicinal ingredient is:
Amiodarone hydrochloride

What the nonmedicinal ingredients are:
Amiodarone Omega in vials: benzyl alcohol, polysorbate-80, sodium hydroxide and/or hydrochloric acid and water for injection.

What dosage forms it comes in:
Amiodarone Omega 50 mg/mL, is available in amber glass vials.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Amiodarone Omega is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.
- Pulmonary fibrosis (permanent scarring of the lungs) can occur and can be fatal.
- Like other antiarrhythmics, Amiodarone Omega can worsen or start an irregular heartbeat (arrhythmias).
- Liver injury is common with Amiodarone Omega, but is usually mild, however it can be serious and even fatal in some cases.

BEFORE you use Amiodarone Omega talk to your doctor or pharmacist if:
- you have hepatitis, thyroid problems or lung abnormalities,
- you are breast feeding, pregnant or planning on becoming pregnant,
- you anticipate undergoing any surgery,
- you have any allergies to this drug or its ingredients or components of the container,
- you are taking any medications (see INTERACTIONS WITH THIS MEDICATION).

Precautions when taking Amiodarone Hydrochloride for Injection
Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted:
- Amiodarone Omega may cause a worsening of the existing arrhythmias or precipitate a new arrhythmia.
- Both hyper- and hypothyroidism (too much or too little thyroid hormone released into the blood by the thyroid gland) may occur during, or soon after treatment with Amiodarone Omega.
- One of the most serious complications is pulmonary (lung) toxicity, characterized by scarring or inflammation of the lungs. Clinical symptoms include

cough, progressive shortness of breath, accompanied by weight loss and weakness.
- Amiodarone Omega induces photosensitization in about 10% of patients. Sunscreen preparations or protective clothing may afford some protection to individual patients experiencing photosensitization. Blue-grey discoloration of exposed skin has been reported during long-term treatment. With discontinuation of therapy, the pigmentation fades slowly over a period of up to several years. 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.
- Loss of vision or other visual disturbances such as visual halos or blurred vision.
- Symptoms of nerve damage (peripheral neuropathy) such as pain, burning, or numbness.
- Progressive skin rash, often with blisters or lesions, which may lead to severe skin reactions that are sometimes fatal.

INTERACTIONS WITH THIS MEDICATION

You should ensure that your doctor and pharmacist know all the medicines you are taking, prescription, non-prescription or herbal.

Drugs that may interact with Amiodarone Omega include:
Azoles, Beta-blockers (e.g., propranolol), Calcium channel antagonists (e.g., verapamil), Cholesterol-lowering medications (e.g., simvastatin, atorvastatin), Cholestyramine, Cimetidine, Cyclosporine, Dabigatran, Digitalis, Digoxin, Disopyramide, Fentanyl, Flecainide, Fluoroquinolones, Lidocaine, Macrolide Antibiotics, Phenytoin, Procainamide, Protease inhibitors (e.g., indinavir), Quinidine, Sofosbuvir (alone or in combination with other antiviral drugs to treat Hepatitis C such as daclatasvir, simeprevir, ledipasvir), Warfarin.

Grapefruit Juice and the herbal preparation St. John's Wort may also interact with Amiodarone Omega.

PROPER USE OF THIS MEDICATION

Amiodarone Hydrochloride for Injection will be administered by a healthcare professional.

Usual dose:
The recommended starting dose of Amiodarone Hydrochloride for Injection is about 1000 mg over the first 24 hours of therapy. Your physician will begin the infusion with a high dose (15 mg/min), and will then reduce the dosage (1 mg/min) over the next 6 hours. After that, the dose will be further reduced (0.5 mg/min) and may be maintained, as needed, for no more than a few weeks (2 to 3 weeks). Your physician will monitor your condition and adjust your dosage as necessary. Once your heartbeat has returned to normal, your physician may switch you to an oral version of this drug.

Overdose:
What to do in case of overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience side effects with the use of Amiodarone Hydrochloride for Injection.

Your doctor should monitor your blood for liver function. The following symptoms may be signs of liver problems: prolonged nausea and vomiting, abdominal pain or discolouration of the skin.

Other symptoms causing discontinuations less often have included disturbances of vision, reactions of the skin to sunlight, blue skin discoloration, life-threatening or even fatal skin reactions, eczema, hyperthyroidism and hypothyroidism.

Should you experience any of these while taking Amiodarone Omega, consult your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist	Stop taking drug and call your doctor or pharmacist
	In all cases	
Tremor/abnormal involuntary movements, lack of coordination, abnormal gait, dizziness		✓
Blue skin discolouration		✓
Severe skin reactions (e.g. progressive skin rash with blisters) or allergic reaction (e.g. swelling of the lips, face, tongue and throat, trouble breathing)		✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist	Stop taking drug and call your doctor or
Low blood pressure (fainting episodes, severe dizziness		✓
Shortness of breath, chest pain, irregular heartbeat, racing heart	✓	
Bleeding abnormalities (excessive bruising, easy bleeding (e.g., when brushing teeth)	✓	
Visual disturbances (halos or blurred vision), visual impairment	✓	
Vomiting, abdominal pain, diarrhea	✓	
Solar dermatitis/ photosensitivity (skin becomes sensitive to light)	✓	
Paresthesias (sensation of tingling, burning, crawling of the skin)	✓	
Peripheral motor and sensory neuropathies (e.g., muscular weakness)	✓	
Cognitive disturbances (e.g., confusion, inability to concentrate)	✓	
Liver problems (e.g., yellowing skin or eyes, abdominal pain or vomiting)	✓	
Alopecia (loss of hair)	✓	

This is not a complete list of side effects. For any unexpected effects while taking Amiodarone Hydrochloride for Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Protect from light and excessive heat.
Use carton to protect contents from light until use.

Keep out of reach of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Omega Laboratories Limited, at:

1-800-363-0584

Or by written request at:
11 177 Hamon
Montreal, Quebec
Canada, H3M3E4

Or by visiting the manufacturer's website:
www.omegalaboratory.com

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