

## Amiodarone Hydrochloride for Injection Antiarrhythmic Agent

### Antiarrhythmic Agent

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Liquid 50 mg/mL	Benzyl Alcohol, NF Polysorbate 80, NF <i>For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

#### 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 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. Because of the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of the arrhythmia, initiation of therapy with amiodarone should be carried out in the hospital.

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

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

#### CONTRAINDICATIONS

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

For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

#### WARNINGS AND PRECAUTIONS

##### General

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

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

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

The difficulty of using amiodarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation 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.

Patients with life-threatening arrhythmias may experience serious adverse events during their treatment and therefore should be properly monitored. Amiodarone hydrochloride should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, who are thoroughly familiar with the risks and benefits of amiodarone 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 caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors in rats was greater than the incidence in controls even at the lowest dose level tested, i.e., 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose\*).

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

#### 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. Although QTc prolongation occurred frequently in patients receiving intravenous amiodarone, torsades de pointes or new-onset VF occurred infrequently (less than 2% of all patients treated with intravenous 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 are administered concurrently.

A careful assessment of the potential risks and benefits of administering intravenous amiodarone and oral amiodarone 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 intravenous 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; therefore, every effort should be made to utilize alternative agents first.

##### Bradycardia and AV Block

Bradycardia was reported as an adverse drug reaction in 4.9% of patients receiving intravenous amiodarone for life-threatening VT/VF in clinical trials. AV block was reported as an adverse drug reaction in 1.4% of patients receiving intravenous 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.

##### 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 have the condition corrected before instituting oral amiodarone 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 balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics. Use caution when administering amiodarone with drugs which may induce hypokalemia and/or hypomagnesemia.

## Hypotension

Hypotension is the most common adverse event seen with intravenous amiodarone therapy. It is uncommon (< 1%) during oral amiodarone therapy. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1,836 patients treated with intravenous 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 intravenous amiodarone therapy was reported in 3% of the 814 patients, with permanent discontinuation required in an additional 2% of the 814 patients. Hypotension should be treated initially by slowing the infusion. Additionally, standard therapy may be needed including vasopressor drugs, positive inotropic agents and volume expansion. **The initial rate of infusion should be monitored closely and should not exceed that recommended in the DOSAGE AND ADMINISTRATION section.**

In some cases, hypotension may be refractory resulting in fatal outcome.

## Hepatic/Biliary

### 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 or intravenous amiodarone 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 should be considered.

Asymptomatic elevations of liver enzymes (AST/SGOT and ALT/SGPT) are frequently associated with the use of oral amiodarone. The mechanism whereby this hepatic effect occurs has not been defined. Phospholipidosis and fibrosis of the liver resembling alcoholic hepatitis or cirrhosis, accompanied by only a mild elevation of hepatic enzymes, have been reported in association with the use of oral amiodarone. Rises in hepatic enzymes, especially when associated with clinical signs and symptoms of hepatitis or with asymptomatic hepatomegaly, may indicate a liver scan and, if needed, a liver biopsy with ultrastructural study. If serum enzyme levels increase significantly, or persist over time, consideration should be given to discontinuation or reducing the dose of amiodarone. Hepatic failure has been a rare cause of death in patients treated with oral amiodarone.

Approximately 54% of patients receiving intravenous 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.

Rare cases of fatal hepatocellular necrosis after treatment with intravenous amiodarone have been reported. Two patients, one 28 and the other 60 years of age, received an initial infusion of 1,500 mg over 5 hours, a rate much higher than recommended. Both patients developed hepatic and renal failure within 24 hours after the start of intravenous 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 because hypotension is related to the rate of infusion, **the initial rate of infusion should be monitored closely and should not exceed that recommended.**

## Respiratory

### Pulmonary Toxicity and Pneumonitis

One of the most serious complications resulting from oral amiodarone 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 of 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 therapy is initiated, a baseline chest x-ray and pulmonary function test, including diffusion capacity, should be performed. 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 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.

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

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

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

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

Only 1 of more than 1,000 patients treated with intravenous amiodarone in clinical studies developed pulmonary fibrosis. For that patient, the condition was diagnosed 3 months after treatment with intravenous amiodarone, during which time she had received oral amiodarone. Intravenous amiodarone therapy should be discontinued if a diagnosis of pulmonary fibrosis is made.

During clinical studies using intravenous 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, intravenous amiodarone played in causing or exacerbating the pulmonary disorder in those patients.

## Sexual Function/Reproduction

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

## 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, 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 i.v. infusion to rats at dosages of 25, 50, or 100 mg/kg per day (about 0.4, 0.7, and 1.4 times the MRHD when compared on a body surface area basis), maternal toxicity (as evidenced by reduced weight gain and food consumption) and embryotoxicity (as evidenced by increased resorptions, decreased live litter size, reduced body weights, and retarded sternum and metacarpal ossification) were observed in the 100 mg/kg group. Intravenous amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

In pregnant rats and rabbits, amiodarone HCl 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\*).

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

Amiodarone Hydrochloride for Injection contains 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.

Intravenous 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 - 14 mg/kg per day), a NOAEL was not identified for rats in the postnatal 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 twofold and sevenfold.

**Geriatrics:** Clinical studies of intravenous amiodarone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## ADVERSE REACTIONS

### Clinical Trial Adverse Drug Reactions

In a total of 1,836 patients in controlled and uncontrolled clinical trials, 14% of patients received intravenous 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 intravenous 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  $\geq 1\%$ ) adverse drug reactions during intravenous amiodarone therapy that were collected from controlled and open-label clinical trials involving 1,836 patients with hemodynamically unstable VT or VF.

Study Events	Controlled Trials (n = 814)	Open-label Trials (n = 1,022)	Total Incidence (n = 1,836)
<b>Any Adverse Reaction</b>	412 (50.6%)	384 (37.5%)	796 (43.3%)
<b>Body as a Whole</b>	54 (6.6%)	32 (3.1%)	86 (4.6%)
Fever	24 (2.9%)	13 (1.2%)	37 (2.0%)
<b>Cardiovascular System</b>	308 (37.8%)	264 (25.8%)	572 (31.1%)
Hypotension	165 (20.2%)	123 (12.0%)	288 (15.6%)
Bradycardia	49 (6.0%)	41 (4.0%)	90 (4.9%)
Heart Arrest	29 (3.5%)	26 (2.5%)	55 (2.9%)

(continued)

**Table 1 – Summary Tabulation of Adverse Drug Reactions in Patients Receiving Intravenous Amiodarone in Controlled and Open-label Studies ( $\geq 1\%$  Incidence) (continued)**

Study Events	Controlled Trials (n = 814)	Open-label Trials (n = 1,022)	Total Incidence (n = 1,836)
Congestive Heart Failure	18 (2.2%)	21 (2.0%)	39 (2.1%)
Atrial Fibrillation	15 (1.8%)	9 (< 1%)	24 (1.3%)
Nodal Arrhythmia	15 (1.8%)	15 (1.4%)	30 (1.6%)
QT Interval Prolonged	15 (1.8%)	4 (< 1%)	19 (1.0%)
Ventricular Tachycardia	15 (1.8%)	30 (2.9%)	45 (2.4%)
AV Block	14 (1.5%)	12 (1.2%)	26 (1.4%)
Shock	13 (1.5%)	12 (1.1%)	25 (1.3%)
Ventricular Fibrillation	12 (1.4%)	13 (1.2%)	25 (1.3%)
<b>Digestive System</b>	102 (12.5%)	97 (9.4%)	199 (10.8%)
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%)
Diarrhea	8 (< 1%)	12 (1.1%)	20 (1.0%)
<b>Hemic and Lymphatic Systems</b>	34 (4.1%)	34 (3.3%)	68 (3.7%)
Thrombocytopenia	14 (1.7%)	16 (1.5%)	30 (1.6%)
<b>Metabolic and Nutritional</b>	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%)
<b>Nervous System</b>	46 (5.6%)	38 (3.7%)	84 (4.5%)
<b>Respiratory System</b>	54 (6.6%)	61 (5.9%)	115 (6.2%)
Respiratory Disorder	11 (1.3%)	8 (< 1%)	19 (1.0%)
Lung Edema	6 (< 1%)	15 (1.4%)	21 (1.1%)
<b>Urogenital System</b>	27 (3.3%)	30 (2.9%)	57 (3.1%)
Kidney Function (Abnormal)	8 (< 1%)	16 (1.5%)	24 (1.3%)

### Postmarket Adverse Drug Reactions

In postmarketing surveillance, sinus arrest, pseudotumor cerebri, toxic epidermal necrolysis (sometimes fatal), exfoliative dermatitis, pancytopenia, neutropenia, erythema multiforme, angioedema, bronchospasm, anaphylactic shock, hypotension (sometimes fatal), and syndrome of inappropriate antidiuretic hormone secretion (SIADH) also have been reported with amiodarone therapy.

Also, in patients receiving recommended dosages (see **DOSAGE AND ADMINISTRATION**), there have been postmarketing reports of the following injection site reactions: erythema, edema, pigment changes, venous thrombosis, phlebitis, thrombophlebitis, necrosis, and skin sloughing.

## DRUG INTERACTIONS

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

### Drug-Drug Interactions

Concomitant Drugs	Interactions
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.
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 concentration of procainamide and n-acetyl procainamide (NAPA) 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 anesthesia. IV: Seizure associated with increased lidocaine concentrations was observed in one patient.

(continued)

Concomitant Drugs	Interactions
Phenytoin	Increases phenytoin serum concentration.
Disopyramide	Increases QT prolongation which could cause arrhythmia.
Fentanyl	May cause hypotension, bradycardia and 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 Antibiotics, Azoles	Are known to cause QTc prolongation, with or without torsades de pointes, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly.

Concomitant Drugs	Interactions
Cholestyramine	Increases enterohepatic recirculation of amiodarone and may reduce serum levels and $t_{1/2}$ .
Cimetidine	Increases serum amiodarone levels.
Phenytoin	Decreases serum amiodarone levels.

#### Volatile Anesthetic Agents

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

#### Beta Blockers

Amiodarone should be used with caution in patients receiving  $\beta$ -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 prothrombin times should be monitored closely.

#### Drugs Affecting Cardiac Conduction

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

#### 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 amiodarone treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. 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). This isozyme is present in both the liver and intestines (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Amiodarone is also known to be an inhibitor of CYP3A4. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4. 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 of amiodarone, potential for drug interactions exist not only with concomitant medication but also with drugs administered after discontinuation of amiodarone.

**HMG-CoA Reductase Inhibitor:** Since amiodarone is a substrate for CYP3A4, drugs/substances that inhibit CYP3A4 may decrease the metabolism and increase serum concentrations of amiodarone, with the potential for toxic effects. Reported examples of this interaction 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 concentrations during concomitant protease inhibitor therapy should be considered.

**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.

#### 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.

## DOSE AND ADMINISTRATION

**Because of the unique pharmacokinetic properties, difficult dosing schedule, and severity of side effects if patients are improperly monitored, amiodarone therapy should be initiated in hospital and continued in a monitored environment until adequate control of the arrhythmia has occurred. Patients treated with amiodarone should be under the supervision of a cardiologist or a physician with equivalent experience in cardiology who is experienced in the treatment of life-threatening arrhythmias, who is thoroughly familiar with the risk and benefit of amiodarone therapy, and who has access to laboratory facilities capable of adequately monitoring effectiveness and side effects of treatment. Dose administration must be individualized, particularly taking into account concomitant antiarrhythmic therapy.**

#### General Considerations

**Amiodarone Hydrochloride for Injection 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 Hydrochloride for Injection should, whenever possible, be administered through a central venous catheter dedicated to that purpose. An in-line filter should be used during administration.

Amiodarone hydrochloride concentrations greater than 3 mg/mL in D<sub>5</sub>W 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 hydrochloride concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

Amiodarone Hydrochloride for Injection infusions exceeding 2 hours must be administered in glass or polyolefin bottles containing D<sub>5</sub>W. Use of evacuated glass containers for admixing Amiodarone Hydrochloride for Injection 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 **DOSE AND ADMINISTRATION** reflect doses identified in these studies. It is important that the recommended infusion regimen be followed closely.

Intravenous 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 amiodarone at higher concentrations and lower flow rates than provided in **DOSE AND ADMINISTRATION** (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Amiodarone Hydrochloride for Injection does not need to be protected from light during administration.

Must be diluted prior to use.

#### Preparation of Infusion Solutions

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

Unused portions of the diluted solution should be discarded. As with all parenteral drug products, the drug product and intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

### Admixture Incompatibility

Amiodarone Hydrochloride for Injection in D<sub>5</sub>W is physically incompatible with the drugs shown below in Table 5.

Drugs	Vehicle	Amiodarone concentration (mg/mL)	Comments
Aminophylline	D <sub>5</sub> W	4	Precipitate
Cefamandole Nafate	D <sub>5</sub> W	4	Precipitate
Cefazolin Sodium	D <sub>5</sub> W	4	Precipitate
Mezlocillin Sodium	D <sub>5</sub> W	4	Precipitate
Heparin Sodium	D <sub>5</sub> W	---	Precipitate
Sodium Bicarbonate	D <sub>5</sub> W	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 1,000 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.

Loading infusions	<b>Rapid: 150 mg over 10 minutes (15 mg/min)</b> Add 3 mL of Amiodarone Hydrochloride for Injection (150 mg) to 100 mL D <sub>5</sub> W (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes.
	<b>Slow: 360 mg over 6 hours (1 mg/min)</b> Add 18 mL of Amiodarone Hydrochloride for Injection (900 mg) to 500 mL D <sub>5</sub> W (concentration = 1.8 mg/mL).
Maintenance infusion	<b>540 mg over 18 hours (0.5 mg/min)</b> Decrease the rate of the slow loading infusion to 0.5 mg/min.

After the first 24 hours, the maintenance infusion rate of 0.5 mg/min (720 mg/24 hours) should be continued utilizing a concentration of 1 to 6 mg/mL (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<sub>5</sub>W may be administered. Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2,100 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 intravenous amiodarone, a maintenance infusion of up to 0.5 mg/min can be cautiously continued for 2 to 3 weeks regardless of the patient's age, renal function, or left ventricular function. There has been limited experience in patients receiving intravenous amiodarone 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 hydrochloride. The optimal dose for changing from intravenous to oral administration of amiodarone will depend on the dose of Amiodarone Hydrochloride for Injection already administered as well as the bioavailability of oral amiodarone. When changing to oral amiodarone 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 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.

Duration of Amiodarone Hydrochloride for Injection Infusion <sup>a</sup>	Initial Daily Dose of Oral Amiodarone Hydrochloride
< 1 week	800 - 1600
1 - 3 weeks	600 - 800
> 3 weeks <sup>b</sup>	400

<sup>a</sup> Assuming a 720 mg/day infusion (0.5 mg/min)  
<sup>b</sup> Amiodarone Hydrochloride for Injection is not intended for maintenance treatment

### OVERDOSAGE

There have been cases, some fatal, of amiodarone overdose. Effects of an inadvertent overdose of intravenous 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 are dialyzable.

### ACTION AND CLINICAL PHARMACOLOGY

#### Mechanisms 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 antisymphathetic 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. The antisymphathetic action and block of calcium and potassium channels are responsible for the negative dromotropic effects on the sinus node, for the slowing of conduction and the prolongation of refractoriness in the atrioventricular (AV) node.

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

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

Formulation	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 intravenous amiodarone hydrochloride, 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. In clinical studies of patients with refractory ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT), drug-related hypotension occurred in 15.6% of 1,836 patients treated with intravenous amiodarone. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of intravenous amiodarone.

#### Pharmacokinetics

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 1,000 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).

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion. Desethylamiodarone (DEA) is the major active metabolite of amiodarone. 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 CYP3A4 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.

There is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA are 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 i.v. (5 mg/kg over 15 min) and oral (400 or 600 mg) studies of healthy subjects and in *in vitro* studies. Pharmacokinetics were similar in males and females.

Drugs	Clearance (mL/h/kg)	V <sub>c</sub> (L/kg)	V <sub>ss</sub> (L/kg)	t <sub>1/2</sub> (days)	Protein binding	F <sub>oral</sub> (%)
Amiodarone	90 - 158	0.2	40 - 84	20 - 47	> 0.96	33 - 35
Desethyl-amiodarone	197 - 290	na	68 - 168	≥ AMI t <sub>1/2</sub>	na	na

Notes: V<sub>c</sub> and V<sub>ss</sub> denote the central and steady-state volumes of distribution from i.v. studies; F<sub>oral</sub> is systemic availability of amiodarone. "na" denotes not available. AMI is Amiodarone. t<sub>1/2</sub> = terminal phase elimination half-life. Desethylamiodarone clearance and volume involve an unknown biotransformation factor.

During short-term intravenous use, age, sex, renal disease, and hepatic disease (cirrhosis) do not have clinically significant effects on the disposition of amiodarone and DEA. No dosage adjustment is necessary for patients in any of these populations. There is no well-established relationship between drug concentration and therapeutic response for 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.

#### Monitoring Effectiveness

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

1. If a patient with a history of cardiac arrest does not manifest a hemodynamically unstable arrhythmia during electrocardiographic monitoring prior to treatment, assessment of the effectiveness of amiodarone requires some provocative approach, either exercise or programmed electrical stimulation (PES).
2. Whether provocation is 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 (a fraction that has varied widely in various series from less than 10% to almost 40%, perhaps due to different stimulation criteria), the prognosis has been almost uniformly excellent, with very low recurrence (ventricular tachycardia or sudden death) rates. More controversial is the meaning of continued inducibility. There has been an impression that continued inducibility in amiodarone patients may not foretell a poor prognosis but, in fact, many observers have found greater recurrence rates in patients who remain inducible than in those who do not. A number of criteria have been proposed, however, for identifying patients who remain inducible but who seem likely nonetheless to do well on amiodarone. These criteria include increased difficulty of induction (more stimuli or more rapid stimuli), which has been reported to predict a lower rate of recurrence, and ability to tolerate the induced ventricular tachycardia without severe symptoms, a finding that has been reported to correlate with better survival but not with lower recurrence rates. While these criteria require confirmation and further study in general, easier inducibility or poorer tolerance of the induced arrhythmia should suggest consideration of a need to revise treatment.

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

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

It is difficult to describe the effectiveness rates of amiodarone, as these depend on the specific arrhythmia treated, the success criteria used, the underlying cardiac disease of the patient, the number of drugs tried before resorting to amiodarone, the duration of follow-up, the dose of amiodarone, the use of additional antiarrhythmic agents, and many other factors. As amiodarone has been studied principally in patients with refractory life-threatening ventricular arrhythmias, in whom drug therapy must be selected on the basis of response and cannot be assigned arbitrarily, randomized comparisons with other agents or placebo have not been possible. 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.

#### STORAGE AND STABILITY

Amiodarone Hydrochloride for Injection should be stored at controlled room temperature, between 15 and 25°C. Protect from light and excessive heat.

Use carton to protect contents from light until use.

The 3 mL and 9 mL fill sizes are multiple-dose vials. Discard unused portion 28 days after initial puncture.

As with all parenteral products, injections and intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion of intravenous admixtures.

#### DOSAGE FORMS, COMPOSITION AND PACKAGING

##### Composition

Each mL of Amiodarone Hydrochloride for Injection contains 50 mg Amiodarone HCl, 20.2 mg Benzyl Alcohol as preservative, 100 mg Polysorbate 80, and Water for Injection.

##### Availability of Dosage Forms

Amiodarone Hydrochloride for Injection is available as the following:

- C601603** A clear, pale yellow solution in a 5 mL, Type I amber glass vial with latex free stopper. Each multiple-dose vial contains 3 mL of 50 mg/mL amiodarone hydrochloride. Available in packages of 25 vials.
- C601609** A clear, pale yellow solution, in a 10 mL, Type I amber glass vial with latex free stopper. Each multiple-dose vial contains 9 mL of 50 mg/mL amiodarone hydrochloride. Available in packages of 10 vials.

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

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