

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use amiodarone safely and effectively. See full prescribing information for amiodarone injection.

AMIODARONE HCl Injection for Intravenous Use

Initial U.S. Approval: 1995

Amiodarone injection is an antiarrhythmic agent indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy (1).

INDICATIONS AND USAGE

DOSEAGE AND ADMINISTRATION

The recommended starting dose is about 100 mg over the first 24 hours of therapy, followed by the following infusion regimen (2):

- o 150 mg per 100 mL (in D₅W) infused over 10 minutes
- o Followed by 1 mg/min for 6 hours
- o Followed by 0.5 mg/min thereafter

In the event of breakthrough episodes of VF or hemodynamically unstable VT (2):

- o Repeat the initial load (described above as needed) (infused over 10 minutes)
- o Increase the rate of the maintenance infusion to achieve effective amiodarone infusion (2)

DOSEAGE FORMS AND STRENGTHS

CONTRAINDICATIONS

Amiodarone is contraindicated in patients with (4):

- Known hypersensitivity to any of the components of amiodarone, including iodine
- Cardiac shock
- Marked sinus bradycardia
- Second- or third-degree atrio-ventricular (AV) block unless a functioning pacemaker is available.

Warnings and Precautions

Amiodarone shows considerable interindividual variability in response. 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 is based on clinical trials in which patients were administered the following infusion regimen:

Table 1: AMIODARONE DOSE RECOMMENDATIONS: FIRST 24 HOURS

Loading Infusions	First Rapid:	150 mg over the FIRST 10 minutes
		Add 3 mL of amiodarone (150 mg) to 100 mL D ₅ W (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes.
	Followed by Slow:	360 mg over the NEXT 6 hours (1 mg/min). Add 18 mL of amiodarone (360 mg) to 500 mL D ₅ W (concentration = 1.8 mg/mL).

Maintenance Infusion

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

After the first 24 hours, continue the maintenance infusion rate of 0.5 mg/min (720 mg per 24 hours) eliciting a concentration of 1 to 2 mg/mL. Use a central venous catheter for amiodarone concentrations greater than 2 mg/mL. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

In the event of breakthrough episodes of VF or hemodynamically unstable VT, use 150 mg supplemental infusions of amiodarone (mixed in 100 mL of D₅W) and infused over 10 minutes to minimize the potential for hypotension.

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. Do not exceed an initial infusion rate of 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 continued for 2 to 3 weeks regardless of the patient's age, renal function, or ventricular function. There has been limited experience in patients receiving intravenous amiodarone for longer than 3 weeks.

The surface properties of solutions containing injectable amiodarone are altered such that the drop size may be reduced. This reduction may lead to underdosage of the patient by up to 30% if drop counter infusion sets are used. Amiodarone must be administered by a volume-controlled infusion pump.

Delivered amiodarone, whenever possible, through a central venous catheter dedicated to that purpose. Use an in-line filter during administration.

Intravenous amiodarone loading infusions at much higher concentrations and rates of infusion much faster than recommended have resulted in hepatocellular necrosis and acute renal failure, leading to death [see Warnings and Precautions (5.3)].

Intravenous amiodarone concentrations greater than 3 mg/mL in D₅W have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/mL, less than or equal to less than 1 hour, do not exceed amiodarone concentrations of 2 mg/mL, unless a central venous catheter is used [see Adverse Reactions (6.2)].

Amiodarone infusions exceeding 2 hours must be administered in glass or polyethylene bottles containing D₅W. Do not use evacuated glass containers for admixing, as incompatibility with a buffer in the container may cause precipitation.

Amiodarone admixtures to polyvinyl chloride (PVC) tubing, but all of the clinical experience has been with PVC tubing and the concentrations and rates of infusion provided in DOSEAGE AND ADMINISTRATION reflecting dosing in these studies.

Amiodarone has been found to leach out plasticizers, including DEHP [bis-(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 DOSEAGE AND ADMINISTRATION. Polybutene 8, a component of amiodarone injection, is also known to leach DEHP from PVC [see Description (17)].

NOTE: Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit.

Table 2: AMIODARONE HCl SOLUTION STABILITY

Solution	Concentration (mg/mL)	Container	Comments
5% Dextrose in Water (D ₅ W)	1 to 6	PVC	Physically compatible, with amiodarone base <10% at 2 hours at room temperature.
5% Dextrose in Water (D ₅ W)	1 to 6	Polyethylene, Glass	Physically compatible, with no amiodarone base at room temperature.

Admixture Incompatibility

Amiodarone in D₅W is incompatible with the drugs shown in Table 3.

Table 3: Y-SITE INJECTION COMPATIBILITY

Drug	Vehicle	Concentration	Comments
Amphotericin B	D ₅ W	4 mg/mL	Precipitate
Cefazolin Sodium	D ₅ W	4 mg/mL	Precipitate
Cefepime Sodium	D ₅ W	4 mg/mL	Precipitate
Mecillinam Sodium	D ₅ W	4 mg/mL	Precipitate
Heparin Sodium	D ₅ W	3 mg/mL	Precipitate
Sodium Bicarbonate	D ₅ W	3 mg/mL	Precipitate

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Warnings and Precautions

Hypotension: Treat initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. (5.1)

Bradycardia and AV block: Treat by slowing the infusion rate or discontinuing amiodarone. (5.2)

ADVERSE REACTIONS

The most common adverse reactions (>1%) leading to discontinuation of intravenous amiodarone are hypotension, asymptotic/arrhythmialess electrical activity, VT, and cardiac shock. (6)

Other important adverse reactions are: torsade de pointes (TdP), congestive heart failure, and liver function test abnormalities. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-425-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone.

Amiodarone inhibits glycolipid and statin CYP450 enzymes, including CYP2C9, CYP2D6, and CYP3A4. This inhibition can result in unexpectedly high plasma levels of other drugs that are metabolized by these CYP450 enzymes or are substrates for glycolipids.

Fluorquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluorquinolones, macrolide antibiotics, or azoles were administered concomitantly.

USE IN SPECIFIC POPULATIONS

Pregnancy: Use amiodarone during pregnancy only if the potential benefit to the mother justifies the risk to the fetus (8.1)

Lactation: Amiodarone and its major metabolites, desethylamiodarone (DEA) and diethylamiodarone (DEA), are excreted in human milk, suggesting that breastfeeding could expose the nursing infant to a significant dose of the drug. Advise mothers to discontinue breastfeeding (8.3).

Pediatric Use: The safety and efficacy of amiodarone in the pediatric population have not been established (8.4).

See 17 for PATIENT COUNSELING INFORMATION

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USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

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13 NONCLINICAL TOXICOLOGY

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*Sections or subsections omitted from the full prescribing information are not listed.

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INSTRUCTIONS FOR TIP CAP REMOVAL



CAUTION: Product-Connector Incompatibility Notice

Certain Neoprene IV sets with Latex Adhesive Devices (LADs) may be incompatible with this syringe. Some LADs that are incompatible with this syringe include the Hospira LifeShield™ Clear™ and other commonly used glass syringes. While the Amiodarone syringe may be connected to these LADs, the physical incompatibility caused by the use of a diameter significantly impairs or even prevents administration of the drug.

Intravenous to Oral Transition

Patients whose arrhythmias have been suppressed by amiodarone may be switched to oral amiodarone. When changing to oral amiodarone therapy, clinical monitoring is recommended, particularly for elderly patients. See package insert for oral amiodarone.

Since grapefruit juice is known to inhibit CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone, do not drink grapefruit juice during therapy with oral amiodarone [see Drug Interactions (7)].

Table 4 provides suggested doses of oral amiodarone to be initiated after varying durations of amiodarone administration. These recommendations are made on the basis of a similar total body amount of amiodarone delivered by the intravenous and oral routes, based on 50% bioavailability.

Table 4: RECOMMENDATIONS FOR ORAL DOSEAGE AFTER INTRAVENOUS INFUSION

Duration of Amiodarone Infusion*	Initial Daily Dose of Oral Amiodarone
< 1 week	800 to 1600 mg
1-3 weeks	800 to 800 mg
> 3 weeks	400 mg

* Assuming a 120 mg/day infusion (0.5 mg/min).

† Intravenous amiodarone is not intended for maintenance treatment.

DOSEAGE FORMS AND STRENGTHS

CONTRAINDICATIONS

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- Known hypersensitivity to any of the components of amiodarone, including iodine
- Cardiac shock
- Marked sinus bradycardia
- Second- or third-degree atrio-ventricular (AV) block unless a functioning pacemaker is available.

WARNINGS AND PRECAUTIONS

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

5.1 Hypotension

Hypotension is the most common adverse reaction seen with intravenous amiodarone. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with intravenous amiodarone. Clinically significant hypotension during treatment was most often in the first several hours of treatment and was not dose related.

Treat hypotension initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. Monitor the initial rate of infusion closely and do not exceed the recommended rate [see Dosage and Administration (2)].

In some cases, hypotension may be refractory and result in a fatal outcome [see Adverse Reactions (6.2)].

5.2 Bradycardia and Atrio-ventricular Block

In 90 (4.9%) of 1836 patients in clinical trials, drug-related bradycardia that was not dose-related occurred while they were receiving intravenous amiodarone for life-threatening VT/VF. Treat bradycardia by slowing the infusion rate or discontinuing amiodarone. In some patients, a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 patient during the controlled study. Treat patients with a known predisposition to bradycardia or AV block with amiodarone in a setting where a temporary pacemaker is available.

5.3 Liver Enzyme Elevations

Amiodarone has been associated with elevated liver enzyme values [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)] in patients with immediately life-threatening VT/VF. Interpreting elevated ALT activity can be difficult because of the high baseline activity of ALT in a body surface area basis, maternal alcohol consumption, heart failure, or multiple electrical defibrillations. Approximately 54% of patients receiving intravenous amiodarone in clinical studies had baseline liver enzyme elevations, and 13% had clinically significant elevations. In 81% of patients with both baseline and follow-up 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.

Acute, centrilobular confluent hepatocellular necrosis leading to hepatic coma, acute renal failure, and death has been associated with the administration of intravenous amiodarone at a much higher loading dose concentration and much faster rate of infusion than recommended [see Dosage and Administration (2)].

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of amiodarone therapy. Careful monitoring and close observation are advised for evidence of progressive hepatic injury. In such cases, consider reducing the rate of administration or withdrawing amiodarone.

5.4 Proarrhythmia

Amiodarone may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsade de pointes (TdP), has been associated with amiodarone therapy in patients with a known predisposition to TdP. Although QTc prolongation occurred frequently in patients receiving intravenous amiodarone, TdP or near-onset VT occurred infrequently (less than 2%). Monitor patients for QTc prolongation during infusion with amiodarone. Report the combination of

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Warnings and Precautions

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Revised: September 2010

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Admixture Incompatibility

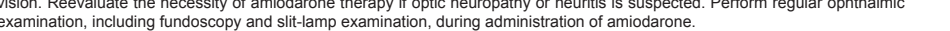
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Sodium Bicarbonate	D ₅ W	3 mg/mL	Precipitate

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Intravenous to Oral Transition

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Since grapefruit juice is known to inhibit CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone, do not drink grapefruit juice during therapy with oral amiodarone [see Drug Interactions (7)].

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