Product Monograph

Including Patient Medication Information

[Pr]Amiodarone Hydrochloride for Injection

Amiodarone hydrochloride for injection

Injectable (sterile solution)

For intravenous use

50 mg/mL of amiodarone hydrochloride

USP

Antiarrhythmic Agent

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Recent Major Label Changes

7. Warnings and Precautions, Peri-Operative Considerations	2026-01

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

Amiodarone Hydrochloride for Injection (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.
- 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.

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 Hydrochloride for Injection may be administered for longer periods, if necessary.

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

Amiodarone Hydrochloride for Injection should be used only by healthcare professionals 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.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of amiodarone hydrochloride for injection in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Clinical studies of amiodarone hydrochloride for injection 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.

2. Contraindications

Amiodarone Hydrochloride for Injection is contraindicated in:

- patients with known hypersensitivity to any of the components of Amiodarone Hydrochloride for Injection,
- patients with cardiogenic shock,
- 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).

3. Serious Warnings and Precautions Box

- 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, healthcare professionals should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

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

- Amiodarone hydrochloride has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with amiodarone hydrochloride, 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 Hydrochloride for Injection 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 hydrochloride for injection 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 hydrochloride is an acceptable risk, Amiodarone Hydrochloride for Injection 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 Hydrochloride for Injection effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Amiodarone Hydrochloride for Injection 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 Hydrochloride for Injection must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone hydrochloride body burden. A similar problem exists when Amiodarone Hydrochloride for Injection is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

4. Dosage and Administration

4.1. Dosing Considerations

BECAUSE OF THE UNIQUE PHARMACOKINETIC PROPERTIES, DIFFICULT DOSING SCHEDULE, AND SEVERITY OF SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, AMIODARONE HYDROCHLORIDE FOR INJECTION THERAPY SHOULD BE INITIATED IN HOSPITAL AND CONTINUED IN A MONITORED ENVIRONMENT UNTIL ADEQUATE CONTROL OF THE ARRHYTHMIA HAS OCCURRED. PATIENTS TREATED WITH AMIODARONE HYDROCHLORIDE FOR INJECTION SHOULD BE UNDER THE SUPERVISION OF A CARDIOLOGIST OR A HEALTHCARE PROFESSIONAL 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 HYDROCHLORIDE FOR INJECTION 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 (see 7. Warnings and Precautions, Monitoring Effectiveness).

Because of the slow rate of elimination of Amiodarone Hydrochloride for Injection, its antiarrhythmic effects may persist for weeks or months after its discontinuation, but the time of arrhythmia recurrence is variable and unpredictable. In general, when the drug is resumed after recurrence of the arrhythmia, control is established more rapidly relative to the initial response, possibly because tissue stores were not wholly depleted at the time of recurrence.

The combination of Amiodarone Hydrochloride for Injection with other antiarrhythmic therapy should be reserved for patients with life-threatening arrhythmias who are unresponsive to adequate doses of a single agent (see 9. Drug Interactions).

Amiodarone Hydrochloride for Injection must be diluted prior to use and is for intravenous infusion only.

Amiodarone Hydrochloride for Injection must be delivered by a volumetric infusion pump. The surface properties of solutions containing injectable amiodarone hydrochloride 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 for injection concentrations greater than 3 mg/mL in Dextrose 5% Injection 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 for Injection concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

4.2 Recommended Dose and Dosage Adjustment

Amiodarone Hydrochloride for Injection 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 hydrochloride losses of approximately 10-12% were observed after 2 hours when Amiodarone Hydrochloride for Injection was diluted in Dextrose 5% Injection in PVC bags. Those losses may be attributed to adsorption of amiodarone hydrochloride to the PVC. However, when diluted in polyolefin or glass containers, 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 5% Injection.

It is well known that amiodarone hydrochloride 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 4. Dosage and Administration reflect doses identified in these studies. It is important that the recommended infusion regimen be followed closely.
Intravenous 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 4. Dosage and

Administration (see 7.1.3. Warnings and Precautions, Pediatrics).

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

Amiodarone hydrochloride 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 infusion regimen in Table 1. It is important that the recommended infusion regimen be followed closely.

Table 1 - Intravenous 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 Dextrose 5% Injection (concentration = 1.5 mg/mL), infuse 100 mL over 10 minutes.
Then, Slow:	**360 mg over 6 hours (1 mg/min).** Add 18 mL of Amiodarone Hydrochloride for Injection (900 mg) to 500 mL Dextrose 5% Injection (concentration = 1.8 mg/mL).
Then, Maintenance Infusion	
	540 mg over 18 hours (0.5 mg/min). Decrease the rate of the slow loading infusion to 0.5 mg/min.

The first 24 hours 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.

After 24 hours
The maintenance infusion rate of 0.5 mg/min should be continued (concentration of 1 to 6 mg/mL). Concentrations greater than 2 mg/mL should be administered via a central venous catheter.

Based on the experience from clinical studies of intravenous amiodarone hydrochloride, 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 hydrochloride for longer than 3 weeks.

Breakthrough episodes of ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT)
150 mg supplemental infusions of Amiodarone Hydrochloride for Injection mixed in 100 mL

of Dextrose 5% Injection 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.

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 hydrochloride will depend on the dose of Amiodarone Hydrochloride for Injection already administered as well as the bioavailability of oral amiodarone hydrochloride. When changing to oral amiodarone hydrochloride 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 Product Monograph for oral amiodarone hydrochloride when switching from intravenous to oral amiodarone hydrochloride therapy.

Table 2 provides suggested doses of oral formulation amiodarone hydrochloride 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 hydrochloride delivered by the intravenous and oral routes, based on a 50% bioavailability of oral amiodarone hydrochloride. **Please refer to the Product Monograph of amiodarone hydrochloride oral formulations for detailed information on dosing and administration of oral amiodarone hydrochloride.**

Table 2 - Recommendations for oral dosage after intravenous infusion

Duration of Amiodarone Hydrochloride for Injection [a]	Initial Daily Dose of Oral Amiodarone hydrochloride (mg)
<1 week	800-1600
1-3 weeks	600-800
>3 weeks[b]	400

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

4.3. Reconstitution

Preparation of IV Solution: Amiodarone Hydrochloride for Injection must be diluted prior to use and is for intravenous infusion only.

Table 3 - Stability of diluted Amiodarone Hydrochloride for Injection in dextrose 5%

Solution	Concentration (mg/mL)	Container	Comments
5% Dextrose in Water	1.0-6.0	PVC	Physically compatible, with amiodarone hydrochloride loss of ≈10-12% at 2 hours at room temperature.
5% Dextrose in Water	1.0-6.0	Polyolefin, Glass	Physically compatible, with no amiodarone hydrochloride loss at 24 hours at room temperature.

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

Admixture Incompatibility: Amiodarone Hydrochloride for Injection in Dextrose 5% Injection (D5W) is physically incompatible with the drugs shown in Table 4.

Table 4 - Y-Site injection incompatibility

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

5. Overdose

There have been cases, some fatal, of amiodarone hydrochloride for injection overdose. Effects of an inadvertent overdose of IV amiodarone hydrochloride for injection 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 hydrochloride nor DEA is dialysable.

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 hydrochloride nor its metabolite is dialysable.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition and Packaging

Table - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous (IV)	Sterile solution, 50 mg/mL amiodarone hydrochloride	Benzyl alcohol, polysorbate-80, sodium hydroxide and/or hydrochloric acid and water for injection.

Description
Amiodarone Hydrochloride for Injection in vials is a clear, colourless to 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.

Amiodarone Hydrochloride for Injection is available in amber glass vials as follows: 3 mL fill in 5 mL vials, cartons of 10.

The vial stopper is not made with natural rubber latex.

Preparation of IV Solution
Amiodarone Hydrochloride for Injection must be diluted prior to use and is for intravenous infusion only.

Amiodarone Hydrochloride for Injection 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 hydrochloride 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 hydrochloride to the PVC. However, when diluted in polyolefin or glass containers, 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.

7. Warnings and Precautions

Please see 3. Serious Warnings and Precautions Box*.*

General

Patients with life-threatening arrhythmias may experience serious adverse events during their treatment and therefore should be properly monitored. Amiodarone Hydrochloride for Injection should be administered only by Healthcare Professionals 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 1. Indications).

Carcinogenesis and Mutagenesis

No carcinogenicity studies were conducted with intravenous amiodarone hydrochloride. 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 hydrochloride. 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 hydrochloride may cause a worsening of the existing arrhythmias or precipitate a new arrhythmia. Amiodarone hydrochloride 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 hydrochloride exhibits a low torsadogenic activity. Although QTc prolongation occurred frequently in patients receiving IV amiodarone hydrochloride, torsades de pointes or new-onset VF occurred infrequently (less than 2% of all patients treated with IV amiodarone hydrochloride in controlled clinical trials). Patients should be monitored carefully for QTc

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

prolongation during amiodarone hydrochloride therapy. Combination of amiodarone hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride, death may result.

Even in patients at high risk of arrhythmic death, in whom the toxicity of amiodarone hydrochloride is an acceptable risk, amiodarone hydrochloride 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 hydrochloride effectively and safely poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone hydrochloride 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 hydrochloride must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone hydrochloride 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.

Bradycardia and AV Block

Bradycardia was reported as an adverse drug reaction in 4.9% of patients receiving IV amiodarone hydrochloride 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 hydrochloride. There was no dose-related increase in bradycardia or AV block in these studies.

During intravenous amiodarone hydrochloride 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 hydrochloride in a setting where a temporary pacemaker is available.

Severe Bradycardia
Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone hydrochloride 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 hydrochloride is not recommended.

If concomitant use with amiodarone hydrochloride 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 hydrochloride, appropriate monitoring should also be carried out for patients who have discontinued amiodarone hydrochloride 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 hydrochloride, 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 hydrochloride 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 hydrochloride. 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 hydrochloride 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 hydrochloride treatment, pacing and defibrillation thresholds should be assessed.

Endocrine and Metabolism

Neonatal Hypo- or Hyperthyroidism
Amiodarone Hydrochloride for Injection can cause fetal harm when administered to a pregnant woman. Although amiodarone hydrochloride 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 Hydrochloride for Injection 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 Hydrochloride for Injection 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 hydrochloride 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

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

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 Hydrochloride for Injection should be considered.

Approximately 54% of patients receiving IV amiodarone hydrochloride 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 IV amiodarone hydrochloride 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 hydrochloride 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.**

Monitoring and Laboratory Tests

Amiodarone hydrochloride should be used only by Healthcare Professionals 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 hydrochloride:

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 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 hydrochloride 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 hydrochloride 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 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/1000 normal beats).

While these issues remain unsettled for amiodarone hydrochloride, as for other agents, the prescriber of Amiodarone Hydrochloride for Injection 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.

Peri-Operative Considerations

Primary graft dysfunction (PGD) post cardiac transplant
There is supportive evidence based on observational studies linking recipient use of amiodarone hydrochloride pre-heart transplant with increased risk of primary graft dysfunction. The certainty of the evidence is low due to the lack of randomization and retrospective nature of these observational studies, that are susceptible to confounding and bias.

PGD is a life-threatening complication of heart transplantation that presents as a left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause. Severe PGD may be irreversible.

For patients who are on a heart transplant waiting list, consideration should be given to use of an alternative antiarrhythmic drug as early as possible before transplant.

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 2. 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 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 hydrochloride 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 hydrochloride are associated with a decreased incidence of amiodarone hydrochloride - induced pulmonary toxicity.

Hypersensitivity pneumonitis usually appears earlier in the course of therapy, and rechallenging these patients with amiodarone hydrochloride 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 hydrochloride 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 hydrochloride-induced pulmonary toxicity; however, these changes also are

present in approximately 50% of all patients on amiodarone hydrochloride therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of amiodarone hydrochloride-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably to withdrawal of the amiodarone hydrochloride to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone hydrochloride-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 hydrochloride at a lower dose has not resulted in return of toxicity.

In a patient receiving Amiodarone Hydrochloride for Injection, 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 Hydrochloride for Injection 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 hydrochloride-induced hypersensitivity pneumonitis is made, amiodarone hydrochloride should be discontinued, and treatment with steroids should be instituted. If a diagnosis of amiodarone hydrochloride-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 hydrochloride-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 hydrochloride in clinical studies developed pulmonary fibrosis. For that patient, the condition was diagnosed 3 months after treatment with IV amiodarone hydrochloride, during which time she had received oral amiodarone hydrochloride. IV amiodarone hydrochloride therapy should be discontinued if a diagnosis of pulmonary fibrosis is made.

During clinical studies of IV amiodarone hydrochloride, 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 hydrochloride 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 8. Adverse Reactions). If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present amiodarone hydrochloride treatment should be discontinued immediately.

7.1. Special Populations

7.1.1. Pregnant Women

Amiodarone hydrochloride 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 hydrochloride use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. Therefore, amiodarone hydrochloride 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 7. Warnings and Precautions, Endocrine and Metabolism, Neonatal Hypo- or Hyperthyroidism), amiodarone hydrochloride has caused a variety of adverse effects in animals.

In a reproductive study in which amiodarone hydrochloride 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 hydrochloride 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 hydrochloride should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

It is not known whether the use of amiodarone hydrochloride 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.

7.1.2. Breast-feeding

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 hydrochloride have demonstrated reduced viability and reduced body weight gains. The risk of exposing the infant to amiodarone hydrochloride should be weighed against the potential benefit of arrhythmia suppression in the mother. The mother should be advised to discontinue nursing.

7.1.3. Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of amiodarone hydrochloride for injection in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

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

The following information is provided in order to help the Healthcare Professionals who considers that critical and treatment-resistant disease in a pediatric patient makes the use of Amiodarone Hydrochloride for Injection 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 Hydrochloride for Injection contains the preservative benzyl alcohol. There have been reports of serious and fatal adverse reactions, including "gasping syndrome" in pediatric patients, particularly in premature neonates and infants that have been administered benzyl alcohol intravenously. Manifestations of the disease included: metabolic acidosis, respiratory distress, gasping respirations, central-nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, hepatic and renal failure, hypotension, cardiovascular collapse and death. Premature and low-birth weight infants may be more likely to develop these adverse reactions because they may be less able to metabolize benzyl alcohol. The minimum quantity of benzyl alcohol at which toxicity may occur is not known.

Amiodarone hydrochloride 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 hydrochloride at higher concentrations and at lower flow rates than provided in 4. 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 hydrochloride 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.

7.1.4. Geriatrics

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.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The most common adverse reactions leading to the discontinuation of IV amiodarone hydrochloride therapy include ventricular tachycardia, hypotension, cardiac arrest (asystole/cardiac arrest/electromechanical dissociation) and cardiogenic shock. In some

cases, IV amiodarone hydrochloride therapy has been associated with organ system abnormalities, such as pulmonary complications, including symptomatic pulmonary disease, cardiovascular complications, such as exacerbation of arrhythmia, bradycardia or sinus arrest, congestive heart failure, vasculitis and angioedema and finally hepatic complications, including symptomatic hepatitis, cholestatic hepatitis and cirrhosis.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Please see Table 5 (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 hydrochloride 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 hydrochloride therapy were ventricular tachycardia (2%), hypotension (2%), cardiac arrest (asystole/cardiac arrest/electromechanical dissociation) (1%), and cardiogenic shock (1%).

Table 5 lists the most common (incidence ≥1%) adverse drug reactions during IV amiodarone hydrochloride therapy that were collected from controlled and open-label clinical trials involving 1836 patients with hemodynamically unstable VT or VF.
If we take into account the overall incidence, there are no adverse reactions with an incidence <1%

Table 5 - Summary tabulation of adverse drug reactions in patients receiving amiodarone hydrochloride iv. in controlled and open-label studies (≥1% incidence)

System organ class/preferred term	Amiodarone hydrochloride Controlled Trials (N=814)	Amiodarone hydrochloride 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%)
Urogenital System	27 (3.3%)	30 (2.9%)	57 (3.1%)
Kidney Function Abnormal	8 (<1%)	16 (1.5%)	24 (1.3%)

Commonly Observed abnormalities

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 7. 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 7. 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 7. 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.

8.5. Post-Market Adverse 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 hydrochloride.

Women receiving amiodarone hydrochloride 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 4. Dosage and Administration).

Injury, poisoning and procedural complications: primary graft dysfunction post cardiac transplant

9. Drug Interactions

9.2. Drug Interaction Overview

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

Beta Blockers
Amiodarone hydrochloride 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 hydrochloride can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

Calcium Channel Antagonists
Amiodarone hydrochloride 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 hydrochloride 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 hydrochloride and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone hydrochloride 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.

Clopidogrel, an inactive thienopyridine prodrug, is metabolized in the liver by CYP3A4 to an active metabolite. A potential interaction between clopidogrel and amiodarone hydrochloride 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 hydrochloride.

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 hydrochloride 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 hydrochloride 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 hydrochloride. During transfer to amiodarone hydrochloride the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of amiodarone hydrochloride, when arrhythmia suppression should be beginning.
The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone hydrochloride 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 hydrochloride is continued. In amiodarone hydrochloride-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 hydrochloride 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 10.3. Pharmacokinetics). Amiodarone hydrochloride is a substrate and an inhibitor of CYP3A4 and a substrate of p-glycoprotein. Therefore, amiodarone hydrochloride 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 hydrochloride 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 hydrochloride, potential for drug interactions exists not only with concomitant medication but also with drugs administered

after discontinuation of amiodarone hydrochloride.

Examples of drugs that may have serum concentrations increased by amiodarone
Amiodarone hydrochloride 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 hydrochloride, interactions may be observed for several months after discontinuation of amiodarone hydrochloride. 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 hydrochloride have been associated with reports of myopathy/rhabdomyolysis.

Immunosuppressives: Oral amiodarone hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone hydrochloride 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 hydrochloride is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentrations of amiodarone hydrochloride, 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 hydrochloride. Monitoring for amiodarone hydrochloride toxicity and serial measurement of amiodarone hydrochloride 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 hydrochloride.

Antiviral drugs
Coadministration of amiodarone hydrochloride 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 hydrochloride inhibits CYP2D6.

Some drugs/substances are known to accelerate the metabolism of amiodarone hydrochloride by stimulating the synthesis of CYP3A4 (enzyme induction). This may lead to low amiodarone hydrochloride 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 hydrochloride has been shown to result in decreases in serum concentrations of amiodarone hydrochloride 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.

9.3. Drug-Behaviour Interactions

The interaction of amiodarone hydrochloride for injection with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

Table 6 - Summary of drug interactions with amiodarone hydrochloride drugs whose effects may be increased by amiodarone hydrochloride

Amiodarone hydrochloride	Effect	Clinical comment
Warfarin	Increases prothrombin time.	N/A
	Oral amiodarone hydrochloride increases digoxin serum	

Amiodarone hydrochloride	Effect	Clinical comment
Digoxin	concentration by 70% after one day. May reach toxic levels with resultant clinical toxicity.	N/A
Digitalis	N/A	With oral amiodarone hydrochloride 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	N/A	Caution should be exercised when amiodarone hydrochloride 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 hydrochloride.
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 hydrochloride.
Flecainide	Plasma levels of flecainide have been reported to increase in the presence of oral amiodarone hydrochloride	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 hydrochloride who was given lidocaine for local anaesthesia. IV: Seizure associated with increased lidocaine concentrations was observed in one patient.	N/A
Phenytoin	Increases phenytoin serum concentration.	N/A

Amiodarone hydrochloride	Effect	Clinical comment
Disopyramide	Increases QT prolongation which could cause arrhythmia.	N/A
Fentanyl	May cause hypotension, bradycardia, decreased cardiac output.	N/A
Cyclosporine	Administered in combination with oral amiodarone hydrochloride, produces persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.	N/A
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 hydrochloride when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly.	N/A

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; PBPK = Physiologically based pharmacokinetic modeling; popPK = Population pharmacokinetic modeling

Table 7 - Summary of drug interactions with amiodarone hydrochloride drugs that may interfere with the actions of amiodarone hydrochloride

Amiodarone hydrochloride	Effect
Cholestyramine	Increases enterohepatic recirculation of amiodarone hydrochloride and may reduce serum levels and t½.
Cimetidine	Increases serum amiodarone hydrochloride levels.
Phenytoin	Decreases serum amiodarone hydrochloride levels.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; PBPK = Physiologically based pharmacokinetic modeling; popPK = Population pharmacokinetic modeling

9.5. Drug-Food Interactions

Grapefruit Juice

Grapefruit juice inhibits CYP3A4-mediated metabolism of oral amiodarone hydrochloride in the intestinal mucosa, resulting in significant increased plasma levels of amiodarone

hydrochloride (C_{max} and AUC increased by 84% and 50%, respectively); therefore, grapefruit juice should not be taken during treatment with oral amiodarone hydrochloride. Therefore, this information should be considered when changing from intravenous amiodarone hydrochloride to oral amiodarone hydrochloride (see 4. Dosage and Administration).

There are no drug-food interactions with Amiodarone Hydrochloride for Injection.

9.6. Drug-Herb Interactions

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

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. 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 hydrochloride 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 hydrochloride in nodal tissues is similar to the effect of Class IV drugs. In addition to blocking sodium channels, amiodarone hydrochloride 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 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.

Table 8 - Effects of oral and intravenous amiodarone hydrochloride 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 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 hydrochloride 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 adrenoreceptor antagonism (Class II activity).

10.2. Pharmacodynamics

Amiodarone hydrochloride has been reported to produce negative inotropic and vasodilating effects in animals and humans. After long-term treatment with oral amiodarone hydrochloride 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 hydrochloride therapy. In clinical studies of patients with refractory ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia, drug-related hypotension occurred in 15.6% of 1836 patients treated with IV amiodarone hydrochloride. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of IV amiodarone hydrochloride.

10.3. Pharmacokinetics

Absorption

The absorption of oral amiodarone hydrochloride is slow and variable, with peak serum amiodarone hydrochloride 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 hydrochloride 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 hydrochloride. The effects of food upon the bioavailability of amiodarone hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride, 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 hydrochloride 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 or hemodynamically unstable ventricular tachycardia 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 hydrochloride mean serum concentrations between 0.7 to 1.4 mg/L were observed (n=260).

Metabolism

Amiodarone hydrochloride is eliminated primarily by hepatic metabolism and biliary excretion. Desethylamiodarone (DEA) is the major active metabolite of amiodarone hydrochloride. At the usual amiodarone hydrochloride daily maintenance dose of 400 mg, mean steady-state DEA/amiodarone hydrochloride ratios ranged from 0.61 to 0.93. High-dose oral amiodarone hydrochloride loading in patients yielded 24-hour DEA/amiodarone hydrochloride ratios of 0.083 to 0.19. High-dose intravenous loading yielded a mean 24-hour DEA/amiodarone hydrochloride 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 hydrochloride. DEA is highly lipophilic and has a very large apparent volume of distribution, showing a higher concentration than amiodarone hydrochloride in all tissue except fat at steady-state. Myocardial concentrations of DEA are approximately 3- to 4.5-fold greater than those of amiodarone hydrochloride during long-term oral amiodarone hydrochloride 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 hydrochloride.

Elimination

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

Table 9 summarizes the mean ranges of pharmacokinetic parameters of amiodarone hydrochloride 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 hydrochloride pharmacokinetic profile

Drug	Clearance (mL/h/kg)	VC (L/kg)	VSS (L/kg)	t½ (days)	Protein Binding	Foral (%)
Amiodarone hydrochloride	90-158	0.2	40-84	20-47	>0.96	33-65
Desethylamiodaron	197-290	-	68-168	≥AMI t½	-	-

Notes: VC and VSS denote the central and steady-state volumes of distribution from IV studies; Foral is systemic availability of amiodarone hydrochloride. "-" denotes not available. AMI is amiodarone hydrochloride. t½ = 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 hydrochloride concentrations of 1 to 2.5 mg/L, however, have been effective with minimal toxicity following chronic oral amiodarone hydrochloride.

Special Populations and Conditions

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **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.

- **Sex:** 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 7. 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.

11. Storage, Stability and Disposal

Amiodarone Hydrochloride for Injection, 50 mg/mL: Store between 15-30°C. Protect from light and excessive heat. Single use vials. Discard unused portion. Keep out of reach and sight of children.

12. 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.

Part 2: Scientific Information

13. Pharmaceutical Information

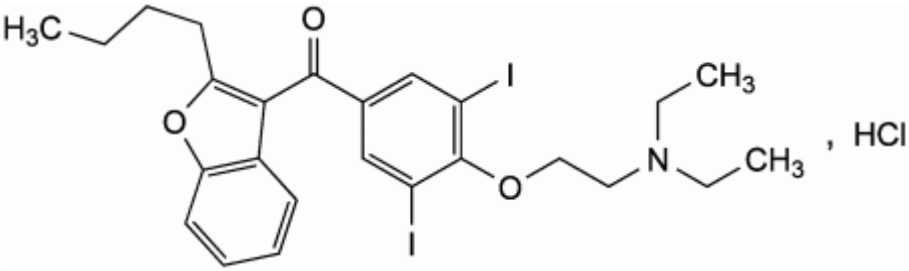
Drug Substance

Non-proprietary name of the drug substance: Amiodarone Hydrochloride

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

Molecular formula and molecular mass: $C_{25}H_{29}I_2NO_3HCl$, 681.8 g / mol

Structural formula:



Physicochemical properties:

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

PKa Value: 6.64

Melting Point: 159-163°C

Pharmaceutical standard: Ph. Eur.

Product Characteristics:

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.

14. Clinical Trials

Trial Design and Study Demographics
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 hydrochloride 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 hydrochloride therapy reduced episodes of VT by 85%.
IV amiodarone	Pharmacokinetic/ pharmacodynamic study evaluating rapid IV loading	Approximately 1500 mg/day IV amiodarone hydrochloride 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 hydrochloride 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	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.

Study Drug/ Route of Administration	Study Type	Dose	Patients/ Indication	Results
		infusion was continued up to hour 48.		

A placebo-controlled study of IV amiodarone hydrochloride 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 hydrochloride were administered using 2- and 3-stage infusion regimens. In the patients with complex ventricular arrhythmias, including sustained and non sustained VT, amiodarone hydrochloride therapy reduced episodes of VT by 85%.
The acute effectiveness of IV amiodarone hydrochloride 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.

15. Microbiology

Amiodarone Hydrochloride for Injection is a sterile solution of amiodarone hydrochloride for intravenous administration.
The products are sterilized by aseptic filtration and are tested for sterility and bacterial

endotoxins.

16. Non-Clinical 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 hydrochloride was administered intravenously in multiple-dose toxicity studies to rabbits (6 weeks), dogs (4 weeks), and baboons (4 weeks).

Table 11 - Oral amiodarone hydrochloride: 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 hydrochloride: 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.

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
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 LD50 for a 5-minute infusion was 75 to 100 mg/kg. The LD50 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 LD50 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

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			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.
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 T4; and decreased protein and T3/T4 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

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			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.
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

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			count, hemoglobin, hematocrit, mean cell hemoglobin, and mean cell hemoglobin concentrations; increased reticulocytes, neutrophils and monocytes) and biochemical (increased bilirubin, triglycerides, BUN, creatinine, and T4 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

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			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 hydrochloride: 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

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			males) were elevated at 75 mg/kg and above. There was an increase in T4 and a decrease in the T3/T4 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 20th 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

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			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 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	Dietary control, 30 or 150 / 3 months*	There were no deaths. At 150 mg/kg, gastrointestinal intolerance (vomiting, diarrhea and anorexia) was observed for

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
	mg/kg)		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

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			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 hydrochloride. 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.
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.

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
			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.

Species / Strain	Mode of Administration	Dosage (mg/kg/day) / Duration	Results
* 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 hydrochloride: 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

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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 and above in the

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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 hydrochloride: 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.

Species/ Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			Changes in thyroid function were characterized by an increase in T4 at dose levels of 12.5 mg/kg/day and above, without any variation in T3 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 hydrochloride 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 hydrochloride: 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 hydrochloride 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.

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
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.

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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. 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 / Gestationday 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.

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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 hydrochloride 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

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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 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 hydrochloride 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 hydrochloride treatment. The mean live litter size and sex ratio were comparable in treated and control groups. The mean fetal weights were significantly

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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 fecundity of the animals.

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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 hydrochloride: 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.

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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. 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

Species/Strain	Mode of Administration	Dosage (mg/kg/day)/Duration	Results
			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

17. Supporting Product Monographs

1. Cordarone, Tablets, 200 mg, control 189723, product monograph, Pfizer Canada Inc. (2016-02-18).

2. Amiodarone Hydrochloride for Injection, Solution, 50 mg / mL, control 291661, product monograph, Sandoz Canada Inc. (2025-05-13).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Amiodarone Hydrochloride for Injection
Amiodarone hydrochloride for injection

This Patient Medication Information is written for the person who will be taking **Amiodarone Hydrochloride for Injection**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Amiodarone Hydrochloride for Injection**, talk to a healthcare professional.

Serious warnings and precautions box

Amiodarone Hydrochloride for Injection can cause serious and potentially life-threatening side effects, including serious issues with the:

- lungs,
- liver, and
- heart.

Because of these risks:

- only take Amiodarone Hydrochloride for Injection if your healthcare professional has prescribed it for you;
- you will begin your treatment in a hospital with experienced healthcare professionals; and
- your health will be closely monitor before, during, and after treatment.

What Amiodarone Hydrochloride for Injection is used for:
Amiodarone Hydrochloride for Injection is used in adults to treat certain life-threatening abnormal heart rhythms (arrhythmias).

How Amiodarone Hydrochloride for Injection works:
Amiodarone Hydrochloride for Injection belongs to a group of medicines known as antiarrhythmic agents. It works by blocking certain channels in the heart. This helps to restore or maintain a normal heart rhythm.

The ingredients in Amiodarone Hydrochloride for Injection are:
Medicinal ingredient: Amiodarone hydrochloride.
Non-medicinal ingredients: Benzyl alcohol, polysorbate-80, hydrochloric acid and/or sodium hydroxide, and water for injection.

Amiodarone Hydrochloride for Injection comes in the following dosage form(s):

Solution: 50 mg/mL of amiodarone hydrochloride.

Do not use Amiodarone Hydrochloride for Injection if:

- you are allergic to amiodarone hydrochloride or any of the other ingredients in Amiodarone Hydrochloride for Injection.
- you are experiencing cardiogenic shock (heart is not able to pump enough blood to the organs of the body).
- you have any of the following heart problems:
    - severe sinus-node dysfunction that causes bradycardia (heart's natural pacemaker does
      not work properly, causing a low heart rate);
    - second- or third-degree atrioventricular block (problem with the electrical signals in the heart, causing a delay or complete block in the heart's rhythm);
    - episodes of bradycardia causing syncope (low heart rate episodes, causing fainting), unless a pacemaker is used to regulate the heart rate.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Amiodarone Hydrochloride for Injection. Talk about any health conditions or problems you may have, including if you:

- have or have had any other heart problems.
- are planning to get a heart transplant or are waiting to get a heart transplant.
- have an implanted defibrillator or pacemaker for your heart.
- have previously received electrical defibrillations (electrical shock that helps the heart return to a normal rhythm).
- have liver problems (e.g., hepatitis).
- have bowel problems (e.g., severe diarrhea or diarrhea for long period of time).
- are low in potassium (hypokalemia) or low in magnesium (hypomagnesemia).
- have or have had any thyroid problems.
- are elderly.
- are breast-feeding or plan to breast-feed. Amiodarone Hydrochloride for Injection can pass into the breast milk.
- are pregnant or plan to become pregnant. If you become pregnant while taking Amiodarone Hydrochloride for Injection, tell your healthcare professional right away to discuss the risks for you and your baby.

Other warnings you should know about:

- **Testing and check-ups:** Your healthcare professional will monitor and assess your health before, during, and after your treatment with Amiodarone Hydrochloride for Injection. This includes monitoring the following:
    - your heart (e.g., heart rhythm, heartbeats, and its electrical system);
    - your thyroid gland;
    - your liver;
    - your electrolyte levels (e.g., potassium, magnesium, etc.);
    - your breathing and lungs; and

    - your eye vision.
- **Pediatrics:** Amiodarone Hydrochloride for Injection contains benzyl alcohol. Serious side effects (e.g., gasping syndrome) including death have happened in newborns or infants who have received benzyl alcohol intravenously (through the veins).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Amiodarone Hydrochloride for Injection:

- beta-blockers, medicines used to lower blood pressure (e.g., propranolol).
- cyclosporine, a medicine used to help prevent organ rejection.
- medicines used to treat depression (e.g., trazodone and St. John's Wort).
- anticoagulants, medicines used to thin the blood or prevent blood clots (e.g., warfarin, clopidogrel, and dabigatran).
- digoxin and digitalis, medicines used to treat certain heart problems.
- medicines used to lower high cholesterol (e.g., cholestyramine, simvastatin and atorvastatin).
- antivirals, medicines used to treat Hepatitis C (e.g., sofosbuvir, daclatasvir, simeprevir, and ledipasvir).
- antiarrhythmics, medicines used to treat irregular heartbeat (e.g., procainamide, quinidine, disopyramide, and flecainide).
- protease inhibitors, medicines used to treat HIV infection (e.g., indinavir).
- phenytoin, a medicine used to prevent seizures.
- calcium channel blockers, medicines used to lower blood pressure (e.g., verapamil and diltiazem).
- cimetidine, a medicine used to treat ulcers.
- Fentanyl, a medicine used to treat pain.
- antibiotics, medicines used to treat bacterial infections (e.g., fluoroquinolones and rifampin).
- antifungals, medicines used to treat fungal infections (e.g., azoles).
- anesthetics, medicines used to prevent pain (e.g., lidocaine).
- antihistamines, medicines used to prevent and treat allergy symptoms (e.g., loratadine).
- dextromethorphan, a medicine used to relieve coughing.
- methotrexate, a medicine used to treat cancer and arthritis.
- stimulating laxative agents, medicines used to treat constipation.

How to take Amiodarone Hydrochloride for Injection:
Your healthcare professional will prepare and give you Amiodarone Hydrochloride for Injection in a hospital. You will receive Amiodarone Hydrochloride for Injection through your veins (i.e., "intravenously" or "IV").

Usual dose:
Your healthcare professional will determine the right dose of Amiodarone Hydrochloride for

Injection for you. This will depend on your age, health, if you take other medication, and how you react to Amiodarone Hydrochloride for Injection. Your healthcare professional may also adjust your dose to ensure that the lowest effective dose is prescribed.

Once your heartbeat has returned to normal, your healthcare professional may switch you to an oral version of amiodarone hydrochloride.

Overdose:

If you think you, or a person you are caring for, have taken too much Amiodarone Hydrochloride for Injection, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using Amiodarone Hydrochloride for Injection:
These are not all the possible side effects you may have when taking Amiodarone Hydrochloride for Injection. If you experience any side effects not listed here, tell your healthcare professional.

The side effects of Amiodarone Hydrochloride for Injection may include:

- feeling disoriented,
- erectile dysfunction,
- low sex drive,
- hallucinations,
- altered sense of smell.

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very Common			
Eye problems: blurred vision, cloudy vision, visual halos, dry eyes, eye discomfort, gritty sensation in the eyes, pain in or around the eye, difficulty with colour vision, blind spots, or vision loss.			**X**
Common			
Heart problems: fainting, dizziness, light-headedness, chest pain, shortness of breath, palpitations, racing heart, rapid or irregular heart beat, fatigue, loss of consciousness, weak pulse, or low blood pressure.		**X**	
Hypotension (low blood pressure): dizziness, fainting, light- headedness, blurred vision, nausea, vomiting, or fatigue (may occur when going from lying or sitting to		**X**	

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
standing up).			
Kidney problems: fatigue, swelling in the legs, ankles, or feet, urinating more or less frequent, confusion, nausea, vomiting, shortness of breath, high blood pressure, low appetite, or chest pain.		**X**	
Liver problems: abdominal discomfort and pain, feeling fullness, yellowing of the skin or eyes, dark urine, pale stools, loss of appetite, fatigue, nausea, or vomiting.		**X**	
Lung problems: shortness of breath, shallow breathing, difficult breathing, cough, weakness, weight loss, fatigue, chest discomfort, wheezing, chest tightness, confusion, blue lips, or fever.			**X**
Thyroid problems: abnormal weight change, abnormally fast or slow heart rate, palpitations, increased sweating, tremors, fatigue, diarrhea, dry skin and hair, muscle weakness, constipation, enlarged thyroid, swelling at the base of the neck, difficulty swallowing, difficulty breathing, tightness in the throat, or cough.		**X**	
Unknown			
Allergic reactions: difficulty swallowing, difficulty breathing, wheezing, drop in blood pressure, nausea, vomiting, hives, rash, or swelling of the face, lips, tongue, or throat.			**X**
Blood problems: easy bruising, unexplained bruising, prolonged bleeding, frequent nosebleeds, fatigue, pale skin, shortness of breath, dark urine, infections, weakness, fever, chills, weight loss, sore throat, or mouth ulcers.		**X**	
Injection site reactions: swelling, irritation, redness, pain, infection, or peeling of the skin at the site of the injection.	**X**		
Movement problems: tremor, abnormal involuntary movements, lack of coordination, change to the normal walking pattern, dizziness, tiredness, tingling, burning sensation, muscular weakness, or loss of sensation.		**X**	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, or tenderness when touching the abdomen.		**X**	
Severe skin reactions: increased sensitivity to sunlight, blue- grey coloured skin, rash, dry skin, itchiness,			**X**

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
blisters, new spot on the skin, redness, blistering, peeling of the skin or inside of the lips, eyes, mouth, nasal passages or genitals, fever, chills, or body aches.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Amiodarone Hydrochloride for Injection will be stored by your healthcare professional between 15-30°C. Protected from light and excessive heat.
Keep out of reach and sight of children.

If you want more information about Amiodarone Hydrochloride for Injection:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-866-399-9091.

This leaflet was prepared by:
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