DESCRIPTION:
Amiodarone Hydrochloride Injection, for intravenous use, contains amiodarone HCl a class III antiarrhythmic drug. Amiodarone HCl is (2-buty1-3-benzofuran-y1) [4-[2-(diethylamino)ethoxy]y]-3,3-diiodophenyl)methanone hydrochloride.

Amiodarone HCl is a white to slightly yellow crystalline powder and is very slightly soluble in water. It contains 57.3% (by weight) amiodarone HCl. Amiodarone HCl Injection is a sterile, pale-yellow, miscellar solution visually free from particulates. Each mL of the Amiodarone HCl Injection formulation contains 50 mg of amiodarone HCl, 20.2 mg of benzy1 alcohol, 100 mg of polysorbate 80, and water for injection.

Amiodarone HCl Injection contains polysorbate 80, which is known to leach di-(2-ethylhexyl)phthalate (DEHP) from polyvinyl chloride (PVC) (see DOSAGE AND ADMINISTRATION).

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

Amiodarone HCl Injection administration prolongs intranodal conduction (Amio-His, AH), and refractoriness of the atroventricular node (ERP AVN), but has little or no effect on sinus cycle length (SCL), refractoriness of the right atrium and right ventricle (ERP RA and ERP RV), repolarization (QTc), intraventricular conduction (QRS), and intranodal conduction (His-ventricular, HV). A comparison of the electrophysiologic effects of amiodarone HCl Injection and oral amiodarone is shown in the table below.

EFFECTS OF INTRAVENOUS AND ORAL AMIODARONE ON ELECTROPHYSIOLOGIC PARAMETERS

<table>
<thead>
<tr>
<th>Formulation</th>
<th>SCL</th>
<th>QRS</th>
<th>QTc</th>
<th>AH</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Oral</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

At higher doses (>10 mg/kg) of amiodarone HCl injection, prolongation of the ERP RV and modest prolongation of the QRS than have been seen. These differences between oral and IV administration suggest that the initial acute effects of amiodarone HCl injection may be predominantly focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel block (class IV activity) and noncompetitive adrenergic antagonism (class II activity).

Pharmacokinetics and Metabolism
Amiodarone exhibits complex disposition characteristics after intravenous administration. Peak serum concentrations after single 5 mg/kg 15-minute intravenous infusions in healthy subjects range between 5 and 41 mg/L. Peak concentrations after 10-minute infusions of 100 mg amiodarone HCl injection in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) were between 7 and 26 mg/L. Due to rapid distribution, 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 over 24 hours) of intravenous amiodarone (150 mg infusions (for recurrent arrhythmias), amiodarone mean serum concentrations between 0.7 to 1.4 mg/L were observed (n=260).

N-Desethylamiodarone (DEA) is the major active metabolite of amiodarone in humans. DEA serum concentrations above 0.05 mg/L are not usually seen until several days of continuous infusions but with prolonged therapy reach approximately the same concentration as amiodarone. Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C. The CYP3A4 isoenzyme is present in both the liver and intestines. This highly variable systemic availability of oral amiodarone may be attributed to highly individual variability in CYP3A4 activity.

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

No data are available on the drug disposition of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA’s precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral amiodarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation. On the other hand (see Clinical Trials), after amiodarone HCl injection administration, there is evidence of activity well before significant concentrations of DEA are attained.

The following table summarizes the mean ranges of pharmacokinetic parameters of amiodarone reported in single-dose IV (5 mg/kg over 15 min) studies of healthy subjects:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance (ml/kg/h)</th>
<th>Vss (L/kg)</th>
<th>t1/2 (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone HCl injection</td>
<td>90-156</td>
<td>40-84</td>
<td>20-47</td>
</tr>
<tr>
<td>Desethylamiodarone 100 mg</td>
<td>88-168</td>
<td>12-74</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Vss and Vc denote the central and steady-state volumes of distribution from IV studies.

Deseethylamiodarone clearance and volume involve an unknown biotransformation factor.

The systemic availability of oral amiodarone in healthy subjects ranges between 33% and 65%. From in vitro studies, the protein binding of amiodarone is >86%.

In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 mL/kg/h. Age, sex, renal, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of amiodarone HCl injection in critically ill patients, significantly lower Cmax and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower clearances (about 100 mL/kg/h) and a decrease in Cmax and an increase in t1/2 from about 20 to 47 days. In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition t1/2 of DEA is prolonged.

Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with oral amiodarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

There is no established relationship between drug concentration and therapeutic response for short-term intravenous use. Steady-state amiodarone concentrations of 1 to 2.5 mg/L have been associated with antarrhythmic effects and acceptable toxicity following chronic oral amiodarone therapy.

Pharmacodynamics
Amiodarone HCl injection has been reported to produce negative inotropic and vasodilatory effects in animals and humans. In clinical studies of patients with refractory VF or hemodynamically unstable VT, treatment emerged. drug-related hypotension occurred in 288 of 1836 patients (16%) treated with amiodarone HCl injection. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of amiodarone HCl injection.

Clinical Trials
Apart from studies in patients with VT or VF, described below, there are no two studies of amiodarone showing an antarrhythmic effect before significant levels of DEA were assessed. A placebo-controlled study of IV amiodarone (300 mg over 2 hours followed by 1300 mg/day) in post-coronary artery bypass graft patients with supraventricular and 2- to 3-fold competitive- ventricular arrhythmias showed a reduction in arrhythmias from 12 hours on. A baseline-controlled study using a similar IV regimen in patients with recurrent, refractory VT also showed a 50% decrease in arrhythmias.

The acute effectiveness of amiodarone HCl injection in suppressing recurrent VF or hemodynamically unstable VT in the preceding 24 hours was randomly assigned to receive doses of approximately 125 or 1000 mg over the first 24 hours, at 8-fold difference. In one study, a middle dose of approximately 500 mg was evaluated. The dose regimen consisted of an 8-hour loading infusion followed by a slower 16-hour maintenance infusion. The maintenance infusion was continued up to hour 48. Additional 10-minute infusions of 150 mg amiodarone HCl injection 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.

This product’s label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.SPPPharm.com or call our medical information and safety department toll-free at 1-800-551-7176.
progressive hepatic injury. Consideration should be injection should be monitored carefully for evidence of potential risk of hepatic injury should be weighed in patients receiving the high dose (FiO2 > 0.60) or 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 with T-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and fulminant hepatic failure required in less than 2% of patients.

Hypothyroidism
Hypothyroidism is the most common adverse effect seen with amiodarone therapy. The most frequent clinical treatment-emergent, drug-related hypothyroidism was reported in 18% of 1836 patients treated with amiodarone HCl injection. Clinically significant hypothyroidism was seen most often in patients receiving the high dose of amiodarone HCl injection but was not dose-related, but appeared to be related to the rate of infusion. Drug-related elevation in serum thyroxine levels in amiodarone HCl injection therapy was in 3% of patients. Drug-related hypothyroidism is a discontinuation required in less than 2% of patients.

Hyperthyroidism should be treated initially by slowing the infusion rate to 100 mg per hour. If hypothyroidism persists or worsens with continued treatment at this rate, the rate of infusion should be monitored closely and may require adjustment. If hyperthyroidism occurs, AMIODARONE HCl injection therapy should be discontinued (see ADVERSE REACTIONS, Post-marketing Reports).

Lever Elevations
Elevations of bilirubin hepatic enzyme values – alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) – are seen in some patients receiving amiodarone HCl injection for life-threatening VT/VT.

Bradydysrhythmias
Drug-related bradycardia occurred in 4.9% of 1836 patients in clinical trials while they were receiving amiodarone HCl injection, including patients with cardiac dysfunction. In one patient, bradycardia and a temporary pacemaker was available. In cases, visual impairment has progressed to permanent blindness. Amiodarone HCl injection is indicated for treatment of recurrent forms of frequently recurring ventricular fibrillation (VF) and hemodynamic unstable patients with tachycardia (VT) in patients refractory to previous therapy and can also be used to treat patients with VT/VF for whom oral amiodarone is administered in the setting of advanced VT/VF. Optic neuropathy and/or neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. If symptoms of ocular impairment, such as changes in visual acuity and decreases in peripheral vision, prompt ophthalmic examination is recommended. Aneurysm and/or retinal neovascularization may be a treatment for amiodarone-induced thyrotoxicosis. Amiodarone-induced hyperthyroidism may be fol-

WARNINGS, Thyroid Dysfunction
When amiodarone-induced thyroid dysfunction has failed or amiodarone-induced hyperthyroidism has failed amiodarone therapy as they may be more sensitive to the potential drug interactions of amiodarone with other drugs. Concomitant medications should be used with caution because of the slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid function tests persist for several weeks or even months following amiodarone withdrawal.

Hypothyroidism is best identified by relevant clinical symptoms and particularly by elevated serum TSH levels. Serum clinical symptoms are hypothyroidism usually occurs in 2% of patients receiving amiodarone, but the incidence may be higher in patients with prior inadequate dietary iodine intake. Amiodarone-induced hypothyroidism usually presents with either reversible hypothyroidism or with permanent hypothyroidism due to the possibility of drug-induced thyroiditis or of death associated with amiodarone-induced thyrotoxicosis. Therefore, surgical and anesthetic management may be a treatment for amiodarone-induced thyrotoxicosis. Amiodarone-induced hyperthyroidism is contraindicated because of the low radioactive uptake associated with amiodarone-induced thyrotoxicosis. Amiodarone-induced hyperthyroidism may be a treatment for amiodarone-induced thyrotoxicosis. Amiodarone-induced hyperthyroidism is contraindicated because of the slow elimination of amiodarone and its metabolites. Because of the slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid function tests persist for several weeks or even months following amiodarone withdrawal.

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interactions should be anticipated. This is especially important for drugs associated with serious toxicity, such as sedation and QT prolongation. If such drugs are needed, their dose should be reassessed and, where appropriate, decreased to avoid exceeding the long and variable half-life of amiodarone, potential for drug-drug interactions. Hemodynamic and electrophysiologic interactions should be considered.

Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit these isozymes may increase the metabolism and increase serum concentration of amiodarone. Recommended dosing should include the following:

- **Protease Inhibitors:** Protease inhibitors are known to inhibit CYP3A4 to varying degrees. A case report of one patient taking amiodarone with ritonavir showed that ritonavir resulted in increases in amiodarone concentrations from 300 to 1,400 ng/mL. In general, amiodarone levels are not affected. There was no evidence of toxicity. Monitoring the need for increased lidocaine serum concentrations during concomitant protease inhibitor therapy should be considered.

- **Histamine H2 antagonists:** Loratadine, a non-sedating antihistaminic, is metabolized primarily by CYP3A4 and CYP2C9 and has the potential to alter amiodarone levels. Studies have shown the presence of oral amiodarone; because of this, the dose of such agents should be approximately half of the usual recommended dose.

- **Antidepressants:** Trazodone, an antidepressant, is metabolized primarily by CYP3A4, QT interval prolongation and torsade de points have been reported with the co-administration of trazodone and amiodarone.

- **Other substances:**
  - **Grapefruit juice:** Given to healthy volunteers increased amiodarone levels by 15% and Cmax by 84%, resulting in increased plasma levels of amiodarone. Grapefruit juice should not be taken during treatment with oral amiodarone. A decrease in the metabolism of amiodarone was observed when changing from intravenous amiodarone to oral amiodarone (see DOSAGE AND ADMINISTRATION). Intravenous to Oral Transition.
  - **Antihypertensives:** A combination of amiodarone with other antiarrhythmics, if such drugs are needed, should be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

All antihypertensives are known to alter amiodarone levels. Amiodarone should be used with caution in patients with hypertension. The concurrent use of amiodarone with thiazides or other diuretics is recommended.

- **Hemodynamic and electrophysiologic interactions** should be considered in patients experiencing severe or prolonged bradycardia, and cardiovascular collapse.

- **Potentiation of other drugs:** Potentiation of warfarin type (CYP3C9 and CYP3A4 substrate) anticoagulant response is almost always avoided, because of the possible prolongation of the prothrombin time, and one should be aware of the potential for drug-drug interactions.

- **Other drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the CYP3A4 enzyme system.** The metabolism of amiodarone may vary in different individuals. When amiodarone is administered concomitantly with drugs known to affect CYP3A4, the AUC and Cmax of amiodarone may be increased, resulting in adverse effects. Concurrent administration of amiodarone with other drugs can affect amiodarone levels. Use of amiodarone in patients receiving protease inhibitors, isoniazid, cyclosporine, and certain herbal products has been extensively studied. Other drugs that inhibit CYP3A4 are known to increase the systemic exposure to amiodarone.

- **Cyclosporine:** Cyclosporine (CYP3A4 substrate) in combination with amiodarone results in an increase in serum digoxin concentrations.

- **Dilantin (phenytoin),** which is an active metabolite of phenytoin, has been shown to increase the serum digoxin concentration. This information should be considered.

- **Cimetidine:** Cimetidine inhibits CYP3A4 and can increase serum amiodarone levels.

- **Quinidine:** Quinidine and proarrhythmias have been reported in patients taking amiodarone in conjunction with quinidine concern. These concern has been shown to increase the serum digoxin concentration. This information should be considered.

- **Lidocaine:** Lidocaine increases the serum digoxin concentration by 70% after 2 weeks.

- **Histamine H1 antagonists:** These drugs may affect the metabolism of amiodarone. This information should be considered.

- **Cyclosporine (CYP3A4 substrate) in combination with amiodarone results in an increase in serum digoxin concentrations.**

- **Protease Inhibitors:** Protease inhibitors are known to inhibit CYP3A4 to vary-}

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**ADVERSE REACTIONS:** In a controlled trial involving 1,836 patients with life-threatening VT/VF, 60% of all adverse events appeared to be dose-related. These were collected in clinical trials involving 1,836 patients with life-threatening VT/VF. Data from all assigned treatment groups are pooled because none of the adverse events appeared to be dose-related.
SUMMARY TABULATION OF TREATMENT-EMERGENT STUDY EVENTS IN PATIENTS RECEIVING AMIODARONE HCL INJECTION IN CONTROLLED AND OPEN-LABEL STUDIES (2% INCIDENCE)

<table>
<thead>
<tr>
<th>Study Event</th>
<th>Controlled Studies</th>
<th>Open-Label Studies</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>24 (2.9%)</td>
<td>13 (1.2%)</td>
<td>37 (2%)</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>13 (1.6%)</td>
<td>21 (2.0%)</td>
<td>34 (1.8%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>18 (2.2%)</td>
<td>21 (2.0%)</td>
<td>39 (2.1%)</td>
</tr>
<tr>
<td>Heart arrest</td>
<td>39 (4.7%)</td>
<td>25 (2.4%)</td>
<td>64 (3.2%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>165 (20.2%)</td>
<td>123 (11.6%)</td>
<td>288 (15.6%)</td>
</tr>
<tr>
<td>Vertebral tachycardia</td>
<td>15 (1.8%)</td>
<td>30 (2.9%)</td>
<td>45 (2.4%)</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35 (4.2%)</td>
<td>29 (2.8%)</td>
<td>64 (3.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (3.5%)</td>
<td>43 (4.2%)</td>
<td>72 (3.9%)</td>
</tr>
</tbody>
</table>

Other treatment-emergent possibly drug-related adverse events reported in less than 2% of patients receiving amiodarone HCl injection in controlled and uncontrolled studies included the following: abnormal kidney function, atelectasis, diarrhea, increased ALT, increased AST, lung edema, nodal arrhythmia, pruritus, pyrexia, renal failure, sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting.

Postmarketing Reports
In postmarketing surveillance, hypotension (sometimes fatal), sinus arrest, and second- or third-degree atrioventricular block (including complete heart block) have been reported. Additionally, severe hypotension has been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/mL or less appear to be less likely. Therefore, for infusions longer than 1 hour, amiodarone HCl injection concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

OVERDOSAGE:
There have been cases, some fatal, of amiodarone overdose. Circulatory failure and inadvertent overdose of amiodarone HCl injection include hypotension, cardiovascular collapse, arrhythmias, and possibly death. Bradycardia and second- or third-degree atrioventricular block should be treated by atropine or a pacemaker. Hypertension and cardiogenic shock should be treated by pressors, fluid therapy, or other 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. Amiodarone is not dialyzable.

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

**AMIODARONE HCl INJECTION Dose Recommendations – First 24 Hours –**

<table>
<thead>
<tr>
<th>Loading</th>
<th>First Rapid</th>
<th>150 mg over the FIRST 10 minutes (15 mg/mL)</th>
<th>Add 3 mL of Amiodarone HCl Injection (150 mg/mL) to 100 mL D/W (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Followed by Slow</td>
<td>360 mg over the NEXT 6 hours (1 mg/mL) and 18 mL of Amiodarone HCl Injection (900 mg/mL) to 500 mL D/W (concentration = 1.8 mg/mL).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maintenance Infusion
540 mL over the REMAINING 18 hours (30 mL/hour), the rate of the slow loading infusion to 0.5 mg/mL.

After the first 24 hours, the maintenance infusion rate (540 mL/hour) should be con- tinued utilizing a concentration of 1 to 6 mg/mL (Amio- darone HCl Injection concentrations greater than 2 mg/mL should be administered via a central venous catheter). In the event of breakthrough episodes of VF or hemodynamically unstable VT, 150 mg supplemental intravenous infusions of amiodarone HCl injection mixed in 100 mL of D/W may be administered. Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of the main- tenance infusion may be increased to achieve effective arrhythmia suppression.

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2300 mg were associated with an increased risk of hypotension. The initial infusion rate should not exceed 0.5 mg/mL (0.5 mg/min).

Based on the experience from clinical studies of amiodarone HCl injection, there has been a report of a first dose reaction 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 amiodarone HCl injection for longer than 3 weeks.

The surface properties of solutions containing injectable amiodarone are 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 HCl injection must be delivered by a volumetric infusion pump.

Amiodarone HCl injection should, whenever possible, be administered through a central venous catheter dedicated to that purpose. An in-line filter should be used as incompatibility with a buffer in the container may cause precipitation.

Amiodarone HCl injection loading infusions at much higher concentrations and rates of infusion much faster than recommended have resulted in hepato- cellular necrosis and acute renal failure, leading to death (see PRECAUTIONS, Liver Enzyme Elevations). Amiodarone HCl injection concentrations greater than 3 mg/mL in D/W have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/mL or less appear to be less likely. Therefore, for infusions longer than 1 hour, amiodarone HCl injection concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

It is well known that amiodarone adorns to polyvinyl chloride (PVC) tubing and the clinical trial dose administra- tion schedule was designed to account for this adsorption. All of the clinical trials were conducted using PVC tubing and its use is therefore recommended. The concentrations and rates of infusion provided in DOSAGE AND ADMINISTRATION section reflect doses identified in these studies. Amiodarone HCl injection has been found to leach out plasticizers, including DEHP (di-(2-ethylhexyl)phthalate) from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing amiodarone HCl injection at higher concentrations and lower flow rates than pro- vided in DOSAGE AND ADMINISTRATION. In addition, polysorbate 80, a component of amiodarone HCl injection, is also known to leach DEHP from PVC (see DESCRIPTION). Therefore, it is important that the recommendations in DOSAGE AND ADMINISTRATION be followed closely. Amiodarone HCl injection does not need to be pro- tected from light during administration.

NOTE: Parenteral drug products should be inspected visually for particulate matter, whenever solution and container permit.

**AMIODARONE HCl INJECTION STABILITY**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Concentration</th>
<th>Container</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Dextrose</td>
<td>1 to 6 D/W</td>
<td>PVC</td>
<td>Physically compatible with amio- darone loss at &lt;10% at 2 hours at room temperature</td>
</tr>
<tr>
<td>5% Dextrose</td>
<td>1 to 6 D/W</td>
<td>Polyradex, Glass</td>
<td>Physically compatible with no amiodarone loss at 24 hours at room temperature</td>
</tr>
</tbody>
</table>

**Amiodarone Incompatibility**

Infusions of amiodarone HCl injection (in D/W) are incompatible with the drugs shown below.

**Y-SITE INJECTION INCOMPATIBILITY**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vehicle</th>
<th>Concentration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline</td>
<td>D/W 4 mg/mL</td>
<td>Precipitate</td>
<td></td>
</tr>
<tr>
<td>Cefamandole Nafate</td>
<td>D/W 4 mg/mL</td>
<td>Precipitate</td>
<td></td>
</tr>
<tr>
<td>Cefazolin Sodium</td>
<td>D/W 4 mg/mL</td>
<td>Precipitate</td>
<td></td>
</tr>
<tr>
<td>Methicillin Sodium</td>
<td>D/W 4 mg/mL</td>
<td>Precipitate</td>
<td></td>
</tr>
<tr>
<td>Heparin Sodium</td>
<td>D/W 4 mg/mL</td>
<td>Precipitate</td>
<td></td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>D/W 3 mg/mL</td>
<td>Precipitate</td>
<td></td>
</tr>
</tbody>
</table>

*Vial stoppers do not contain natural rubber latex.
*Store at 20° to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

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