# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 75-761

# FINAL PRINTED LABELING

ENLARGED TO 115% BY DIDP STAFF (F01)

AMERICAN PHARMACEUTICAL PARTNERS, INC.

45887A/Issued: July 2002

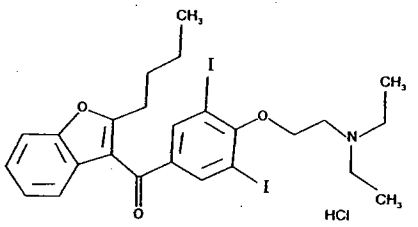
# AMIODARONE HYDROCHLORIDE
*INJECTION*

APPROVED
OCT 15 2002

Rx only

**DESCRIPTION:**
Amiodarone Hydrochloride Injection, for intravenous use, contains amiodarone HCl ($C_{25}H_{29}I_2NO_3$•HCl), a class III antiarrhythmic drug. Amiodarone HCl is (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl] methanone hydrochloride.

Amiodarone HCl has the following structural formula:



Amiodarone HCl is a white to slightly yellow crystalline powder, and is very slightly soluble in water. It has a molecular weight of 681.78 and contains 37.3% iodine by weight. Amiodarone HCl Injection is a sterile clear, pale-yellow solution visually free from particulates. Each mL of the Amiodarone HCl Injection formulation contains 50 mg of amiodarone HCl, 20.2 mg of benzyl alcohol, 100 mg of polysorbate 80, and water for injection.

**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 atrioventricular (AV) node. Its vasodilatory action can decrease cardiac workload and consequently myocardial oxygen consumption.

Amiodarone HCl Injection administration prolongs intranodal conduction (Atrial-His, AH) and refractoriness of the atrioventricular 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 infranodal 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**

| Formulation | SCL | QRS | QTc | AH |
|---|---|---|---|---|
| IV | ↔ | ↔ | ↔ | ↑ |
| Oral | ↑ | ↔ | ↑ | ↑ |

| Formulation | HV | ERP RA | ERP RV | ERP AVN |
|---|---|---|---|---|
| IV | ↔ | ↔ | ↔ | ↑ |
| Oral | ↔ | ↑ | ↑ | ↑ |

↔ No change

At higher doses (> 10 mg/kg) of Amiodarone HCl Injection, prolongation of the ERP RV and modest prolongation of the QRS have been seen. These differences between oral and IV administration suggest that the initial acute effects of Amiodarone HCl Injection may be predominately focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel blockade (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 150 mg Amiodarone HCl Injection in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) range 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/day) plus supplemental (150 mg) infusions (for recurrent arrhythmias), amiodarone mean serum concentrations between 0.7 to 1.4 mg/L were observed (n=260).

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 after several days of continuous infusion but with prolonged therapy reach approximately the same concentration as amiodarone. The enzymes responsible for the N-deethylation are believed to be the cytochrome P-450 3A (CYP3A) subfamily, principally CYP3A4. This isozyme is present in both the liver and intestines. The highly variable systemic availability of oral amiodarone may be attributed potentially to large interindividual variability in CYP3A4 activity.

Amiodarone is eliminated primarily by hepatic metabolism and billiary 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 activity 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.

**PHARMACOKINETIC PROFILE AFTER AMIODARONE HCl INJECTION ADMINISTRATION**

| Drug | Clearance (mL/h/kg) | Vc (L/kg) | Vss (L/kg) | t½ (days) |
|---|---|---|---|---|
| Amiodarone | 90-158 | 0.2 | 40-84 | 20-47 |
| Desethylamiodarone | 197-290 | — | 68-168 | ≥ AMI t½ |

Notes: Vc and Vss denote the central and steady-state volumes of distribution from IV studies.
"—" denotes not available.

Desethylamiodarone 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 >96%.

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/hr/kg. Age, sex, renal disease, 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 cirrhotic patients, significantly lower $C_{max}$ 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/hr/kg) than younger subjects (about 150 mL/hr/kg) and an increase in t½ 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 t½ 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 antiarrhythmic 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-emergent, 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 two other studies of amiodarone showing an antiarrhythmic effect before significant levels of DEA could have accumulated. A placebo-controlled study of IV amiodarone (300 mg over 2 hours followed by 1200 mg/day) in post-coronary artery bypass graft patients with supraventricular and 2- to 3-consecutive-beat ventricular arrhythmia showed a reduction in arrhythmias from 12 hours on. A baseline-controlled study using a similar IV regimen in patients with recurrent, refractory VT/VF also showed rapid onset of antiarrhythmic activity; amiodarone therapy reduced episodes of VT by 85% compared to baseline.

The acute effectiveness of Amiodarone HCl Injection 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 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.

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 Amiodarone HCl Injection) was deemed necessary.

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

Amiodarone HCl 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 Amiodarone HCl Injection may be safely administered for longer periods if necessary.

**CONTRAINDICATIONS:**
Amiodarone HCl Injection is contraindicated in patients with known hypersensitivity to any of the components of Amiodarone HCl Injection or in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block unless a functioning pacemaker is available.

**WARNINGS:**
***Hypotension***
Hypotension is the most common adverse effect seen with Amiodarone HCl Injection. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with Amiodarone HCl Injection. 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 alterations in Amiodarone HCl Injection therapy was reported in 3% of patients, with permanent discontinuation required in less than 2% of patients. Hypotension should be treated initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. ***The initial rate of infusion should be monitored closely and should not exceed that prescribed in*** **DOSAGE AND ADMINISTRATION.**

***Bradycardia and AV Block***
Drug-related bradycardia occurred in 90 (4.9%) of 1836 patients in clinical trials while they were receiving Amiodarone HCl Injection for life-threatening VT/VF; it was not dose-related. Bradycardia should be treated by slowing the infusion rate or discontinuing Amiodarone HCl Injection. In some patients, inserting a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 patient during the controlled trials. Patients with a known predisposition to bradycardia or AV block should be treated with Amiodarone HCl Injection in a setting where a temporary pacemaker is available.

***Long-Term Use***
See labeling for oral amiodarone. There has been limited experience in patients receiving Amiodarone HCl Injection for longer than 3 weeks.

***Neonatal Hypo- or Hyperthyroidism***
Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with its oral administration. If Amiodarone HCl Injection is administered during pregnancy, the patient should be apprised of the potential hazard to the fetus.

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

***Liver Enzyme Elevations***
Elevations of blood hepatic enzyme values – alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) – are seen commonly in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because the values may be elevated in patients who have had recent myocardial infarction, congestive heart failure, or multiple electrical defibrillations. Approximately 54% of patients receiving Amiodarone HCl Injection in clinical studies had baseline liver enzyme elevations, and 13% had clinically significant elevations. In 81% of patients with both 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.

Two (2) cases of fatal hepatocellular necrosis after treatment with Amiodarone HCl Injection have been reported. The patients, one 28 years of age and the other 60 years of age, were treated for atrial arrhythmias with 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 Amiodarone HCl Injection 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 with possible rate-related hypotension, ***the initial rate of infusion should be monitored closely and should not exceed that prescribed in*** **DOSAGE AND ADMINISTRATION.**

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of Amiodarone HCl Injection therapy, but patients receiving Amiodarone HCl Injection should be monitored carefully for evidence of progressive hepatic injury. Consideration should be given to reducing the rate of administration or withdrawing Amiodarone HCl Injection in such cases.

***Proarrhythmia***
Like all antiarrhythmic agents, Amiodarone HCl Injection may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsades de pointes, has been associated with prolongation by Amiodarone HCl Injection of the QTc interval to 500 ms or greater. Although QTc prolongation occurred frequently in patients receiving Amiodarone HCl Injection, torsades de pointes or new onset VF occurred infrequently (less than 2%). Patients should be monitored for QTc prolongation during infusion with Amiodarone HCl Injection.

***Pulmonary Disorders***
ARDS
Two percent (2%) of patients were reported to have adult respiratory distress syndrome (ARDS) during clinical studies. 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, Amiodarone HCl Injection played in causing or exacerbating the pulmonary disorder in those patients.

Postoperatively, occurrences of ARDS have been reported in patients receiving ***oral*** amiodarone therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that $FiO_2$ and the determinants of oxygen delivery to the tissues (e.g., $SaO_2$, $PaO_2$) be closely monitored in patients on amiodarone.

Pulmonary Fibrosis
Only 1 of more than 1000 patients treated with Amiodarone HCl Injection in clinical studies developed pulmonary fibrosis. In that patient, the condition was diagnosed 3 months after treatment with Amiodarone HCl Injection, during which time she received oral amiodarone. Pulmonary toxicity is a well-recognized complication of long-term amiodarone use (see labeling for oral amiodarone).

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

***Drug Interactions***
Amiodarone can inhibit metabolism mediated by cytochrome P-450 enzymes, probably accounting for the significant effects of oral amiodarone (and presumably Amiodarone HCl Injection) on the pharmacokinetics of various therapeutic agents including digoxin, quinidine, procainamide, warfarin (CYP2C9), dextromethorphan (CYP2D6), and cyclosporine (CYP3A4). Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with propranolol, diltiazem, and verapamil. Conversely, agents producing a significant effect on amiodarone pharmacokinetics include phenytoin, cimetidine, and cholestyramine. Because of the long half-life of amiodarone, drug interactions may persist long after discontinuation of drug administration. Few data are available on drug inter-

actions with Amiodarone HCl Injection. Except as noted, the following tables summarize the important reactions between *oral* amiodarone and other therapeutic agents.

**SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE**

**Drugs Whose Effects May Be Increased by Amiodarone**

| Concomitant Drug | Interaction |
|---|---|
| Warfarin | Increases prothrombin time. |
| Digoxin | Increases serum concentration. |
| Quinidine | Increases serum concentration. |
| Procainamide | Increases serum concentration, NAPA concentration. |
| Disopyramide | Increases QT prolongation which could cause arrhythmia. |
| Fentanyl | May cause hypotension, bradycardia, decreased cardiac output. |
| Flecainide | Reduces the dose of flecainide needed to maintain therapeutic plasma concentrations. |
| Lidocaine | **Oral:** Sinus bradycardia was observed in a patient receiving oral amiodarone who was given lidocaine for local anesthesia. **IV:** Seizure associated with increased lidocaine concentrations was observed in one patient. |
| Cyclosporine | Produces persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine. |

**SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE**

**Drugs that May Interfere with the Actions of Amiodarone**

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

*Potential drug class interactions with Amiodarone*

Beta Blockers: Since amiodarone has weak beta blocking activity, use with beta blocking agents could increase risk of hypotension and bradycardia.

Calcium Channel Blockers: Amiodarone inhibits atrioventricular conduction and decreases myocardial contractility, increasing the risk of AV block with verapamil or diltiazem or of hypotension with any calcium channel blocker.

Volatile Anesthetic Agents: (see **PRECAUTIONS, *Surgery***)

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

***Electrolyte Disturbances***

Patients with hypokalemia or hypomagnesemia should have the condition corrected whenever possible before being treated with Amiodarone HCl Injection, as these disorders can exaggerate the degree of QTc prolongation and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***

No carcinogenicity studies were conducted with Amiodarone HCl Injection. However, ***oral*** amiodarone caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors in rats was greater than the incidence in controls even at the lowest dose level tested, i.e., 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).

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

No fertility studies were conducted with Amiodarone HCl Injection. However, in a study in which amiodarone HCl 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*).

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

***Pregnancy***

**Category D. See WARNINGS, *Neonatal Hypo- or Hyperthyroidism.***

In addition to causing infrequent congenital goiter/hypothyroidism and hyperthyroidism, amiodarone has caused a variety of adverse effects in animals.

In a reproductive study in which amiodarone was given intravenously to rabbits at dosages of 5, 10, or 25 mg/kg per day (about 0.1, 0.3, and 0.7 times the maximum recommended human dose [MRHD] on a body surface area basis), maternal deaths occurred in all groups, including controls. Embryotoxicity (as manifested by fewer full-term fetuses and increased resorptions with concomitantly lower litter weights) occurred at dosages of 10 mg/kg and above. No evidence of embryotoxicity was observed at 5 mg/kg and no teratogenicity was observed at any dosages.

In a teratology study in which amiodarone was administered by continuous 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.

Amiodarone HCl Injection should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

***Nursing Mothers***

Amiodarone is excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered amiodarone have demonstrated reduced viability and reduced body weight gains. The risk of exposing the infant to amiodarone should be weighed against the potential benefit of arrhythmia suppression in the mother. The mother should be advised to discontinue nursing.

***Labor and Delivery***

It is not known whether the use of amiodarone during labor 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.

***Pediatric Use***

The safety and efficacy of amiodarone in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended.

Amiodarone HCl Injection contains the preservative benzyl alcohol (see **DESCRIPTION**). There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

***Geriatric Use***

Clinical studies of amiodarone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**ADVERSE REACTIONS:**

In a total of 1836 patients in controlled and uncontrolled clinical trials, 14% of patients received Amiodarone HCl Injection for at least one week, 5% received it for at least 2 weeks, 2% received it for at least 3 weeks, and 1% received it for more than 3 weeks, without an increased incidence of severe adverse reactions. The mean duration of therapy in these studies was 5.6 days; median exposure was 3.7 days.

The most important treatment-emergent adverse effects were hypotension, asystole/cardiac arrest/ electromechanical dissociation (EMD), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. Overall, treatment was discontinued for about 9% of the patients because of adverse effects. The most common adverse effects leading to discontinuation of Amiodarone HCl Injection therapy were hypotension (1.6%), asystole/cardiac arrest/EMD (1.2%), VT (1.1%), and cardiogenic shock (1%).

The following table lists the most common (incidence ≥ 2%) treatment-emergent adverse events during Amiodarone HCl Injection therapy considered at least possibly drug-related. These data were collected from clinical trials involving 1836 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 DRUG-RELATED STUDY EVENTS IN PATIENTS RECEIVING AMIODARONE HCL INJECTION IN CONTROLLED AND OPEN-LABEL STUDIES[1] (≥ 2% INCIDENCE)**

| Study Event | Controlled Studies (n = 814) | Open-Label Studies (n=1022) | Total (n=1836) |
|---|---|---|---|
| **Body as a whole** | | | |
| Fever | 24 (2.9%) | 13 (1.2%) | 37 (2.0%) |
| **Cardiovascular System** | | | |
| 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%) |
| Ventricular tachycardia | 15 (1.8%) | 30 (2.9%) | 45 (2.4%) |
| **Digestive System** | | | |
| Liver function tests abnormal | 35 (4.2%) | 29 (2.8%) | 64 (3.4%) |
| Nausea | 29 (3.5%) | 43 (4.2%) | 72 (3.9%) |

[1]Clinical trials and studies conducted by Wyeth-Ayerst.

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, atrial fibrillation, diarrhea, increased ALT, increased AST, lung edema, nodal arrhythmia, prolonged QT interval, respiratory disorder, shock, sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting.

In postmarketing surveillance, toxic epidermal necrolysis, pancytopenia, neutropenia, angioedema, and anaphylactic shock also have been reported with amiodarone therapy.

**OVERDOSAGE:**

There have been cases, some fatal, of amiodarone overdose. Effects of an inadvertent overdose of Amiodarone HCl Injection are 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.

Amiodarone is not dialyzable.

**DOSAGE AND ADMINISTRATION:**

Amiodarone shows considerable interindividual variation in response. Thus, although a starting dose adequate to suppress life-threatening arrhythmias is needed, close monitoring with adjustment of dose 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 regimen:

**AMIODARONE HCL INJECTION DOSE RECOMMENDATIONS**

**– FIRST 24 HOURS –**

| | | |
|---|---|---|
| **Loading Infusions** | ***First* Rapid:** | **150 mg over the FIRST 10 minutes (15 mg/min).** Add 3 mL of Amiodarone HCl Injection (150 mg) to 100 mL $D_5W$ (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes. |
| | ***Followed by* Slow:** | **360 mg over the NEXT 6 hours (1 mg/mL).** Add 18 mL of Amiodarone HCl Injection (900 mg) to 500 mL $D_5W$ (concentration = 1.8 mg/mL). |
| **Maintenance infusion** | | **540 mg over the REMAINING 18 hours (0.5 mg/min).** Decrease the rate of the slow loading infusion to 0.5 mg/min. |

**After the first 24 hours,** the maintenance infusion rate of 0.5 mg/min (720 mg/24 hours) should be continued utilizing a concentration of 1 to 6 mg/mL (Amiodarone 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 infusions of Amiodarone HCl Injection mixed in 100 mL of $D_5W$ may be administered. Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2100 mg were associated with an increased risk of hypotension. The initial infusion rate should not exceed 30 mg/min.

Based on the experience from clinical studies of Amiodarone HCl Injection, 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 Amiodarone HCl Injection for longer than 3 weeks.

**The surface properties of solutions containing injectable amiodarone are altered such that the drop size may be reduced. This reduction may lead to underdosage of the patient by up to 30% if drop counter infusion sets are used. Amiodarone 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 during administration.

Amiodarone HCl Injection concentrations greater than 3 mg/mL in $D_5W$ have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/mL or less appear to be less irritating. Therefore, for infusions longer than 1 hour, Amiodarone HCl Injection concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

Amiodarone HCl Injection infusions exceeding 2 hours must be administered in glass or polyolefin bottles containing $D_5W$. Use of **evacuated glass containers** for admixing Amiodarone HCl Injection is not recommended as incompatibility with a buffer in the container may cause precipitation.

It is well known that amiodarone adsorbs to polyvinyl chloride (PVC) tubing and the clinical trial dose administration schedule was designed to account for this adsorption. All of the clinical trials were conducted using PVC and its use is therefore recommended. The concentrations and rates of infusion provided in **DOSAGE AND ADMINISTRATION** reflect doses identified in these studies. It is important that the recommended infusion regimen be followed closely.

Amiodarone 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 provided in **DOSAGE AND ADMINISTRATION.**

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

**AMIODARONE HCL INJECTION SOLUTION STABILITY**

| Solution | Concentration (mg/mL) | Container | Comments |
|---|---|---|---|
| 5% Dextrose in Water ($D_5W$) | 1-6 | PVC | Physically compatible, with amiodarone loss <10% at 2 hours. |
| 5% Dextrose in Water ($D_5W$) | 1-6 | Polyolefin, Glass | Physically compatible, with no amiodarone loss at 24 hours. |

***Admixture Incompatibility***

Amiodarone HCl Injection in $D_5W$ is incompatible with the drugs shown below.

**Y-SITE INJECTION INCOMPATIBILITY**

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

***Intravenous to Oral Transition***

Patients whose arrhythmias have been suppressed by Amiodarone HCl Injection may be switched to oral amiodarone. The optimal dose for changing from intravenous to oral administration of amiodarone will depend on the dose of Amiodarone HCl Injection already administered, as well as the bioavailability of oral amiodarone. When changing to oral amiodarone therapy, clinical monitoring is recommended, particularly for elderly patients.

The following table provides suggested doses of oral amiodarone to be initiated after varying durations of Amiodarone HCl Injection administration. These recommendations are made on the basis of a comparable total body amount of amiodarone delivered by the intravenous and oral routes, based on 50% bioavailability of oral amiodarone.

**RECOMMENDATIONS FOR ORAL DOSAGE AFTER IV INFUSION**

| Duration of Amiodarone HCl Injection Infusion# | Initial Daily Dose of Oral Amiodarone |
|---|---|
| <1 week | 800-1600 mg |
| 1-3 weeks | 600-800 mg |
| > 3 weeks* | 400 mg |

#Assuming a 720 mg/day infusion (0.5 mg/min).
*Amiodarone HCl Injection is not intended for maintenance treatment.

**HOW SUPPLIED:**

| Product No. | NDC No. | Amiodarone HCl Injection per mL | Volume |
|---|---|---|---|
| 601603 | 63323-616-03 | 50 mg | 3 mL in a 3 mL Single Dose Vial |

Amiodarone HCl Injection is supplied in packages of 25 vials.

Vial stoppers do not contain natural rubber latex.

**Store at room temperature 15° to 25°C (59° to 77°F).**

**Protect from light and excessive heat.**

**Use carton to protect contents from light until used.**

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Schaumburg, IL 60173

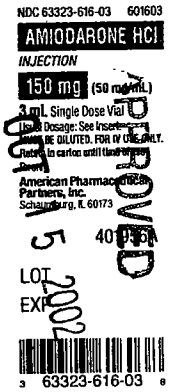
45887A
Issued: July 2002

ENLARGED TO 121%
BY FOI STAFF

**ANDA 75-761** **Minor Amendment**

**Amiodarone Hydrochloride Injection** **Final Approval Notification**

## FINAL PRINTED VIAL LABEL




## FINAL PRINTED TRAY LABEL