PRODUCT MONOGRAPH

[Pr] ratio-AMIODARONE
Amiodarone Hydrochloride Tablets BP

200 mg

Antiarrhythmic Agent

ratiopharm inc.
17800 rue Lapointe
Mirabel, QC
Canada, J7J 1P3

Date of Preparation:
March 31, 2010

Control#: 137656

ratio-AMIODARONE
Amiodarone Hydrochloride Tablets BP
200 mg

THERAPEUTIC CLASSIFICATION

Antiarrhythmic Agent

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ratio-AMIODARONE is generally considered a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all 4 Vaughan Williams classes. Like Class I drugs, amiodarone 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 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 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 has vasodilatory action that can decrease cardiac workload and consequently myocardial oxygen consumption.

At higher doses (>10 mg/kg) of amiodarone IV 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 IV may be predominantly focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to calcium channel blockade (Class IV activity) and β-adrenoreceptor antagonism (Class II activity).

Pharmacodynamics

Amiodarone has been reported to produce negative inotropic and vasodilating effects in animals and humans. After long-term treatment with **oral** amiodarone 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 therapy. In clinical studies of patients with refractory ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT), drug-related hypotension occurred in 15.6% of 1 836 patients treated with amiodarone IV. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of amiodarone IV.

Pharmacokinetics

The absorption of **oral** amiodarone is slow and variable, with peak serum amiodarone concentrations being attained from 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 50 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 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 amiodarone. The effects of food upon the bioavailability of amiodarone have been studied in 30 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 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%.

Amiodarone has a very high apparent volume of distribution (approximately 5 000 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, desethylamiodarone, has been identified, but the pharmacological activity of this metabolite is not known. During chronic treatment, the plasma ratio of metabolite to parent compound approximates 1.

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion. Desethylamiodarone (DEA) is the major active metabolite of amiodarone. At the usual amiodarone daily maintenance dose of 400 mg, mean steady-state DEA/amiodarone ratios ranged from 0.61 to 0.93. High-dose oral amiodarone loading in patients yielded 24-hour DEA/amiodarone ratios of 0.083 to 0.19. High-dose IV loading yielded a mean 24-hour DEA/amiodarone ratio of 0.041. No data are presently available on the activity of DEA in humans, but animal studies have shown that it has significant electrophysiologic and antiarrhythmic properties. The major enzyme responsible for the N-deethylation to DEA is believed to be cytochrome P-450 3A4. Large interindividual variability in CYP-450 3A4 activity may explain the variable systemic availability of

amiodarone. DEA is highly lipophilic and has a very large apparent volume of distribution, showing a higher concentration than amiodarone in all tissue except fat at steady state. Myocardial concentrations of DEA are approximately 3- to 4.5-fold greater than those of amiodarone during long-term oral amiodarone therapy. However, after either acute oral or acute IV administration, both mean serum and mean myocardial DEA concentrations are quite low compared to those of amiodarone.

There is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable. Amiodarone and DEA cross the placenta and both appear in breast milk.

A biostudy conducted in healthy volunteers under fed conditions with Ratio-AMIODARONE 200 mg tablets *vs* the Canadian reference drug has shown that the products are bioequivalent (see following table).

Summary Table of the Comparative Bioavailability Data
ratio-AMIODARONE (1 x 200 mg) Tablets From Measured Data (Fed State)

Parameter	**Geometric Mean Arithmetic Mean (CV %)**		
	Test ratio-AMIODARONE	**Reference Cordarone***	**% Ratio of Geometric Mean**
AUC_T (ng.h/mL)	5 917.94 6 135.44 (27.7)	6 365.43 6 599.43 (28.5)	93
AUC (ng.h/mL)	6 580.76 6 894.12 (26.6)	7 080.67 7 342.66 (28.4)	93
C_{max} (ng/mL)	327.10 355.24 (44.0)	376.47 394.07 (30.7)	87
T_{max} (h)	4.65 (42.2)	3.81 (45.2)	--
$T½_{el}$ (h)	22.43 (29.9)	22.82 (27.1)	--

For T_{max} and $T½_{el}$, the arithmetic mean only is presented.
* Cordarone (Wyeth-Ayerst) purchased in Canada.

Another study was conducted in healthy volunteers under fasting conditions with ratio-AMIODARONE 200 mg tablets *vs* the Canadian reference drug and has also shown that the products were bioequivalent (see following table).

Summary Table of the Comparative Bioavailability Data
ratio-AMIODARONE (1 x 200 mg) Tablets From Measured Data (Fasting State)

Parameter	Geometric Mean Arithmetic Mean (CV %)		
	Test ratio-AMIODARONE	**Reference Cordarone***	**% Ratio of Geometric Mean**
AUC_T (ng.h/mL)	2 969.71 3 103.19 (29.6)	3 202.71 3 333.39 (29.6)	93
AUC (ng.h/mL)	3 403.34 3 576.74 (32.5)	3 602.38 3 762.16 (31.0)	94
C_{max} (ng/mL)	129.54 137.02 (33.0)	141.74 150.37 (35.0)	91
T_{max} (h)	7.08 (27.4)	7.15 (34.7)	--
$T½_{el}$ (h)	24.33 (35.4)	23.6 (28.2)	--

For T_{max} and $T½_{el}$, the arithmetic mean only is presented.
* Cordarone (Wyeth-Ayerst) purchased in Canada.

During chronic treatment with oral amiodarone, close monitoring may be prudent for elderly patients and those with severe left ventricular dysfunction.

There is no well-established relationship between drug concentration and therapeutic response for long-term oral or short-term IV use. Steady-state amiodarone concentrations of 1 to 2.5 mg/L, however, have been effective with minimal toxicity following chronic **oral** amiodarone.

INDICATIONS

No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

Amiodarone therapy should be initiated in hospital and continued in a monitored environment until adequate control of the arrhythmia has occurred.

Patients treated with amiodarone should be under the supervision of a cardiologist or a physician with equivalent experience in cardiology.

Because of its potential for serious toxicity and the substantial management difficulties associated with its oral use, amiodarone is indicated only for the treatment of patients with the following documented, life-threatening, recurrent ventricular arrhythmias refractory to all other treatment or when alternative agents could not be tolerated.

• hemodynamically unstable ventricular tachycardia (VT).

• recurrent ventricular fibrillation (VF).

Amiodarone is normally initiated by the intravenous route for acute treatment of ventricular arrhythmias. Most patients will require this form of therapy for 48 to 96 hours or until the patient's ventricular arrhythmia has stabilized.

CONTRAINDICATIONS

In patients with known hypersensitivity to any of the components of oral amiodarone (tablets) and in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block unless a functioning pacemaker is available. In addition, oral amiodarone is contraindicated in patients with evidence of acute hepatitis (see **PRECAUTIONS**), thyroid dysfunction (see **WARNINGS**), or pulmonary interstitial abnormalities (see **WARNINGS**).

WARNINGS

Mortality

The results of the Cardiac Arrhythmia Suppression Trial (CAST) in postmyocardial infarction patients with asymptomatic ventricular arrhythmias showed a significant increase in mortality and in nonfatal cardiac arrest rate in patients treated with encainide or flecainide compared with a matched placebo-treated group. CAST was continued using a revised protocol with the moricizine and placebo treatment groups only. The trial was prematurely terminated because of a trend towards an increase in mortality in the moricizine-treated group.

The applicability of these results to other populations or other antiarrhythmic agents is uncertain, but at present, it is prudent to consider these results when using any antiarrhythmic agent.

Thyroid Dysfunction

Amiodarone inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine levels, decreased T_3 levels, and increased levels of inactive reverse T_3 (rT_3) in clinically triiodothyronine patients. It is also a potential

source of large amounts of inorganic iodine. Both hyper and hypothyroidism may occur during, or soon after treatment with **oral** amiodarone. Because of its release of inorganic iodine, or perhaps for other reasons, amiodarone can cause either hypothyroidism or hyperthyroidism. Thyroid function should be monitored prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid function tests may persist for several weeks or even months following amiodarone withdrawal.

Hypothyroidism has been reported in 2 to 4% of patients in most series, but in 8 to 10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Hypothyroidism is best managed by amiodarone dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue amiodarone in some patients.

Hyperthyroidism occurs in about 2% of patients receiving amiodarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Amiodarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation. In fact, **if any new signs of arrhythmia appear, the possibility of hyperthyroidism should be considered**. Hyperthyroidism is best identified by relevant clinical symptoms and signs, accompanied usually by abnormally elevated levels of serum T_3 RIA, and further elevations of serum T_4, and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany amiodarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of amiodarone. The institution of antithyroid drugs, beta-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism. Experience with thyroid surgery in this setting is extremely limited, and this form of therapy runs the theoretical risk of inducing thyroid storm. Amiodarone-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

In a rat carcinogenicity, at doses of 5, 16 and 50 mg/kg/day, amiodarone produced statistically significant dose-related changes in the thyroid gland, including follicular adenomas and carcinomas. The significance of these changes for the long-term use of amiodarone in humans is unknown.

Neonatal Hypo- or Hyperthyroidism: Pregnancy
Amiodarone can cause fatal harm when administered to a pregnant woman. Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If amiodarone is used during pregnancy, or if the patient becomes pregnant while taking amiodarone, the patient should be apprised of the potential hazard to the fetus.

In general, amiodarone 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 in doses 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*).

Loss of Vision
Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with amiodarone. In some cases, visual impairment has progressed to permanent blindness. 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 visual impairment appear, such as changes in visual acuity and decreases in peripheral vision, prompt ophthalmic examination is recommended. Appearance of optic neuropathy and/or neuritis calls for re-evaluation of amiodarone therapy. The risks and complications of antiarrhythmic therapy with amiodarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including fundoscopy and slit-lamp examination, is recommended during administration of ratio-AMIODARONE (see **ADVERSE REACTIONS**).

Pulmonary Toxicity
One of the most serious complications resulting from **oral** amiodarone therapy is pulmonary toxicity, characterized by pneumonitis. Clinical symptoms include cough, dyspnea, weight loss, and weakness.

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

On chest x-ray, there is a diffuse interstitial pattern of lung involvement frequently with patchy alveolar infiltrates, particularly in the upper lobe. Predicting which patient will develop pulmonary toxicity has been difficult (see **CONTRAINDICATIONS**). Pulmonary toxicity can appear abruptly either early or late during therapy and it commonly mimics viral or bacterial infection or worsening congestive heart failure. The relationship of pulmonary toxicity to duration of therapy, maintenance dose, and total dose is unclear. The majority of patients have recovered with this management, although some fatalities have occurred. Therefore, when amiodarone therapy is initiated, a baseline chest x-ray and pulmonary-function 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 seems to result from either indirect or direct toxicity as represented by hypersensitive pneumonitis or interstitial/alveolar pneumonitis, respectively at rates as high as 10-17% in patients with ventricular arrhythmia given doses around 400 mg/day. Pulmonary toxicity has been fatal about 10% of the time.

Hypersensitivity Pneumonitis: Usually appears earlier in the course of therapy, and rechallenging these patients with amiodarone results in a more rapid recurrence of greater severity. Bronchoalveolar lavage is the procedure of choice to confirm this diagnosis, which can be made when a T suppressor/cytotoxic (CD8-positive) lymphocytosis is noted. Steroid therapy should be instituted and amiodarone therapy discontinued in these patients.

Interstitial/Alveolar Pneumonitis: May result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), due to inhibition of phospholipase, will be present in most cases of amiodarone-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on amiodarone therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of amiodarone-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably to withdrawal of the amiodarone to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone-induced pulmonary toxicity was usually noted within the first week, and a clinical improvement was greatest in the first two to three weeks. Chest x-ray changes usually resolve within two to four months. According to some experts steroids may prove beneficial. Prednisone in doses of 40 to 60 mg/day or equivalent doses of other steroids have been given and tapered over the course of several weeks depending upon the condition of the patient. In some cases rechallenge with amiodarone at a lower dose has not resulted in return of toxicity. Recent reports suggest that the use of lower loading and maintenance doses of amiodarone are associated with a decreased incidence of amiodarone-induced pulmonary toxicity.

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

Fatalities, secondary to pulmonary toxicity, have occurred in approximately 10% of cases.

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

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

Liver Enzyme Elevations

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of amiodarone therapy. However, patients receiving oral or intravenous amiodarone should be monitored carefully for evidence of progressive hepatic injury.

Elevations of blood hepatic enzyme values-alanine aminotransferase (ALT) aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) are seen commonly in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because the values may be elevated in patients with recent myocardial infarction, congestive heart failure, and in those who have received multiple electrical defibrillations.

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

Proarrhythmia/QT Interval Prolongation

Amiodarone may cause a worsening of the existing arrhythmias or precipitate a new arrhythmia. Amiodarone causes prolongation of the QT interval. Proarrhythmia, primarily torsades de pointes, has been associated with prolongation of the QTc interval to 500 ms or greater. Proarrhythmia has been reported (2 to 5%) with oral amiodarone, especially in the presence of concomitant antiarrhythmic therapy and has included new-onset VF, incessant VT, increased resistance to cardioversion, and paroxysmal polymorphic VT associated with QT prolongation (torsades de pointes). Although QTc prolongation occurred frequently in patients receiving amiodarone IV, torsades de pointes or new-onset VF occurred infrequently (less than 2% of all patients treated with amiodarone IV in controlled clinical trials). Patients should be monitored carefully for QTc prolongation during amiodarone therapy.

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

The difficulty of using amiodarone effectively and safely poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance dose selection is difficult and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when amiodarone must be stopped will be made difficult by the

gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when amiodarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

Bradycardia and AV Block
In patients treated with **oral** amiodarone, symptomatic bradycardia or sinus arrest with suppression of escape foci occurred in approximately 2 to 4% of patients.

In patients who develop symptomatic bradycardia while taking **oral** amiodarone, dose reduction or discontinuation, and possibly pacing, may be considered. Due to the large body load of amiodarone that accumulates with chronic dose administration, and the long half-life of the drug, levels may drop slowly after dose reduction or discontinuation.

PRECAUTIONS

General
Patients with life-threatening arrhythmias may experience serious adverse events during their treatment and therefore should be properly monitored. Amiodarone should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, who are thoroughly familiar with the risks and benefits of amiodarone therapy, and who have access to facilities adequate for monitoring the effectiveness and adverse events of treatment (see **INDICATIONS**).

Loading Phase
The higher doses of oral amiodarone used in the loading phase may sometimes be associated with adverse effects such as nausea or tremor. The nausea may respond to dividing the total dose into 2 or 3 fractions taken with meals, or by decreasing the total daily dose. The tremor may respond to dose reduction as well.

Cardiac Disorders
Oral amiodarone should be used with caution in patients with latent or manifest heart failure because this condition may be worsened by its administration. In these cases, oral amiodarone should be given with appropriate concurrent therapy.

Oral amiodarone therapy may be considered in the treatment of patients with Wolff Parkinson White (WPW) syndrome, atrial flutter, or atrial fibrillation, when these conditions are complicated by life-threatening ventricular tachyarrhythmias. In such cases, care is required since the effect of oral amiodarone in these conditions does not appear to be uniform. Electrophysiologic studies may be of value in the selection of these patients who may respond to oral amiodarone, particularly in WPW syndrome.

Nervous System Disorders
Chronic administration of oral amiodarone in rare instances may lead to the development of peripheral neuropathy that may resolve when amiodarone is discontinued, but this resolution has been slow and incomplete.

Dermatologic Disorders
Oral amiodarone may induce photosensitization in some patients. Sunscreen preparations or protective clothing may afford some protection to individual patients experiencing photosensitization. Blue-grey discolouration of exposed skin has been reported during long-term treatment. With discontinuation of therapy, the pigmentation regresses slowly over a period of up to several years. The risk of this phenomenon appears to be related to dose and duration of therapy.

Ocular Abnormalities
Microdeposits appear in the cornea in the majority of patients treated with oral amiodarone. The deposits are usually discernible only by slit-lamp examination and occasionally give rise to symptoms such as visual halos, which are experienced in as many as 10% of patients. Corneal microdeposits are reversible with reduction of dose or termination of treatment. Asymptomatic microdeposits alone are not a reason to reduce or discontinue treatment (see **ADVERSE REACTIONS**).

Cases of optical neuropathy and optical neuritis have been reported (see **WARNINGS**).

Postsurgical Disorders
Occurrences of adult respiratory syndrome (ARDS) and low cardiac output syndrome have been reported postoperatively in patients receiving oral amiodarone therapy who have undergone either cardiac or noncardiac surgery. An intra-aortic balloon pump augmentation has been required in some patients with the low cardiac output syndrome at discontinuation of cardiopulmonary bypass. In the case of ARDS, although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. A number of patients who developed ARDS were subjected to a high concentration of oxygen in the inspired air; this could have been a factor in the respiratory complications. 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.

Caution should also be exercised in considering amiodarone patients for surgery in the presence of preoperative pulmonary dysfunction. However, as amiodarone has a very long half-life, withdrawal before surgery implies delaying operations by several weeks and putting patients at increased risk of malignant dysrhythmias. The ARDS in these cases has rarely been fatal.

Hypotension independent of, or associated with, discontinuation of cardiopulmonary bypass following open-heart surgery has been reported. Blood vessels may respond poorly to adrenoreceptor agonists. Atropine-resistant bradycardia and complete heart block have also been reported in patients being weaned from cardiopulmonary bypass.

Urogenital System Disorders
Oral amiodarone-induced epididymitis has been observed in some patients. This form of epididymitis is rare, benign, self-limited, and requires no treatment. Physicians should be aware of it to protect their patients from unnecessary invasive urologic examinations and antibiotic therapy.

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

Children
The safety and efficacy of amiodarone in children have not been established; therefore, its use in children is not recommended. Experience with the use of oral amiodarone in children is very limited. The following information is provided in order to help the physician who considers that critical and treatment-resistant disease in a pediatric patient makes the use of amiodarone necessary. In a study of 26 patients aged 6 weeks to 29 years (mean 13 years), an amiodarone 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 was 7.5 mg/kg/day (range 2.5 to 21.5 mg/kg/day).

Pregnancy
Amiodarone has been shown to be embryotoxic in some animal species. In 3 different human case reports, both the parent drug and its DEA metabolite have been shown to pass through the placenta, quantitatively ranging between 10 and 50% of human maternal serum concentrations. Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. Therefore, amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

Labour and Delivery
It is not known whether the use of amiodarone during labour or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect on the duration of gestation or on parturition.

Lactation

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

Drug Interactions

Amiodarone can inhibit the metabolism mediated by cytochrome P-450 enzymes, probably accounting for the significant effects of oral amiodarone on the pharmacokinetics of various therapeutic agents including digoxin, quinidine, procainamide, warfarin, dextromethorphan, and cyclosporine. 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. The potential for drug interactions may persist long after discontinuation of amiodarone administration because of its long half-life.

Few data are available on drug interactions with amiodarone IV. Except as noted, **TABLE I** and **TABLE II** summarize the key interactions between oral amiodarone and other therapeutic agents.

TABLE I: 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.

TABLE II: Summary of Drug Interactions with Amiodarone
Drugs That May Interfere With the Actions of Amiodarone

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

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 may have additive effects on atrioventricular conduction or myocardial contractility, increasing the risk of hypotension.

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

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

In general, combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to amiodarone the dose levels of previously administered agents should be reduced by 30 to 50% several days after the addition of amiodarone, when arrhythmia suppression should be beginning. The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as amiodarone is continued. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

ADVERSE EFFECTS

Because of the extensive distribution of amiodarone in body tissues, and the prolonged time required for its elimination from the body following discontinuation of long-term therapy, the relationship between adverse reactions and dosage and duration of therapy, has not been fully established. For some adverse reactions, for example, corneal microdeposits, a relationship to dosage and duration of therapy has been established, so

that corneal deposits are reversible with dose reduction or with discontinuation of therapy. However, for other adverse reactions, for example, fibrosing alveolitis or peripheral neuropathy, the dose relationship and the reversibility of the adverse reaction have not been established.

Certain gastrointestinal reactions (e.g. nausea, vomiting, constipation, and bad taste) and CNS reactions (e.g. fatigue, headaches, vertigo, nightmares, and sleeplessness) occur frequently at the initiation of therapy when high doses are used. These may disappear on reduction of the dose. The time and dose relationship of adverse events are under continued study.

The most serious and potentially life-threatening adverse effects associated with the use of amiodarone are pulmonary fibrosis, the aggravation of arrhythmias, and cirrhotic hepatitis.

Published data reflecting the North American experience with chronic oral amiodarone therapy suggest that amiodarone-associated adverse drug reactions are very common, having occurred in approximately 75% of patients taking 400 mg or more/day; these adverse events have led to the discontinuation of amiodarone treatment in 7 to 18% of patients. The adverse reactions most frequently requiring discontinuation of amiodarone have included pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, congestive heart failure, and elevation of liver enzymes. Other symptoms causing discontinuations less often have included visual disturbances, solar dermatitis, blue skin discolouration, hyperthyroidism, and hypothyroidism.

Ophthalmological Abnormalities
Corneal microdeposits are apparent upon slit-lamp examination in virtually all adult patients who have taken amiodarone for longer than 6 months. These deposits may give rise to symptoms such as visual halos or blurred vision (see **PRECAUTIONS**). Other reported amiodarone-associated abnormalities have included corneal degeneration, papilledema, photosensitivity, eye discomfort, dry eyes, scotoma, lens opacities, and macular degeneration, optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness (see **WARNINGS).**

Neurological Abnormalities
Occurring in 20 to 40% of patients, these common disorders have included ataxia, tremor, fatigue, dizziness, weakness, sleep disorders, headaches, cognitive disorders, disturbances of alertness, peripheral motor and sensory neuropathies, proximal muscle weakness, impotence (see **PRECAUTIONS**) and pseudotumour cerebri.

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 **WARNINGS**).

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 have 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. Hypotension independent of, as well as associated with, discontinuation of cardiopulmonary bypass following open-heart surgery has also been reported (see **WARNINGS** and **PRECAUTIONS**).

Gastrointestinal Abnormalities
Complaints of this nature have occurred in about 25% of patients and have included nausea, vomiting, constipation, anorexia, abnormal taste, dyspepsia, abdominal pain, and diarrhea (see **PRECAUTIONS**).

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 **PRECAUTIONS**). Overt liver disease can occur however, and has been fatal in a few cases.

Dermatologic Abnormalities
These have occurred in approximately 15% of patients, with photosensitivity (10% of patients) being the most common. Blue-grey skin pigmentation has been reported in 2 to 3% of patients. Hair loss (alopecia) has been observed in up to 4% of patients. Other amiodarone-associated phenomena reported with less than 1% incidence have included nonspecific skin eruptions, pruritus, acquired keratoderma, hyperhidrosis, onycholysis, generalized pustular psoriasis, vasculitis and polyserositis, and toxic epidermal necrolysis (see **PRECAUTIONS**).

Thyroid Abnormalities
Amiodarone-associated hypothyroidism has been reported in 2 to 4% of patients in most series but in 8 to 10% of patients with other series: hyperthyroidism has been reported in 1 to 3% of patients (see **WARNINGS**).

The following adverse events are based upon retrospective multicentre analysis of 241 patients treated at various doses of amiodarone for 2 to 1 515 days (mean duration: 441.3 days) (see **TABLE III**).

TABLE III: Incidence of Adverse Events in Patients Receiving Oral Amiodarone

Body System	Incidence, % n=241	Adverse Event
Gastrointestinal	10-33 4-9 1-3	Nausea, vomiting. Constipation, anorexia. Abdominal pain, dyspepsia, diarrhea, abnormal taste, dry mouth.
Dermatologic	4-9 1-3 <1	Solar dermatitis/photosensivity. Blue skin discolouration, rash. Alopecia, onycholysis.
Neurologic	4-9 1-3 <1	Malaise/fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias. Decreased libido/impotence, insomnia and other sleep disturbances, headache, cognitive disturbances and disorders of alertness, general weakness, peripheral motor and sensory neuropathies. Tinnitus.
Ophthalmologic	10-33 4-9 up to 2	Corneal microdeposits. Visual disturbances. Optic neuropathy with visual impairment/decreased acuity*.
Hepatic	4-9 1-3	Hepatomegaly, abnormal liver function test results. Nonspecific hepatic disorders.
Respiratory	4-9	Pulmonary inflammation or fibrosis.
Cardiovascular	1-3 <1	Congestive heart failure, cardiac arrhythmias, SA node dysfunction. Hypotension, cardiac conduction abnormalities.
Thyroid	1-3 <1	Hyperthyroidism, hypothyroidism. Goiter.
Other	1-3 <1	Flushing, coagulation abnormalities. Spontaneous ecchymosis, epididymitis.

***** Based on 1 retrospective study from 1981 to June 1986 at the Mayo Clinic, up to 2%; Optic neuropathy with visual impairment/decreased acuity.

OVERDOSE SYMPTOMS AND TREATMENT

Overdose may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or patients on digitalis therapy.

One report of the acute ingestion of a single 8 g dose of oral amiodarone by a healthy 20 year old female has been reported. At first assessment, the patient was conscious and profuse perspiration and a slight tachycardia were the only abnormal findings on clinical observation. Slight bradycardia was observed during the second and third day; thereafter,

QT interval and heart rate returned to normal. No clinical adverse events were documented over the subsequent 3-month monitoring period.

If an overdose should occur, gastric lavage or induced emesis should be employed to reduce absorption, in addition to general supportive measures. The patient's cardiac rhythm and blood pressure should be monitored, and if clinically significant bradycardia ensues, a temporary pacemaker should be used.

Neither amiodarone nor DEA is dialyzable.

DOSAGE AND ADMINISTRATION

General Considerations

Amiodarone therapy should be initiated in hospital and continued in a monitored environment until adequate control of the arrhythmia has occurred. Patients treated with amiodarone should be under the supervision of a cardiologist or a physician with equivalent experience in cardiology. Dose administration must be individualized, particularly taking into account concomitant antiarrhythmic therapy.

The dosage schedule for amiodarone is still somewhat controversial, probably in part due to its poor absorption, unusually long elimination half-life, and huge volume of distribution. Extensive tissue stores of amiodarone must be established before the effects on the heart of oral dose administration are apparent. Intersubject variability as well as differences in dosage regimens and methods of assessment have made it difficult to precisely define the time of onset of initial and maximal antiarrhythmic effect in an individual patient. In order to ensure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. Amiodarone's antiarrhythmic effect after oral administration may be noted in as early as 3 days (72 hours) but more often takes 1 to 3 weeks.

Because of the slow rate of elimination of amiodarone, 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 with other antiarrhythmic therapy should be reserved for patients with life-threatening arrhythmias who are unresponsive to adequate doses of a single agent (see **PRECAUTIONS, DRUG INTERACTIONS**).

Adults
Ventricular Arrhythmias
Loading Dose:
Loading doses of 800 to 1 600 mg/day are required for 1 to 3 weeks (occasionally longer) until therapeutic response occurs. (Administration of amiodarone in divided doses at meals is suggested for total daily doses of 1 000 mg or higher, when gastrointestinal intolerance occurs).

Maintenance Dose:
When adequate arrhythmia control has been achieved, or if adverse drug reactions become prominent, the amiodarone dose should be reduced to 600 to 800 mg/day for 1 month and then to the maintenance dose, usually 200 to 400 mg/day (occasionally 600 mg/day). Amiodarone may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a b.i.d. dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation, and by patient tolerance. Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity.

The lowest effective dose should be used to prevent the occurrence of adverse drug reactions. In all instances, the physician must be guided by the severity of the individual patient's arrhythmia and response to therapy. When dose adjustments are necessary, the patient should be closely monitored for an extended period of time because of the long and variable half-life of amiodarone and the difficulty in predicting the time required to attain a new steady-state level of drug. Dosage suggestions are summarized in **TABLE IV**.

TABLE IV: Oral Amiodarone Dosages for Ventricular Arrhythmia Suppression

Loading Dose-Daily	Adjustment and Maintenance Dose-Daily	
1-3 weeks	1 month	Usual Maintenance
800-1 600 mg	600-800	200-400 mg (some 600 mg)

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

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

Table V: Recommendations for Oral Dosage After IV Infusion

[a] Duration of Amiodarone IV Infusion	Initial Daily Dose of Oral Amiodarone (mg)
<1 week	800-1 600
1-3 weeks	600-800
>3 weeks [b]	400

[a] Assuming a 720 mg/day infusion (0.5 mg/min).

[b] Amiodarone IV is not intended for maintenance treatment.

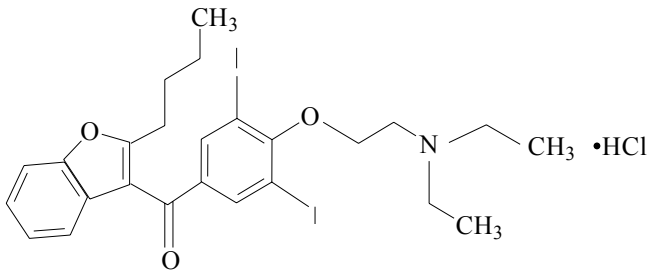
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Amiodarone Hydrochloride

Chemical Name: (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride

Structural Formula:



Molecular Weight: 681.78

Physical Form: White to slightly yellow crystalline powder

Solubility:

Water	0.25 mg/mL at 25°C
Ethanol (96%)	30 mg/mL at 25°C
Ethanol (100%)	13 mg/mL at 25°C
Hexane	0.0015 mg/mL at 25°C
Methylene Chloride	294 mg/mL at 25°C
Methanol	114 mg/mL at 25°C

pKa & pH Values: pKa of 6.64 at 25°C a 5% aqueous solution has a pH of 3.2-3.8

Melting Point: 156-163°C

Partition Coefficient: Approximately 82 (N-octanol/pH 7.4 phosphate buffer)

COMPOSITION

Medicinal Ingredients: Amiodarone HCl (200 mg)

Nonmedicinal Ingredients: cornstarch, lactose, polyvidone, anhydrous colloidal silica, colloidal silicon dioxide, magnesium stearate, erythrosine

STABILITY AND STORAGE RECOMMENDATIONS

ratio-AMIODARONE tablets should be stored between 15 and 30°C . Protect from light. Store unused tablets in the original carton.

AVAILABILITY OF DOSAGE FORMS

Oral
Each ratio-AMIODARONE tablet 200 mg, pink, round, biconvex with a single score notch on one side and "R-200" on the other contains 200 mg of amiodarone hydrochloride and is available in HDPE bottles of 100 tablets, and in polypropylene and aluminum blisters, packaged in boxes of 50 or 100.

PHARMACOLOGY

In anesthetised dogs, amiodarone, in two separate single-dose studies of 2.5, 5, and 10 (n=7/dose, and 10 (n=10) and 20 (n=5) mg/kg IV, caused a decrease in cardiac contractility (maximal at 10 mg/kg), systemic pressure and heart rate, and an increase in left ventricular end-diastolic pressure.

Direct injection of amiodarone (10 to 1 000 mcg) into the anterior descending branch of the left coronary artery of isolated, blood-perfused, dog ventricular muscle (n=8) electrically-paced at 1.5 to 2.0 Hz, produced dose-dependent decreases left ventricular dp/dt and developed tension to a maximum decrease of 50%.

In anesthetised dogs, single intravenous doses of 3, 5, or 10 mg/kg increased coronary blood flow and decreased coronary artery resistance, left ventricular work, heart rate, total peripheral vascular resistance, and myocardial oxygen consumption in a dose-dependent manner.

In anesthetised dogs, single intravenous doses of amiodarone, 10 mg/kg, reduced heart rate an additional 23% after it had been maximally reduced by intravenous propranolol and atropine. Under similar conditions, amiodarone reduced an isoprenaline-mediated increase in heart rate. Further combinations of single doses of intravenous amiodarone

with intravenous propranolol, with intravenous glucagon and with intraperitoneal reserpine led the investigators to conclude that the observed antiadrenergic actions of amiodarone were not mediated by competitive blockade of beta-adrenoceptors.

In 19 anesthetised dogs administered single, rapid, intravenous doses of amiodarone percutaneously-introduced intracardiac probes measured the monophasic action potentials (MAP) of right atria and ventricles, bundle of His potentials, and atrial and ventricular stimulation. Under the conditions of the experiment, the peak activity of amiodarone was found between the fifth and the tenth minutes. The rate of discharge of the sinus node was lowered by 36%. At the atrial level, the duration of the MAP was increased by 9% and its dv/dt was lowered slightly, the total refractory period was increased by 22%, the effective refractory period was increased by 27%, the functional refractory period was increased by 19%, the ratio of the length of the effective period/duration of the MAP became slightly greater than unity, conduction facilitation disappeared, and the period of slow conduction increased. In the AV node, the AH interval increased by 44% under normal rhythm, while atrial stimulation at 200/msec resulted in conversion to total AV block in more than half of the cases. The potential of the bundle of His and the HV interval were not altered. At the ventricular level, the duration of the monophasic action potential increased by 25%, its dv/dt decreased slightly, the total refractory period increased by 8%, and the effective refractory period increased by 14%.

Amiodarone, 20 mg/kg, given daily for 6 weeks intraperitoneally to rabbits, had no effect on the resting potential or action potential height and only a small effect on the maximum rate of depolarization of isolated rabbit atrial or ventricular muscle fibres as shown by intracellular recording. It caused a considerable prolongation of the action potential in both issues.

Using a microelectrode technique, the action of amiodarone (1.5×10^{-5}M) on the sinus node activity of spontaneously-beating, isolated right atria of rabbits was discovered to consist of a significant increase of the action potential duration and a decrease of the slope of diastolic depolarization, both effects leading to a reduction in the sinus rate.

In *in vitro* experiments using voltage clamp conditions by mean of the double sucrose gap technique in both frog atrial and ferret ventricular fibres, an aqueous solution of amiodarone (2.10^{-4} to 2.10^{-5}M) decreased outward K+-mediated currents and decreased reactivation of inward currents.

In an experiment involving the simultaneous daily administration by intraperitoneal injection to live rabbits (n=5) for a period of 3 weeks (beginning at week 4) of 5 mcg of thyroxine (assumed normal daily thyroxine requirement for these rabbits: approximately 7 mcg/day) and 20 mg/kg of amiodarone (for a period of 6 weeks), the prolongation by amiodarone of the action potential of isolated rabbit atria and ventricular strips was prevented. Treatment of similar rabbits (n=5) with 10 mg/kg of potassium iodine (equivalent to the iodine content of 20 mg/kg of amiodarone) given daily,

intraperitonealy, for 6 weeks had no effect upon cardiac action potential duration. It was concluded by the investigators conducting the rabbit tissue experiments that amiodarone had effects on cardiac action potentials similar to those which occur after thyroidectomy.

Amiodarone has been shown to exhibit antiarrhythmic activity in several experimental animal models. At a single intravenous dose of 5 mg/kg, amiodarone suppressed multifocal ventricular ectopic beats induced by the intravenous injection of epinephrine in an anesthetised dog: at 10 to 15 mg/kg, intravenous amiodarone suppressed polymorphic ventricular systoles provoked by the intravenous injection of barium chloride in anesthetised rabbits (n=2) and dogs (n=2). At 10 mg/kg, intravenous amiodarone suppressed ventricular extrasystoles induced by ligature of the anterior descending coronary artery in an anesthetised dog. At 10 to 20 mg/kg, intravenous amiodarone suppressed atrial fibrillation induced by acetylcholine in anesthetised dogs (n=2). At 10 mg/kg, intravenous amiodarone suppressed the ventricular tachycardia induced by aconitine in an anesthetised dog and the ventricular tachycardia induced by strophantine in morphinized dogs (n=16).

In the isolated hearts of rats pretreated intravenously with single doses (21 to 42 μmol/kg, 3.5 to 7.5 mg), amiodarone prevented (in a dose-related fashion) both ventricular tachycardia and ventricular fibrillation during regional myocardial ischemia and during reperfusion of ischemic muscle. In anesthetised guinea pigs (n=10/group) amiodarone administered intravenously at single doses of 25 and 50 mg/kg statistically significantly protected against ouabain-induced ventricular flutter-fibrillation although it did not provide significant protection against cardiac arrest.

TOXICOLOGY

Amiodarone 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 was administered intravenously in multiple dose toxicity studies to rabbits (6 weeks), dogs (4 weeks), and baboons (4 weeks).

Reproductive toxicology studies were performed by both oral and intravenous administration. Amiodarone 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.

Summaries of these studies appear in the following tables (categorized below).

TOXICOLOGY TABLES

TABLE 13: Oral Amiodarone: Acute Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Mouse/NMRI	Oral (gavage)	500 to 3 000 single dose	The oral LD_{50} was greater than 3 000 mg/kg. For technical reasons (high viscosity of the solutions at concentrations greater than 10%, the highest dose that could be administered was 3 000 mg/kg.
Rat/Wistar	Oral (gavage)	500, 750, 1 000, 2 000, 3 000/single dose	The oral LD_{50} was greater than 3 000 mg/kg. No deaths occurred at the highest dosage.
Dog*	Oral (diet)	0, 1 000, 3 000, or 5 000 in feed	The oral LD_{50} was greater than 5 000 mg/kg. No deaths occurred. All dogs vomited within 6 hours of ingestion. One dog given 5 000 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 14: Oral Amiodarone: Chronic Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Rat/Wistar	Oral (gavage)	100, 200, 300, 450, or 600/for 3weeks[a]	The oral LD_{50} was 420 mg/kg.
Rat/Wistar	Oral (gavage)	0, 100, 200, 300, 450, or 600/for 3 weeks [a]	The oral LD_{50} was greater than 600 mg/kg. A dose-related decrease in mean body weights of both males and females occurred.
Rat/Crl Bc	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 examination 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 thigh-dose treatment group. Clinical chemistry values of BUN, alkaline phosphatase, and total and esterified cholesterol (dose-related in males) were elevated at 75 mg/kg and above. There was an increase in T_4 and a decrease in the T_3/T_4 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 historic appearance of increased activity.

[a] animals were dosed 5 days/week.

TABLE 14: (cont'd) Oral Amiodarone: Chronic Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Rat/Fisher 344	Oral (gavage)	Vehicle-control, 160/7 days [a]	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 on the 20th days. 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. 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 [b]	Dose-related increases in mortality were observed (0 at 100 mg/kg, 15% at 200 mg/kg and 25% at 300 mg/kg. Body weight 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 and red blood cell counts in male and female rats were 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 those 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 myocardium were present.

[a] Treatment was followed by a sequential sacrifice of 7 animals on days 11, 18, 25, 39, 67, and 121 of the study.

[b] Animals were dosed 5 days/week.

TABLE 14: (cont'd) Oral Amiodarone: Chronic Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Dog/Beagle	Oral (capsule)	Vehicle-control or 100/4 weeks	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 the bile contained in the gallbladder 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 gallbladder 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**	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. 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.

** Report does not identify strain.

TABLE 14: (cont'd) Oral Amiodarone: Chronic Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
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 1 ½ months, 2 high-dose animals died during blood collecting. An autopsy revealed only gastritis and gastric ulceration. At 2 ½ 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. 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 2 ½ months. In the liver, this was characterized by a disorganization of the hepatic parenchyma, focal necrosis, sclerosed Kleman'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.
		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.

* Animals were dosed 5 days/weeks.

TABLE 15: Oral Amiodarone: Chronic Toxicity Studies/Carcinogenicity

Species/Strain	Mode of Administration	Dosage (mg/kg/d) 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 month of the study only; the effect was not dose related. A dose-related increase in the thyroid weight in both sexes 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 nonneoplastic 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 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.

TABLE 15: (cont'd) Oral Amiodarone: Chronic Toxicity Studies/Carcinogenicity

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
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 per 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 per 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 per day, an increased incidence of thyroid enlargement in all treated male groups, increased incidence of liver masses in males given 50 mg/kg per 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 per day, and thyroid weight was markedly higher in males given 50 mg/kg per 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 per day and above in the female. Nonneoplastic 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 per day. Lymph node changes occurred in males and females given 16 to 50 mg/kg per day, and systemic and thymic lesions occurred in males given 50 mg/kg per day.

TABLE 16: Oral Amiodarone: Chronic Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Dog/Beagle	Oral (gavage)	0, 12.5, 25, 50, 100 mg/kg/ 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 per day and above. Electrocardiograms were altered at 50 and 100 mg/kg per day. Dyslipidosis, characterized by the presence of foam cells was observed at 25 mg/kg per day and above in the lymph nodes and lungs. In the lungs these lesions appeared to be totally reversible after 3 months without treatment at 25 mg/kg per 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 per 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. Changes in thyroid function were characterized by an increase in T_4 at dose levels of 12.5 mg/kg per day and above, without any variation in T_3 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 disappearence of the thymus, amyotrophy, and altered spermatogenesis in males were also recorded at dosage levels of 50 and 100 mg/kg per day.

TABLE 17: Oral Amiodarone: Reproductive Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) 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 was embyotoxic 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. 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 implantation 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 estrous cyclicity and precoital 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 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. 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 estrous cycles from day 80 to day 100 postpartum.

TABLE 17: (cont'd) Oral Amiodarone: Reproductive Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Rat/Wistar	Oral (gavage)	Water control and 200/ Gestation day 1 to 21	Drug-treated females demonstrated adverse physical examination findings (listless, shaggy, and dull fur) and reduced weight gain. Conjunctivitis and nasal suppuration mixed with blood were observed in several of the treated rats. Six 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. 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 premating, during mating and from gestation day 1 to 19 (females only)	Prior to mating, treated animals showed no changes in behaviour, food consumption, or estrous cyclicity. Mean body weight gain was slightly depressed in females receiving 90 mg/kg. Although seven deaths occurred during the premating period, none were considered related to amiodarone 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 group may partially explain the reduced fertility rate. Because total litter loss due to resorptions 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 was without teratogenic potential in rats.

TABLE 17: (cont'd) Oral Amiodarone: Reproductive Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
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 treatment. The mean litter size and sex ratio were comparable in treated and control groups. The mean fetal weights were significantly reduced (18% smaller than control) only at 90 mg/kg. This difference was increased on days 4 and 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 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.
Rats/Sprague-Dawley	Oral (gavage)	0 (water control), 5, 50, or 100/ Gestion 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 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/ Gestion 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. Examination of the fetuses revealed no malformations.

TABLE 18: Mutagencicity

Mutagenicity Studies	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 GT4015	Not identified	At concentrations that approached toxic levels (100 micrograms/dish), no increase in spontaneous lysis occurred.
Micronucleus Test	Mouse/Charles River	50, 100, 225 mg/kg (each animal received 2 intra-peritoneal 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: Acute Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Rat/Wistar	IV	100, 150, 200/single dose	The IV LD_{50} was 135 mg/kg. Dyspnea, resulting in cyanosis, was observed.
Rat/Wistar	IV	100, 120, 140, 160, 180, 200/ single dose	The IV LD_{50} was 150 mg/kg.
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 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 LD_{50} for 5-minute infusion was 75 to 100 mg/kg. The LD_{50} for a 20-minute infusion was 150 mg/kg. Injections were followed by excitation with redness of the skin and mucous membrane, sedation, dyspnea, convulsions, and electrocardiographic alterations.
Dogs [(a)]	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 LD_{50} was 110 to 125 mg/kg for an infusion rate of 0.6 to 0.75 mg/kg per min and was >90 mg/kg for an infusion rate of 0.45 mg/kg per min.

IV Intravenous administration

TABLE 20: Intravenous Amiodarone: Subchronic Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) 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 (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 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 hematological 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 dosage 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 level), biochemical increased cholesterol (122% to 216%), triglycerides, alanine aminotransferase, alkaline phosphatase, potassium, and T_4; and decreased protein and T_3/T_4 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 segment, increased T wave amplitude) occurred at 60 mg/kg. Liver weights were increased in all drug-treated 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, crepitations, foamy discharge at sectioning) were observed in 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.

IV Intravenous administration

TABLE 20: (cont'd) Intravenous Amiodarone: Subchronic Toxicity Studies

Species/Strain	Mode of Administration	Dosage (mg/kg/d) Duration	Results
Dog/Beagle (cont'd)	IV	0, 7.5, 15, 30, and 60/ 4 weeks (cont'd)	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 was 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. Change in hemoglobin, (decreased red blood cell count, hemoglobin, hematocrit, mean cell hemoglobin, and mean cell hemoglobin concentration; increased reticulocytes, neutrophils, and monocytes) and biochemical (increased bilirubin, triglycerides, blood urea nitrogen, creatinine, and T_4 levels) parameters were observed in all drug-related 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 of the animals that died during the study exhibited cardiac lesions, 2 of which had a clot adherent to the endocardium and valvulæ in the right side of the heart, while the third showed discolouration of the myocardium and necrotic magma in the muscle.
Baboon/ *Papio papio*	IV	0, 12.5, 25 and 50/ 4 weeks	These changes were probably attributable to the irritative properties of amiodarone HCl when the compound is repeatedly administered into the cephalic or saphenous veins. Intravenous treatment with amiodarone HCl 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 at all dose levels, changes in the gallbladder 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 21: Intravenous Amiodarone: Reproductive Studies

Species/Strain	Mode of Administration	Dosage(mg/kg/d) Duration	Results
Rat/CD®BR	IV (infusion)	0 (saline, 0 (stock), 25, 50, 100/ Gestion 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 groups compared to the saline and/or stock control group. Food consumption was decreased for animals in the 100 mg/kg dosage group compared to either control group. Resorptions were increased, and liver litter size and fetal body weights were decreased at a dosage of 100 mg/kg. Delayed ossification of the sternum and metacarpals occurred at a 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 development NTEL was 50 mg/kg based on resorptions, reductions in liver 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 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

BIBLIOGRAPHY

1. Bopp P, Rasoamanambelo L, Crevoisier JL, et al. Acute hemodynamic effects of intravenous amiodarone in patients with coronary artery disease. J Cardiovasc Pharmacol 1985; 7:286-9.

2. Borowski GD, Garofano CD, Rose LI, et al. Effect of long-term amiodarone therapy on thyroid hormone levels and thyroid function. Am J Med 1985; 7:443-50.

3. Burger A, Dinichert D, Nicod P, Jenny M, Lemarchand Beraud T, Vallotton MD. Effect of amiodarone on serum triiodothyronine, reserve triiodothyronine, thyroxin, and thyrotropin. J Clin Invest 1976; 58:255-9.

4. Cordon-Lopez A, et al. Acute intracranial hypertension during amiodarone infusion. Crit Care Med 1985; 13:688-9.

5. Controlled Clinical Trials on Cordarone Intravenous. Data on file. Wyeth-Ayerst Canada Inc.

6. Duane PG, Rice KL, Charboneau DE, Niewoehner DE. Amiodarone-induced endothelial injury is associated with phospholipase C-mediated hydrolysis of membrane phospholipids. J Lab Clin Med 1992; 120:955-63.

7. Falik R, Flores BT, Shaw L, Gibson GA, Josephson ME, Marchlinsk FE. Relationship of steady-state serum concentrations of amiodarone and desethylamiodarone to therapeutic efficacy and adverse effects. Am J Med 1987; 82:1102-08.

8. Feiner LA, Younge BR, Kazmier FJ, Stricker BH, Fraunfelder FT. Optic neuropathy and amiodarone therapy. Mayo Clinic Proceed 1987; 62:702-17.

9. Figa FH, et al. Clinical efficacy and safety of intravenous amiodarone in infants and children. Am J Cardiol 1994; 74:573-7.

10. Finerman WB, Hamer A, Peter T, et al. Electrophysiologic effects of amiodarone therapy in patients with ventricular arrhythmias. Am Heart J 1982; 104:987-96.

11. Flaker CG, Alpert MA, Webel RR, et al. Amiodarone and sustained ventricular arrhythmias: statistical evidence of drug effectiveness. Am Heart J 1985; 110:371-6.

12. Forgoros EN, Anderson KP, Winkle RA, et al. Amiodarone: Clinical efficacy and toxicity in 96 patients with recurrent, drug refractory arrhythmias. Circulation 1983; 68:88-94.

13. Fraire AE, Guntupalli KK, Greenberg SD, Cartwright J Jr, Chasen MH. Amiodarone pulmonary toxicity: A multidisciplinary review of current status. Southem Med J 1993; 86:67-77.

14. Freedman MD, Somberg JC. Pharmacology and pharmacokinetics of amiodarone. J Clin Pharmacol 1991; 31:1061-9.

15. Garson A, Gillette P, McVey P, et al. Amiodarone treatment of critical arrhythmias in children and young adults. J Am Coll Cardiol 1984; 4:749-55.

16. Gill J, Heel RC, Fitton A. Amiodarone: an overview of its pharmacological properties, and a review of its therapeutic use in cardiac arrhythmias. Drugs 1992; 43:69-110.

17. Gittinger JW, et al. Papillopathy caused by amiodarone. Arch Ophthalmol 987; 105:349-51.

18. Green HL, et al. The efficacy of amiodarone in the treatment of ventricular tachycardia or ventricular fibrillation. Prog Cardiovasc Dis 1989; 31:319-54.

19. Haffajee CI, Love JC, Canada AT, Lesko LJ, Asdourian G, Alpert JS. Clinical pharmacokinetics and efficacy of amiodarone for refractory tachyarrhythmias. Circulation 1983; 67(6):1347-55.

20. Hansten PD, Horn JR. Drug interactions and updates. 6th ed. Philadelphia: Lea and Febiger; 1989, p.2.

21. Harris L, Roncucci R. editors. Amiodarone: pharmacology, pharmacokinetics, toxicology, clinical effects. Paris: MEDSI, Medicine and Sciences Internationales, 1986.

22. Harris L, McKenna WJ, Holt DW, et al. Renal elimination of amiodarone and its desethyl metabolite. Postgard Med J 1983; 59:440-2.

23. Harris L, et al. Side effects and possible contraindications of amiodarone use. Am Heart J 1983; 106:916.

24. Harrison RF, Elias E. Amiodarone-associated cirrhosis with hepatic and lymph node granulomas. Histopathology 1993; 22:80-2.

25. Heger JJ, Prystowsky EN, Jackman WM, et al. Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. N Engl J Med 1981; 305:539-45.

26. Helmy I, Herre JM, Garwood G, et al. Use of intravenous amiodarone for emergency treatment of life-threatening ventricular arrhythmias. J Am Coll Cardiol 1988; 12:1015-22.

27. Hohnloser SH, et al. Amiodarone-associated proarrhythmic effects. A review with special reference to torsade de pointes tachycardia. Ann Intern Med 1994; 121:529-35.

28. Hohnloser SH, et al. Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: Results of a prospective, placebo-controlled study. Am Heart J 1991; 121:80-95.

29. Kalantzis N, Gabriel P, Mouzas P, et al. Acute amiodarone-induced hepatitis. Hepato-gastroenterol 1991; 38:71-4

30. Kay GN, et al. Fatal postoperative amiodarone pulmonary toxicity. Am J Cardiol 1988; 62:490-2

31. Keidar S, Grenadier E, Palant A. Sinoatrial arrest due to lidocaine injection in sick sinus syndrome during amiodarone administration. Am Heart J 1982; 104:1384-5.

32. Kowey PR et al. Electrophysiologic testing in patients who respond acutely to intravenous amiodarone for incessant ventricular tachyarrhythmias. Am Heart J 1993; 125:1628-32.

33. Kupferschmid JP, et al. Amiodarone-induced complications after cardiac operation for obstructive hyperthrophic cardiomyopathy. Ann Thoracic Surg 1989; 48:359-64.

34. Leak D, Eydt JN. Control of refractory cardiac arrhythmias with amiodarone. Arch Intern Med 1979;139:425-8.

35. Lee TH, Friedman PL, Goldman K, et al. Sinus arrest and hypotension with combined amiodarone-diltiazem therapy. Am Heart J 1985; 109:163-4.

36. Liberman BA, et al. Anæsthesia and amiodarone. Can Anæsth Soc J 1985;32:629.37.

37. Martin WJ. Mechanisms of amiodarone pulmonary toxicity. Clin Chest Med 1990; 1:131-8.

38. Mitchell LB, Wyse DG, Gillis AM, Duff HJ. Electropharmacology of amiodarone therapy initiation: time courses of onset of electrophysiologic and antiarrhythmic effects. Circulation 1989; 80:34-42.

39. Mooss AN, Mohiuddin SM, Hee TT, et al. Efficacy and tolerance of high-dose intravenous amiodarone for recurrent, refractory ventricular tachycardia. Am J Cardiol 1990; 65:609-14.

40. Morady F, DiCarlo L, Krol R, et al. Acute and chronic effects of amiodarone on ventricular refractoriness, intraventricular conduction, and ventricular tachycardia induction. J Am Coll Cardiol 1986; 7:148-57.

41. Morady F, et al. Long-term efficacy and toxicity of high-dose amiodarone therapy for ventricular tachycardia or ventricular fibrillation. Am J Cardiol 1983; 52:975-9.

42. Mostow ND, Vrobel TR, Noon D, Rakita L. Rapid suppression of complex ventricular arrhythmias with high-dose oral amiodarone. Circulation 1986; 72(6):1231-38.

43. Myers JL, Kennedy JL, Plumb VJ. Amiodarone lung: Pathologic findings in clinical toxic patients. Hum Pathol 1987; 18:349-54.

44. Nalos PC, et al. Intravenous amiodarone for short-term treatment of refractory ventricular tachycardia or fibrillation. Am Heart J 1991; 122:1629-32.

45. Nattel S, Talajic M, Fermini B, Roy D. Amiodarone: pharmacology, clinical actions, and relationship between them. J Cardiovasc Electrophysiol 1992; 3:266-80.

46. Ochi RP, Goldenberg IF, Almquist A, et al. Intravenous amiodarone for the rapid treatment of life-threatening ventricular arrhythmias in critically ill patients with coronary artery disease. Am J Cardiol 1989; 64:599-603.

47. Polikar R, Goy JJ, Schlapfer J, Lemarchand-Beraud T, Biollaz J, Magnenat P, Nicol P. Effect of oral triiodothyronine during amiodarone treatment for ventricular premature complexes. Am J Cardiol 1986: 58:987-91.

48. Pollak PT, Sharma AD, Carruthers SG. Correlation of amiodarone dosage, heart rate, QT interval, and corneal microdeposits with serum amiodarone and desethylamiodarone concentrations. Am J Cardiol 1989; 64:1138-43.

49. Remme WJ, et al. Hemodynamic effects and tolerability in intravenous amiodarone in patients with impaired left ventricular function. Am Heart J 1991; 122:96-103.

50. Saksena S, Rothbart ST, Shah Y, Capello G. Clinical efficacy and electropharmacology of continuous intravenous amiodarone infusion and chronic oral amiodarone in refractory ventricular tachycardia. Am J Cardiol 1984; 54:347-52.

51. Schwartz A, Shen E, Morady R, et al. Hemodynamic effects of intravenous amiodarone in patients with depressed left ventricular function and recurrent ventricular tachycardia. Am Heart J 1983; 106:848-56.

52. Touboul P, Atallah G, Kirkorian G. Effect of intravenous amiodarone in patients with intraventricular conduction disorders. Eur Heart J 1982; 3:546-52.

53. Van Dyck M, et al. Should amiodarone be discontinued before cardiac surgery? Acta Anæsthesiologica Belg 1988; 39:3-10.

54. Vrobel TR, Miller PE, Moslow ND, Rakita L. A general overview of amiodarone toxicity. Its prevention, detection and management. Prog Cardiovasc Dis 1989; 31:393-426.

55. Weir SJ, et al. Sorption of amiodarone to polyvinyl chloride infusion bags and administration sets. Am J Hosp Pharm 1985; 42:267.