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APPROVAL PACKAGE FOR

APPLICATION NUMBER

18-972

Pharmacology Review(s)

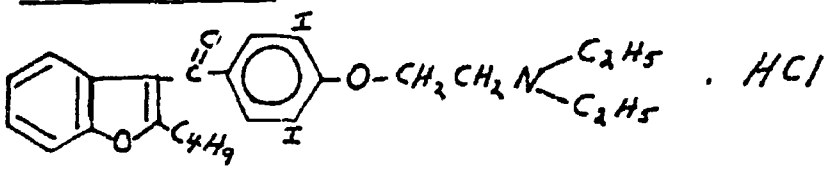
FEB 6 1984

Review and Evaluation of Pharmacology and Toxicology Data
(Original Summary; Corresp. date, March 14, 1983)

NDA. 18-972

Sponsor: American Home Products Corp.
New York, New York 10017

Drug
Generic name: Amiodarone hydrochloride
Trade name: Cordarone
Chemical name
2-butyl-3-(3,5-diiodo-4-beta-diethylaminoethoxybenzoyl)-benzofuran hydrochloride
Chemical structure



Category: Antiarrhythmic

Related NDA: [redacted]

Clinical Dosage

Loading (1-2 weeks) dose per day	600-1200 mg
Maintenance dose per day	200-800 mg

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1. Pharmacology

The pharmacological properties of amiodarone in animals have been extensively described in the published literature Presented herein is a synopsis of the sponsor's expanded optional summary of the more significant studies.

1.1 Antiarrhythmic Effects

Intraperitoneal injection of amiodarone (50-200 mg/kg) prevented chloroform-induced ventricular fibrillation in mice in a dose dependent manner (ED 50=150 mg/kg) Amiodarone was apporoximately 1/2 as potent as diphenylhydantoin or procainamide, 1/6 as potent as quinidine and 60 times less active than propranolol When administered orally, amiodarone was 6 times less active than quinidine and 50 times less active than propranolol, ED 50 values of 500 mg/kg, 85 mg/kg and 10 mg/kg, respectivley. Chronic oral dosing with amiodarone (50-100 mg/kg/day for 3-6 weeks) showed a residual antiarrhythmic effect which persisted for more than 48 but less than 72 hours

Amiodarone (15 mg/kg i v.) gave only partial protection against $CaCl_2$-inducted ventricular fibrillation in rats. In this model, lidocaine (5 & 7 5 mg/kg i v) and aprindine (15 mg/kg i.v.) were inactive, verapamil (0 5 mg/kg i v) was active, but only at near toxic doses

Amiodarone (5 & 10 mg/kg i v) effectively prevented the ventricular tachycardia evoked in rats by aconitine.

Intravenous administration of amiodarone (10 mg/kg) suppressed various experimental cardiac arrhythmias in the anesthetized dogs (1) epinephrine and $Ba\ Cl_2$ induced multifocal ventricular ectopic beats, (2) ventricular extrasystoles occurring after ligation of the anterior descending coronary, (3) atrial fibrillation induced by application of a solution of acetylcholine on the anterior wall of the right atrium, (4) ventricular tachycardia induced by placing a crystal of aconitine on the anterior wall of the right ventricle, or by i v. injection of a large dose of strophantine.

In anesthetized guina-pigs, acutely administered amiodarone (5 25 - 50 mg/kg i.v) provided significant, dose-related protection against omabain-induced ventricular arrhythmias but not cardiac arrest

Pretreatment (2 min and 3 wks) of rats with amiodarone (130-260 umol/kg i.p , 21-42 umol/kg i v) before the excision of their hearts caused a dose-related decrease in heart rate and an increase in the ventricular fibrillation threshold both before and after coronary arterial ligation Similarly, amiodarone (30-260 umol/kg i v , 7-56 umol/kg i v.) decreased the incidence of ventricular premature extrasystoles, ventricular tachycardia and ventricular fibrillation during the period of regional ischemia after coronary arterial ligation and also after reperfusion of the ischemic myocardium.

Orally administered amiodarone (10-40 mg/kg/day for 1-4 weeks) prevented the occurrence of ventricular fibrillation produced by coronary artery ligation in all of 10 pretreated dogs, whereas ventricular fibrillation occurred in 7 or 8 control dogs.

1 2 Electrophysiological Effects.

1 2.1 Heart rate

Intravenous infusion of amiodarone to chloralose anesthetized dogs produced a dose-related bradycardia at doses of more than 1 mg/kg. The amiodarone-induced bradycardia persisted in atropinized dogs, indicating that it is not evoked by parasympathetic stimulation. Propranolol pretreatment did not appreciably affect the negative chronotropic action of amiodarone (10 mg/kg i.v), demonstrating that the bradycardia produced by amiodarone was not due to blockade of beta-adrenoceptors.

1.2.2 Conduction rate

The effect of intravenously administered amiodarone upon conduction rate was studied in dogs by measuring potentials in the Bundle of His. Amiodarone reduced intra-auricular conduction rate (elongation of SA segment) as well as the rate of conduction in the atrio-ventricular mode (elongation of AH segment) Intra-ventricular conduction in the Bundle of His was not modified.

1 2 3 Refractory Periods

Several investigators have shown that amiodarone increases the refractory periods of the atrio-ventricular node, the atrial muscle, and to a lesser extent, the ventricular muscle This effect was demonstrated in dogs when amiodarone was given by (1) slow i v injection (2 mins) in successive doses of 1, 2, 4 and 8 mg/kg at intervals of 10 mins. or (2) chronic oral doses of 25 mg/kg/day over 4 weeks The same effect has also been demonstrated in isolated hearts from rabbits pretreated with amiodarone (25 mg/kg/day) for 4 weeks.

1.2 4 Effect on monophasic action potential

Rabbits were pretreated with amiodarone 20 mg (24 9 m mole/kg), given intraperitoneally, for a period of one to six weeks. Amiodarone had no effect on the resting membrane potential or action potential height or rate of rise of the action potential in either atrial or ventricular muscle. It caused a marked increase in action potential duration in both tissues--the increase being 23 7% at three weeks and 33 5% at six weeks The effect of amiodarone on intracelluar potentials was prevented by the simultaneou. administration of a dose of thyroxine equivalent to less than the normal daily thyroxine secretion

Rabbits that had been pretreated for 4 weeks with 100 mg/kg/day p o with amiodarone had a prolongation of the action potential in atrial and ventricular tissue and to a lesser degree in Purkinje fibers

Amiodarone (1.5×10^{-5}M) increased the action potential duration and decreased the slope of diastolic depolarization in sinus node cells of the isolated right atria of the rabbit In contrast to beta-adrenoceptor blockers, amiodarone reduced but did not entirely abolish the adrenergic effects on the sinus node activity The study suggests that the bradycardia induced by amiodarone is mainly due to a direct action on the autonomic cells of the sinus node

Rapid i v. injection of 10 mg/kg amiodarone in the dog lowered the rate of sinus node discharge. At the atrial level, the duration of the monophasic action potential (MAP) increased and the dv/dt was slightly lowered, the total refractory period, the effective refractory period, and the functional refractory period were increased The ratio of the length of the effective period/duration of the MAP was slightly greater than one, conduction facilitation dissappeared and the period of slow conduction increased. In the AV node, the AH interval increased under normal rhythm, while atrial stimulation at 200/min caused conversion to total AV block in many dogs. At the ventricular level, the duration of the MAP increased, its dv/dt decreased slightly, and the total refractory period and the effective refractory period increased.

1 3 Hemodynamic Effects.

Intravenous administration of amiodarone (3-10 mg/kg) to barbiturate anesthetized dogs caused bradycardia, a reduction in arterial blood pressure (diastolic greater than systolic) an increase in coronary blood flow and partial non-competitive inhibition of the effect of sympathetic nerve stimulation and the actions of catecholamines mediated by both alpha and beta adrenoreceptors Left ventricular work and total vascular resistance decreased Cardiac output was not significantly changed At doses of 10 and 20 mg/kg i v, amiodarone reduced myocardial contractility, increased the end-diastolic ventricular pressure (i e, increased cardic preload) Myocardial oxygen consumption decreased in a dose-dependent manner

In thyroidectomized rats and rabbits, i v. injection of 10 mg/kg of amiodarone produced reductions in heart rate and blood pressure similar to that seen in normal animals Thus, the hemodynamic properties of amiodarone are independent of thyroid function

1 4 Antiadrenergic Effects

The dose-response curves to isoproterenol-induced tachycardia in anesthetized dogs after i v amiodarone showed dose dependent decreased slopes. These features were consistent with a non-competitive inhibition pattern

The inhibition by amiodarone and propranolol of the chronotropic effect of isoproterenol was examined on spontaneously beating rabbit right atria The inhibition caused by proprarolol was of the competitive type pA_2 = 8 33)

In contrast, the non-parallel shift of the dose-response curves and the lowering of their respective maximum with increasing doses of amiodarone were typical of a non-competitive inhibition (p D_2 ca 4 17) Amiodarone also acted as a non-competitive type inhibitor of norepinephrine-induced contractions of isolated rat aortic strips (p D_2 ca 4 06)

2 Absorption, Distribution, Metabolism, Excretion (Taken from sponsor's Optional Expanded Summary)

2.1 Studies with ^{131}I-Labeled Amiodarone.

In acute studies, radiolabeled amiodarone (2 or 5 mg/kg, p o) was administered to male Wistar rats and tissues collected for analysis up to 48 hours after drug administration

Absorption was significant (approximately 50%) but variable No remarkable accumulation was observed in any of the organs and tissues examined

In another series of experiments, amiodarone was administered to rats at a dose level of 2 5 mg/kg/day, p o. for 24 days, and animals were sacrificed 3, 8, 14, 24 and 36 days, after the start of the experiment The concentration of iodine in various organs had no tendency to rise (except in the thyroid where an accumulation was noted during the first 2 weeks of treatment which subsequently declined despite continued treatment) Twelve days after the end of the treatment there was practically no iodine remaining in the tissues examined.

Chronic treatment of several animal species at elevated doses (30 to 60 mg/kg, p o. for 8 to 39 weeks) produced variable tissue concentrations of iodine from species to species Increasing the dose or prolonging the treatment did not necessarily lead to an increased concentration of iodine being retained These study results indicate that the highest levels of iodine occurred in the dog and cat and the lowest levels in the rat, guinea pig and monkey

The highest uptake of iodine occurred in the liver (cat and dog), the spleen (cat and dog), the adrenals (dog, cat and mouse) and the kidney (cat and dog), the lowest concentrations of iodine were found in striated and smooth muscle and the central nervous system

2 2 Studies with High Performance Liquid Chromatography.

A study was performed by injecting 2 dogs with 10 mg/kg, i v. Blood samples were obtained over 8 hours, and a final sample 24 hours after dosing. Pharmacokinetic coefficients were computed assuming a 2-compartment model.

	Dog 1	Dog 2
terminal t 1/2 (hr)	8.4	9 1
apparent V_D (l/kg)	3 037	2.635
body clearance (l h^{-1} kg^{-1})	3.0	2 6
elimination constant (h^{-1})	0 40	0 24
area (mg.h.l^{-1})	3.3	3 8

It should be noted that in spite of a rather short observation period, the half-life was long, and the apparent volume of distribution very large. Such an elevated volume of distribution was also evident from a study in the rat Amiodarone was injected i.v. in 10 rats and assayed in plasma and myocardial muscle 3 hours later The ratio of myocardial/plasma concentration ranged from 40 to 155 with a mean of 93. Compared with the dog, the plasma levels were higher by a factor of about 1 8, indicating that amiodarone in rats might be distributed in a smaller volume than in dogs.

Amiodarone (50 mg/kg) was administered intravenously to male rats which were then sacrificed at various time intervals for collection of blood and tissue samples

The drug disappeared from the blood with an eliminiation half-life of approximately 8.5 hours and distributed extensively into tissues, the apparent volume of distribution was 29 5 l/kg Drug concentrations were highest in well perfused oragans such as the liver, kidney and heart, and lowest at all times in the brain. The highest concentrations were found within 5 to 30 minutes of administration Amiodarone accumlated extensively in adipose tissue and reached a fat/blood concentration of about 1,000 at 16 hours

3. Toxicology

3 1 Acute Toxicity

Species	Route	LD_{50}, mg/kg
Mouse	i p.	450
	p o.	3000
Rat	i p.	610
	p o	3000
	i v	135
	i v	150
Dog	p o	5000

Clinical signs observed by the parenteral routes in rats and mice included motor stimulation, aggressiveness, Straubs' phenomenon, respiratory difficulties, sedation and tremors followed by convulsions Within 6 hours of ingesting amiodarone, all dogs vomited One dog given 5000 mg/kg showed tremor 24 hours after dosing, which lasted more than 96 hours and was accompained by paresis of the hindquarter.

Lethal doses of amiodarone in anesthetized dogs following various i.v infusion rates were

Dog No	Anesthesia	Infusion Rate, (mg/kg/min)	Time	Lethal dose (mg/kg)
1	Nembutal	0 75	145	110
2	Chloralose	0 75	125	95
3	Nembutal	0 62	200	124
4	Chloralose	0 45	7 hr *	190

*Animal still alive after 7 hours of infusion.

3 2 Subchronic and Chronic Toxicity.

3.2 1 Rat

3 2 1 1 Four-week oral (Clin Midy Research Ctr, France)

Strain Cvl Br (Charles River)
Duration 4 weeks
Route Oral (gavage)
Dose Levels 0(tap-water), 10, 19, 37 5, 75 or 150 mg/kg/day
Number/Sex/Dose 10
Results Animals treated with 75 mg/kg and 150 mg/kg were in a poor general condition with signs of piloerection, dehydration and sedation, the symptoms being more pronounced in females than males Nine animals (6 male, 3 female) in the 150 mg/kg dose group died, in addition, 3 animals (2 male, 1 female) in this group, and one 75 mg/kg treated female were moribund sacrificed. Autopsy revealed that rats which died during the study were cachectic No clinical signs or mortalities occurred at doses of 37 5 mg/kg and lower No significant changes in blood pressure (measured pre- and day 36) were observed in treated rats Electrocardiographic examinations (performed pre- and day 36) showed a dose-related decrease in heart rate at the two highest dose levels and a significant increase of the PR interval at doses of 37 5 mg/kg and greater At 150 mg/kg the QTa segment was increased and the QRS complex slighty prolonged The T wave amplitude was elevated at the two highest dose levels

No drug-related ocular lesions were reported Bodyweight gains decreased in both sexes at 150 mg/kg and in females at 75 mg/kg Food consumption was also reduced in animals from these dose groups

At 150 mg/kg, the number of neutrophils greatly increased and the lymphocyte count decreased, the total count remained unchanged

Clinical chemistry evaluation showed increases in BUN, total and esterified cholesterol, SGPT, and alkaline phosphatase in the 150 mg/kg group and to a lesser extent in the 75 mg/kg group At 75 and 150 mg/kg, thyroid hormones T_4 increased and the T_3/T_4 ratio decreased

At doses of 75 and 150 mg/kg, there was an increase in lung and adrenal weights, and a decrease in thymus, prostate, seminal vesicles, uterus, and ovarian weights At 37 5 mg/kg and greater, female liver relative weights slightly increased

Microscropic examination revealed at doses of 75 mg/kg and 150 mg/kg a dose-dependent accumulation of foamy macrophages involving the mesenteric lymph nodes with spreading to the liver, spleen and lungs. The adrenal cortex contained islets of clear cells and birefringent bodies and moderate thymic regression at the high dose level In another study, it was demonstrated that mesenteric lymph node and lung lesions induced by amiodarone given to rats at 160 mg/kg p o for 7 consecutive days were totally reversible within 2 weeks after termination of treatment

3 2 1 2 Three-months oral (Labaz Laboratories, Belgium)

Strain Wistar
Duration 3 months
Route Oral (gavage)
Dose Levels 0(water), 100, 200 or 300 mg/kg/day
Number/Sex/Dose 10
Results Mortalities were $^{0}/_{20}$, $^{0}/_{20}$, $^{3}/_{20}$ and $^{5}/_{20}$ in the control, 100 mg/kg, 200 mg/kg and 300 mg/kg dose groups, respectively Body weight gains were reduced relative to control by 19% in 200 mg/kg males, 30% in the 300 mg/kg males and 14% in 300 mg/kg females At the 200 mg/kg and 300 mg/kg levels, there were dose related decreases in hemoglobin and erythrocyte concentrations

At 300 mg/kg, the ratio of circulating lymphocytes to polymorphonuclear leukocytes increased, especially in females BUN was significantly increased in the 200 mg/kg and 300 mg/kg groups

Histomorphological hypertrophic changes of the thyroid were evident in 100 mg/kg rats Centrilobular congestion of the liver was noted at both 200 mg/kg and 300 mg/kg Myocardial lesions occurred in 2 of 14 rats receiving 300 mg/kg

3 2 2 Dog.

3 2 2.1 Four-week oral (Clin-Midy Research Ctr , France)

Strain Beagle (CREP)
Duration 4 weeks
Route Oral (capsule)
Dose Level 0 or 100 mg/kg/day
Number/Sex/Dose treated-2, control-1
Results Bodyweight and food consumption were decreased in treated animals, resulting in the sacrifice of one female on day 30 due to its cachectic state Autopsy of this dog showed an abnormal increase in the quantity of bile in the gallbladder and intestine ECG analysis (performed pre- and day 34) from treated dogs showed a lengthening of the ST segment with a reduction in heart rate, although there were no arrhythmias. Slight, but statistically significant increases in cholesterol and triglycerides were noted in treated animals In addition, clinically significant increases SGPT (129%), SGOT (300%) and LDH (363%) were noted in 3 of 4, 1 of 4 and 3 of 4 treated dogs, respectively Urinary pH was increased in treated groups

Postmortum examination revealed increases in the absolute and relative weights of the adrenal and liver and the disappearance of the thymus in treated dogs Microscopic changes in drug treated animals were the presence of foam cells in the mesenteric lymph nodes, the spleen and the lymphoid tissue of the digestive tract. The foamy cells were characterized by an abundance of polymorphic cytoplasic inclusions of probable dyslipdic origin

3 2 2 2 Three-month oral (Labaz Research Center, Belgium)

Strain Beagle
Duration 3 months
Route Oral (capsule or in diet)
Dose Levels 0, 30, or 150 mg/kg/day, administered 5 days a week
Number/Sex/Dose 2
Results No deaths occurred Signs of gastrointestinal intolerance (vomiting, diarrhea, anorexia) were noted at 150 mg/kg, especially during the first 1 1/2 months of the study. Excessive salivation occurred throughout the study Concurrent with the period of digestive distrubance, high dose dogs showed a 20% loss in body weight The leukocyte count increased in a dose-related manner at both dosage levels During the last month of the study, all high dose dogs showed decreases in neutrophils and 3 of 4 high dose dogs showed increases in lymphocytes A slight, progressive increase in BUN occurred in one high dose dog SGPT increased in dogs given 150 mg/kg during the first month of dosing but returned to normal thereafter Alkaline phosphatase levels increased in the high dose group but remained within the normal range Total cholesterol increased in one high dose dog BSP clearance remained normal Postmortem examination showed necrosis of the stomach in 1 high dose dog and thyroid hypertrophy in another

3 2 2 3 Nine-month oral (Labaz Laboratories, Belgium, dated April 1969)

Strain Mongrel
Duration 9 months
Route Oral (diet)
Dose Levels 0, 30 or 60 mg/kg/day
Number/Sex/Dose 2
Results No changes in appetite or behavior were noted Body weight gains were similar in each group Serum cholesterol levels were increased at the high dose level, although it was noted that pre-dosing levels for this group were higher than either control or low-dose values.

Free fatty acid levels showed dose-related increases Blood and tissue iodine levels and PBI were elevated in drug treated dogs Macroscopic and microscopic tissue examinations revealed no drug-related lesions

3 2 3 Pig

3.2 3 1 Three-month oral (Labaz Research Center, Belgium)

Duration 3 months
Route Oral (diet)
Dose Levels 0, 10, 20, 50 or 150 mg/kg/day
Number/Sex/Dose 2
Results Signs of toxicity in 150 mg/kg treated animals included ataxia, hypotonia, and no weight gain, appetite was not affected at 1 1/2 months, two 150 mg/kg dosed pigs died during blood collecting Autopsy showed gastritis and a recent gastric ulceration of the stress ulcer type The other two high-dose pigs were sacrificed in extremis at 2 1/2 months Autopsy findings were unremarkable Hematology and blood chemistry values were within normal limits in drug treated animals (blood testing was not performed on high dose animals) Histopathological lesions were found in the liver and endocrine glands in pigs treated at the 15 mg/kg dose for 2 1/2 months The liver lesion was characterized as disorganization of the hepatic parenchyma, focal necrosis, sclerosed interlobular spaces, and brown pigmented macrophages in the interstitial spaces The adrenal cortex had lympho-monocyte clusters and hemorrhagic foci in the zona fasciculota Evidence of hyperfunction was found in both the zona glomerulosa and the zona fasciculata In the thyroid, numberous follicles had epithelial cells that were higher than normal with vacuolar cytoplasm, suggesting increased activity In one pig, the basophil cells of the pituitary were more numberous and larger than normal

3 2 3 2 Ten-month oral (Labaz Research Center, Belgium, dated January, 1970

Strain Mini-pig
Duration 10 months
Route Oral (diet)
Dose Levels 0 or 50 mg/kg/day
Number/Sex/Dose treated-3, control -2,
Results There were no deaths or clinical signs of toxicity One treated male pig had low RBC, ESR, hemoglobin and hematocrit No macroscopic abnormalities were found Histological examinations were not reported

3 2.4 Rabbits

Strain Dutch
Duration 6 weeks
Route Intravenous
Dose Levels 0, 5, 10, or 25 mg/kg/day, 5 days/week
Number/Sex/Dose 8
Results There were no drug related deaths or clinical signs of toxicity. Hemoglobin and red blood cell counts were significantly reduced in the mid and high dose groups. Total cholesterol values were above control in all dose groups, although the difference was statistically significant only at dose levels above 10 mg/kg. Total lipids were significantly increased in high dose males and low and mid dose females. Hepatic changes (white patches, signs of cirrhosis) were seen in several treated rabbits. Histologically, treated animals (2 low, 2 m'd, 1 high) showed hepatic parenchyma degeneration which was replaced by zones of necrosis surrounded by fibrous tissue giving a cirrhotic appearance.

3 3 Reproduction

3 3.1 Fertility and general reproductive performance study in rats (two-generation study) (Labaz Research Center, Belgium dated February 2, 1982, April, 1982)

Strain OFA (Sprague-Dawley)
Route Oral (gavage)
Dose Levels 0, 10, 30, 60 or 90 mg/kg/day.
Number/Sex/Dose 16 males, 25 females.
Treatment Schedule (F1 generation)· Males treated for 64 days prior to mating and throughout the mating period. Females treated for 64 days prior to mating, throughout the mating period, gestation, and until termination on day 21 post-partum
Results The general condition and survival of the F_1 generation animals were similar in all groups during the pre-mating period Body weight gain of 60 mg/kg females was slightly decreased from week 8 onwards, a.. that of 90 mg/kg females was decreased throughout the pre-matings, mating, and gestation periods During the lactation period, the mean body weight gain of 90 mg/kg females was significantly decreased during the first 10 days Since the body weights at parturition were similar among the groups, the reduced body weight during the gestation period may be attributed to the decreased litter weight and sizes of these groups. Male bodyweight gain was slightly decreased only at the higher doses. Food consumption was similar in all groups.

Drug treatment had nc adverse effect on the regularity of the estrus cycle or the mating performance The fertility index was significantly decreased in the 90 mg/kg groups Mean gestation lengths were similar among the groups Drug treatment had no adverse effect upon parturition with the exception of one female (60 mg/kg) which died suddenly after delivery

No drug-related gross abnormalities were observed among the F_1 offspring (F_2 generation). Post-natal viability was reduced at the highest dose level. Body weight gain of the F_1 offspring from the highest dose group was markedly decreased from day 1 to day 10 post-partum but not thereafter.

The fertility index and the duration of gestation were similar in all F_2 generation groups. Body weight gain among the 60 mg/kg and 90 mg/kg F_2 generation dams was significantly increased

Various parameters of the F_3 generation (live litter size, body weight, viability index, lactation index, functional development) were unaffected by drug treatment.

3 3 2 Teratology Studies

3 3 2.1 Rat (Labaz Research Center, Belgium)

(a) Study No 1 (dated February, 1982)

Strain OFA (Sprague-Dawley)
Route Oral (gavage)
Dose Levels 0, 10, 30 or 90 mg/kg/day
Number/Sex/Dose 16 males, 25 females.
Treatment Schedule 64 days pre-mating, during mating and during gestation days 1 to 19 (females only)
Results During the pre-mating period, there were no drug-related effects on behavior, food consumption or survival Mean body weight gain of high dose females was significantly depressed during the pre-mating and gestation periods (with and without the fetuses) The fertility index was significantly decreased in the high dose groups. At this dose level, the mean number of corpora lutea and implantation sites per litter decreased, resulting in a significant increase in pre-implantation loss Histological examination of the reproductive organs of treated males revealed no abnormalities Total litter loss due to resorptions occurred in 1 or 2 of the dams from each treatment group and none occured in the control group. As a result, the percentage of resorbed fetuses was increased in treated groups No significant increase in fetal resorptions occurred in the treated groups when these total litter losses were not included.

Mean fetal weight was significantly decreased at the high dose level.

No drug-related major fetal abnormalities were detected, higher incidences of minor fetal abnormalities (mainly incomplete skeletal ossifications) were present in drug treated groups i.e, 1 5% control, 9 3% low, 11 6% mid, 17 8% high

b) Study No. 2 (dated February 1969)

Strain Wistar
Route Oral (gavage)
Dose Levels 0, 5, 50 or 100 mg/kg/day
Number Pregnant/Dose at least 21.
Treatment Schedule Days 1 to 15 of gestation
Results The average number of implantations, resorptions, and living and dead fetuses were comparable among the groups. No drug-induced external, visceral or skeletal abnormalities of the fetuses were reported (actual data not supplied).

c) Study No 3 (not dated)

Strain Wistar
Route Oral (gavage)
Dose Levels 0 or 200 mg/kg/day
Number Pregnant/Dose 27
Treatment Schedule Days 1 to 21 of gestation
Results The treated dams were listless, the fur was shaggy and dull, and lost weight Six treated rats died and were shown at autopy to have macerations of the abdominal viscera and severe enteritis. The number of resorptions was significantly increased in the treated group compared to control

	Control	200 mg/kg amiodarone
No females presenting only resorption	0/26	17/21 (81%)
No. full-term live fetuses (% of implant)	354 (98.3)	50 (17 3)

3.3 2 1 Mouse

(a) Study No 1 (Labaz Research Center, Belgium, dated June, 1967)

Strain NMRI
Route Oral (gavage)
Dose Levels 0, 5, 50 or 100 mg/kg/day
Number Pregnant/Dose at least 19
Treatment Schedule Days 1 to 15 of gestation
Results Live litter size was reduced in all drug treated groups (126 control, 111 low, 76 mid, 27 high) as a result of an increased number of resorptions (59 control, 109 low, 137 mid, 180 high) There was no evidence of gross, visceral or skeletal abnormalities of the fetuses due to drug treatment (actual data not supplied)

b) Study No. 2 (Dr P. Lechat, France, date February, 1969

Strain: Charles River
Route: Oral (gavage)
Dose Levels: 0, 5, 50, 50, or 100 mg/kg/day
Number Pregnant/Dose: at least 5
Treatment Schdule: Days 1 to 16 of gestation and in an additional 50 mg/kg group, days 6 to 16 of gestation
Results: The average number of implantations, live and dead fetuses, and resorptions were similar among the groups. No fetal malformations were reported (methods for fetal examination were not specified).

3.3.2.2 Rabbit

a) Study No 1 (Dr Deltour, France, dated February, 1969)

Strain: Belgian hare
Route: Oral (gavage)
Dose Levels: 0, 5, 50, or 100 mg/kg/day
Number Pregnant/Dose: 15
Treatment Schedule: Days 1 to 18 of gestation
Results: Drug treatment had no affect on the number of implantations, live and dead fetuses, or resorptions. Examination of the fetuses revealed no external or skeletal malformations (methods for fetal examination were not specified).

b) Study No 2 (Labaz Research Center, Belgium, dated August, 1975)

Strain: Dutch.
Route: Intravenous
Dose Levels: 0, 5, 10, or 25 mg/kg/day
Number Pregnant/Dose: at least 11
Treatment Schedule: Days 8 to 16 of gestation
Results: A greater number of deaths occurred among drug treated females compared to control, i.e., 1/20 (5%) control, 3/20 (15%) low, 5/20 (25%) mid, 8/20 (40%) high. Autopsies revealed brochopneumonia and peritonitis. The number of resorption (% of implantations) was significantly increased at the 2 highest doses, i.e., 4.9% control, 0.9% low, 20.6% mid, 19,8% high. No drug-related teratogenic effects were seen

3.3.3 Peri-and postnatal study in rats (Labaz Research Center, Belgium, dated January, 1980

Strain: Sprague-Dawley
Route: Oral (gavage)
Dose Levels: 0, 10, 30 or 90 mg/kg/day
Number/Dose: 25
Treatment Schedule: Day 14 of gestation to day 21 of loctation
Results: No clinical signs of drug-induced toxicity was observed and there were no mortality. High dose females had a decreased body weight gain during gestation from day 16 onwards, weight gain during lactation was normal, however The duration of gestation and parturition were unaffected by drug treatment. Mean live litter size and sex ratio were similar among the groups. Mean fetal weight at birth was siginificantly

decreased at the high dose level, pup body weight gain at this dose remained decreased until weaning. Neonatal mortality was higher in the high dose group than control i.e, survival index was 98% control vs 59% high dose. Offspring mortality was higher in the lactation period (between the 5th day and weaning) than in the perinatal period (between birth and the 4th day).

3.4 Mutagenicity

3.4 1 Ames Test

Amiodarone was not mutagenic in S typhimurium tester strain TA 1535, TA 1537, TA 1538, TA 98 and TA 100 with and without rat liver microsomal activation.

3 4 2 Lysogenic Induction Test

At concentrations approaching toxic levels (ca 100 mcg/plate), amiodarone caused no increase in spontaneous lysis in a lysogenic bacterial strain GY 5027 with a GY 4015 indicator.

3.4 3 Micronucleus Test

Charles River male mice (5/gp) received 2 i p injections of vehicle (distilled water) or amiodarone (50, 100 or 225 mg/kg) over a 24 hr. period The number of polychromatophilic erythrocytes with micronuclei was not increased by the drug

4 Package Insert

The following changes are suggested with respect to the preclinical portions of the proposed labeling

(1) Carcinogenesis, Mutagenesis, Impairment of Fertility.

Fertility of male and female rats was reduced with dose levels above 60 mg/kg/day (or 5 times the maximum recommended maintenance dose)

(2) Teratogenic effects Pregnancy category C.

Cordardone has been shown to be embryotoxic (increased fetal resorption and growth retardation) in the rat when given orally at a dose of 200 mg/kg/day (greater than 13 times the maximum recommended maintenance dose) Similar findings have been noted in one strain of mouse at doses of 5 mg/kg (approximately 1/2 the maximum recommended maintenance dose) and above but not in a second strain of mouse nor in the rabbit at dose levels up to 100 mg/kg/day (approximately 7 times the maximum recommended maintenance dose). There are no adequate etc , etc

(3) Overdose

Animal studies indicate that Cordarone has a high oral LD_{50}(>3g/kg), etc., etc.

5. SUMMARY AND EVALUATION

5.1 Pharmacodynamics

The antiarrhythmic activity of amiodarone was assessed using various animal models. Amiodarone showed activity against chloroform-induced ventricular fibrillation in mice and, to a lesser extent, calcium chloride-induced ventricular fibrillation in rats. In rats pretreated for 2 minutes to 3 weeks before the excision of their hearts, amiodarone increased the ventricular fibrillation threshold in a dose related manner After coronary arterial ligation, the incidence of spontaneous arrhythmias decreased Amiodarone pretreatment also protected against the occurrence of ventricular fibrillation induced by reperfusion of the ischemic myocardium. In anesthetized dogs, the drug suppressed multifocal ventricular ectopic beats induced by epinephrine or by barium chloride, ventricular extrasystoles occurring after occlusion of the anterior descending coronary artery, atrial fibillation induced by application of acetylcholine to the anterior wall of the right atrium, ventricular tachycardia induced by application of aconitine to the anterior wall of the right ventricle, or by intravenous injection of strophantine

Electrophysiological studies in animals suggested that the mode of action of amiodarone as an antiarrhythmic agent results mainly from prolongation of the action potential duration of atrial and ventricular muscle without altering the resting membrane potential Prolongation of the action potential duration with the consequent lengthening of the effective refractory period is the basis for classifying amiodarone electrophysiologically as a Cass III antiarrhythmic agent Other drugs with Class III antiarrhythmic action include bretylium, sotalol and clofilium When given intravenously to dogs, amiodarone depressed AV nodal conduction, as evidenced by prolongation of the AH interval, an effect also considered to be due to a prolongation of the action potential duration

Hemodynamic effects of intravenously administered amiodarone to anesthetized dogs were an atropine-resistant bradycardia, decreased peripheral vascular resistance and increased coronary blood flow Cardiac work and myocardial oxygen demand decreased Anti-adrenergic effects of amiodarone consisted of a partial, non-competitive blockade of both alpha- and beta-adrenoceptors

5.2 Pharmacokinetics

Specific HPLC methods were used to study the pharmacokinetics of amiodarone in rats and dogs

Following intravenous administration of amiodarone (50 mg/kg) to rats, the drug disappeared from the blood with an elimination half-life of approximately 8 5 hours and distributed extensively into tissues, the apparent volume of distribution was 29 5 L/kg Drug concentrations were highest in the liver, kidney and heart, and lowest in the brain The highest concentrations were attained within 5 to 30 minutes of administration Amiodarone accumulated extensively in adipose tissue

In dogs, the elimination half-life of amiodarone (10 mg/kg, i.v.) was approximatley 8.7 hours and the apparent volume of distribution was 36 L/kg.

The oral absorption of ^{131}-I-amiodarone (2 or 5 mg/kg, single dose) in rats was slow and variable and was estimated to be approximately 50%.

No information of the biotransformation of amiodarone in laboratory animals was submitted.

5.3 Toxicology

The acute lethality (LD 50) of amiodarone in both mice and rats was greater than 3000 mg/kg by the oral route and greater than 450 mg/kg by the intraperitoneal route. For rats, i.v. LD 50 values of 135 mg/kg and 150 mg/kg were obtained in two separate studies. The oral LD 50 value for amiodarone in dogs was greater than 5000 mg/kg.

Signs of acute toxicity in rodents after parenteral administration of amiodarone included CNS stimulation followed by sedation, tremors, convulsions and respiratory difficulties. For dogs, emesis and paresis of the hindlimbs were noted with oral dosing.

Subacute oral toxicity studies of up to 3 months in duration were conducted in rats. Animals receiving daily doses of 75 or 150 mg/kg of amiodarone for up to 4 weeks showed a marked deterioration in general health, increased mortality, an altered ECG (increased PR interval and QTa segment, prolonged QRS complex, elevated T-wave), hypercholesterolemia, azotemia, elevated thyroxine (T_4) levels and a decreased triiodothyronine (T_3)/T_4 ratio, elevated liver enzymes (SGPT, alkaline phosphatase) and organ weight changes (lung and adrenal increased, reproductive organs and thymus decreased). Microscopic examination revealed an accumulation of foamy macrophages in the mesenteric lymph node as well as the spleen, liver and lungs. These lesions have been described in animals as drug-induced lipidosis-like cellular alterations and are characteristic of amphiphilic cationic compounds (Bockhardt et al., Verh. Anat. Ges. 72. S417-418, 1978). In another study conducted by Bockhardt et al (Arch. Klin. Exp. Ophthalmol, 207 91-96, 1978) similar lipidoses like changes in ocular tissues of rats were produced by amiodarone at oral doses of 200 mg/kg/day for 3 weeks. In subsequent studies, the reversibility of the lesions caused by amiodarone (160-200 mg/kg) was demonstraced within 4 weeks after discontinuing dosing. No adverse effects were observed with doses of 37.5 mg/kg or lower of amiodarone.

Clinical observations in the 3-month rat study revealed increased mortality, reduced body weight gains, anemia and azotemia at daily doses of 200 mg/kg or greater. Histopathologic examination showed centrilobular congestion of the liver at doses of 200 mg/kg or greater and myocardial lesions at 300 mg/kg. Other than hypertrophic changes of the thyroid gland, no microscopic lesions were evident at 100 mg/kg.

Subacute oral toxicity studies were conducted in dogs at dose levels of amiodarone ranging from 30 to 150 mg/kg Dogs receiving 100 mg/kg for 1 month showed a decrease in body weight gain and food consumption which resulted in the moribund sacrifice of one female and elevations in serum enzyme levels (SGPT, SGOT, LDH), cholesterol, triglycerides and urinary pH Postmortum examination revealed increases in adrenal and liver weight, the disappearance of the thymus gland and a generalized dyslipidosis In another study, dogs receiving 150 mg/kg (5 days/week) of amiodarone for 3 months exhibited excessive salivation and signs of gastrointestinal distress (i e, vomiting, diarrhea, anorexia) which was accompanied by some loss in body weight The leukocyte count increased in a dose-related manner at each dosage level (30 and 150 mg/kg) and high dose dogs showed decreases in neutrophils and increases in lymphocytes during the end of the study. Apart from occasional increases in BUN, SGPT, alkaline phosphatase and cholesterol reported in several high dose dogs, clinical chemistry values were generally similar to the control values.

Postmortem examination revealed hypertrophy of the thyroid in one high dose dog and necrosis of the stomach in another.

In a chronic (9 months) oral toxicity study in dogs, amiodarone caused no clinical signs of toxicity at daily dose levels of 30 and 60 mg/kg Serum cholesterol levels were increased in the high dose group and terminal serum free fatty acids increased at both dose levels Increases in blood and tissue iodine levels and in PBI were found in drug treated dogs Histopathology was unremarkable.

A 3 month oral toxicity study with amiodarone (10, 20, 50, or 150 mg/kg) in pigs demonstrated that the drug was well tolerated at doses up to 50 mg/kg. Dose levels of 150 mg/kg caused ataxia, hypotonia and lack of weight gain Two high dose animals died within 1 1/2 months and autopsy showed gastritis and gastric ulceration The remaining pigs at the high dose level were sacrificed in extremis at 2 1/2 months Histopathological lesions of the liver and endocrine (pituitary, thyroid, adrenal) glands were present in these animals

Other than anemia in one treated animal, amiodarone (50 mg/kg) appeared to be well tolerated in a chronic (10 months) oral toxicity study in pigs. Histopatholoical examinations were not reported in this study, however

A 6 week intravenous toxicity study in rabbits at doses of 5, 10, or 25 mg/kg revealed anemia, hyperlipidemia and hypercholesterolemia at the high dose level Non dose-related hepatic degenative lesions were found in rabbits from each treated group (2/8 low, 2/8 mid, 1/8 high)

Amiodarone had no adverse effect on fertility or mating performance when administered to male or female rats at daily oral doses up to 30 mg/kg Higher doses of the drug (60 and 90 mg/kg) adversely affected female fertility and significantly decreased litter size and litter weight For the F_1 generation offspring (F_2 pups), those obtained from the high dose amiodaron group were less viable and gained less weight than their control counterparts for the first 10 days postpartum, but developed normally thereafter

The teratogenic potential of orally administered amiodarone was investigated in mice, rats and rabbits. In rats, 200 mg/kg of amiodarone administered during gestation caused maternal toxicity and marked embryotoxicity, therefore, no conclusions regarding tertogenicity could be made With 90 mg/kg of amiodarone, fertility decreased and pre-implantation loss increased Increased fetal resorption and growth retardation (mainly delayed skeletal ossification) at 90 mg/kg were indicative of drug-induced embryotoxicity In another study, however, doses of up to 100 mg/kg administered from gestation days 1 to 15 produced no embryotoxicity or skeletal abnormalities. Amiodarone was not teratogenic in rats at any dose level

Mice receiving 5, 50 or 100 mg/kg of amiodarone on gestation days 1-15 showed a dose-related reduction in litter size and an increase in the number of fetal resorptions There was no suggestion of drug-related teratogenicity In another study employing a different mouse strain, up to 100 mg/kg administered during days 1-16 of gestation was not teratogenic nor embryotoxic

In rabbits, amiodarone administered orally during gestation days 1-18 at doses up to 100 mg/kg was not teratogenic. In a second rabbit study, intravenous administration of 5, 10, or 25 mg/kg amiodarone during days 8 to 16 of gestation caused maternal death at the high dose level and a non-dose related increase in the number of resorptions at the two higher dose levels. No fetal abnormalities were observed

In a perinatal and postnatal development study in rats, pregnant dams gained less weight during gestation at a dose level of 90 mg/kg amiodarone Weanling body weight and neonatal survival were also reduced at this dose level. Dose levels of 10 and 30 mg/kg produced no adverse effects In vitro, amiodarone exibited no mutagenic potential in the Ames and the micronucleus test (with and without metabolic activation) and was not lysogenic to bacterial indicator strains GY 5027 or GY 4015

Many of the nonclinical safety studies with amiodarone were conducted prior to the promulgation of the FDA Good Laboratory Practice (GLP) Regulation As such, the sponsor states that laboratory procedures and operations in effect at the time of these studies were often not in compliance with those specified in the June 20, 1979 GLP Regulations The sponsor further states that those studies conducted after June 20, 1979 were effected under conditions which were not entirely in compliance with GLP Pegulations In addition to the deviations from GLP Regulations, some of the toxicity and teratology studies with amiodarone were unacceptable according to present day guidelines Specifically, in the chronic dog and mini-pig studies the drug was incorporated in the diet Since food consumptions were not measured in these studies, the actual amount of drug consumed could not be ascertained In addition, histopathological data from the mini-pig study were not reported.

With respect to the teratology studies, only the summary reports without adequate supportive data were submitted for Mouse Study No 1 and Rat Study No 2. Due to the marked drug-related embryotoxicity in Rat Study No 3, no conclusions regarding potential teratogenicity could be made

In Rat Study No 1 the drug was given to females 64 days pre-mating, during mating and throughout pregnancy with no consideration of possible drug-induced induction of liver microsomal catabolizing enzymes Finally, the methods for examination of the fetuses were not stated for Mouse Study No. 1 and Rabbit Study No 2.

6. Recommendation

The adverse reactions during long term amiodarone therapy in humans are fairly well established (Harris et al , Circulation 67 45, 1983, McGovern et al Br Med. J., 287 175, 1983), Forgoros et at., Circulation 68 88, 1983). Therefore with the exception of potential carcinogenic risk, it seems unlikely that repeat chronic toxicity studies with the drug in animals would offer any additional useful information with respect to human risks The negative results obtained in in vitro mutagenicity testing are reassuring in that the drug is probably not a genotoxic carcinogen.

In view of the deficiencies in the animal teratology studies we feel that the teratogenic potential of amiodarone has not been adequately assessed We therefore recommend that repeat teratology (Segment II) studies be conducted with amiodarone in two species according to FDA Guidelines for Reproduction Studies

M A Commarato 2/2/84
M A. Commarato, Ph D

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dmu/11-21-83/2886c
R/D init JBurns/11-17-83

APPENDIX ----

IND/NDA 18972 Clinical Chemistry Parameters Measured in Safety Assessment Studies.

Species	Rat			Dog			Pig	Mini Pig		Rabbit		
Duration & Route	1 mo PO	3 mo PO		1 mo PO	3 mo PO	9 mo PO	3 mo PO	12 mo PO		6 wk IV		
albumin	X			X								
alk phosphatase	X			X	X	X	X	X		X		
bilirubin				X	X	X		X				
BSP												
calcium				X								
chloride	X			X								
cholesterol	X			X	X	X	X	X		X		
CPK										X		
creatinine	X			X								
globulin												
glucose	X	X		X	X	X	X	X		X		
iron												
LDH				X						X		
potassium	X	—		X								
prot. (tot) elect	X			X	X	X		X		X		
PSP												
SGOT				X	X	X	X	X		X		
SGPT	X			X	X	X	X	X		X		
sodium	X			X								
triglycerides	X			X		X						
uric acid										X		
urea nitrogen	X	X		X	X	X	X			X		
Other												
Thyroid hormones	X			X								
phospholipids												
Bromsulphalein Test					X	X						

APPENDIX ------

IND/(NDA) 18972 Hematology Parameters Measured in Safety Assessment Studies

Species	Rat			Dog			Pig	Mini Pig		Rabbit		
Duration & Route	1 mo IC	3 mo po		1 mo IC	3 mo PO	9 mo PO	3 mo PO	12 mo PO		6 wk IV		
ESR	X	X			X	X		X				
hematocrit	X							X				
hemoglobin	X	X			X			X		X		
MCH	X											
MCHC	X											
MCV	X											
platelet count	X											
prothrombin time					X	X						
PTT								X				
RBC	X	X			X	X	X	X		X		
reticulocyte												
WBC, tot & diff	X	X			X	X	X	X		X		
bands												
basophils	X	X			X	X	X			X		
lymphocytes	X	X			X	X	X			X		
leukocytes, seg												
monocytes	X	X			X	X	X			X		
neutrophils	X	X			X	X	X			X		
Other blood smear	X											
coagulation time		X				X		X				
3												

APPENDIX C

IND/NDA 18972 Tissues Examined Microscopically in Safety Assessment Studies.

Species	Rat			Dog			Pig	Rabbit			
Duration & Route	1 mo PO	3 mo PO		1 mo PO	3 mo PO	9 mo PO	3 mo PO	6 wk IV			
adrenals	X			X	X	X	X	X			
aorta	X			X				X			
bone marrow											
brain	X			X	X		X	X			
eye	X			X				X			
heart	X	X		X	X	X	X	X			
intestine, large	X	X		X		X	X	X			
intestine, small	X	X		X	X	X	X	X			
kidneys	X	X		X	X	X	X	X			
liver	X	X		X	X	X	X	X			
lungs	X			X	X	X	X	X			
lymph nodes	X			X							
mammary gland	X			X							
esophagus	X			X							
ovaries	X			X	X	X	X	X			
pancreas	X			X	X	X	X	X			
peripheral n	X			X							
pituitary	X			X	X		X	X			
prostate	X										
salivary gland	X			X	X	X		X			
seminal vesicle											
skeletal muscle	X			X	X						

[redacted] NDA [redacted]

APPENDIX ——— (Cont'd)

Species	Rat			Dog			Pig	Rabbit			
Duration & Route	1 mo PO,	3 mo PO		1 mo PO,	3 mo PO	9 mo PO	3 mo PO	6 wk iv			
skin	X			X	X	X					
spinal cord				X							
spleen	X	X		X	X	X	X	X			
stomach	X			X	X	X	X	X			
testes	X			X	X	X	X	X			
thymus	X			X				X			
tongue											
trachea				X							
thyroid	X	X		X	X	X	X	X			
uterus	X			X							
urinary bladder	X			X							
Other parathyroid	X			X				X			
rectum	X			X							
epididymus	X										
seminal vesicles	X										
vagina	X			X							
bone	X										
gallbladder				X							
larynx				X							
optic nerve				X							

NDA# 18-972 Amiodarone· Efficacy in Animal Models of Arrhythmias

Model	Results	Ref.
Chloroform-induced ventricular fibrillation in anesthetized mouse.	IP doses of 50,100 & 200 mg/kg gave 0, 30 & 50% protection, resp, ED50 = 160 mg/kg. Oral doses of 250, 500 & 1000 mg/kg (30 mins. before experiment) gave 25, 50 & 75% protection, ED50 = 500 mg/kg.	(1)
Aconitine-induced ventricular tachycardia in anesthetized rat.	IV doses of amiodarone prolonged time interval before v. tachycardia occurred during aconitine infusion, i e, 3.56± 0 25 min. control vs 9.07 *± 1.36 min. 5 mg/kg amiodarone & 10.72*± 2.59 min 10 mg/kg amiodarone. *$p < .05$.	(2)
Ba Cl2-induced polymorphic ventricular extrasystole in conscious dog and rabbit.	10 mg/kg i.v. amiodarone restored sinus rhythm.	(3)
Coronary artery ligation-induced ventricular arrhythmias in conscious dog.	10 mg/kg i v. amiodarone restored sinus rhythm.	(3)
Strophantine induced ventricular tachycardia in conscious dog	10 mg/kg i.v. amiodarone restored sinus rhythm within 30 sec and 6 min after end of injection	(3)
Coronary artery ligation-induced ventricular fibrillation in isolated rat heart	Pretreatment with i p. (30-260 m M/kg) or iv (7-56 m M/kg) amiodarone 2 min -3 wks before excision of hearts caused dose-related increase in VF threshold (both before and after coronary arterial ligation) and dose related decreased incidence of VPE, VT, VF during ligation and after reperfusion of ischemic myocardium	(4)
Coronary artery ligation-induced ventricular fibrillation in conscious dog	Amiodarone pretreatment, 10-40 mg/kg/day po for 1-4 wks, prevented VF in all 10 pretreated dogs whereas VF occurred in 7 of 8 control dogs.	(5)

Ouabain-induced ventricular fibrillation in anesthetized guinea-pig.	6.25-50 mg/kg iv amiodarone caused dose related protection against ouabain-induced arrhythmias but not against cardiac arrest.	(6)
Coronary artery ligation-induced ventricular arrhythmias in conscious dog.	Amiodarone pretreatment, 30 mg/kg/day p.o. for 3-4 weeks, markedly attenuated frequency of early ventricular arrhythmias; incidence of VF was 9% (1/11) in treated dogs compared with 29% (4/14) in controls.	(7)
Left circumflex intimal injury and thrombosis in presence of anterior myocardial infarction ("sudden coronary death") in conscious dog.	Both acute iv (10 mg/kg/hr) and chronic oral (10 mg/kg/day for 24 days) amiodarone administration significantly reduced incidence of VF (iv amiodarone, incidence of 60% vs control incidence of 100%; oral amiodarone, incidence of 20% vs control incidence of 91%).	(8)
Coronary artery ligation/ reperfusion-induced ventricular arrhythmias in conscious dog	Amiodarone pretreatment, 10 mg/kg/day p.o for 2 weeks, did not significantly reduce incidence of VA (78% vs 82% control) and VF (44% vs 49% control) during coronary ligation or the incidence of VA (79% vs 68% control) and VF (64% vs 60% control) during coronary reperfusion Other antiarrhythmics (lidocaine, procainamide, verapamil) also not effective in this model.	(9)

References

(1) Full report not available.
(2) Full report not available
(3) Charlier R. and Deltour G., J Pharmacol (Paris) 1, 2; 175, 1970.
(4) Lubbe WF et al., Am J. Cardiol, 43: 84, 1979.
(5) Rosenbaum, MB, Am. J. Cardiol, 38: 934, 1976.
(6) Singh BN and Vaughan Villiams, Br. J. Pharmacol. 39 657, 1970.
(7) Chew CYC et al., J. Caridovas. Pharmacol 4 1028, 1982
(8) Patterson E., et al, Lab Invest. 68: 857, 1983.
(9) Naito, M. et al, J. Pharmacol, exp. Therap 218 129, 1981

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MA Commarato 12/8/83

Attachment for NDA No 18-972,
Cordarone (amiodarone hydrochloride)
Tablets, Paragraph 8p

July 12, 1983

DETERMINATION OF AMIODARONE IN CORDARONE TABLETS BY HPLC

Apparatus - High-pressure liquid chromatograph operable at pressures up to 3000 psi, equipped with an injector capable of 20 0-microliter injections, a detector measuring absorbance at 242 nm, and a chromatographic column (25-cm x 4 6-mm I D , 10-micron Microbondapak C-18, or an equivalent column)

Mobile Phase - Dissolve 2 04 g of monobasic potassium phosphate in 315 ml of water Add 900 ml of acetonitrile, deaerate under vacuum for 15 minutes, and adjust the pH to 3 9 with 50-percent phosphoric acid (v/v)

Standard Preparation - Transfer about 50 mg of Amiodarone Hydrochloride Reference Standard, accurately weighed, to a 50-ml volumetric flask Add about 35 ml of Mobile Phase, shake well, sonicate to dissolve it, and dilute to volume with Mobile Phase Transfer 5 0 ml of this solution to a 50-ml volumetric flask and dilute to volume with Mobile Phase

System Suitability Tests - Transfer about 3 mg of 2-butyl-3-(3,5-diiodo-4-hydroxybenzoyl)benzofuran (BDI) and 3 mg of 2-butyl-3-(3-iodo-4-hydroxy-benzoyl)benzofuran (BMI) to a 25-ml volumetric flask Dissolve and dilute to volume with Standard Preparation Inject 20 microliters of this solution into the chromatograph, operated typically as follows, flow rate, 2 ml per minute, detector, 242 nm, sensitivity, 0 3 AUFS; chart speed not less than 2 cm per minute Calculate the resolution factors (see USP Sec. 621) for BMI and amiodarone, and for amiodarone and BDI The typical retention times for BMI, amiodarone and BDI are 3 6, 4.4 and 5.4 minutes, respectively In a suitable system resolution in each case is not less than 1 5. If necessary, resolution of BMI and amiodarone can be increased by increasing the pH of the Mobile Phase or decreasing the amount of monobasic potassium phosphate; resolution of amiodarone and BDI can be increased by decreasing the pH or increasing the amount of water Precision: Inject 4 replicate portions of 20 0 microliters each of the Standard Preparation Measure the peak responses and calculate the relative standard deviation (RSD) In a suitable system the RSD is not more than 2 0 percent

Sample Preparation - Weigh and finely powder not less than 20 tablets Transfer a portion of the powder, accurately weighed and equivalent to about 200 mg of amiodarone hydrochloride, to a 100-ml volumetric flask Add about 75 ml of Mobile Phase, shake for 2 minutes, sonicate for 5 minutes, and dilute to volume with Mobile Phase Mix and then centrifuge a portion of the mixture, then transfer 5 0 ml of the clear supernatant to a 100-ml volumetric flask and dilute to volume with Mobile Phase

continued

Attachment for NDA No 18-972,
Cordarone (amiodarone hydrochloride)
Tablets, Paragraph 8p

July 12, 1983

DETERMINATION OF AMIODARONE IN CORDARONE TABLETS BY HPLC
(concluded)

Procedure - Inject 20 0-microliter portions of the Standard and Sample Preparations into the chromatograph Measure the amiodarone peak heights or areas and calculate as follows

$$(Pu/Ps)(4\ Ws/Wu)(Wav/K)(100) = \%\ \text{of claim}$$

Pu = sample peak response
Ps = standard peak response
Ws = standard weight, in mg
Wu = sample weight, in mg
Wav = average tablet weight, in mg
K = claim, in mg of amiodarone HCl per tablet