

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75135

BIOEQUIVALENCE REVIEW(S)

Amiodarone Hydrochloride
200 mg Tablet
ANDA # 75-135
Reviewer: James Chaney

Upsher-Smith Laboratories, Inc.
Minneapolis, MN
Submission Dated:
May 19, 1997

REVIEW OF AN IN VIVO FASTING BIOEQUIVALENCE STUDY AND IN VITRO DISSOLUTION TESTING DATA

I. INTRODUCTION

Amiodarone, a benzofuran, is a class III anti-arrhythmic drug (Vaughan Williams classification). Because of its life-threatening side effects and substantial difficulties associated with its use amiodarone hydrochloride is indicated for the treatment of recurrent life-threatening ventricular fibrillation or hemodynamically unstable ventricular tachycardia when these have not responded to documented adequate doses of other available anti-arrhythmic drugs or when alternative agents cannot be tolerated. Administration of amiodarone in hospital setting in divided doses with meals is suggested for total daily doses of 1,000 mg or higher, or when gastrointestinal intolerance occurs.

Amiodarone's oral bioavailability has been shown to vary from 35-65%, with maximum plasma concentrations attained in 3-7 hours after a single dose. Onset of action may occur in 2-3 days, more commonly one to three weeks is required. Amiodarone is about 96-99% bound to plasma proteins and has a low plasma clearance with negligible renal excretion. There is a large degree of first-pass metabolism of amiodarone to N-desethylamiodarone, which also possesses some antiarrhythmic activity. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one. The terminal elimination half-life of amiodarone ranges from 3-80 hours (mean 30-40 hours) following a single dose. The elimination is much longer following chronic administration.

The referenced drug is manufactured by Sanofi Pharmaceuticals, Paris, France, and is marketed in the U.S. by Wyeth-Ayerst Laboratories as Cordarone[®] Tablets, 200 mg.

II. OBJECTIVE

The objective of this study was to evaluate the bioequivalence of amiodarone hydrochloride 200 mg tablets by Upsher-Smith Laboratories, Inc. with that of Cordarone[®] by Wyeth Laboratories following a single oral dose (1 x 200 mg tablet) in healthy adult male volunteers under fasting conditions using a randomized, crossover design.

III. INVESTIGATORS AND FACILITIES

Clinical Study Site:

investigator.

Analytical Site:

IV. STUDY DATES

For Group 1 the drug was administered November 9, 1996 and January 4, 1997 .

For Group 2 the drug was administered December 7, 1996 and February 1, 1997.

All subjects returned to the facility for the 48, 72, 96, 168, 336, and 672 hour blood sample collections.

Sample analysis began on February 4, 1997 and was completed on April 5, 1997,

V. CLINICAL

Subject Eligibility: Medical histories, physical examinations (including vital signs and electrocardiograms), and diagnostic laboratory results, obtained within 28 days of study start, were reviewed and approved by the investigating physicians for all subjects. A urine sample for detection of drugs of abuse was obtained from all subjects at screening and at entry of each period. A negative result was required at all times for continued participation.

Institutional Review Board: The study Protocol and Informed Consent were reviewed and approved by the National Institutional Review Board.

Design: The protocol was designed as a double-blind, randomized, single oral dose, two-treatment, two-period, two-sequence crossover study.

Washout Period: Eight weeks wash-out between drug administrations.

Number of Subjects: Forty-two subjects were enrolled in the study in two groups after being screened from the general population. Subjects 1 to 28 were included in Group 1 and Subjects 30 to 43 were included in Group 2. Subject 29 was assigned number 43 to prevent a delay in dosing when his period 1 electrocardiogram was delayed. Thirty-six completed both periods of the study.

Formulations:

Test (A) Amiodarone HCL tablets, (Pacerone™), 200 mg
Manufactured by Upsher-Smith Laboratories, Inc.,
Lot # 62185, (On page 123 of Volume 1.2 the lot
number is indicated as 16461 but this number is
actually only the packaged lot number.) The

expiration date not available. The content uniformity is 103.8% (1.5 %CV, 99.7-105.8). The potency is 100.9%.

Ref (B) Amiodarone HCL tablets, (Cordarone[®]), 200 mg
Manufactured by Sanofi-Winthrop Industrie for
Wyeth Laboratories, Inc., Lot = 9960379, The
expiration date is March 1999. The content
uniformity is 100.9% (2.3 %CV, 97.1-106.1). The
potency is 99.1%.

Drug Administration: One 200 mg amiodarone tablet was administered with 240 mL of water according to the randomization schedule. The subjects were dosed each period at the same time, at two minute intervals starting at 0900 hours for group 1 and 0902 hours for group 2. Subjects were not allowed to be supine for 4 hours postdose.

Blood Collection: Ten milliliters of venous blood were obtained in EDTA Vacutainers[™] for analysis of amiodarone and N-desethylamiodarone at: 0 (prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 168 (7 days), 336 (14 days), and 672 hours (28 days). The samples were placed in an ice-water bath upon collection, until centrifugation at 4°C for 15 minutes at 2400 RPM. Immediately after centrifugation, equal aliquots of the plasma were pipetted with polyethylene pipettes into two labeled polypropylene tubes and placed into a -20°C freezer to await analysis.

Subject Monitoring: Blood pressure, pulse, and electrocardiograph monitoring was performed at 0 (predose), 2, 3, 4, 5, 6, 7, 8, 24 and 36 hours postdose.

Foods and Fluids: The subjects fasted for at least 10 hours prior to and 4 hours after the drug administration. No fluid except that given with drug administration was permitted from 1 hour prior to dose administration until 2 hours after dosing. At 2 hours post-dose, all subjects consumed 240 mL of water. Four hours after the dose, water was generally allowed *ad lib*, but was monitored, recorded, and limited to approximately 2400 mL up to 24 hours postdose.

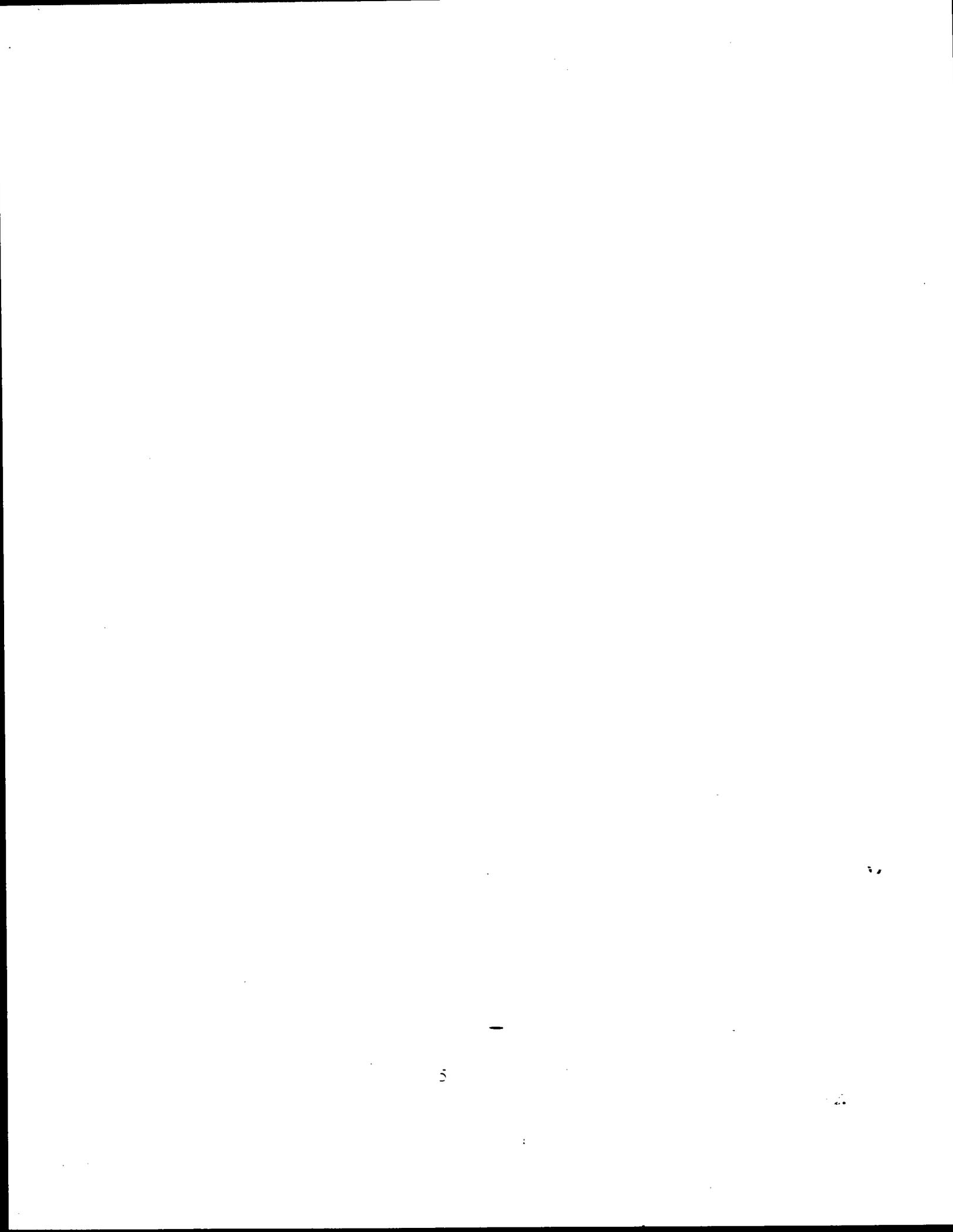
Housing: The subjects were housed in a dormitory facility from approximately 10 hours prior to drug administration until at least 36 hours after drug administration for each period.

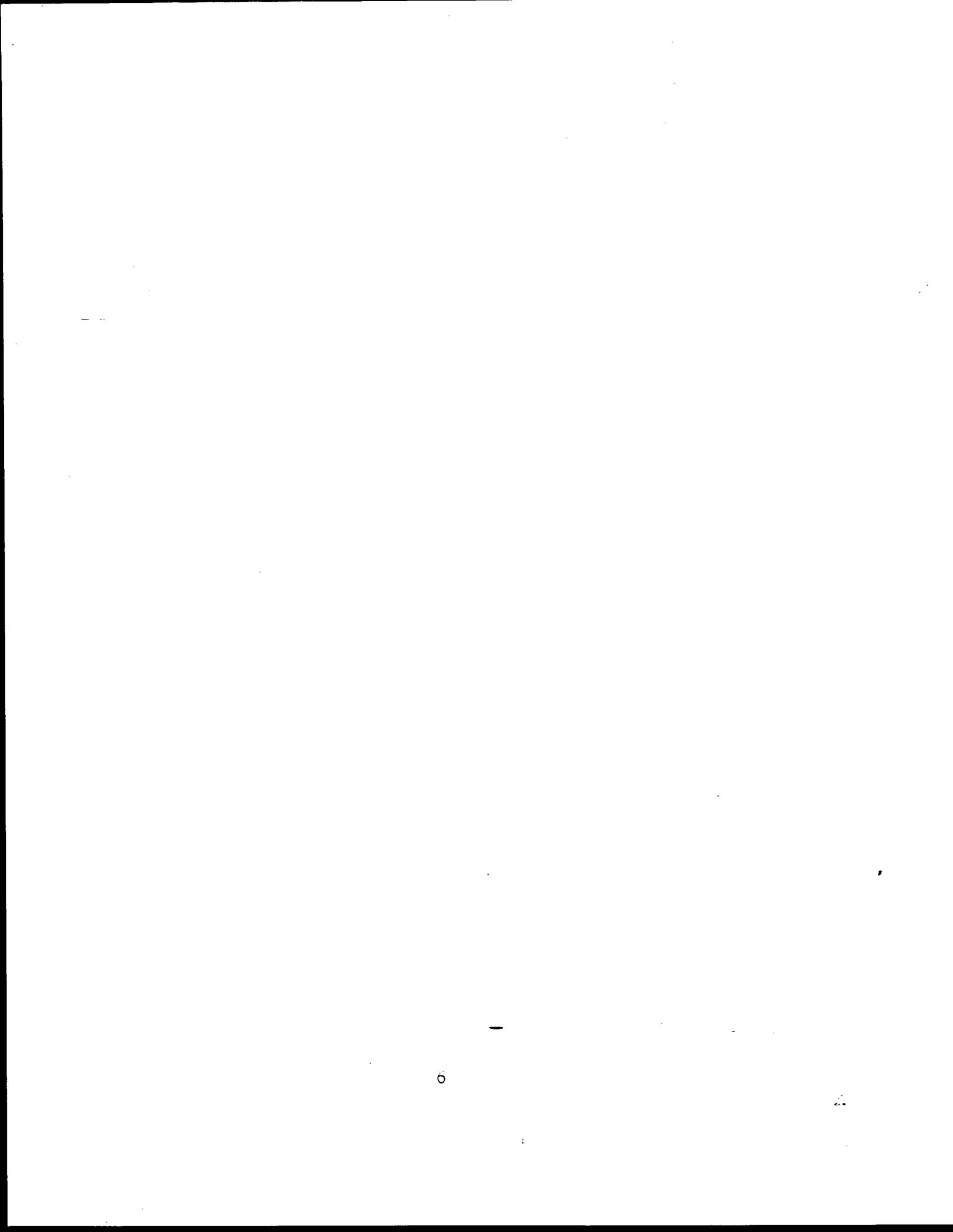
VI. PHARMACOKINETICS AND STATISTICAL ANALYSIS

All parameters were analyzed by analysis of variance (ANOVA) and an F-test to determine statistically significant differences ($\alpha=0.05$). The power to detect a 20% difference between drug formulation means as statistically significant and the 90%

confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the difference in formulations from the analysis of variance. The ANOVA included enrollment group, sequence, subject nested within group-by-sequence, phase nested within group, and drug treatment in the statistical model. An initial test of enrollment group interaction effects was provided by an additional ANOVA including effects for group-by-drug and group-by-sequence.

VII. ANALYTICAL





VIII. STUDY RESULTS

Forty-two subjects who met the protocol inclusion/exclusion criteria were entered into the study. Thirty-six subjects completed the study (27 from enrollment group 1 and 9 from group 2). Six subjects failed to complete the study. Subjects 28, 31, 33, and 35 failed to return to the facility for Period II. Subjects 34 and 38 were withdrawn due to potentially clinically significant laboratory test results.

There was no statistically significant sequence effect ($p > 0.10$) for any analysis of AUC or C_{max} . There were no statistically significant differences between the formulations for any parameter.

Statistically significant period or phase effects ($p < 0.05$) were observed for log transformed AUC_{0-12} and AUC_{0-24} for both the parent compound and the metabolite. There was no evidence that the period effect resulted from a carry-over of drug from period 1 to period 2, since there was no drug or metabolite detectable for any subject at predose in period 2.

The firm conducted the study in four groups. The group effect was included in the SAS GLM (Model $y = \text{group seq seq*group sub(seq*group) trt per}$). The SAS analysis showed that there was no significant group effect when evaluated with sub(seq*group) as an error term. There were no statistically significant group-by-drug interaction effects for any parameter for drug or metabolite. The group term was eliminated from the model statement of the SAS GLM and the data were handled as if the study were conducted in two groups instead of four groups.

Amiodarone: The mean concentrations amiodarone of at each time point after each product are summarized in Table 1. There were no statistically significant differences in mean concentrations ($p > 0.05$) at any time after dosing. A linear plot of the mean plasma concentration for Amiodarone as a function of time is shown in Figure 1.

Table 1. Mean Plasma Concentrations (ng/mL) of Amiodarone Following a Single-Dose of Upsher-Smith's Amiodarone Hydrochloride, 200 mg, Tablet or Wyeth Laboratories' Cardarone[®], 200 mg Tablet under Fasting Conditions to 36 Subjects

Time (Hr)	TEST			REFERENCE			T/R
	N	Mean	%CV	N	Mean	%CV	
0	36	0.00	--	36	0.00	--	--
0.5	36	2.729	183	36	4.126	192	0.66
1	36	25.82	92	36	21.60	106	1.20
1.5	36	42.24	74	36	37.54	83	1.13
2	36	55.79	69	36	52.50	62	1.06
3	36	72.06	52	36	78.11	49	0.92
4	36	83.53	47	36	85.88	45	0.97
5	36	113.3	42	36	112.5	45	1.01
6	36	127.7	50	36	119.9	43	1.06
7	36	128.5	46	36	126.5	45	1.02
8	36	126.3	49	36	122.4	42	1.03
10	36	116.1	51	36	107.9	44	1.07
12	36	113.7	56	36	103.3	46	1.10
16	36	73.81	56	35	69.44	47	1.05
24	36	42.53	52	36	39.13	41	1.09
36	36	31.46	49	36	29.82	44	1.06
48	35	18.20	52	36	16.72	47	1.09
72	35	9.880	62	36	9.292	48	1.06
96	36	5.805	87	36	5.117	84	1.13
168	35	1.968	175	33	1.226	219	1.61
336	36	0.0000	--	35	0.0000	--	--
672	36	0.0000	--	36	0.0000	--	--

(%CV's were calculated by reviewer.)

The pharmacokinetic parameters for amiodarone are shown in Tables 2 and 3. Based on the least squares means of the logarithmically transformed variables, the AUC_{0-12} and AUC_{0-24} of the Upsher-Smith formulation were both 5% higher than the respective means for the Wyeth formulation. The test C_{max} value was 3% higher than that of the reference product and occurred 7% earlier (32 minutes). Based upon the logarithmic transformations, the 90% confidence intervals about the ratios of test/reference means for AUC_{0-12} , AUC_{0-24} and C_{max} were within the 80 - 125% limits for bioequivalence when the Upsher-Smith product was compared to the Wyeth product (AUC_{0-12} , 97.7-113.4; AUC_{0-24} , 97.6-112.6; and C_{max} , 96.1-110.9 (Table 3)).

Table 2. Comparison of Amiodarone arithmetic and geometric mean pharmacokinetic results between Upsher-Smith's Amiodarone Hydrochloride, 200 mg, Tablet (Test) and Wyeth Laboratories, Cardarone[®], 200 mg Tablet (Reference) administered as 200 mg doses under fasting conditions.

PARAMETER	TEST			REFERENCE			T/R
	N	Mean	%CV	N	Mean	%CV	
Arithmetic Means							
AUC _{0-∞} (ng-hr/mL)	36	3386	54.5	36	3133	46.4	1.08
AUC _{0-∞} (ng-hr/mL)	35	3747	55.7	36	3480	46.4	1.08
C _{max} (ng/mL)	36	139.3	47.5	36	134.3	44.0	1.04
T _{1/2} (hr)	35	39.0	55.4	36	35.1	58.1	1.11
T _{max} (hr)	36	6.83	27.4	36	7.39	24.5	0.92
Geometric Means							
AUC _{0-∞} (ng-hr/mL)	36	2945	--	36	2775	--	1.06
AUC _{0-∞} (ng-hr/mL)	35	3266	--	36	3095	--	1.06
C _{max} (ng/mL)	36	125.4	--	36	120.6	--	1.04

The blood sampling proved adequate for this bioequivalence study for the products under study. Eighty percent or more of the AUC_{0-∞} was measured by AUC_{0-t} for 68 of 72 estimates of AUC_{0-∞} (Table 9). The first postdose sample was not the maximum observed concentration after any dose.

Individual test/reference ratios of the pharmacokinetic parameters AUC_{0-t}, AUC_{0-∞} and C_{max} for amiodarone are shown in Table 8 (appended). Individual AUC_{0-t}/AUC_{0-∞} ratios for amiodarone are shown in Table 9 (appended). The elimination rate constant and half-life could not be reliably estimated for amiodarone for subject #10 administered the test formulation due to pharmacokinetic anomalies in the terminal phase of elimination. As a result, AUC_{0-∞} was not obtained.

Table 3. LSMeans and 90% Confidence Intervals (C.I.) For Amiodarone Following a Single-Dose of Amiodarone Hydrochloride 200 mg Tablet and Reference Cardarone[®] (200 mg) Tablet Under Fasting Conditions

PARAMETER	Test	Ref	T/R	90% C.I.
LSMeans				
AUC _{0-∞} (ng-hr/mL)	3425	3190	1.07	--
AUC _{0-t} (ng-hr/mL)	3793	3549	1.07	--
C _{max} (ng/mL)	139.1	134.8	1.03	--
Geometric LSMeans				
AUC _{0-∞} (ng-hr/mL)	2995	2845	1.05	97.7-113.4
AUC _{0-t} (ng-hr/mL)	3327	3174	1.05	97.6-112.6
C _{max} (ng/mL)	126.5	122.5	1.03	96.1-110.9

N-Desethylamiodarone: The mean concentrations of N-desethylamiodarone at each time point after each product are summarized in Table 4. There were no statistically significant differences in mean concentrations ($\alpha=0.05$) at any time after dosing. A linear plot of the mean plasma concentration for N-desethylamiodarone as a function of time is shown in Figure 2.

Table 4. Mean Plasma Concentrations (ng/mL) of N-Desethylamiodarone Following a Single-Dose of Upsher-Smith's Amiodarone Hydrochloride, 200 mg, Tablet or Wyeth Laboratories' Cardarone[®], 200 mg Tablet under Fasting Conditions to 36 Subjects

Time (Hr)	TEST			REFERENCE			T/R
	N	Mean	%CV	N	Mean	%CV	
0	36	0.0000	--	36	0.0000	--	--
0.5	36	0.0000	--	36	0.0000	--	--
1	36	0.0000	--	36	0.3869	430	0.00
1.5	34	1.554	183	35	1.490	238	1.09
2	36	3.518	120	35	3.155	149	1.15
3	36	7.284	69.1	36	7.606	74.8	0.96
4	36	11.56	55.0	36	12.37	57.0	0.93
5	36	21.07	43.8	36	21.66	43.8	0.97
6	36	25.38	35.5	36	25.84	39.3	0.98
7	36	29.14	34.1	36	31.00	36.9	0.94
8	36	32.43	32.3	36	33.33	32.7	0.97
10	36	37.59	30.6	36	36.6	33.4	1.03
12	36	44.06	32.1	36	42.46	33.5	1.04
16	36	38.04	32.4	36	38.41	32.7	0.99
24	36	37.29	33.4	36	35.75	29.3	1.04

(continuation of Table 4)

36	36	37.99	32.0	36	36.53	32.2	1.04
48	35	31.93	34.4	36	30.91	32.2	1.03
72	35	29.86	31.5	36	29.05	30.2	1.02
96	36	25.23	32.1	36	24.73	31.7	1.02
168	36	19.52	33.9	33	18.93	40.2	1.04
336	35	11.45	42.0	35	10.64	43.8	1.07
672	36	2.597	140.0	35	2.547	137	1.05

(%CV's were calculated by reviewer.)

The pharmacokinetic parameters for N-desethylamiodarone are shown in Tables 5 and 6. Based on the least squares means of the log-transformed variables, the AUC_{0-t} and $AUC_{0-\infty}$ of the Upsher-Smith formulation were 5% and 4% higher than the respective means for the Wyeth formulation. The test C_{max} value was 2% higher than that of the reference product and occurred 1% later (13 minutes). Based upon the logarithmic transformations, the 90% confidence intervals about the ratios of test/reference means for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were within 80 - 125% limits for bioequivalence when the Upsher-Smith product was compared to the Wyeth product (AUC_{0-t} , 95.7-114.8; $AUC_{0-\infty}$, 97.1-110.4; and C_{max} , 95.7-108.2) (Table 6).

Table 5. Comparison of N-Desethylamiodarone arithmetic and geometric pharmacokinetic results between Upsher-Smith's Amiodarone Hydrochloride, 200 mg, Tablet (Test) and Wyeth Laboratories, Cardarone[®], 200 mg Tablet (Reference) administered as 200 mg doses under fasting conditions.

PARAMETER	TEST			REFERENCE			T/R
	N	Mean	%CV	N	Mean	%CV	

Arithmetic Means							
AUC_{0-t} (ng-hr/mL)	36	8535	45.8	36	8106	46.6	1.05
$AUC_{0-\infty}$ (ng-hr/mL)	36	11331	39.0	35	10764	38.8	1.05
C_{max} (ng/mL)	36	45.19	31.9	36	44.24	30.6	1.02
$T_{1/2}$ (hr)	36	225.3	36.12	35	220.4	36.5	1.02
T_{max} (hr)	36	15.67	50.1	36	15.42	49.0	1.02

Geometric Means							
AUC_{0-t} (ng-hr/mL)	36	7659	--	36	7223	--	1.06
$AUC_{0-\infty}$ (ng-hr/mL)	36	10479	--	35	9951	--	1.05
C_{max} (ng/mL)	36	43.03	--	36	42.11	--	1.02

Table 6. LSMeans and 90% Confidence Intervals (C.I.) For N-Desethylamiodarone Following a Single-Dose of Amiodarone Hydrochloride 200 mg Tablet and Reference Cardarone[®] (200 mg) Tablet Under Fasting Conditions

PARAMETER	Test	Ref	T/R	90% C.I.
----- LSMeans -----				
AUC _{0-∞} (ng-hr/mL)	8728	8381	1.04	--
AUC ₀₋₂₄ (ng-hr/mL)	11477	11061	1.04	--
C _{max} (ng/mL)	45.78	44.94	1.02	--
----- Geometric LSMeans -----				
AUC _{0-∞} (ng-hr/mL)	7905	7544	1.05	95.7-114.8
AUC ₀₋₂₄ (ng-hr/mL)	10678	10311	1.04	97.1-110.4
C _{max} (ng/mL)	43.78	43.01	1.02	95.7-108.2

Individual test/reference ratios of the pharmacokinetic parameters AUC_{0-∞}, AUC₀₋₂₄ and C_{max} for N-desethylamiodarone are shown in Table 10 (appended). Individual AUC_{0-∞}/AUC₀₋₂₄ ratios for N-desethylamiodarone are shown in Table 11 (appended). The elimination rate constant and half-life could not be reliably estimated for the metabolite in plasma for subject #39 administered the reference formulation, due to pharmacokinetic anomalies in the terminal phase of elimination. As a result, AUC_{0-∞} was not obtained.

Adverse Events

Sixteen subjects reported 20 adverse events. Three of the events were moderate in severity and 17 of the events were mild in severity. The events appear with approximately equal frequency for the test and the reference products. Headache was the most frequently reported event (6 subjects, 6 events). Subjects 34 and 38 were withdrawn from the study because of adverse events.

IX. DISSOLUTION TESTING

There is no USP dissolution for the amiodarone hydrochloride 200 mg tablet. The firm proposes the following dissolution method, and tolerance specifications for its product:

Apparatus:	USP Apparatus I (Basket)
Spindle Speed:	50 rpm
Medium:	0.05M Sodium Acetate Buffer, pH 4 with 1% Polysorbate 80
Volume:	900 mL
Tablets Tested:	12 Test vs. 12 Reference
Tolerance:	Q = in 60 minutes

The dissolution data obtained using the above method are shown in Table 7.

Dissolution Developmental Work

On May 24, 1996 the firm sent a letter to the Division of Bioequivalence that briefly outlined the firm's development work on dissolution and its proposed methodology. Amiodarone hydrochloride, is only very slightly soluble in water, making an aqueous dissolution method difficult. Screening dissolutions were performed with Cordarone^s, the innovator product, in various buffers and surfactants, alone and in combination. Based on the screening dissolutions, the most successful media were 0.05M acetate buffer containing either isopropyl alcohol, 1% SDS or 1% polysorbate 80. Acetate buffer (0.05M) at pH 4 containing 1% polysorbate 80 was chosen as the dissolution media based on the screening dissolutions which established it as the ideal media to meet the development objectives.

For evaluation purposes, dissolutions were initially performed using both USP apparatus II (paddle) and USP apparatus I (basket). Using baskets in place of paddles was very effective in reducing the variability observed using paddles. A spindle speed of 50 rpm was chosen to benefit from the more discriminating profile compared to the very rapid profile obtained using the 100 rpm stirring speed.

The firm's method of quantitation was validated and shown to have a linear response at to amiodarone concentration and it was shown to be precise and accurate.

On July 22, 1996 in the response from the Division of Bioequivalence to the firm's above May 24, 1996 correspondence the firm was advised that a dissolution test method for amiodarone HCl tablets had been established (900 mL sodium acetate buffer, pH 5.0, 1% SDS (1% sodium lauryl sulfate), paddles at 75 rpm, NLT in 60 min. The firm was asked to submit comparative dissolution test data when the ANDA is submitted using the above FDA recommended method for the test versus the referenced product. Also, the firm was advised that should it find the recommended method to be unacceptable for the test product, to submit relevant supporting data.

Upsher-Smith Laboratories informed the Division of Bioequivalence by telephone on 8/9/96 that the FDA method had been found to give highly variable results for its product and for the brand name Cordarone^s Tablets (due to tablets sticking to the sides of the dissolution vessels).

On 8/22/96 the Division of Bioequivalence determined that the NDA dissolution specifications were listed as paddle 100 rpm in 1000 mL 1% SLS in water with a tolerance specification of Q=NLT in 60 minutes. On 8/22/96 the firm was informed of the innovator specifications. The firm was told that it should perform comparative testing using the innovator specifications,

but that our Division generally does not recommend the 100 rpm paddle speed. The firm was asked to submit all comparative dissolution data with its ANDA, including any proposals to establish a revised dissolution procedure.

X. FORMULATION

Upsher-Smith Laboratories' formulation of its drug product, Amiodarone Hydrochloride 200 mg Tablet follows:

(NOT FOR RELEASE UNDER FOI)

Component	%W/W	mg/Tablet
Amiodarone Hydrochloride	53.33	200.00
Lactose Monohydrate, NF		
Pregelatinized Corn Starch, NF		
FD&C Red No. 40		
FD&C Yellow No. 6		
Povidone, U.S.P.		
Purified Water, U.S.P.		
Sodium Starch Glycolate, NF		
Stearic Acid, NF		
Magnesium Stearate, NF		
TOTAL	100.00	375.0

Manufacturing Lot # 62185 was used in the bioequivalence study.
The batch size was

XI. COMMENTS

1. The pharmacokinetic parameters and statistics were calculated by the reviewer and were in satisfactory agreement with what the firm reported.
2. The dissolution method developed by the firm was validated. Accuracy, reproducibility and release profile continuity are acceptable. The Division of Bioequivalence agrees that the method proposed by Upsher-Smith Laboratories is an appropriate option for evaluating the dissolution of amiodarone HCl 200 mg tablets for the test product.
3. The firm's proposed tolerance specifications are those recommended by the Agency in the Division of Bioequivalence July 22, 1996 response letter (i.e., NLT Q) in 60 minutes).
4. The analytical data is acceptable.
5. The assayed potencies of the test and reference products and content uniformity of the test product are satisfactory.
6. The N-desethylamiodarone (metabolite) quality control sample concentrations are 750, 75 and 12.5 ng/mL. All of the plasma concentrations after the 200 mg amiodarone dose are less than 75 ng/mL. Only one quality control sample is within the observed concentration range. In the future the

concentrations of the control samples should be more relevant to the levels in the study.

RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study conducted by Upsher-Smith Laboratories, Inc. on its amiodarone hydrochloride, 200 mg tablet, lot # 62185 comparing it to Wyeth-Ayerst Laboratories, Inc.'s Cordarone^s, 200 mg tablet, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Upsher-Smith Laboratories, Inc.'s amiodarone hydrochloride, 200 mg tablet is bioequivalent to the reference product, Cordarone^s, 200 mg tablet manufactured by Wyeth-Ayerst Laboratories, Inc.

2. The *in vitro* dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.05M sodium acetate buffer, pH 4, with 1% polysorbate 80 at 37°C using USP XXIII apparatus 1 (basket) at 50 rpm. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of amiodarone hydrochloride in the dosage form is dissolved in 60 minutes.

3. From the Bioequivalence point of view the firm has met the requirements of *in vivo* bioavailability and *in vitro* dissolution testing and the application is approvable.

The firm should be advised of the recommendations and comment 6.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang _____
FT INITIALED YCHuang _____

Concur:
Dale Connér, Pharm.D.
Director, Division of Bioequivalence

Date: 12/23/97

cc: ANDA 75-135 (original, duplicate), HFD-630
(Hare), HFD-652 (Huang, Chaney), HFD-650
(Director), Drug File, Division File

JEC/120297

WP# x:\new\firmnsz\upsher\ltrs&rev\75135SD.597

Table 7. In Vitro Dissolution Testing

Drug (Generic Name): Amiodarone Hydrochloride
 Dose Strength: 200 mg
 ANDA No.: 75-135
 Firm: Upsher-Smith Laboratories, Inc.
 Submission Date: May 19, 1997
 File Name: wp# 750135SD.597

I. Conditions for Dissolution Testing:

U.S.P. XXIII Basket: X Paddle: RPM: 50
 No. Units Tested: 12
 Medium: 0.05 acetate buffer (pH4) with 1% Polysorbate 80
 Volume: 900 mL
 Specifications: NLT in 60 min
 Reference Drug: Cordarone[®]
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 62185 Composite Strength(mg) 200			Reference Product Lot # 9960379 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	36.8		7.6	32.1		9.0
20	74.8		7.3	75.6		8.1
40	99.6		2.1	96.1		2.2
60	98.4		1.8	95.5		1.6

Table 8. Individual Amiodarone Test/Reference Ratios for AUC_{0-24} , AUC_{0-12} , and C_{max} Following Oral Dosing of Test Amiodarone Hydrochloride 200 mg Tablet and Reference Cardarone[®] (200 mg) Tablet Under Fasting Conditions

SUBJ	AUC_{0-24}	AUC_{0-12}	C_{max}
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
30			
32			
36			
37			
39			
40			
41			
42			
43			
Mean	1.11	1.11	1.09
Minimum	0.56	0.59	0.60
Maximum	2.07	2.15	2.30
N	36	35	36

Table 9. Individual Amiodarone AUC₀₋₂₄ to AUC₀₋₁₂ Ratios Following Oral Dosing of Test Amiodarone Hydrochloride 200 mg Tablet and Reference Cardarone[®] 200 mg Tablet Under Fasting Conditions

SUBJECT	TEST	REFERENCE
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
30		
32		
36		
37		
39		
40		
41		
42		
43		
Mean	0.89	0.90
Minimum	0.78	0.79
Maximum	0.96	0.95
N	35	36

Table 10. Individual N-Desethylamiodarone Test/Reference Ratios for AUC₀₋₁₂, AUC₀₋₂₄, and C_{max} Following Oral Dosing of Test Amiodarone Hydrochloride 200 mg Tablet and Reference Cardarone[®] (200 mg) Tablet Under Fasting Conditions

SUBJ	AUC ₀₋₁₂	AUC ₀₋₂₄	C _{max}
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
30			
32			
36			
37			
39			
40			
41			
42			
43			
Mean	1.17	1.11	1.05
Minimum	0.41	0.43	0.67
Maximum	3.43	2.72	2.15
N	36	35	36

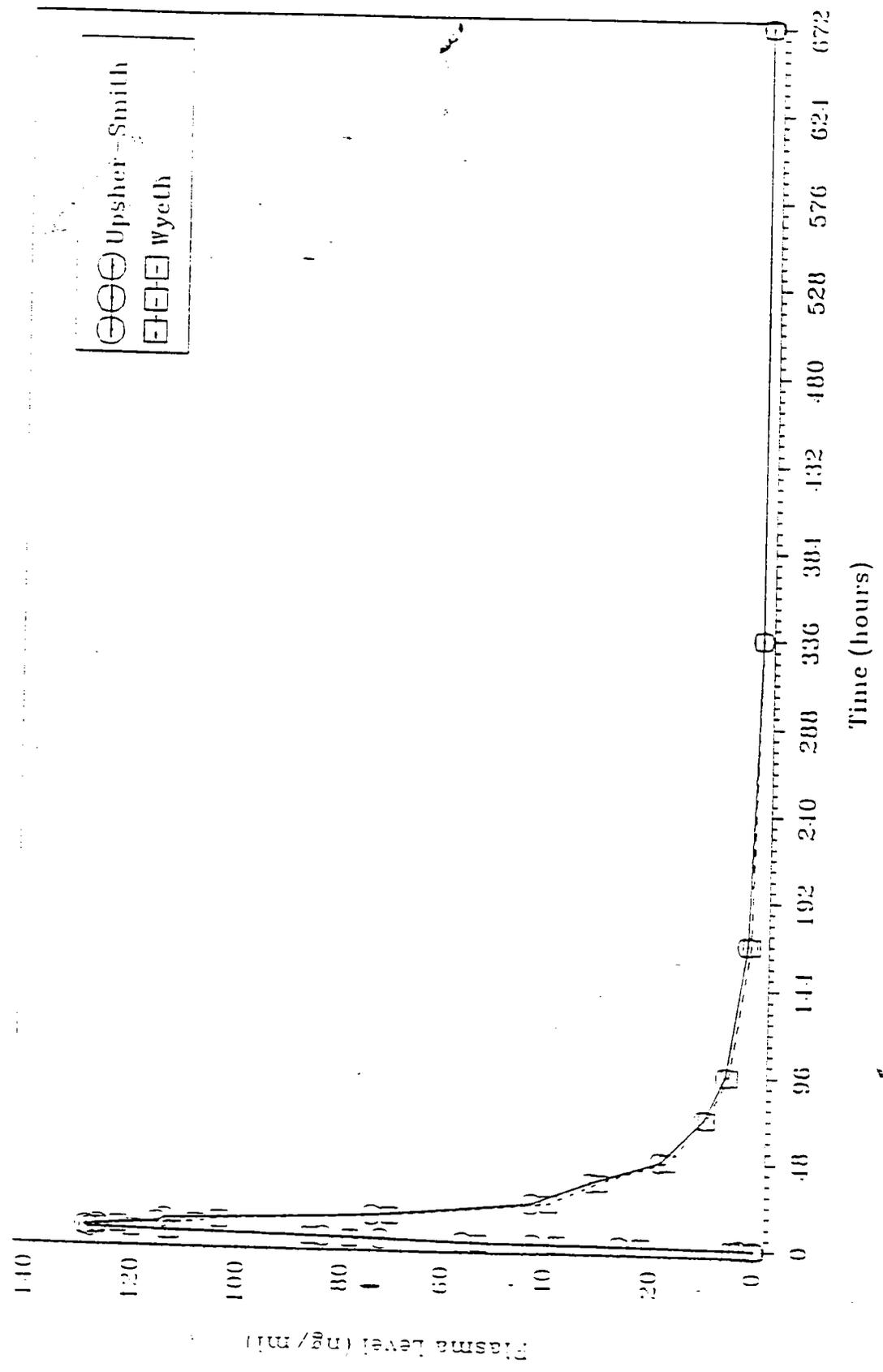
Table 11 Individual N-Desethylamiodarone AUC_{0-12} to AUC_{0-24} Ratios Following Oral Dosing of Test Amiodarone Hydrochloride 200 mg Tablet and Reference Cardarone^s 200 mg Tablet Under Fasting Conditions

SUBJECT	TEST	REFERENCE
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
30		
32		
36		
37		
39		
40		
41		
42		
43		
Mean	0.74	0.73
Minimum	0.41	0.38
Maximum	0.91	0.93
N	36	35

Figure 1: Mean Amiodarone Plasma Levels

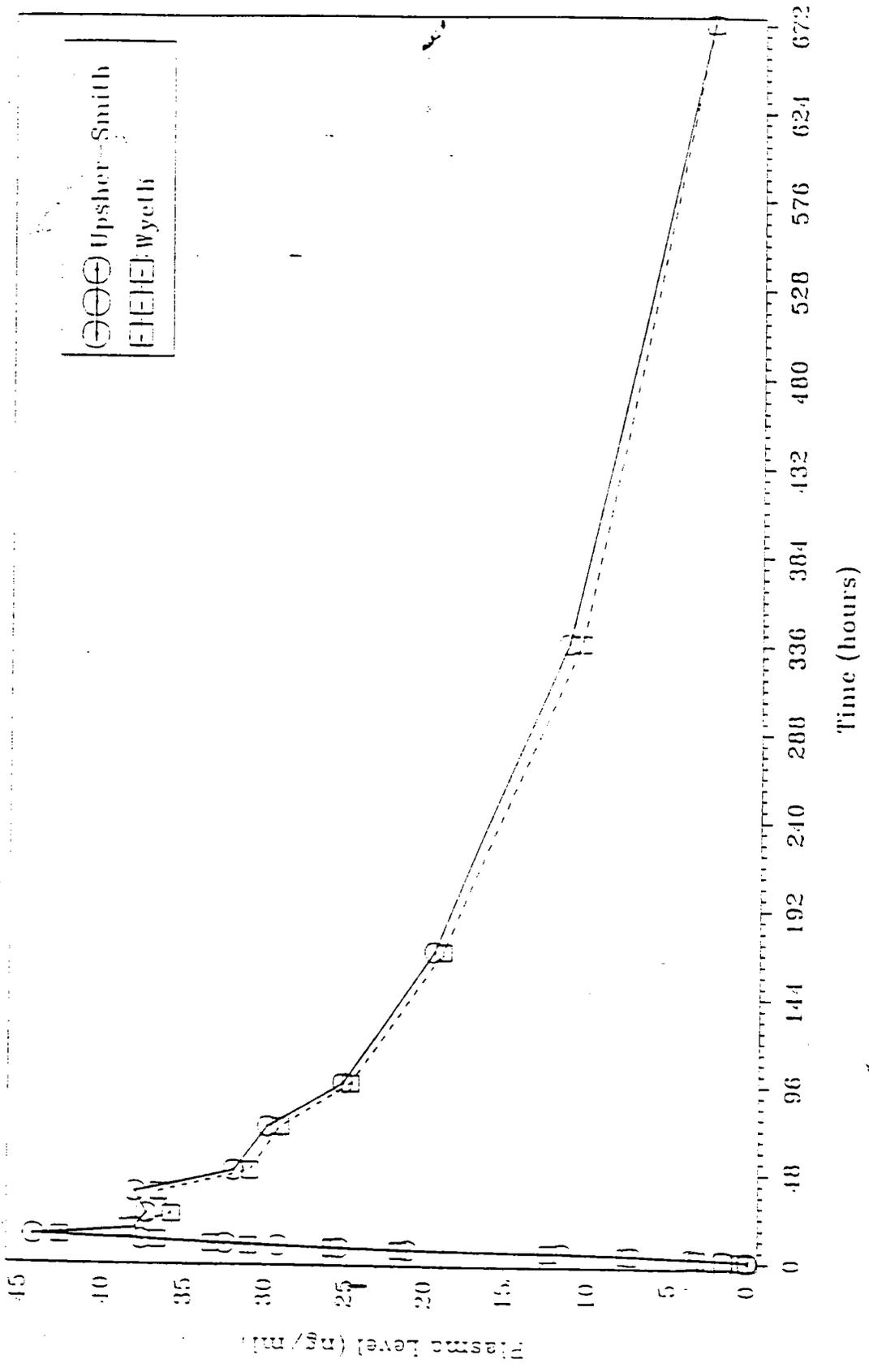
#110-02-11166

N = 36



~~1100~~ Fig 2

2
 Figure X: Mean N-desethylamiodarone Plasma Levels
 #140-02-11166
 N = 36



~~00140~~ fig 22

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-135

APPLICANT: Upsher Smith

DRUG PRODUCT: Amiodarone 200 mg tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.05M sodium acetate buffer, pH 4, with 1% polysorbate 80 at 37°C using USP XXIII apparatus 1 (basket) at 50 rpm. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of amiodarone hydrochloride in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **75135** _____

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-135 Dates of Submission: December 31, 1997 &
January 30, 1998

Applicant's Name: Upsher-Smith Laboratories, Inc.

Established Name: Amiodarone Hydrochloride Tablets 200 mg

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 60s and 500s
Satisfactory as of January 30, 1998 submission.

Unit Dose Blister Label:
Satisfactory as of January 30, 1998 submission.

Unit Dose Carton Label: 100s (10 x 10)
Satisfactory as of January 30, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of January 30, 1998 submission.

Revisions needed post-approval: Replace "CAUTION: Federal law...
statement with "Rx only" symbol on labels and labeling; container
labels and carton labeling - established name should include
"tablet"

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cordarone®

NDA Number: 18-972

NDA Drug Name: Cordarone® (Amiodarone Hydrochloride) Tablets

NDA Firm: Wyeth Ayerst Labs

Date of Approval of NDA Insert and supplement #: 10/18/95 (S-014)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: labels on file and side-by-sides

Basis of Approval for the Unit Dose Carton Labeling: side-by-sides

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
	Yes	No	N.A.
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? NO List reasons in FTR, if so. Consider: Misleading? NO Sounds or looks like another name? NO USAN stem present? NO Prefix or Suffix present? SUFFIX "RONE" present		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified? LNC found the name acceptable provided that no emphasis put on ONE in name.	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? FOR THE UNIT DOSE Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? HDPE containers Must the package insert accompany the product? Yes		X	
Are there any other safety concerns?		X	
Labeling			

	Yes	No	N.A.
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the PTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (PTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) Tablets are "debossed"		X	
USP Issues: (PTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? HAVE ASKED THE CHEMIST THIS			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			
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FOR THE RECORD: (portions taken from previous review)

1. The labeling review for this ANDA was based on the reference listed drug Cordarone® (NDA 18-972/S-014; approved 10-18-95). New labeling pending approval.
2. Upsher-Smith is the manufacturer. Other firms share some of the manufacturing operations (v 1.8, p 3348). The firm has included the statement "Certain manufacturing operations have been performed by other firms." on all their labeling pieces. This is satisfactory
3. Both the RLD and this ANDA are scored.
4. Container/Closure

The containers are made of HDPE; the 60s size has a CRC while the 500s does not (v 1.9, p 3766).
5. Container sizes

RLD - 60s and UD 100s
ANDA - 60s, 500s and UD 100s
6. The proposed proprietary name Pacerone™ has been submitted to the LNC and has been found unobjectionable provided that the firm does not emphasize the "one" part of the name, e.g. "PacerONE".
7. There are no patents or exclusivities for this drug product.
8. This is a "first generic".

Date of Review: 2-4-98 Dates of Submission: 12-31-97 & 1-30-98

Primary Reviewer: Adolph Vezza Date:

Team Leader: Charlie Hoppes Date:
