CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75315

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 75-315 APPLICANT: Eon Labs

DRUG PRODUCT: Amiodarone HCl Tablets, 200 mg

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

The following dissolution testing should be incorporated into your stability and quality control programs, only as an interim method, until more uniform in vitro dissolution testing requirements and specifications for amiodarone HCl tablet products are made available and official by the USP.

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,

/S/

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA #75-315 SPONSOR : Eon Labs
DRUG & DOSAGE FORM : Amiodarone HCl Tablets
STRENGTHS : 200 mg

TYPE OF STUDY: SD
STUDY: XAcceptable ☐Not Applicable

DISSOLUTION: XAcceptable ☐Not Applicable

REVIEWER: Hoainhon Nguyen BRANCH: I
INITIAL: HN DATE : 10-16-98

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : Yih-Chain Huang DATE: 10/16/98

DIRECTOR: Dale Conner, Pharm.D. DIVISION OF BIOEQUIVALENCE
INITIAL : DC DATE: 10/19/98

Amiodarone Hydrochloride Tablets, 200 mg
ANDA #75-315
Reviewer: Hoainhon Nguyen
WP # 75315a.698

Eon Labs
Laurelton, NY
Submission Date:
June 19, 1998
October 9, 1998 (Tel. Amend.)

Review of a Study Amendment: Stability Study and Dissolution Data

The firm has recently amended the ANDA in response to the Division of Bioequivalence's deficiency comments sent to the firm in the letter dated June 9, 1998 concerning the long-term stability data for the single-dose, fasting bioequivalence study, and dissolution testing of the test product. The comments were as follows:

"1. The single-dose, fasting bioequivalence study conducted by Eon Labs on the test product, Amiodarone Hydrochloride Tablets, 200 mg, lot # 970604, comparing it with the reference product, Wyeth-Ayerst's Cordarone® Tablets, 200 mg, lot # 9961276, has been found incomplete for the reason that the long-term stability study is deficient. Since the first plasma sample was collected on August 5, 1997 and the last sample was analyzed on December 17, 1997, the maximum storage duration was 134 days. The stability of amiodarone and desethylamiodarone in plasma at -22 °C for that length of time has not been demonstrated. The study results are not considered valid until the long-term stability study is found acceptable.

2. The in vitro dissolution data for the test and reference products are unacceptable. The paddle speed of rpm was not recommended by the agency for the paddle apparatus, especially for amiodarone hydrochloride drug products. You should repeat the dissolution testing using the correct paddle speed of 75 rpm.

The FDA-recommended dissolution testing for the test product should be conducted in 900 mL of pH 5.0 sodium acetate buffer with 1% SLS at 37 °C using USP XXIII apparatus II(paddle) at 75 rpm."

Firm's Responses:

1. The firm has submitted the stability study data to demonstrate that amiodarone and desethylamiodarone are stable at -25°C for at least 270 days.

2 a. The firm has repeated the dissolution testing as requested. The results are summarized below.

Dissolution Testing:

Drug (Generic Name): Amiodarone HCl Tablets Firm: Eon Labs
Dose Strength: 200 mg ANDA # 75-315
Submission Date: June 19, 1998

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXI Basket ____ Paddle X RPM 75 No. Units Tested: 12
Medium: pH 5.0 sodium acetate buffer with 1% SLS Volume: 900 ml
Reference Drug: (Manuf.) Cordarone^{R} Tablets; Wyeth-Ayerst
Assay Methodology:

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 970604 Strength (mg) 200		Reference Product Lot # 9961276 Strength (mg) 200	
	Mean %	Range (CV)	Mean %	Range (CV)
15	72.7	(31%)	68.9	(30%)
30	86.6	(23%)	87.2	(19%)
45	90.2	(19%)	91.2	(16%)
60	92.1	(17%)	93.4	(13%)

The firm explained that tablets of both the test and reference products *'are sticking to the bottom of the dissolution vessel, which significantly affected their release rate. This sticking tendency, inducing a drop of release rate, has been consistently observed during the product development phase. A paddle speed increase to rpm eliminated the sticking in both the referenced and test drugs. Consequently, rpm paddle speed was selected over the recommended speed of 75 rpm.'* The firm *'would prefer to abstain from changing the paddle speed of rpm to 75 rpm, as the sticking of the tablets to the bottom of the dissolution vessels, clearly impairs the reliability of the data.'*

2b. Due to the dissolution problem using the FDA-recommended testing procedure

as described above, on October 7, 1998, the Division of Bioequivalence requested through telephone that the firm repeats dissolution testing of the test product using another dissolution procedure which has been approved for ANDA #75-135 (Upsher Smith). The dissolution testing procedure is as follows:

Medium: 0.05M sodium acetate buffer, pH 4, with 1% polysorbate 80
Volume: 900 mL
USP XXIII apparatus: I(basket)
Speed: 50 and 100 rpm

The firm submitted the additional dissolution testing results on October 9, 1998. The results are summarized below.

Drug (Generic Name): Amiodarone HCl Tablets Firm: Eon Labs
Dose Strength: 200 mg ANDA # 75-315
Submission Date: October 9, 1998

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXI Basket X Paddle ____ RPM 50 & 100 No. Units Tested: 12
Medium: pH 4.0 sodium acetate buffer (0.05M) with 1% polysorbate 80(Tween 80) Volume: 900 ml
Reference Drug: (Manuf.) None
Assay Methodology:

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 970604 Strength (mg) 200 @50 rpm		Test Product Lot # 9961276 Strength (mg) 200 @100 rpm		
	Mean %	Range (CV)	Mean %	Range	(CV)
15	94.7	3.0%)	101.0		(2.7%)
30	101.8	(1.2%)	101.0		(2.4%)
60	101.8	(1.3%)	100.9		(2.7%)
~~60~~ 75	101.8	(1.3%)	100.9		(2.6%)

DBE's Comments:

1. The long-term stability data for amiodarone and desethylamiodarone, as submitted in the current amendment, are acceptable.

The single-dose, fasting bioequivalence study which was submitted on January 28, 1998 and reviewed June 3, 1998 has now been found acceptable. See the review of

the original submission for the summary of the study results. The study demonstrated that the test and reference products are equivalent in the rate and extent of absorption, as measured by CMAX and AUCs, respectively, of amiodarone and desethylamiodarone.

2. The dissolution data for the test product obtained using the alternative dissolution testing procedure (as submitted on October 9, 1998) above are acceptable. The basket speed of **50 rpm** yielded more discriminating release rate data than the speed of **100 rpm**. The basket speed of 50 rpm is therefore recommended for the dissolution testing of the test product.

Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Eon Labs on its test product, Amiodarone HCl Tablets, 200 mg, lot # 970604, comparing it with the reference product, Wyeth-Ayerst's Cordarone® Tablets, 200 mg, lot # 9961276, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Eon's Amiodarone HCl Tablets, 200 mg, is bioequivalent to the reference product, Cordarone® Tablets, 200 mg, manufactured by Wyeth-Ayerst, under fasting conditions.

2. The in-vitro dissolution testing conducted by Eon Labs on its Amiodarone HCl Tablets, 200 mg, has been found **acceptable.**

The following dissolution testing should be incorporated into the firm's stability and quality control programs, **as an interim method,** until more uniform *in vitro* dissolution testing requirements and specifications for amiodarone HCl tablet products are made available and official by the USP.

/S/
Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 10/16/98

Concur: /S/ Date: 10/19/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-315 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
Hnguyen/09-23-98/WP #75315a.698/Revised 10-16-98

Attachments: 0page

JUN 9 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-315 APPLICANT: Eon Labs

DRUG PRODUCT: Amiodarone Hydrochloride Tablets, 200 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The single-dose, fasting bioequivalence study conducted by Eon Labs on the test product, Amiodarone Hydrochloride Tablets, 200 mg, lot # 970604, comparing it with the reference product, Wyeth-Ayerst's Cordarone® Tablets, 200 mg, lot # 9961276, has been found **incomplete** for the reason that **the long-term stability study is deficient**. Since the first plasma sample was collected on August 5, 1997 and the last sample was analyzed on December 17, 1997, the maximum storage duration was **134 days**. The stability of amiodarone and desethylamiodarone in plasma at -22°C for that length of time has not been demonstrated. The study results are not considered valid until the long-term stability study is found acceptable.

2. The in vitro dissolution data for the test and reference products are **unacceptable**. The paddle speed of rpm was not recommended by the agency for the paddle apparatus, especially for amiodarone hydrochloride drug products. You should repeat the dissolution testing using the correct paddle speed of **75 rpm**.

The FDA-recommended dissolution testing for the test product should be conducted in 900 mL of pH 5.0 sodium acetate buffer with 1% SLS at 37°C using USP XXIII apparatus II(paddle) at **75 rpm**.

Sincerely yours,

/S/

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

Amiodarone Hydrochloride Tablets
200 mg
ANDA #75-315
Reviewer: Hoainhon Nguyen
WP #75315sd.198

Eon Labs
Laurelton, NY
Submission Date:
January 6, 1998

Review of A Bioequivalence Study and Dissolution Data

I. Background:

Amiodarone hydrochloride is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects which may be due to at least two major properties: 1) a prolongation of the myocardial cell-action potential duration and refractory period and 2) noncompetitive alpha- and beta-adrenergic inhibition. Because of its life-threatening side effects and the substantial management difficulties associated with its use, the drug is indicated only for the treatment of the following documented, life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated: 1) recurrent ventricular fibrillation, and 2) recurrent hemodynamically unstable ventricular tachycardia. Amiodarone hydrochloride is slightly soluble in water.

Following oral administration in man, amiodarone hydrochloride is slowly and variably absorbed. The bioavailability of the drug is approximately 50%, but has varied between 35 and 65% in various studies. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses. The drug has a very large but variable volume of distribution, averaging about 60L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of amiodarone, mono-N-desethylamiodarone, has some arrhythmic activity and accumulates to an even greater extent in almost all tissues. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one.

The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. Amiodarone has a very low plasma clearance with negligible renal excretion. In patients, following discontinuation of chronic oral therapy, the drug has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26 to 107 days, with a mean of approximately 53 days and most patients in the 40- to 55-day range. In the absence of a loading-dose period, steady-state plasma concentrations, at constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of the drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat. The drug is highly protein-bound (approximately 96%).

Common adverse effects associated with amiodarone include nausea, vomiting, solar dermatitis/photosensitivity, malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias, constipation, anorexia, and visual disturbances. Most serious adverse effects of amiodarone are pulmonary toxicity, exacerbation of arrhythmia, and rare serious liver injury.

Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading doses of amiodarone of 800 to 1,600 mg/day are required for 1 to 3 weeks until initial therapeutic response occurs. When adequate arrhythmia control is achieved, the dose should be reduced to 600 to 800 mg/day for one month, then to the maintenance dose, usually 400 mg/day.

Amiodarone hydrochloride is available commercially as Cordarone® tablets, 200 mg, manufactured by Wyeth-Ayerst.

The firm has submitted the results of a fasting, single-dose bioequivalence study comparing its Amiodarone Hydrochloride Tablets, 200 mg, with Cordarone® Tablets, 200 mg. Comparative dissolution data for the test and RLD products are

also submitted.

II. Bioequivalence Study (Protocol No. GP310): Two-Way Crossover Bioequivalence Study of Eon Laboratories and Wyeth-Ayerst Amiodarone H Cl 200 mg Tablets (Cordarone®) in Fasting Volunteers

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Eon's Amiodarone Hydrochloride Tablets compared to Wyeth-Ayerst's Cordarone® 200 mg Tablets following a single 2x200 mg dose.

Study Investigators and Facilities:

The study was conducted at the between August 5 and October 23, 1997. The principal investigator was Plasma samples were assayed also by under the supervision of , between November 6 and December 17, 1997.

Demographics:

Forty-two normal, healthy male volunteers between 20-45 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were divided into 2 groups: Group 1 (Subjects # 1-26) was dosed on August 5(Period I) and October 7, 1997(Period II); Group 2 (Subjects #27-42) was dosed on August 21(Period I) and October 23, 1997(Period II). The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 61.4-86.6 kg and 157-186 cm.

Inclusion/exclusion criteria:

Subjects did not have any history of: hypotension or hypertension; clinically

significant cardiovascular, hepatic, renal, CNS, hematological or gastrointestinal disease; clinically significant bradycardia; alcoholism or drug abuse within the last year; hypersensitivity or idiosyncratic reaction to amiodarone or any other antiarrhythmic; using tobacco products in the previous 3 months.

Restrictions:

They were free of all prescription and over-the-counter medications for at least 14 days and allowed no concomitant medications during the study sessions. No alcoholic beverages and no xanthine-containing beverages or food were allowed for 48 hours prior to and during each study period. The subjects fasted for 10 hours overnight prior to and 4 hours after each drug administration. The washout duration between the two phases was 9 weeks. Duration of confinement was approximately 10 hours pre-dose to approximately 72 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 2x200 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product (Treatment A): Eon's Amiodarone HCL tablets, 200 mg, lot # 970604 (Batch size of units, potency of 99.5%).

Reference product (Treatment B): Wyeth's Cordarone® tablets, 200 mg, lot # 9961276 (Potency of 98.7%).

Blood samples were collected at predose, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36, 48, 72, 96 hours and 6, 10, 14, 21 and 28 days following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -20°C until assayed by the

Assay Methodology:

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Assay methodology

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters. Group(GRP) effect analysis was performed using MODEL Y= GRP SUBJ(GRP) PER(GRP) TRT GRP*TRT. As the GRP*TRT term was found not statistically significant, MODEL Y = SEQ SUBJ(SEQ) PER TRT was used with pooled data from both groups of subjects (Group I: Subjects 1-26, Group II: Subjects 26-41). In addition, a second check on the *poolability* of the two groups of subjects was performed on the equality of the residual mean squares from the two groups. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Thirty-eight of 42 enrolled volunteers completed the clinical portion of the study. Subject #3 was withdrawn due to a serious adverse event, depression and adjustment disorder, 31 days after dosing Period 1. Subject #28 was withdrawn due to abnormal EKG screening. Subject #36 withdrew for a personal reason. Subject #36 did not show up for check-in. Per protocol, data was to be analyzed on the first 36 subjects who completed the study. However, there was no data available for Subject #21 and data were analyzed from Subject #41.

NOTE: According to Don Schuirmann, the FDA statistician, MODEL Y=SEQ SUBJ(SEQ) PER(GRP) TRT; should be used for the study design such as that of this study (See a consult example attached). Reanalyzed results are given in the

result summary tables **in bold** below.

Amiodarone: There was no significant difference (alpha=0.05) between treatments for LAUC(0-T), LAUC(0-Inf) or LCMAX when Schuirmann's model was used. The results are summarized in the tables below:

Table I
Amiodarone Comparative Pharmacokinetic Parameters
Dose=2x200 mg; n=36
Fasting Study

Parameters	Eon's Mean (CV%)	Cordarone® Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	5835.6*	6530.3*	[0.82;0.98] **[0.82;0.98]****	0.89
AUC (0-Inf) ng.hr/ml	6658.6*	7221.4*	[0.82;1.00] **[0.82;1.00]****	0.92
CMAX(ng/ml)	286.7*	316.9*	[0.82;1.00] **[0.82;1.00]****	0.90
TMAX (hrs)	6 (23)	6 (30)		
KEL (1/hrs)	0.023(49)	0.021(43)		
T1/2 (hrs)	39 (72)	44 (72)		

*Geometric LSMeans
**Calculated using Don Schuirmann's model

For mean plasma **amiodarone** concentrations at each sampling time point, see Table II, Attachment 1 at the end of the review.

Desethylamiodarone: There was no significant difference (alpha=0.05) between treatments for LAUC(0-T), LAUC(0-Inf) or LCMAX when Schuirmann's model was used. The results are summarized in the tables below:

Table III
Desethylamiodarone Comparative Pharmacokinetic Parameters
Dose=2x200 mg; n=36
Fasting Study

Parameters	Eon's Mean (CV%)	Cordarone® Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	8431.7*	9162.5*	[0.84;1.01] **[0.84;1.01]****	0.92
AUC (0-Inf) ng.hr/ml	13082*	13829*	[0.87;1.03] **[0.86;1.03]****	0.95
CMAX(ng/ml)	58.7*	59.5*	[0.91;1.07] **[0.91;1.08]****	0.99
TMAX (hrs)	15(79)	15(75)		
KEL (1/hrs)	0.0037(40)	0.0035(39)		
T1/2 (hrs)	216(38)	223(35)		

*Geometric LSMeans
**Calculated using Don Schuirmann's model

For mean plasma **desethylamiodarone** concentrations at each sampling time point, see Table IV, Attachment 2 at the end of the review.

Adverse Effects:

There was no serious adverse event reported. There were 28 study-related complaints: 22 complaints by 9 subjects during the Test treatment, and 6 complaints by 3 subjects during the Reference treatment. The summary of the adverse events is attached to this review.

III. Dissolution Testing: **FDA-recommended** methods (NOTE: Amiodarone Hydrochloride Tablets are non-compendial).

Drug (Generic Name): Amiodarone Hydrochloride Tablets Firm: Eon Labs
Dose Strength: 200 mg ANDA # 75-315
Submission Date: January 6, 1998

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket __ Paddle X RPM 100 Units Tested: 12
Medium: pH 5.0 Sodium Acetate Buffer with 1% SLS Volume: 900 ml
Reference Drug: (Manuf.) Cordarone (Wyeth-Ayerst)
Assay Methodology: _____
Specifications: NLT % in 60 minutes

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 970604 Strength (mg) 200 Mean % Dissolved(CV%)	Range	Reference Product Lot # 9961276 Strength (mg) 200 Mean % Dissolved(CV%)	Range
10	75.9(12.2)		61.7(14.5)	
15	93.7(5.4)		84.3(10.3)	
20	98.5(2.1)		93.3(5.5)	
30	100.2(1.0)		72.1	
45	100.9(0.7)		80.7	
60	101.2(0.7)		87.3	

IV. Deficiency:

1. Since the first plasma sample was collected on August 5, 1997 and the last sample was analyzed on December 17, 1997, the maximum storage duration was **134 days**. The stability of amiodarone and desethylamiodarone in plasma at -22°C for that length of time has not been demonstrated. The long-term stability study is therefore deficient. The study results are not considered valid until the long-term stability study is found acceptable.

2. The in vitro dissolution data for the test and reference products are **unacceptable**. The paddle speed of rpm was not recommended by the agency for the paddle apparatus, especially for amiodarone hydrochloride drug products. The firm should repeat the dissolution testing using the correct paddle speed of **75 rpm**.

V. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Eon Labs on the test product, Amiodarone Hydrochloride Tablets, 200 mg, lot # 970604, comparing it with the reference product, Wyeth-Ayerst's Cordarone® Tablets, 200 mg, lot # 9961276, has been found **incomplete** for the reason cited in the Deficiency #1 above.

2. The in-vitro dissolution testing conducted by Eon Labs on its Amiodarone Hydrochloride Tablets, 200 mg, has been found **unacceptable** for the reason cited in the Deficiency #2 above. The firm is required to repeat the dissolution testing using the correct paddle speed of **75 rpm**.

The FDA-recommended dissolution testing should be conducted in 900 mL of pH 5.0 sodium acetate buffer with 1% SLS at 37°C using USP XXIII apparatus II(paddle) at **75 rpm**.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 5/26/98

Concur: /S/ Date: 6/3/98

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 75-315 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File, HFD-650 (Director)

HNguyen/05-07-98/WP #75315sd.198
Also in x:\new\firmsam\eon\ltrs&rev\75315sd.198
Attachment: 8 pages

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-315 APPLICANT: Eon Labs

DRUG PRODUCT: Amiodarone Hydrochloride Tablets, 200 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The single-dose, fasting bioequivalence study conducted by Eon Labs on the test product, Amiodarone Hydrochloride Tablets, 200 mg, lot # 970604, comparing it with the reference product, Wyeth-Ayerst's Cordarone® Tablets, 200 mg, lot # 9961276, has been found **incomplete** for the reason that **the long-term stability study is deficient**. Since the first plasma sample was collected on August 5, 1997 and the last sample was analyzed on December 17, 1997, the maximum storage duration was **134 days**. The stability of amiodarone and desethylamiodarone in plasma at -22°C for that length of time has not been demonstrated. The study results are not considered valid until the long-term stability study is found acceptable.

2. The in vitro dissolution data for the test and reference products are **unacceptable**. The paddle speed of rpm was not recommended by the agency for the paddle apparatus, especially for amiodarone hydrochloride drug products. You should repeat the dissolution testing using the correct paddle speed of **75 rpm**.

The FDA-recommended dissolution testing for the test product should be conducted in 900 mL of pH 5.0 sodium acetate buffer with 1% SLS at 37°C using USP XXIII apparatus II(paddle) at **75 rpm**.

Sincerely yours,

/S/

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

WP #75315sd.198 Attachment 1:

Table II

Comparative Mean Plasma Levels of Amiodarone

Dose=2x200 mg; n=36

ng/ml(CV%)

Fasting Study

TIME (hours)	A: EON LABS mean(CV%)	B: WYETH-AYERST mean(CV%)
pre-dose	0.0	0.0
1 hour	45.0(126)	52.8 (104)
2 hours	121.5(85)	134.7(63)
3 hours	165.8(57)	188.4(49)
4 hours	195.9(44)	206.3(48)
5 hours	267.3(43)	278.8(46)
6 hours	298.8(49)	291.4(42)
7 hours	287.0(56)	293.9(49)
8 hours	273.5(55)	278.4(48)
12 hours	181.9(60)	188.4(56)
24 hours	77.1(45)	87.5(47)
36 hours	52.3(51)	56.5(52)
48 hours	33.0(50)	36.3(43)
72 hours	20.2(46)	22.1(45)
96 hours	11.8(83)	15.1(71)
120 hours	8.6(93)	8.2 (121)
216 hours	0.7(412)	2.5 (223)
312 hours	0.3(583)	0.7 (407)
480 hours	0.0	0.0
648 hours	0.0	0.0
AUC(0-T)ng.hr/mL	6594.6(51)	7265.7(49)
AUC(0-I)ng.hr/mL	7508.3(50)	8074.3(51)
CMAX	321.5(52)	343.1(42)

WP #75315sd.198 Attachment 2:

Table IV

Comparative Mean Plasma Levels of Desethylamiodarone

Dose=2x200 mg; n=36

ng/ml(CV%)

Fasting Study

TIME (hours)	A: EON LABS mean(CV%)	B: WYETH-AYERST mean(CV%)
pre-dose	0.0	0.0
1 hour	0.4(600)	0.0
2 hours	3.5(233)	4.6(155)
3 hours	9.7(115)	10.4 (112)
4 hours	18.0(73)	19.6(67)
5 hours	35.5(42)	37.4(50)
6 hours	45.3(37)	43.3(39)
7 hours	48.6(42)	47.2(37)
8 hours	55.0(36)	54.2(33)
12 hours	57.5(32)	55.5(31)
24 hours	45.3(27)	48.3(24)
36 hours	45.9(30)	49.2(24)
48 hours	39.4(32)	40.8(22)
72 hours	34.7(26)	36.7(24)
120 hours	27.3(28)	29.6(32)
216 hours	18.7(33)	20.5(35)
312 hours	13.2(56)	14.9(51)
480 hours	4.9(137)	5.1(127)
648 hours	1.0(337)	1.3(288)
AUC(0-T)ng.hr/mL	9250.6(41)	9968.7(41)
AUC(0-I)ng.hr/mL	13883(34)	14589(31)
CMAX	62.1(34)	61.4(26)

CC:ANDA 75-315
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 5/26/98
HFD-617/ L. Sanchez or N.Chamberlin
HFD-650/ D. Conner 6/3/98

BIOEQUIVALENCY - INCOMPLETE
(DISSOLUTION - UNACCEPTABLE)

Submission date: 1-6-98

1. FASTING STUDY (STF)
   Clinical:
   Analytical:

Strengths: 200 MG
Outcome: IC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

WP # 75315sd.1"15

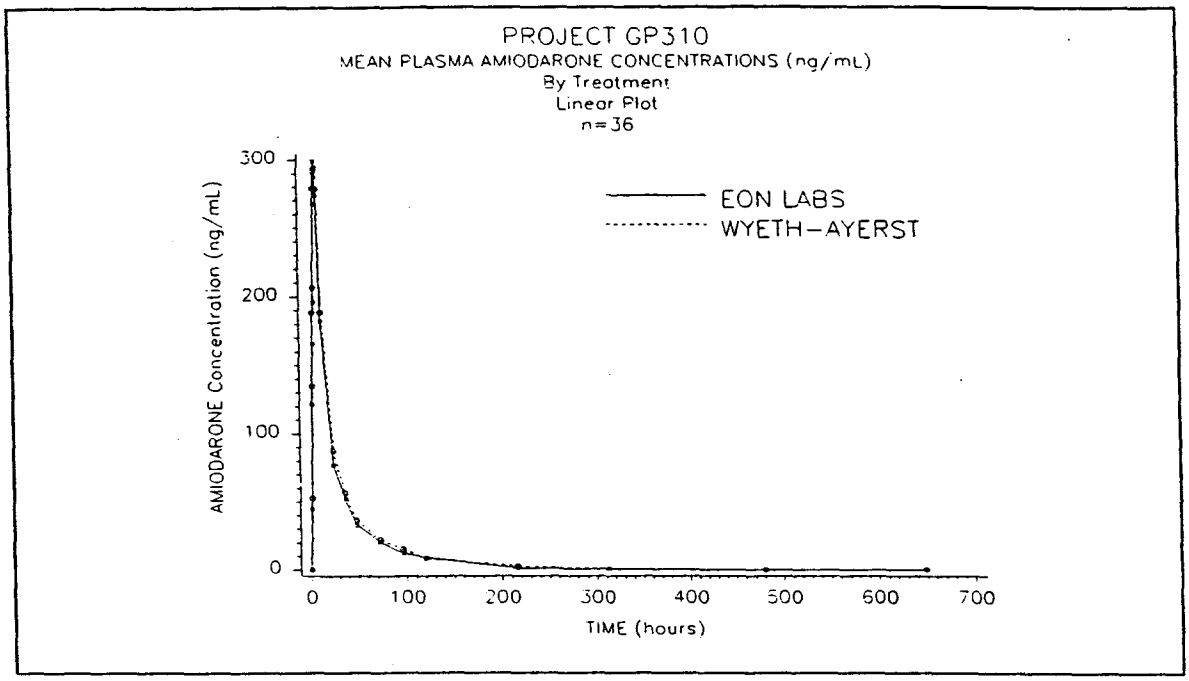

Figure 1

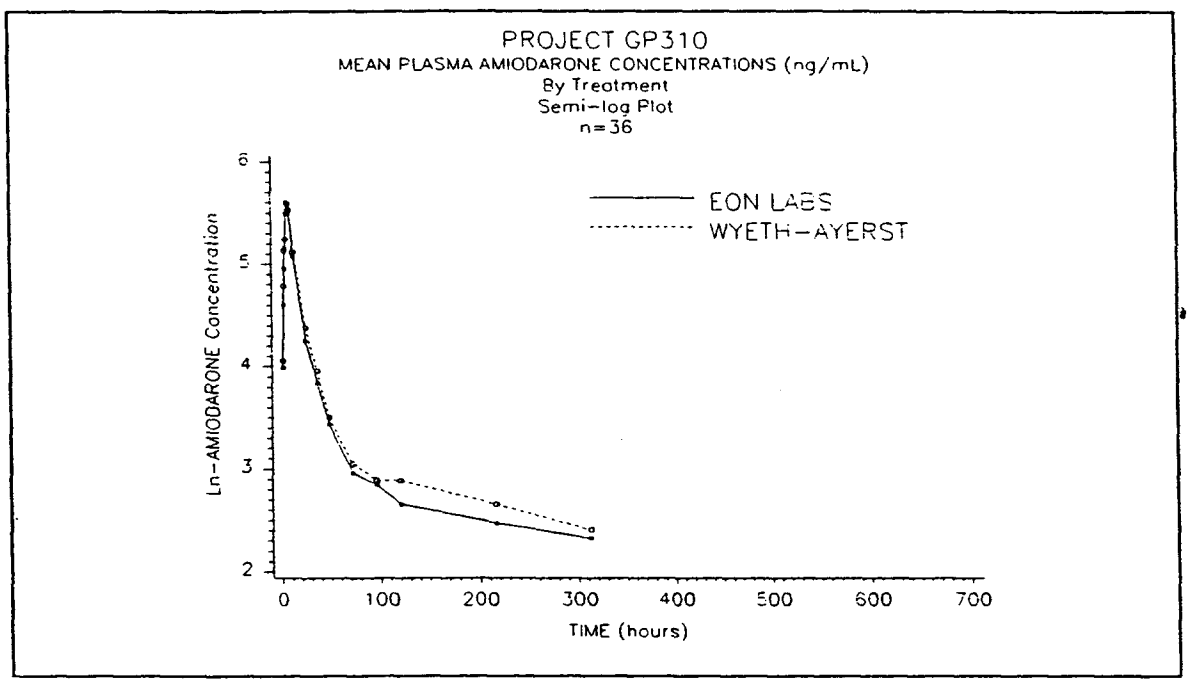

Figure 2

WI# 152155d, 1 10 Attachment 4

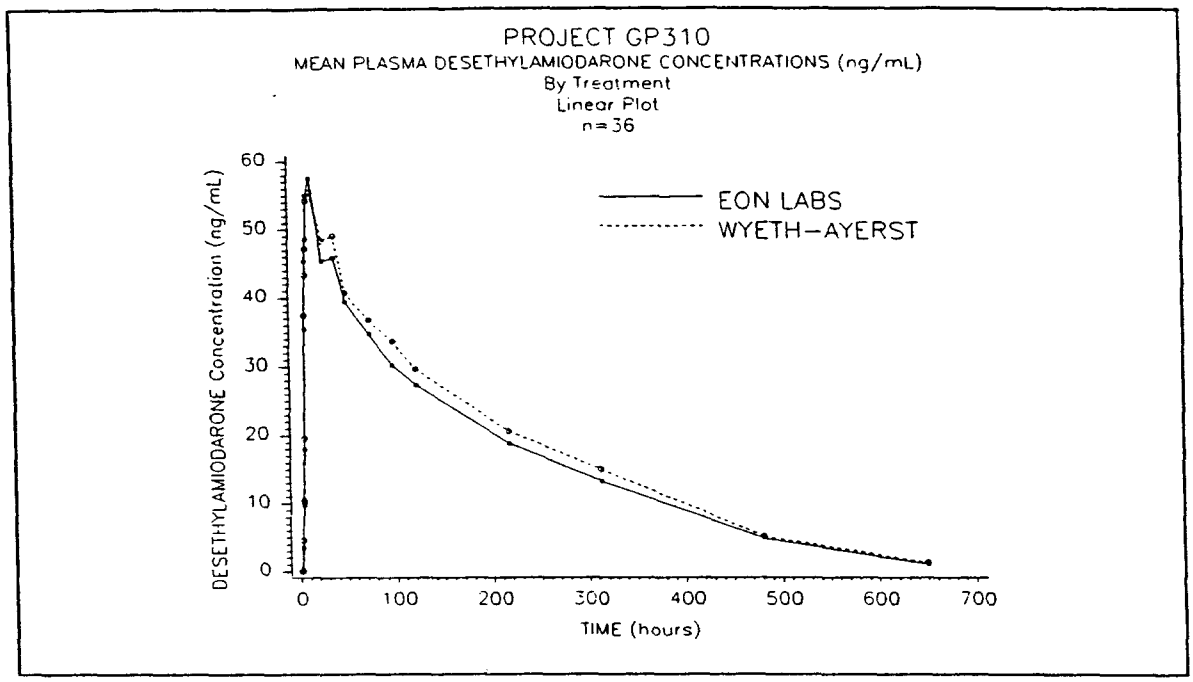

Figure 3

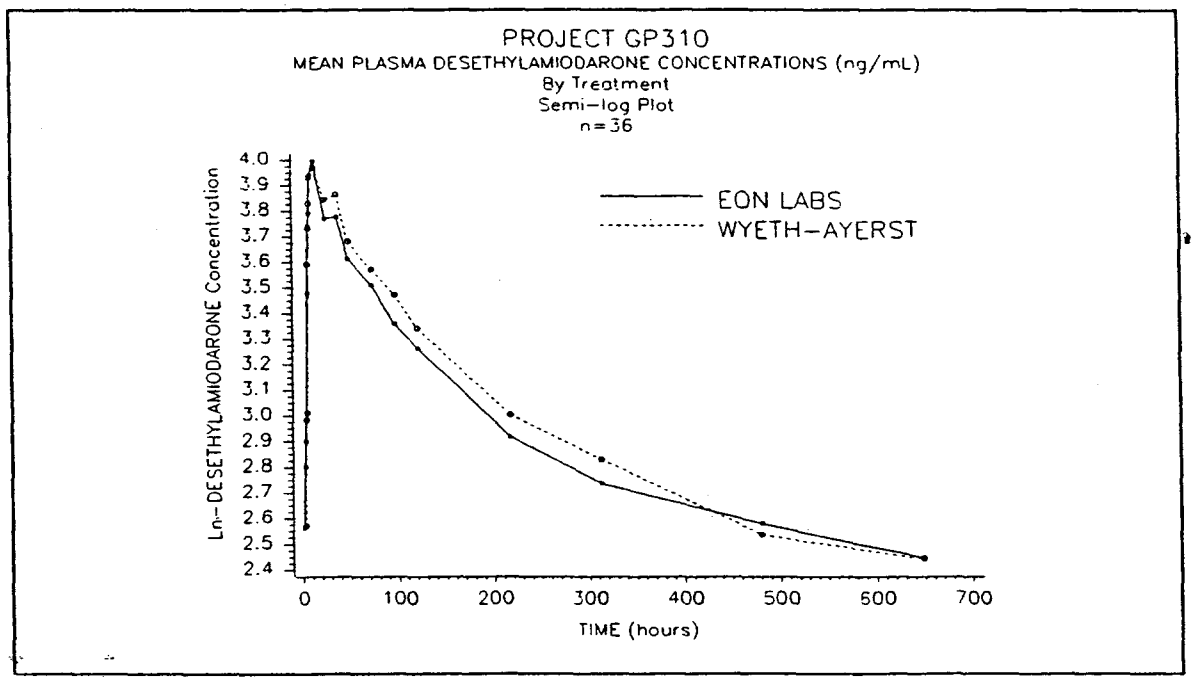

Figure 4

WP# 15315d, 198 Attachment 5

0093

A Full Statement of the Composition of the Drug Product for Amiodarone Hydrochoride Tablets, 200 mg:

Component	Amount per Tablet (mg)	%w/w	Amount per Tablet Batch (g)	Amount per Tablet Batch (g)
Amiodarone Hydrochoride				
Lactose Monohydrate, NF				
Corn Starch, NF				
Povidone, USP (K30)				
Colloidal Silicon Dioxide, NF				
D&C Yellow #10 Aluminum Lake (pure dye 15-21%)				
Magnesium Stearate, NF				
Total				