CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75315

CORRESPONDENCE

ANDA 75-315

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, New York 11413

FEB 10 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Amiodarone Hydrochloride Tablets, 200 mg

DATE OF APPLICATION: January 6, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 13, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

January 6 1998

Douglas L. Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **Original ANDA**
Amiodarone Hydrochloride Tablets, 200 mg

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Amiodarone Hydrochloride Tablets, 200 mg. This application consists of the following volumes:

Volume 1	Debarment, patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, dissolution profiles, certificates of analysis, and components and composition.
Volume 2	Raw material control data, manufacturing and packaging data including executed batch record.
Volume 3	Container/closure, finished product control, methods validation, stability data, control numbers, samples, and environmental impact statement.

Volume 4 through 9 Biostudy summary and test results. Also included are diskettes

A full table of contents precedes each appropriately paginated volume.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the District Field Office, Brooklyn, New York. Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

If there are any comments or questions about this application, please contact me at (718) 276-8600, extension 330.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs

D. Sporn **January 6, 1998**

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
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June 19, 1998

AMENDMENT
N/AB

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
JUN 22 1998
GENERIC DRUGS

Re: BIOEQUIVALENCY AMENDMENT
Amiodarone Hydrochloride Tablets, 200 mg
ANDA 75-315

Dear Mr. Dale:

We refer to Mrs L. Sanchez letter of June 9, 1998 regarding the above referenced abbreviated new drug application. The following are our responses to the deficiency noted in the letter.

1. Comment:
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.

Response:

Our , has provided stability data to support long term storage of the plasma samples in -22 C for amiodarone and desethylamiodaronet. The data are provided in **EXHIBIT 1**.

2. Comment:
The in vitro dissolution data for the test reference product are unacceptable. The paddle speed of 100 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 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.

Response:

The dissolution testing was repeated using a paddle speed of 75 rpm. A comparative dissolution profile report is included for your review, **EXHIBIT 2**.

The referenced drug and the test drug both exhibit very similar dissolution rates as seen from the data. However, tablets were 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 100 rpm eliminated the sticking in both the referenced and test drugs. Consequently, 100 rpm paddle speed was selected over the recommended speed of 75 rpm.

We would prefer to abstain from changing the paddle speed of 100 rpm to 75 rpm, as the sticking of the tablets to the bottom of the dissolution vessels, clearly impairs the reliability of the data. Unless there is a strong argument against this rationale, we will maintain our current specification of NLT % Q in 60 minutes at 100 rpm.

We hope the responses satisfactorily address the deficiencies noted in your letter. We have included a copy of the facsimile deficiency, **EXHIBIT 3**. If additional information is required, please contact me at (718) 276-8607, extension 393.

Sincerely,
Eon Labs Manufacturing, Inc.

Zohra E. Lomri
Sr. Regulatory Affairs Associate

Eon Labs
The Pharmacy Drug Company

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227-15 N. Conduit Avenue
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September 16, 1998

NEW CORRESP
NC to
FA

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Reference: Facsimile Amendment – Chemistry
Amiodarone Hydrochloride Tablets, 200 mg
ANDA # 75-315

Dear Dr. Holcombe:

Reference is made to your September 9, 1998 letter commenting on our original abbreviated new drug application submitted January 6, 1998 for Amiodarone Hydrochloride Tablets, 200 mg. The following are our responses to the Chemistry deficiencies noted in your fax:

1. **Comment:**

Regarding the controls for amiodarone hydrochloride drug substance (page 107), please explain the limits for related substances by including limits for "any secondary impurity" and "NMT one impurity".

Response:

As seen by the **"Raw Material Specification and Analysis Report"** testing for related compounds for the drug substance is performed by two different analytical methods, Comment No. 1 refers specifically to the specifications of NMT % for "any secondary impurity" and NMT one impurity exceeding %. The method and specifications are included as release criteria on the specification sheet to be in conformance with the manufacturer's test requirements to meet BP standards.

The intention of the specification is to allow **only one** secondary impurity to fall

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SEP 17 1998
GENERIC DRUGS

between the % limit, while all other secondary impurities must be below %. The specification expressed in this way controls and limits the number of spots having higher concentrations thereby reducing the overall cumulative effect for total impurities in the raw material.

We commit to re-phrasing the **"Raw Material Specification and Analysis Report"** form at the time of the next revision date for improved clarity. The revised form will be filed in the first periodic report for the product.

2. **Comment:**

Please revise the particle size limit on page 107 to account for 100% of the material.

Response:

In providing an appropriate reply, we hope that we correctly understand your comment to mean that 100% of the material should be accounted for when performing particle size analysis. In that regard, the actual value reported on the raw material specification sheet after applying the method, (the method filed in our original application), is derived in the following manner:

If the intention of your comment is to request a change to the particle size specification to allow % of the particles to pass through the screen, then such a specification would not control particle size at all and would be of little value. A manufacturer could select a screen size large enough (an extreme mesh size) to ensure that all the particles would meet the specification each time.

In the case of the amiodarone hydrochloride active drug substance, particle size is not a critical element. Specifically since the finished product is manufactured by a

The particle size of the active drug substance is changed from the very beginning of the manufacturing processing.

In summary, we feel that the particle size specification of NLT % through mesh is acceptable and that % of the material is accounted for during the process.

3. **Comment:**

Regarding in-process controls for the manufacture of the drug product, please include an individual tablet weight limit as an in-process control.

Response:

According to Eon Lab's internal SOP, , **In-Process Product Material Sampling and Testing**, ***(ATTACHMENT 1).*** In accordance with the SOP, requirements for performing in process tablet weight checks depend on the final weight of the product. Finished products with a unit dose weight under 100 mg are weighed individually while unit dose weights over 100 mg are based on a composite of ten units. The rationale for using this approach is that small differences in a large tablet have little impact whereas small differences in a small tablet can have an effect.

Eon Lab's practice of performing individual tablet weight checks versus average tablet weight checks in relation to the finished product unit weight has been reviewed and accepted by the FDA District Field Office during numerous pre-approval inspections. For the above reasons, we feel that our current in-process tablet weight checks on a composite of ten tablets is acceptable.

4. **Comment:**

The reconciled yield limit of % for the process is wide (see page 234). Please justify or tighten the limits.

Response:

We acknowledge that the in-process limits of % are very broad. However, the manufacturing process for Amiodarone Hydrochloride Tablets require the manufacturing of

Upon closer review of our data on the Bio/ANDA batch, Eon Lab's agrees to tighten the in-process specifications to _____% at this time. We are reluctant to

tighten the yield limits further until more data is evaluated from the prospective validation studies. At that time, we commit to re-evaluating the manufacturing losses and tighten the yield limits even further if the data supports tighter specifications. An updated **"Formulation Manufacturing Record"** is being submitted reflecting the tighter in-process limits (***ATTACHMENT 2)***.

5. Comment:

The limits for individual known and unknown impurities and total related compounds for drug product release and stability are high (see pages 453 and 560, respectively). These limits are not supported by data. Please revise and resubmit to include tighter limits.

Response:

We propose the following tighter limits:

Total Related Compounds	NMT	%
Known Impurities	NMT	%
Unknown Impurities	NMT	%

An updated **"Product Monograph"**, **"Quality Control Tablet Specification & Report Form"**, and a **"Post Approval Stability Commitment"** are submitted for your review in ***ATTACHMENTS 3, 4, and 5*** respectively.

6. Comment:

Please submit available room temperature stability data accrued to date.

Response:

Updated stability reports with 12 months data are being submitted (***ATTACHMENT 6)***.

B. Comment:

Please note and acknowledge the following;

The analytical methods will be submitted for validation by the FDA laboratories after the review and approval of your dissolution method and limits by the Division of Bioequivalence.

Response:

We acknowledge that the analytical methods will be submitted for validation to the FDA field laboratories after the review and approval of our dissolution method and limits by the Division of Bioequivalence.

We hope that our responses satisfactorily address the deficiencies noted in your facsimile. If you need further information or clarification, please do not hesitate to call me at (718) 276 - 8607, extension 393.

Sincerely,
Eon Labs Manufacturing, Inc.

Zohra E. Lomri
Sr. Regulatory Affairs Associate

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
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FA noted,
To Chem reviewer for review. 11/19/98
NEW CORRESP
(N/FA)

November 13, 1998

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Reference: Facsimile Amendment – Chemistry
Amiodarone Hydrochloride Tablets, 200 mg
ANDA # 75-315

Dear Dr. Holcombe:

Reference is made to your November 12, 1998 facsimile chemistry deficiency commenting on our original abbreviated new drug application submitted January 6, 1998 for Amiodarone Hydrochloride Tablets, 200 mg. The following are our responses to the Chemistry deficiencies noted in your fax:

Comment:

The division of Bioequivalence has determined that 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 hydrochloride tablet products are made available and official by the USP.

Please submit revised specifications and testing procedures consistent with the above requirements.

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NOV 16 1998
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Response:

To address your comments we are submitting an updated product monograph incorporating the dissolution changes required, ***ATTACHMENT 1***. This monograph is in effect until official USP methods are adopted.

The *in vitro* dissolution specifications on the **"Quality Control Finished Tablet Specification & Report Form"** and in the **"Post Approval Stability Commitment for Amiodarone Hydrochloride Tablets, 200 mg"** are already set at "not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes". A copy of the **"Quality Control Finished Tablet Specification & Report Form"** and in the **"Post Approval Stability Commitment for Amiodarone Hydrochloride Tablets, 200 mg"** are included for your convenience, ***ATTACHMENT 2 and 3***, respectively.

We acknowledge our analytical methods have been submitted for validation by the FDA laboratories, including specifications and procedures as indicated by the Division of Bioequivalence. We also commit to resolve any analytical method issues with the district should they still be pending at the time of the approval.

We hope that our responses satisfactorily address the deficiency noted in your facsimile. If you need further information or clarification, please do not hesitate to call me at (718) 276 - 8607, extension 393.

Sincerely,
Eon Labs Manufacturing, Inc.

Zohra E. Lomri
Sr. Regulatory Affairs Associate

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
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October 9, 1998

NDA ORIG AMENDMENT

N/AB

Ms. Lizzie Sanchez
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: Bioequivalence Telephone Amendment — ANDA 75-315
Amiodarone Hydrochloride Tablets, 200 mg

Dear Ms. Sanchez:

Reference is made to your telephone conversation October 7, 1998 with Ms. Sadie Ciganek commenting on Eon's original Abbreviated New Drug Application submitted January 6, 1998 and our previous bioequivalence amendment dated June 19, 1998 for Amiodarone Hydrochloride Tablets, 200 mg. As requested, the dissolution testing was repeated using

EXHIBIT 1.

We hope this response is satisfactory. If you need further clarification or additional information regarding this Telephone Amendment, please do not hesitate to contact me at (718) 276-8607, extension 393.

Sincerely,
Eon Labs Manufacturing, Inc.

RECEIVED

OCT 15 1998

Zohra E. Lomri
Sr. Regulatory Affairs Associate

Eon Labs
The Pharmacy Drug Company

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ORIG AMENDMENT
N/AF

August 26, 1998

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
AUG 27 1998
GENERIC DRUGS

Reference: Facsimile Amendment – Labeling
Amiodarone Hydrochloride Tablets, 200 mg
ANDA # 75-315

Dear Dr. Holcombe:

Reference is made to your August 12, 1998 letter commenting on our original abbreviated new drug application submitted January 6, 1998 for Amiodarone Hydrochloride Tablets, 200 mg. The following are our responses to the labeling deficiencies noted in your fax:

1. **GENERAL COMMENTS**:

As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx Only" or Rx Only" throughout your labels and labeling. The symbol should appear prominently on the principal display panel. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", the internet site: http://www.fda.gov/cder/guidance/index.htm for guidance. The Agency, encourages the use of this symbol beneath the title of the package insert labeling.

Response:

The statement "CAUTION: Federal law....." has been replaced with the symbol "Rx Only" as per the FDA Modernization Act of 1997. In addition the symbol "Rx Only" was added beneath the title package insert labeling.

2. CONTAINER 60s and 500s

a. See GENERAL COMMENT above.

b. **The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturers when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed container of 60s appears to be in this category, therefore we believe that this package must comply with the Act, please comment.**

Response:

To comply with the Poison Prevention Packaging Act for unit of issue containers, we commit to marketing the 60s with a 38 mm child resistant closure (CRC). The CRC closure system will use the same

In accordance with **"Guidance for Industry — Stability Testing of Drug Substances and Drug Products"**, draft Guidance, changes of this nature are permitted provided the liner and innerseal components remain unchanged. A copy of the relevant page taken from the guideline is provided for your review, ***ATTACHMENT 1.*** Although the guidance is a draft, it reflects FDA's current thinking on the matter. To further support this change, we commit to perform stability testing on the first three production/validation batches with the CRC closure. The data from the studies will be filed in the first periodic report.

3. INSERT

a. GENERAL COMMENT

Please make the revisions as noted in the "mocked-up" copy of your submitted draft insert labeling.

b. TITLE

See GENERAL COMMENT (1) above.

c. WARNINGS

Add the following subsection immediately following the "Liver injury" subsection:

Loss of Vision
Cases of optic neuropathy and /or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and/or neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. If symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral vision, prompt ophthalmic examination is recommended. Appearance of optic neuropathy and/or neuritis calls for re-evaluation of amiodarone therapy. The risks and complications of antiarrhythmic therapy with amiodarone must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including fundoscopy and slit-lamp examination, is recommended during administration of amiodarone (see "ADVERSE REACTIONS').

d. PRECAUTIONS

i Revise the beginning of this section as follows:

Impairment of vision
Optic Neuropathy and/or Neuritis
Cases of optic neuropathy and optic neuritis have been reported (see "WARNINGS").

Corneal Microdeposits
Corneal microdeposits appear in 'the ... treatment (see "ADVERSE REACTIONS").

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

Photosensitivity
Amiodarone has....

ii Surgery — Adult Respiratory Distress Syndrome — Replace the last sentence with the following text:

Until further Studies have been performed, it is recommended that FiO_2 and the determinants of oxygen delivery to the tissues

(e.g., SaO_2, PaO_2) be closely monitored in patients on amiodarone.

a. ADVERSE REACTIONS

i. Second paragraph — ...to dose reductions or discontinuation (see "PRECAUTIONS").

ii. Add the following text as the fourth paragraph:

...or divided doses.

Ophthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to blindness, papilledema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities, and macular degeneration have been reported (see "WARNINGS"),

Asymptomatic corneal ...

iii Add the following paragraph to immediately follow the paragraph beginning "Bradycardia usually responds..."

"...of drug"

Hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, vasculitis, pseudomotor cerebri, thrombocytopenia, angioedema, bronchiolitis obliterans organizing pneumonia (possibly fatal), pleuritis, pancreatitis, toxic epidermal necrolysis, pancytopenia, and neutropenia also have been reported in patients receiving amiodarone.

The following ...

iv Delete the following paragraph: Rare occurrences of hepatitis ... receiving amiodarone hydrochloride.

a. HOW SUPPLIED

i. See GENERAL COMMENT (1) above.

ii. We note that you include the statement "Use carton to protect contents from light." in this section, yet you have not submitted any carton labeling. Please comment.

iii. **You have not noted in this section if the tablet is embossed, debossed, or imprinted.**

RESPONSE:

The statement "CAUTION: Federal law....." has been replaced with the symbol "Rx Only" as per the FDA Modernization Act of 1997 on labels and labeling. In addition, the symbol "Rx Only" was added beneath the title package insert labeling.

The package insert was revised according to your comments, and the statement "Use carton to protect contents from light" has been deleted.

In addition, we are including in the "How Supplied " section of the package insert, bulk containers of 100 with screw cap closure, the container/closure configuration being covered by the stability data submitted in the original application.

To facilitate the review process, we are providing you with a side-by-side comparison of our the previous and the proposed labeling. We are also providing twelve copies (12) of final printed labels and insert labeling.

We hope the responses satisfactorily address the deficiencies noted in your letter. If additional information is required, please contact me at (718) 276-8607, extension 393.

Sincerely,
Eon Labs Manufacturing, Inc.

Zohra E. Lomri
Sr. Regulatory Affairs Associate