CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75315

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-315 DRUG PRODUCT: Amiodarone Hydorchloride Tablets

FIRM: Eon Labs
227-15 N. Conduit Ave
Laurelton, NY 11413

DOSAGE FORM: Tablet STRENGTHS: 200 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 200) in original submission. Paragraph 306(k) certification submitted.

EIR acceptable for drug product manufacturer and drug substance manufacturer, 2/11/98.

Facilities included:

Manufacturing, testing, packaging, labeling, and stability testing:

Eon Labs Manufacturing, Inc.
227-15 North Conduit Avenue
Laurelton, NY 11413

Drug Substance Manufacturer:

BIO STUDY:

Bioequivalence study conducted on the 200 mg tablets, Lot #970604, batch size tablets, was found acceptable by the Division of Bioequivalence per H. Nguyen, 10/16/98.

In-vitro dissolution study for 200 mg tablets was found acceptable. Firm indicated conformance to release specifications proposed by the Office of Bioequivalence.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Both drug substance and drug product noncompendial. Methods for Amiodarone Hydrochloride drug substance and drug product found acceptable by the
Laboratory description of dosage form was the same as firm's.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability for the following included:

Lot #	Batch Size	Sample	Test Conditions
970604	tablets	60's	40°C/75% RH/3 months
		500's	25° - 30°C/12 months

Container/Closure system:

60's in 100 cc white HDPE bottle, 38 mm plastic screw cap, innerseal/liner, cotton coil.

500's in 250 cc white HDPE bottle, 45 mm plastic screw cap, innerseal/liner, cotton coil.

All container/closure systems are as described in the Container/Closure section.

Expiration date: 24 months based on accelerated stability data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, A. Vezza, 7/31/98.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Bio batch: 200 mg product, Lot #970604, batch size tablets, stability data included.

DMF Amiodarone Hydrochloride, satisfactory, L. Tang, 12/4/97, no amendments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

An executed batch record for the 200 mg batch (bioequivalence/stability batch) included. A blank batch record was submitted in the application for kilogram granulation and compression for tablets. All scale-ups consistent with current Office policy. Proposed manufacturing processes are the same as the bio/stability batches.

CHEMIST: Gsmith /S/ DATE: 11/23/98

SUPERVISOR: UVenkataram DATE: 11/20/98

/S/ 12/8/98.

cc: ANDA 75-315

ANDA 75-315

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-315

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Cordarone® brand of Amiodarone Hydrochloride Tablets, 200 mg manufactured for Wyeth-Ayerst by Sanofi Winthrop Industrie. The applicant certifies that there are no effective patents or exclusivities for NDA 18-972.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Amiodarone Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: January 6, 1998
Amendment (Bio): June 19, 1998

FDA:
Acknowledgement: February 10, 1998
Bio Review: June 3, 1998
Bio letter to applicant: June 9, 1998

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

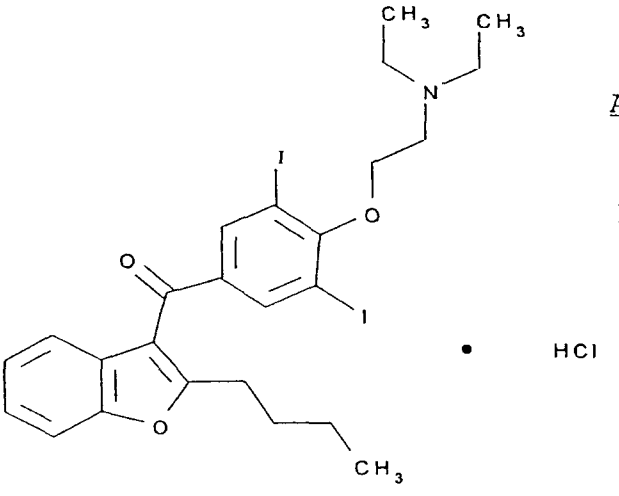
12. RELATED IND/NDA/DMF(s)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Tablet

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Amiodarone Hydrochloride
$C_{25}H_{29}I_2NO_3.HCl$; M.W. = 681.77



2-Butyl-3-benzofuranyl 4-[2-(dimethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride. CAS [1977-82-4]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. CMC issues satisfactory. (see note below)
b. EIR overall recommendation is acceptable per EES 7/9/98.
c. Label review is pending.
d. Review of the 6/19/98 bio amendment is pending.
e. Methods validation package to be prepared and issued after bio is found to be satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA can be approved upon satisfactory bio review, label review and methods validation.

Note: During the secondary review several deficiencies were identified by the team Leader and will be conveyed to the applicant. See review element #38. The review has been revised accordingly.

19. REVIEWER:	DATE COMPLETED:
Donald Shostak	July 31, 1998; revised 8/12/98

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Chem #1

SEP 9 1998

ANDA 75-315

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-315 Applicant: Eon Labs Manufacturing, Inc.

Drug Product: Amiodarone Hydrochloride Tablets, 200 mg.

The deficiencies presented below represent FACSIMILE deficiencies.

1. 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".

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

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

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

5. 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.

6. Please submit available room temperature stability data accrued to date.

B. 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.

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA #75-315

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-315

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Cordarone® brand of Amiodarone Hydrochloride Tablets, 200 mg manufactured for Wyeth-Ayerst by Sanofi Winthrop Industrie. The applicant certifies that there are no effective patents or exclusivities for NDA 18-972.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Amiodarone Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: January 6, 1998
Amendment (Bio): June 19, 1998
Response to Facsimile: September 16, 1998.

FDA:
Acknowledgement: February 10, 1998
Bio Review: June 3, 1998
Bio letter to applicant: June 9, 1998
Minor Facsimile: September 9, 1998.

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
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13. DOSAGE FORM
Tablet

14. POTENCY
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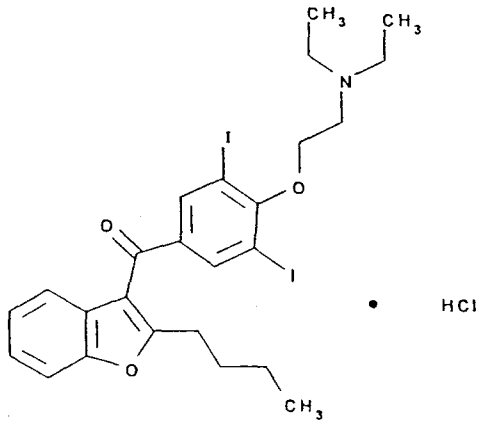
15. CHEMICAL NAME AND STRUCTURE

Amiodarone Hydrochloride

$C_{25}H_{29}I_2NO_3.HCl$; M.W. = 681.77



2-Butyl-3-benzofuranyl 4-[2-(dimethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride. CAS [1977-82-4]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
a. CMC issues satisfactory.
b. EIR overall recommendation is acceptable per EES 7/9/98.
c. Label review is pending.
d. Review of the 6/19/98 bio amendment is pending.
e. Methods validation package to be prepared and issued after bio is found to be satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
The ANDA can be approved upon satisfactory bio review, label review and methods validation.

19. REVIEWER: Glen Jon Smith
DATE COMPLETED: 10.21.98

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Chem #2

NOV 12 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-315 Applicant: Eon Labs Manufacturing, Inc.

Drug Product: Amiodarone Hydrochloride Tablets, 200 mg.

The deficiency presented below represents a FACSIMILE deficiency.

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 HCl tablet products are made available and official by the USP.

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

Please note and acknowledge the following:

Your analytical methods have been submitted for validation by the FDA laboratories, including Dissolution testing using the specifications and procedures as indicated by the Division of Bioequivalence.

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-315

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION
The reference listed drug is Cordarone® brand of Amiodarone Hydrochloride Tablets, 200 mg manufactured for Wyeth-Ayerst by Sanofi Winthrop Industrie. The applicant certifies that there are no effective patents or exclusivities for NDA 18-972.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Amiodarone Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: January 6, 1998
Amendment (Bio): June 19, 1998
Response to Facsimile: September 16, 1998.
Response to Facsimile: November 13, 1998.

FDA:
Acknowledgement: February 10, 1998
Bio Review: June 3, 1998
Bio letter to applicant: June 9, 1998
Minor Facsimile: September 9, 1998.
Minor Facsimile: November 12, 1998.

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
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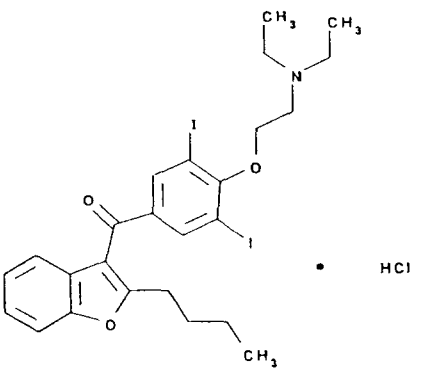
DMF

13. DOSAGE FORM
Tablet

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Amiodarone Hydrochloride
$C_{25}H_{29}I_2NO_3.HCl$; M.W. = 681.77



2-Butyl-3-benzofuranyl 4-[2-(dimethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride. CAS [1977-82-4]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
a. CMC issues satisfactory.
b. EIR overall recommendation is acceptable.
c. Labeling satisfactory.
d. Bioequivalence satisfactory.
e. Methods validation pending.

18. CONCLUSIONS AND RECOMMENDATIONS
The ANDA can be approved upon satisfactory methods validation.

19. REVIEWER: Glen Jon Smith
DATE COMPLETED: November 19, 1998

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Chem #3