CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75315

ADMINISTRATIVE DOCUMENTS

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

FIELD COPY CERTIFICATION

I certify that a true copy of the technical sections of Eon Labs Manufacturing Inc.'s pending ANDA #75-315 for Amiodarone Hydrochloride Tablets, 200 mg has been sent to the Food and Drug Administration New York District Office, 850 Third Avenue, Brooklyn, New York.

Sadie Ciganek
Vice President, Regulatory Affairs
Eon Labs Manufacturing, Inc.

9/16/98
Date

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
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FIELD COPY CERTIFICATION

I certify that a true copy of the technical sections of this Abbreviated New Drug Application for Amiodarone Hydrochloride Tablets, 200 mg has been sent to the Food and Drug Administration New York District Office, 850 Third Avenue, Brooklyn, New York.

Sadie M. Ciganek
Vice President Regulatory Affairs
Eon Labs Manufacturing, Inc.

Jan 6, 98
Date

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

ANDA Number: 75-315 Date of Submission: **August 26, 1998**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Amiodarone Hydrochloride Tablets 200 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 60s and 500s
Satisfactory as of August 26, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of August 26, 1998 submission.

Revisions needed post-approval: There are a number of extra "hydrochloride"s throughout the text of the insert not needed.

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 #: 6/15/98 (S-018)

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: side-by-sides and generic labeling on file

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	
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? NO.		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	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
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? See REVIEW and FOR THE RECORD			
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 FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	

	Yes	No	N.A.
Inactive Ingredients: (FTR: 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) See FOR THE RECORD and comment in review under HOW SUPPLIED			
USP Issues: (FTR: 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? See NOTE TO CHEMIST and FOR THE RECORD	X		
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.			

NOTES/QUESTIONS TO THE CHEMIST:

I asked UV if amiodarone is light-sensitive. He indicated that since it is a diazo compound that it likely would be light-sensitive. Product will be marketed in white HDPE containers which are impervious to light.

FOR THE RECORD:

1. The labeling review for this ANDA was based on the reference listed drug Cordarone® (NDA 18-972/S-018; approved 6-15-98). The insert for Copley's unapproved ANDA 74-739 was used to determine the location of the salts in the insert. There are a few extra "hydrochloride"s throughout the text of the insert.

2. There are no patents or exclusivities for this drug product.

3. The inactives as listed in the DESCRIPTION section are accurate (see p 93 B 1.1).

4. Eon Labs is the sole manufacturer (p 198 B 1.2).

5. The tablet description as seen in the HOW SUPPLIED section is accurate.

6. There are at least three other unapproved generics (no approved ones). ANDA 75-135 and ANDA 74-739 both have pink tablets, as does the innovator. ANDA 75-188 has white tablets. This ANDA is proposing yellow tablets.

7. Container sizes:

   RLD - 60s and UD 100s
   ANDA - 60s and 500s

   Both containers are made of HDPE, impervious to light and come with screw-on lids (p 340 B 1.3).

8. Both the innovator and this ANDA have scored tablets.

9. The following statements for the RLD and the ANDA are the same:

   Keep tightly closed. Protect from light.
   Dispense in a light-resistant, tight container.

   RLD: Store at room temperature, approximately 25°C (77°F).
   ANDA: Store at controlled room temperature 15°-30°C (59°-86°F) - firm has shown no problems at this temperature range per G. Smith.

10. The innovator has the statement "SEALED FOR YOUR PROTECTION" on the front panel of their container labels. I have not asked the firm to put this on their container labels.

11. Review done on red jacket.

Date of Review: 9-1-98 Date of Submission: 8-26-98

Primary Reviewer: Adolph Vezza /S/ Date: 9/2/98

Team Leader: Charlie Hoppes /S/ Date: 9/3/98

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

ANDA Number: 75-315 Date of Submission: January 6, 1998

Applicant's Name: Eon Labs Manufacturing, Inc.

Established Name: Amiodarone Hydrochloride Tablets 200 mg

Labeling Deficiencies:

1. GENERAL COMMENT:

   As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "℞ 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...", at 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.

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.

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:

PRECAUTIONS

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.

e. 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 permanent 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.

f. 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.

Please revise your container labels and insert labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

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

Attachment: "Mocked up" copy of draft insert labeling.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 60s and 500s

Professional Package Insert Labeling:

Revisions needed post-approval:

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 #: 6/15/98 (S-018)

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: side-by-sides and generic labeling on file

Other Comments:

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	
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? NO.		X	
Packaging			

	Yes	No	N.A.
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	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
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? See REVIEW and FOR THE RECORD			
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 FTR			
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: (FTR: 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	

	Yes	No	N.A.
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) See FOR THE RECORD and comment in review under HOW SUPPLIED			
USP Issues: (FTR: 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? See NOTE TO CHEMIST and FOR THE RECORD	X		
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.			

NOTES/QUESTIONS TO THE CHEMIST:

1. I asked UV if amiodarone is light-sensitive. He indicated that since it is a diazo compound that it likely would be light-sensitive. Product will be marketed in white HDPE containers which are impervious to light.

2. See comment iii under INSERT - HOW SUPPLIED. Do you concur?

FOR THE RECORD:

1. The labeling review for this ANDA was based on the reference listed drug Cordarone® (NDA 18-972/S-018; approved 6-15-98). The insert for Copley's unapproved ANDA 74-739 was used to determine the location of the salts in the insert.

2. There are no patents or exclusivities for this drug product.

3. The inactives as listed in the DESCRIPTION section are accurate (see p 93 B 1.1).

4. Eon Labs is the sole manufacturer (p 198 B 1.2).

5. The tablet description as seen in the HOW SUPPLIED section is not accurate. See comment (iii) under INSERT - HOW SUPPLIED and page 453 B 1.3. The firm has not specified if the tablet is embossed, debossed, or imprinted.

6. There are at least three other unapproved generics (no approved ones). ANDA 75-135 and ANDA 74-739 both have pink tablets, as does the innovator. ANDA 75-188 has white tablets. This ANDA is proposing yellow tablets.

7. Container sizes:

   RLD - 60s and UD 100s
   ANDA - 60s and 500s

   Both containers are made of HDPE, impervious to light and come with screw-on lids (p 340 B 1.3).

8. Both the innovator and this ANDA have scored tablets.

9. The storage and dispensing statements for the RLD and the ANDA are the same:

   Keep tightly closed.
   Store at room temperature, approximately 25°C (77°F).
   Protect from light.
   Dispense in a light-resistant, tight container.

   The ANDA's PI includes the statement "Use carton to protect contents from light.". I have asked the firm to comment on the presence of this statement since they have not submitted carton labeling.

10. The innovator has the statement "SEALED FOR YOUR PROTECTION" on the front panel of their container labels. I have not asked the firm to put this on their container labels.

11. Review done on red jacket.

Date of Review: 8-4-98 Date of Submission: 1-6-98

Primary Reviewer: Adolph Vezza /S/ Date: 8/11/98

Team Leader: Charlie Hoppes /S/ Date: 8/12/98

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cc:

ANDA: 75-315
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)

Review