# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**76018**

# ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

| | |
|---|---|
| Molly Rapp was contacted regarding the post-approval stability data limits for this particular ANDA. Sema Basaran, Ph.D., asked that Molly tighten the spec from %, and the the total impurities limit from %. Based on 1-year stability data, the total impurities need to be tightened to %. Molly agreed to the above and will submit a telephone amendment to this application. | DATE:14-Dec-2001<br><br>APPLICATION NUMBER<br>76-018<br><br>TELECON<br><br>INITIATED BY AGENT FOR SPONSOR<br><br>PRODUCT NAME<br>Amiodarone Hydrochloride Injection 50mg/ml 3ml vial.<br><br>Firm Name:<br>Bedford Laboratories<br><br>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD<br><br>Molly Rapp<br><br>TELEPHONE NUMBER<br>(440)201-3576<br><br>SIGNATURE<br>/S/ |

Orig: ANDA
Cc: Division File
Chem. II telecon binder

RECORD OF TELEPHONE CONVERSATION

Called the firm and told them we have only one thing to resolve. This concerns the media fill. Dr. Ensor explained that normally we do not accept a commitment to perform a media fill in the future (as was made by the firm in their last submission). Dr. Ensor asked if the firm now has data from a media fill on their smallest vial size.

Ms. Rapp answered that they do have media fill data for filling rooms 111 and 112 for their smallest vial size which is listed as 2 cc. She said she could fax it to us immediately. She was also asked to submit a hard copy to the document room.

**DATE:** January 18, 2002

**APPLICATION NUMBER**
76-018

**TELECON**

**INITIATED BY FDA**

**PRODUCT NAME**
Amiodarone Hydrochloride Injection 50mg/ml

Firm Name:
Bedford Laboratories

**NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD**

Molly Rapp, Reg. Affairs and Margaret VanDyne, Reg. Assoc.

**TELEPHONE NUMBER**
440 01-3576

**RE**

L.Enso /S/ 1/18/02
M. Stevens-Riley
B.McNeal /S/ 1/18/02

CC: ANDA 76-018
Division File

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

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ANDA Number: **76-018** Date of Submission: **February 20, 2002**

Applicant's Name: **Bedford Laboratories**

Established Name: **Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials**

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**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: 3 mL vials
*Satisfactory in FPL as of September 25, 2001 submission.*
Carton Labeling: 10 x 3 mL
*Satisfactory in FPL as of September 25, 2001 submission.*
Professional Package Insert Labeling:
*Satisfactory in FPL as of the February 20, 2002 submission.*
Revisions needed post-approval: None

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Cordarone® Injection
NDA Number: 20-377
NDA Drug Name: Cordarone® (amiodarone hydrochloride) Injection
NDA Firm: Wyeth Ayerst
Date of Approval of NDA Insert and supplement #: 7/11/01 (S-004, S-005)
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
Basis of Approval for the Carton Labeling: side-by-sides
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** | | | |
| 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 | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | | 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? NO Issues for FTR: Innovator individually cartoned? NO Light sensitive product which might require cartoning? YES Must the package insert accompany the product? YES | X | 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 | |
| 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 | |
| **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)? HAS BENZYL ALCOHOL - PRODUCT NOT INDICATED FOR NEONATES | X | 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 | |
| **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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | | X |
| Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? NO | X | 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. | | | |

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Cordarone® Injection (Wyeth Ayerst - Approved 7/11/01; Revised 10/27/00 - NDA 20-377/S-004, S-005).

2. The inactives are accurately listed in the DESCRIPTION section (p 68 v B 1 .1).

3. Orphan Drug Exclusivity for this drug product expires 8/3/02. The firm has stated that they will not market their product until that time.

4. Ben Venue is the manufacturer (p 105 v B 1.1).

5. Storage recommendations:

   RLD - carton and PI - Store at room temperature 15°-25°C (59°-77°F). Protect from light and excessive heat. Use carton to protect contents from light until used.

   ANDA - vial and carton - Store at room temperature 15° to 25°C (59o to 77oF). Retain in carton until time of use. - The vial and both cartons also have "Protect from light and excessive heat."

   PI - Store at room temperature 15°-25°C (59°-77°F) Protect from light and excessive heat. Retain in carton until time of use.

6. CARTONING:

   RLD - 5 x 3 mL amps
   ANDA - 10 x 3 mL vials

7. The September 25, 2001 submission provides for the addition of an vial. A suitability petition was previously approved for another ANDA for this size vial. The firm proposes a multiple dose vial (MDV) while the RLD is a single dose vial. We will need input from Micro (sterility), and Chemistry (stability). I spoke to Dr. Stockbridge of Cardio-Renal concerning this issue. Both he and Dr. Lipicky feel that an MDV is okay for this drug product and that we do not have to send them anything. I spoke to Dr. Nath of Micro and he said that they routinely look to see if the firm has submitted a PET and then they review it. He checked into this application. The firm did submit a modified PET study and Micro found it acceptable. I also spoke to Nashed Samaan of Chem - He said that they look to check to see if the firm has submitted stability data and whether or not it supports an MDV. The vial amendment was withdrawn. An ANDA cannot contain a single dose vial and a multiple dose vial. The - vial was resubmitted as a new ANDA.

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Date of Review: 2-25-02 Date of Submission: 2-20-02

Primary Reviewer: Adolph Vezza Date: 2/25/02

Team Leader: Charlie Hoppes /S/ Date: 2/25/02

cc: ANDA: 76-018
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)

Review

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

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ANDA Number: **76-018** Date of Submission: **January 22, 2002**

Applicant's Name: **Bedford Laboratories**

Established Name: **Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials**

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Labeling Deficiencies:

INSERT

1. PRECAUTIONS (Carcinogenesis, Mutagenesis, Impairment of Fertility)

   a. First paragraph, second sentence - "adenoma" rather than

   b. Third paragraph - Delete the last sentence

2. DOSAGE AND ADMINISTRATION

   Paragraph which discusses "plasticizers", first sentence - "[di-(2- ethyl..." (add parenthesis)

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**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: 3 mL vials
*Satisfactory in FPL as of September 25, 2001 submission.*
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*Satisfactory in FPL as of September 25, 2001 submission.*
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® Injection
NDA Number: 20-377
NDA Drug Name: Cordarone® (amiodarone hydrochloride) Injection
NDA Firm: Wyeth Ayerst
Date of Approval of NDA Insert and supplement #: 7/11/01 (S-004, S-005)
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
Basis of Approval for the Carton Labeling: side-by-sides
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** | | | |
| 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 | |
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| Individual cartons required? NO Issues for FTR: Innovator individually cartoned? NO Light sensitive product which might require cartoning? YES Must the package insert accompany the product? YES | X | X | |
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| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
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| | | | |
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FOR THE RECORD: (portions taken from previous review)

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Date of Review: 2-11-02 Date of Submission: 1-22-02

Primary Reviewer: Adolph Vezza Date: 2/11/02

Team Leader: Charlie Hoppes /S/ Date: 2/11/02

/S/

cc: ANDA: 76-018
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)

Review

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

3.1

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ANDA Number: 76-018 Date of Submission: **September 25, 2001**

Applicant's Name: **Bedford Laboratories**

Established Name: **Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials**

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Labeling Deficiencies:

INSERT

1. DESCRIPTION

   Distinguish the "I's" (iodine) from the "I" (HCl) in the molecular formula.

2. WARNINGS

   Neonatal Hypo- or Hyperthyroidism, revise the first sentence as follows:

   Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with its oral administration. If ...

3. PRECAUTIONS

   a. Pulmonary Disorders. ARDS - Add the following as the last paragraph:

      Postoperatively, occurrences of ARDS have been reported in patients receiving ***oral*** amiodarone therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. 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.

   b. Surgery - "... conduction defects of ..." rather than

   c. Carcinogenesis, Mutagenesis, Impairment of Fertility

      i. First paragraph

         A). Second sentence - "... in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence ..."

         B). Third sentence - "The incidence of thyroid tumors in rats ... even at the lowest dose level tested, i.e., 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).

      ii. Third paragraph, second sentence - "However, in a study in which amiodarone hydrochloride was orally administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*).
      *600 mg in a 50 kg patient (doses compared on a body surface area basis)

d. Pediatric Use - Add the following paragraph as the last paragraph:

AMIODARONE HCl INJECTION contains the preservative benzyl alcohol (see DESCRIPTION). There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

e. Add the following as the last subsection:

**Geriatric Use**
Clinical studies of AMIODARONE HCl INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4. ADVERSE REACTIONS

Revise the last sentence as follows:

In postmarketing surveillance, toxic epidermal necrolysis, pancytopenia, neutropenia, angioedema, and anaphylactic shock also have been reported with amiodarone therapy.

5. DOSAGE AND ADMINISTRATION

Add the following paragraph to immediately follow the paragraph beginning "It is well known ..."

AMIODARONE HCl INJECTION has been found to leach out plasticizers, including DEHP [di-(2-ethylhexyl)phthalate] from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing AMIODARONE HCl INJECTION at higher concentrations and lower flow rates than provided in **DOSAGE AND ADMINISTRATION.** Rename the first table as follows: "AMIODARONE HYDROCHLORIDE DOSE RECOMMENDATIONS" (you may substitute "HCl" if you wish)

6. HOW SUPPLIED

See comment under CONTAINER above.

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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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/ 12/3/01

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**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: 3 mL . . vials
*Satisfactory (3 mL) in FPL as of September 25, 2001 submission.*

Carton Labeling: 10 x 3 mL
*Satisfactory (3 mL) in FPL as of September 25, 2001 submission.*

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® Injection

NDA Number: 20-377

NDA Drug Name: Cordarone® (amiodarone hydrochloride) Injection

NDA Firm: Wyeth Ayerst

Date of Approval of NDA Insert and supplement #: 7/11/01 (S-004, S-005)

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

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

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 | |
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| 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 | |
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| **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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | | X |
| Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? NO | X | 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. | | | |

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Cordarone® Injection (Wyeth Ayerst - Approved 7/11/01; Revised 10/27/00 - NDA 20-377/S-004, S-005).

2. The inactives are accurately listed in the DESCRIPTION section (p 68 v B 1 .1).

3. Orphan Drug Exclusivity for this drug product expires 8/3/02. The firm has stated that they will not market their product until that time.

4. Ben Venue is the manufacturer (p 105 v B 1.1).

5. Storage recommendations:

   RLD - carton and PI - Store at room temperature 15°-25°C (59°-77°F). Protect from light and excessive heat. Use carton to protect contents from light until used.

   ANDA - vial and carton - Store at room temperature 15° to 25°C (59o to 77oF). Retain in carton until time of use. - The vial and both cartons also have "Protect from light and excessive heat."

   PI - Store at room temperature 15°-25°C (59°-77°F) Protect from light and excessive heat. Retain in carton until time of use.

6. CARTONING:

   RLD - 5 x 3 mL amps
   ANDA - 10 x 3 mL vials al

7. The September 25, 2001 submission provides for the addition of an vial. A suitability petition was previously approved for another ANDA for this size vial. The firm proposes a multiple dose vial (MDV) while the RLD is a single dose vial. We will need input from , Micro (sterility), and Chemistry (stability). I spoke to Dr. Stockbridge of Cardio-Renal concerning this issue. Both he and Dr. Lipicky feel that an MDV is okay for this drug product and that we do not have to send them anything. I spoke to Dr. Nath of Micro and he said that they routinely look to see if the firm has submitted a PET and then they review it. He checked into this application. The firm did submit a modified PET study and Micro found it acceptable. I also spoke to Nashed Samaan of Chem - He said that they look to check to see if the firm has submitted stability data and whether or not it supports an MDV.

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Date of Review: 10-3-01 Date of Submission: 9-25-01

Primary Reviewer: Adolph Vezza Date: 10/12/01

/S/

Team Leader: Charlie Hoppes Date: 10/15/01

/S/

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cc: ANDA: 76-018
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)

Review

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

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ANDA Number: **76-018** Date of Submission: **June 27, 2002**

Applicant's Name: **Bedford Laboratories**

Established Name: **Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials**

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**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: 3 mL vials
*Satisfactory in FPL as of June 27, 2002 submission; Vol 5.1*
Carton Labeling: 10 x 3 mL
*Satisfactory in FPL as of June 27, 2002 submission; Vol 5.1*
Professional Package Insert Labeling: (code # AMI-POO)
*Satisfactory in FPL as of the June 27, 2002 submission; Vol 5.1*
*Revisions needed post-approval: Add "3 mL" to the container label

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Cordarone® Injection
NDA Number: 20-377
NDA Drug Name: Cordarone® (amiodarone hydrochloride) Injection
NDA Firm: Wyeth Ayerst
Date of Approval of NDA Insert and supplement #: 7/11/01 (S-004, S-005)
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
Basis of Approval for the Carton Labeling: side-by-sides
*Other Comments: **I spoke to Molly Rapp of the firm on 7-9-02 concerning the revision above. She said the firm will commit to adding "3 mL" to the container label before the product is launched.**

## 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 | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | | 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? NO Issues for FTR: Innovator individually cartoned? NO Light sensitive product which might require cartoning? YES Must the package insert accompany the product? YES | X | 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 | |
| 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 | |
| **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)? HAS BENZYL ALCOHOL - PRODUCT NOT INDICATED FOR NEONATES | X | 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 | |
| **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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | | X |
| Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? NO | X | 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. | | | |

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Cordarone® Injection (Wyeth Ayerst - Approved 7/11/01; Revised 10/27/00 - NDA 20-377/S-004, S-005).

2. The inactives are accurately listed in the DESCRIPTION section (p 68 v B 1 .1).

3. Orphan Drug Exclusivity for this drug product expires 8/3/02. The firm has stated that they will not market their product until that time.

4. Ben Venue is the manufacturer (p 105 v B 1.1).

5. Storage recommendations:

   RLD - carton and PI - Store at room temperature 15°-25°C (59°-77°F). Protect from light and excessive heat. Use carton to protect contents from light until used.

   ANDA - vial and carton - Store at room temperature 15° to 25°C (59o to 77oF). Retain in carton until time of use. - The vial and both cartons also have "Protect from light and excessive heat."

   PI - Store at room temperature 15°-25°C (59°-77°F) Protect from light and excessive heat. Retain in carton until time of use.

6. CARTONING:
   RLD - 5 x 3 mL amps
   ANDA - 10 x 3 mL vials

7. The September 25, 2001 submission provides for the addition of an vial. A suitability petition was previously approved for another ANDA for this size vial. The firm proposes a multiple dose vial (MDV) while the RLD is a single dose vial. We will need input from Micro (sterility), and Chemistry (stability). I spoke to Dr. Stockbridge of Cardio-Renal concerning this issue. Both he and Dr. Lipicky feel that an MDV is okay for this drug product and that we do not have to send them anything. I spoke to Dr. Nath of Micro and he said that they routinely look to see if the firm has submitted a PET and then they review it. He checked into this application. The firm did submit a modified PET study and Micro found it acceptable. I also spoke to Nashed Samaan of Chem - He said that they look to check to see if the firm has submitted stability data and whether or not it supports an MDV. The vial amendment was withdrawn. An ANDA cannot contain a single dose vial and a multiple dose vial. The vial was resubmitted as a new ANDA.

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Date of Review: 7-8-02 Date of Submission: 6-27-02

Primary Reviewer: Adolph Vezza /S/ Date: 7/9/02

Team Leader: Lillie Golson /S/ Date: 7/9/02

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cc: ANDA: 76-018
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)

Review

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

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ANDA Number: **76-018** Date of Submission: **October 27, 2000**

Applicant's Name: **Bedford Laboratories**

Established Name: **Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials**

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Labeling Deficiencies:

1. GENERAL COMMENT

   Revise your storage temperature recommendations throughout your labels and labeling as follows:

   Store at room temperature 15° - 25°C (59° - 77°F).

2. CONTAINER 3 mL vial

   a. See GENERAL COMMENT above.

   b. Add the statement "Single Use Vial"

   c. We encourage you to include the statement: "Retain in carton until time of use."

3. CARTON 10 x 3 mL

   a. See GENERAL COMMENT above.

   b. "10 x 3 mL single use vials"

4. INSERT

   a. GENERAL COMMENTS

      i. Include "I.V." with the established name throughout the insert where the innovator has "Cordarone I.V.".

      ii. Delete "HCl" (or "hydrochloride") from the established name except in the TITLE, DESCRIPTION, INDICATIONS AND USAGE (first instance), CONTRAINDICATIONS (first instance), and HOW SUPPLIED sections and in general wherever the name is associated with a specific dose.

   b. DESCRIPTION

      i. First sentence - "Amiodarone Hydrochloride Injection, for intravenous use, contains ..."

      ii. Second paragraph, first sentence - "... white to slightly yellow crystalline ..."

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics and Metabolism

      i. Fifth paragraph - "dose" rather than

ii. Notes after table - "--" denotes not available (delete hyphen)

d. WARNINGS

Neonatal Hypo- or Hyperthyroidism - upper case "H"s

e. PRECAUTIONS

Table - The "Cyclosporine" entry should be the last entry of this table. Construct another table with the remaining information in the following format:

SUMMARY OF DRUG INTERACTIONS WITH AMIODARONE

Drugs that May Interfere with the Actions of Amiodarone

| Concomitant Drug | Interaction |
|---|---|
| Cholestyramine | Increases enterohepatic elimination of amiodarone and may reduce serum levels and $t_{1/2}$. |
| Cimetidine | Increases serum amiodarone levels. |
| Phenytoin | Decreases serum amiodarone levels. |

f. DOSAGE AND ADMINISTRATION

Rename the first table as follows: "AMIODARONE HYDROCHLORIDE DOSE RECOMMENDATIONS" (you may substitute "HCl" if you wish)

g. HOW SUPPLIED

i. See GENERAL COMMENT above.

ii. Add "Single Use Vial"

Please revise your container labels and carton and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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/

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**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: 3 mL vials

Carton Labeling: 10 x 3 mL

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® Injection

NDA Number: 20-377

NDA Drug Name: Cordarone® (amiodarone hydrochloride) Injection

NDA Firm: Wyeth Ayerst

Date of Approval of NDA Insert and supplement #: 12/10/97 (S-002)

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

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

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** | | | |
| 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 | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | | 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? NO Issues for FTR: Innovator individually cartoned? NO Light sensitive product which might require cartoning? YES Must the package insert accompany the product? YES | X | 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 | |
| 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. | ? | ? | |
| **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)? HAS BENZYL ALCOHOL - PRODUCT NOT INDICATED FOR NEONATES | X | 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 | |
| **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 | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | | X |
| Is the product light sensitive? YES If so, is NDA and/or ANDA in a light resistant container? NO | X | 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:

**Has the firm submitted adequate stability data to support the stability and incompatibility information found in the DOSAGE AND ADMINISTRATION section?**

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FOR THE RECORD:

1. **This review was based on the labeling for Cordarone® Injection (Wyeth Ayerst - Approved 12/10/97; Revised 8/6/97 - NDA 20-377/S-002).**

2. **The inactives are accurately listed in the DESCRIPTION section (p 68 v B 1 .1).**

3. **Orphan Drug Exclusivity for this drug product expires 8/3/02. The firm has stated that they will not market their product until that time.**

4. **Ben Venue is the manufacturer (p 105 v B 1.1).**

5. **Storage recommendations:**

   **RLD - carton and PI - Store at room temperature 15°-25°C (59°-77°F). Protect from light and excessive heat. Use carton to protect contents from light until used.**

   **ANDA - vial - Store at 25°C (77°F).[See USP].**
   **carton - Store at 25°C (77°F)., excursions permitted to 15° to 30°C (59° to 86°F). [See USP]. Protect from light and excessive heat. Retain in carton until time of use.**
   **PI - Store at 25°C (77°F)., excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]. Protect from light and excessive heat. Retain in carton until time of use.**

6. **CARTONING:**

   **RLD - 5 x 3 mL amps**
   **ANDA - 10 x 3 mL vials**

**Date of Review:** 1-26-01 **Date of Submission:** 10-27-00

**Primary Reviewer:** Adolph Vezza **Date:** 1/29/01

**Team Leader:** Charlie Hoppes /S/ **Date:** 1/29/01

/S/ 1/29/01

cc: ANDA: 76-018
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)

Review