

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76394

ADMINISTRATIVE DOCUMENTS

1.1

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

ANDA Number: 76-394

Date of Submission: April 4, 2002

Applicant's Name: Apotex Corp.

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

Labeling Deficiencies:

1. CONTAINER 3 mL
 - a. Improve the legibility of the "Rx" symbol.
 - b. Relocate "**Must be diluted**" to the principal display panel.
 - c. Add the statement "**Protect from light.**"
2. CARTON
 - a. See comment 1 (a) above.
 - b. "50 mg/mL" (add a space between "50" and "mg")
3. INSERT
 - a. CLINICAL PHARMACOLOGY
 - i. Mechanisms of Action, first paragraph, seventh line - Delete the excess space between the words "channels," and "amiodarone"
 - ii. Pharmacokinetics and Metabolism, first paragraph, seventh line - Delete the excess space between the words "end" and "of"
 - iii. Clinical trials, second paragraph, last sentence - "125 mg" (delete the hyphen)
 - b. PRECAUTIONS
 - i. Liver Enzyme Elevations, second paragraph, sixth line - Delete the excess space between the words "of" and "hepatic" ..
 - ii. Pulmonary Disorders, ARDS, second paragraph
 - A). Fifth line - "FiO₂"
 - B). Sixth line
 - 1). "SaO₂"
 - 2). "PaO₂"
 - iii. Drug Interactions, first paragraph
 - A). Fourth line - Delete the excess space between the word "dextromethorphan" and "(CYP2D6)".

- B). Eleventh line - Delete the excess space between the words "tables" and "summarize"
 - iv. Carcinogenesis, Mutagenesis, Impairment of Fertility
 - A). Add a blank line space between the first and second paragraphs.
 - B). Third paragraph, second sentence - "... in which amiodarone HCl was **orally** administered ..."
 - v. Pediatric Use - Add a blank line space between the second and third paragraphs.
 - c. DOSAGE AND ADMINISTRATION
 - i. First table - "3 mL" rather than "3 MI"
 - ii. Second paragraph, fifth line - "150 mg" (delete hyphen)
-

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

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?

Container Labels: 3 mL

Carton Labeling: 10 x 3 mL

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:**ORPHAN DRUG EXCLUSIVITY EXPIRES 8-3-02 - The firm will not market their product until after this date.**

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 24		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: (PTR: 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)? NOT FOR PEDIATRIC USE	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: (PTR: 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? 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?: PTR: 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:

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 147 - section VII - v B1.1).
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. This exclusivity is "for the acute treatment and prophylaxis of life-threatening ventricular tachycardia or ventricular fibrillation".
4. Novex Pharma is the manufacturer (p 213 - section IX - v B1.1).

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 - container - Store at controlled room temperature 15°-30°C (59°-86°F)[see USP].
carton and PI - Store at controlled room temperature 15°-30°C (59°-86°F)[see USP].
Protect from light and excessive heat. Use carton to protect contents from light until used.

6. CARTONING:

RLD - 2 x 5 x 3 mL amps

ANDA - 10 x 3 mL vials

Date of Review: 6-20-02

Date of Submission: 4-4-02

Primary Reviewer: Adolph Vezza

Date:

7/9/02

Team Leader: Lillie Golson

Date:

7/9/02

CC:

ANDA: 75-761
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)

Review

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

ANDA Number: 76-394

Date of Submission: October 11, 2002

Applicant's Name: Apotex Corp.

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

Labeling Deficiencies:

CONTAINER 3 mL

The color contrast between the background color and the print color of the established name and the statement of strength is insufficient thus resulting in poor legibility. We suggest that you lighten the background color to improve the legibility of the name and strength.

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

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
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?

Container Labels: 3 mL

Carton Labeling: 10 x 3 mL

Satisfactory in FPL as of the October 11, 2002 submission (Vol 1.1 - Section IV)

Professional Package Insert Labeling:

Satisfactory in FPL as of the October 11, 2002 submission (V1.1 - Section IV -204026 - rev 8-02)

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 24		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)? NOT FOR PEDIATRIC USE	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	
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:

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 147 - section VII - v B1 .1).
3. There are no active patents or exclusivities for this drug product.
4. Novex Pharma is the manufacturer (p 213 - section IX - v B1.1).

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 - container - Store at controlled room temperature 15°-30°C (59°-86°F)[see USP].
carton and PI - Store at controlled room temperature 15°-30°C (59°-86°F)[see USP].
Protect from light and excessive heat. Use carton to protect contents from light until used.

6. CARTONING:

RLD - 2 x 5 x 3 mL amps
ANDA - 10 x 3 mL vials

Date of Review: 10-22-02

Date of Submission: 10-11-02

Primary Reviewer: Adolph Vezza

Date:

10/24/02

Team Leader: Lillie Golson

Date:

10/24/02

cc:

ANDA: 75-761
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)

Review

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

ANDA Number: **76-394** Dates of Submission: **October 25 and November 5, 2002**

Applicant's Name: **Apotex Corp.**

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

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

Do you have 12 Final Printed Labels and Labeling?
 Container Labels: 3 mL
Satisfactory in FPL as of the November 5, 2002 submission (Vol 2.1 - Section III)

Carton Labeling: 10 x 3 mL
Satisfactory in FPL as of the November 5, 2002 submission (Vol 2.1 - Section III)

Professional Package Insert Labeling:
Satisfactory in FPL as of the October 11, 2002 submission (V1.1 - Section IV -204026 - rev 8-02)

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 24		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 PTR.		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)? NOT FOR PEDIATRIC USE	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	
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.			

NOTE TO THE CHEMIST:

Does the stability data submitted support the proposed storage temperature recommendations of "Store at controlled room temperature 15°-30°C (59°-86°F)[see USP]."?

FOR THE RECORD:

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 147 - section VII - v B1 .1).
3. ~~There are no active patents or exclusivities for this drug product.~~
4. Novex Pharma is the manufacturer (p 213 - section IX - v B1.1).
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 - container - Store at controlled room temperature 15°-30°C (59°-86°F)[see USP].
carton and PI - Store at controlled room temperature 15°-30°C (59°-86°F)[see USP].
Protect from light and excessive heat. Use carton to protect contents from light until used.
6. CARTONING:

RLD - 2 x 5 x 3 mL amps
ANDA - 10 x 3 mL vials

Date of Review: 11-13-02

Dates of Submission: 10-25-02 and 11-5-02

Primary Reviewer: Adolph Vezza

Date:

/S/

11/18/02

Team Leader: Lillie Golson

Date:

/S/

11/18/02

cc:

ANDA: 76-394
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)

Review