CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76394

CHEMISTRY REVIEW(S)

Chemistry Review Data Sheet

1. **ANDA # 76-394**

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2. **REVIEW #: 1**

3. **REVIEW DATE: July 19**
4. **, 2002**

4. **REVIEWER: Mouna P. Selvam, Ph.D.,**

5. **PREVIOUS DOCUMENTS:**

Previous Documents	**Document Date**
Firm:	
Original Submission.	04-04-2002
FDA:	
Acceptable for Filing	04-10-2002
Acknowledgement.	06-06-2002
Labeling Review	06-20-2002
Bio Review	07-30-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	04-04-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Apotex Corp.

Address: 50 Lakeview Parkway
Suite #127
Vernon Hills
IL-60061

Representative: Marcy MacDonald

Telephone: 847-573-9999

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): AMIODARONE Hydrochloride Injection

9. LEGAL BASIS FOR SUBMISSION:

Cordarone Injection (50 mg/mL) manufactured by Wyeth-Ayerst Company is the RLD, NDA 20-377. The expiration of Orphan Drug Exclusivity is on 08/03/02. Patent certification
on page #7.

10. PHARMACOL. CATEGORY:

Antiarrhythmic (class III)

11. DOSAGE FORM:

Injection

12. STRENGTH/POTENCY:

50 mg/mL, 3 mL vial

13. ROUTE OF ADMINISTRATION:

IM, IV

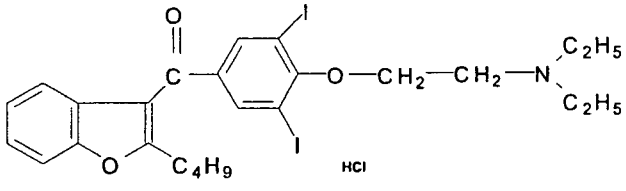
14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Amiodarone Hydrochloride

$C_{25}H_{29}I_2NO_3.HCl$ 617.27 CAS#[1977-82-4]

(2-butyl-3-benzofuranyl)[4-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Drug substance	1	Adequate	07-26-2002	Mouna Selvam
	~~III~~		~~Stopper~~	4			
	~~III~~		Stopper	4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Wyeth-Ayerst Laboratories	NDA 20-377	RLD
	DMF	Drug substance

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending for review		
EES	Pending		
Methods Validation	Pending		
Labeling	Not Approved	06/20/2002	A.Vezza
Bioequivalence	Acceptable	07/30/2002	M.Gokhale
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-394

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
The application should be considered Not Approvable -

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Description of drug product: Appearance; Clear, light yellow to yellow solution free from visible contaminants. Target pH: 4.2, sterile injectable solution. It meets USP particulate and BET tests. Potency and container is 50 mg/mL in 20 cc vial.

Description of drug substance: Very slightly soluble in water Freely soluble in
✓ . Sparingly soluble in
.. Very slightly soluble in The solution at
% must be clear

B. Description of How the Drug Product is Intended to be Used
This product 50 mg/mL , 3 mL vials will be used for the treatment of irregular heart beat.

C. Basis for Approvability or Not-Approval Recommendation
This application is considered as not approvable . The NA Minor letter will be issued based on CMC issues regarding drug substance, manufacturing, finished product and stability. Also, Microbiology review and EER are pending.

III. Administrative

A. Reviewer's Signature

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commercial

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Chem. Review #1

36. Chemistry Comments to be Provided to the Applicant

ANDA: 76-394 APPLICANT: APOTEX Corp.

DRUG PRODUCT: AMIODARONE Hydrochloride Injection, 50 mg/mL 3 mL vial.

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. Regarding Drug Substance:

   a. Please provide the quantitative test for

   b. Please provide the test for particle size.

2. Regarding Manufacturing:

   a. Please indicate the target limit for the in-process pH test, in your blank production batch records and resubmit.

3. Regarding the finished product:

   a. Please submit the specification limits for the degradation products for the finished dosage form at release.

4. Regarding Stability:

   a. Please include tests, methods and limits for content in the stability studies.

   b. Please tighten your related substance limits based on the actual room temperature stability data. Also, resubmit the revised stability protocol and report formats.

   c. Please submit the accrued room temperature stability data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A satisfactory compliance evaluation of the firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending.

2. The microbiology review is pending. We may request additional information based on this review.

3. Methods Validation will be requested for both DS and DP, since they are non-compendial.

Sincerely yours,

for 8/12/02

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Review Data Sheet

1. ANDA # 76-394

2. REVIEW #: 2

3. REVIEW DATE: 30-NOV- 2002

4. REVIEWER: Mouna P. Selvam, Ph.D.,

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm:	
Original Submission.	04-APR-2002
FDA:	
Acceptable for Filing	10-APR-2002
Acknowledgement.	06-JUN-2002
NA Letter (Chemistry)	13-AUG-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	15-OCT-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Corp.
Address:	50 Lakeview Parkway Suite #127 Vernon Hills, IL 60061
Representative:	Marcy MacDonald
Telephone:	847-573-9999 x223

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): AMIODARONE Hydrochloride Injection

9. LEGAL BASIS FOR SUBMISSION:

Cordarone Injection (50 mg/mL) manufactured by Wyeth-Ayerst Company is the RLD, NDA 20-377. The expiration of Orphan Drug Exclusivity is on 08/03/02. Patent certification

on page #7.

10. PHARMACOL. CATEGORY:

Antiarrhythmic (class III)

11. DOSAGE FORM:

Injection

12. STRENGTH/POTENCY:

50 mg/mL, 3 mL vial

13. ROUTE OF ADMINISTRATION:

IM, IV

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

_____SPOTS product – Form Completed

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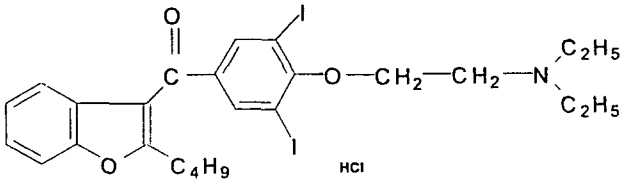

Amiodarone Hydrochloride

$C_{25}H_{29}I_2NO_3.HCl$ 617.27 CAS#[1977-82-4]

(2-butyl-3-benzofuranyl)[4-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Chemistry Assessment Section

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Wyeth-Ayerst Laboratories	NDA 20-377	RLD
	DMF	Drug substance

18. STATUS:

~~CONSULTS/ CMC~~ RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not satisfactory	04-NOV-02	N. Nath
EES	Acceptable	04-SEP-02	
Methods Validation	Pending		Submitted on 09.10.02
Labeling	Satisfactory	18-NOV-02	L.Golson
Bioequivalence	Acceptable	29-JUL-02	M.Gokhale
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _x__ Yes ____ No If no, explain reason(s) below:

Chemistry Assessment Section

The Chemistry Review for ANDA 76-394

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application should be considered Not Approvable -

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Description of drug product: Appearance; Clear, light yellow to yellow solution free from visible contaminants. Target pH: 4.2, sterile injectable solution. It meets USP particulate and BET tests. Potency and container is 50 mg/mL in 20 cc vial. The product formulation is 50 mg/ml amiodarone, 20.2 mg/mL of benzyl alcohol, 100 mg/mL of polysorbate 80 and water (qs). It is Q and Q with the RLD. It is manufactured by

Description of drug substance:

Very slightly soluble in water; freely soluble in
Sparingly soluble in Very slightly soluble in The solution at % must be clear.

B. Description of How the Drug Product is Intended to be Used

This product 50 mg/mL , 3 mL vials will be used for the treatment of irregular heartbeat.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable . The NA Minor letter will be issued based on CMC deficiency. Microbiology review is not satisfactory.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Mouna P. Selvam/~~30-NOV-2002~~ /S/ 12/12/02

U.V. Venkataram/12.9.02 /S/ 12/13/02

S.Shepperson/12-11-02

C. CC Block

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information

Chem Review #2

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

36. Chemistry Comments to be Provided to the Applicant DEC 18 2002

ANDA: 76-394 **APPLICANT: APOTEX Corp.**

DRUG PRODUCT: AMIODARONE Hydrochloride Injection, 50 mg/mL, 3 mL vials.

The deficiencies presented below represent Minor deficiencies.

A. Chemistry Deficiencies:

1. Please submit particle size data for the test lot in support of your specification.

2.

3. Please submit data for the test. Tighten the specification based on available data.

B. Please note and acknowledge the following:

1. Methods Validation has been requested for both the Drug Substance and Drug Product.

2. Please submit available data.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Chemistry Review Data Sheet

1. **ANDA # 76-394**

2. **REVIEW #: 3**

3. **REVIEW DATE:12-APR- 2003**

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4. **REVIEWER: Mouna P. Selvam, Ph.D.,**

5. **PREVIOUS DOCUMENTS:**

Previous Documents	**Document Date**
Firm:	
Original Submission.	04-APR-2002
Minor Amendment	11-OCT-2002
Minor Amendment	29-JAN-2003
FDA:	
Acceptable for Filing Acknowledgement.	10-APR-2002
NA Letter (Chemistry)	06-JUN-2002
Bio Review	13-AUG-2002
Labeling Review	30-JUL-2002
NA Letter (Chemistry)	24-OCT-2002
Micro Review	18-DEC-2002
Micro Review	10-FEB-2003
Labeling Review	18-NOV-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	29-JAN-2003

24 Jan, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Apotex Corp.

Address: 50 Lakeview Parkway
Suite #127
Vernon Hills, IL 60061

Representative: Marcy MacDonald

Chemistry Assessment Section

Telephone: 847-573-9999 x223

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
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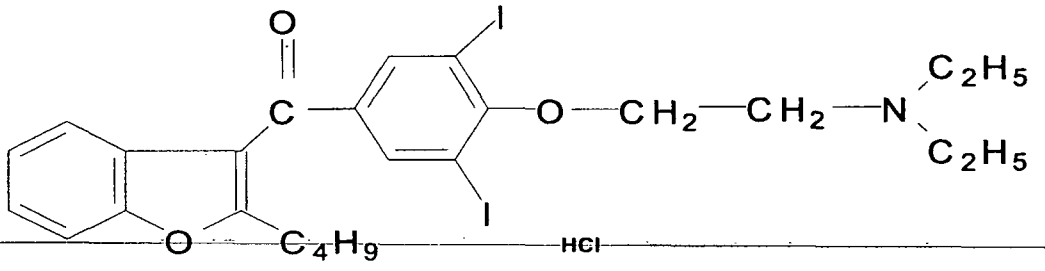

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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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	DMF;	Drug substance

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Satisfactory	10-FEB-03	N. Nath
EES	Acceptable	04-SEP-02	
Methods Validation	Pending		Lab received the samples
Labeling	Satisfactory	18-NOV-02	L.Golson
Bioequivalence	Acceptable	29-JUL-02	M.Gokhale
EA	N/A		
Radiopharmaceutical	N/A		

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Chemistry Assessment Section

The Chemistry Review for ANDA 76-394

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approved.

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N/A

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This product 50 mg/mL , 3 mL vials will be used for the treatment of irregular heartbeat.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable .

III. Administrative

A. Reviewer's Signature

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Chem. Review #3