CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76018

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

A: 76-018 DRUG PRODUCT: Amiodarone Hydrochloride

FIRM: Bedford Laboratories DOSAGE FORM: Injection

STRENGTH: 50 mg/mL, 3 mL per vial

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Page 102).
EIR update : EER acceptable on 3-13-2002.

BIO STUDY: Satisfactory.
The waiver of in vivo bioequivalence requirements for 50 mg/mL was granted on 1–23-2001.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
They have submitted MV commitment on 10-27-2000.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability testing are the same as described in the container section.

Container: Vials

5 mL, clear, amber color, glass tubing vial, the dimensions 5 cc, 13 mm amber tubing vial, manufactured by (DMF

Closure:
13 mm, Gray plug stoppers (DMF

Seal:
13 mm Flip-Off Aluminum seal (DMF

LABELING:
Acceptable per vezza on 2-25-2002.

STERILIZATION VALIDATION (IF APPLICABLE):
Microbiology status is acceptable on 1-25-2002.

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

odarone Hydrochloride Injection, Lot 211146: 70 L is compared to the ted drug Cordarone Injection (50 mg/mL, 3 mL fill in a 3 mL vial). A waiver of in vivo bioavailability testing for the Amiodarone Hydrochloride Injection requested and granted.

The size of the bio batch was L, vial(lot #211146).
Firm's source of NDS OK : Yes Amiodarone HCl; DMF

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
Lot 211146: L

Yes, they are manufactured via the same process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
Blank production batch records: L vials)

Manufacturing process is the same as bio and stability.

CHEMIST: S. Basaran /S/ DATE:3-1-2002 3/21/02

Team Leader: U. Venkataram DATE:3-5-2002 /S/ 3/21/2002.

1. CHEMIST'S REVIEW NO. 1

2. ANDA # 76-018

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
300 Northfield Road
Bedford, Ohio 44146

4. LEGAL BASIS for ANDA SUBMISSION

Cordarone Injection (50 mg/mL, 3 mL fill in a 3 mL vial) manufactured by Wyeth-Ayerst Company is the RLD. The expiration of Orphan Drug Exclusivity is on 08/03/02.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

AMIODARONE Hydrochloride Injection

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

9. AMENDMENTS AND OTHER DATES:

Firm:

10-27-2000: Original Submission.

FDA:

11-30-2000: Acknowledgement.

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic (class III)

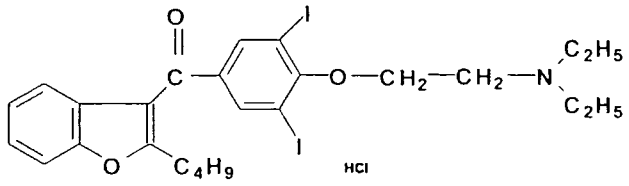
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA 20-377 -Wyeth-Ayrerst Laboratories
DMF Drug Substance, Amiodarone Hydrochloride,

13. DOSAGE FORM
Injection

14. POTENCY
50 mg/mL, 3 mL per vial

15. CHEMICAL NAME AND STRUCTURE



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

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Status:

a. EER status: Acceptable

EER was requested for Ben Venue Laboratories Inc., by B.McNeal on November 1, 2000. Acceptable 2-13-2001.

b. Method Validation status: Pending

Not compendial.

Method validation for samples of the active ingredient and finished product will be issued when NA letter sent out.

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per Sikta Pradhan reviewed on 1-23-2001.

d. Micro-review status: Pending

It will be reviewed by microbiologist.

e. Labeling review status: Not Satisfactory

Not Satisfactory per A. Vezza reviewed on 1-29-2001.

e. DMF Unsatisfactory

DMF was reviewed and found unsatisfactory by INN. on 2-7-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

The application should be considered Not Approvable - Minor Amendment.

19. REVIEWER: DATE COMPLETED:

Sema Basaran, Ph.D. 3-8-2001; 3-15-2001(revised)

Redacted 13

pages of trade

secret and/or

confidential

commercial

information

Chem. Review #1

38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-018 APPLICANT: Bedford Laboratories

DRUG PRODUCT(s): Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL in 5 cc vial.

The deficiencies presented below represent Minor deficiencies.

A. Chemistry Deficiencies

1. Regarding drug substance:

   a. Your individual unknown impurity level is NMT % whereas the drug substance (DS) manufacturer's limit is NMT %. Please tighten your limit to be consistent with drug substance manufacturer's limit.

   b. Please include a test for Organic Volatile Impurities in your DS specifications per USP 24 <467>. You may submit certification from the DS manufacturer in lieu of actual testing.

2. Regarding Manufacturing:

   a. Please indicate target and range limits for the in-process pH test on of your blank production batch records and resubmit.

   b. Please include the in-process tests with limits for the process in your blank production batch records and resubmit.

   c. You have submitted yield accountability limits. Please also set the percent yield limits for the bulk solution and packaged vials. Revise your blank production batch records accordingly.

3. Regarding the finished product:

   a. Please include a test, method and limit for content and pH for the finished dosage form at release.

b. Please submit data including chromatograms comparing impurities in your product with those in the innovator product (RLD).

4. Regarding Stability:

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

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

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

a. Please indicate excipient functionality in the composition statement.

b. DMF has been reviewed and found deficient. A fax letter outlining the deficiencies was sent to This ANDA cannot be approved until these deficiencies have been resolved.

c. Methods validation will be performed on the drug substance and drug product by an FDA laboratory.

Sincerely yours,

/S/

3/26/01

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

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 76-018

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
300 Northfield Road
Bedford, Ohio 44146

4. LEGAL BASIS for ANDA SUBMISSION

Cordarone Injection (50 mg/mL, 3 mL fill in a 3 mL vial) manufactured by Wyeth-Ayerst Company is the RLD. The expiration of Orphan Drug Exclusivity is on 08/03/02.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

AMIODARONE Hydrochloride Injection

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

9. AMENDMENTS AND OTHER DATES:

Firm:
10-27-2000: Original Submission.
9-25-2001: Minor amendment
11-5-2001: Telephone amendment withdrawing the minor amendment and adding 50 mg/mL,
11-19-2001:, The minor amendment and withdrawing the additional
12-19-2001: Telephone amendment
1-18-2002: Telephone amendment(micro.)
1-22-2002: Labeling amendment
2-20-2002: Labeling amendment
2-21-2002: Gratuitions amendment

FDA:

11-30-2000: Acknowledgement.
3-27-2001: Minor CMC letter
7-3-2001: Microbiology deficiency letter
10-4-2001: Telephone conversation
12-14-2001: Telephone conversation
1-18-2002: Telephone conversation

10. PHARMACOLOGICAL CATEGORY
Antiarrhythmic (class III)

11. Rx or OTC
Rx

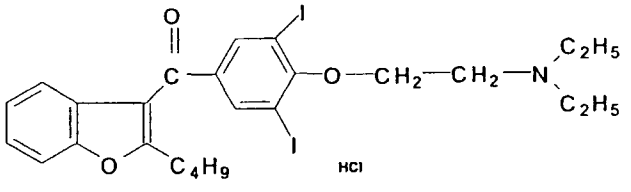
12. RELATED IND/NDA/DMF(s)
NDA 20-377 -Wyeth-Ayrerst Laboratories

DMF Drug Substance, Amiodarone Hydrochloride,

13. DOSAGE FORM
Injection

14. POTENCY
50 mg/mL, 3 mL per vial

15. CHEMICAL NAME AND STRUCTURE



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

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Status:

a. EER status: Satisfactory

EER was requested for Ben Venue Laboratories Inc., by B.McNeal on November 1, 2000. Acceptable 2-13-2001. A subsequent EER was requested on 12-21-01 for the new drug substance manufacturing site included in the amendment to the DMF Received commitment that site never used for API manufacturing.

b. Method Validation status: Pending

Not compendial.

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per Sikta Pradhan reviewed on 1-23-2001.

d. Micro-review status: Acceptable

Acceptable as of 1-25-2002.

e. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 2-25-2002.

f. DMF Satisfactory

DMF was reviewed and found satisfactory by S.Basaran on 11-2-2001.

g. CMC: The Bedford Laboratories submitted for review an additional dosage size, a multiple dose This dosage form has the exact formulation as that previously submitted in the original application and the same manufacturing process. I talked to A. Vezza and he notified Pat Beers Block. She called the company and told them that with submission of this new strength (50 mg/ml, the amendment would be considered a major amendment. See telephone conversation memo by Pat Beer Block on 10-4-2001. In

their amendment of November 19, 2001 the firm withdrew the new strength but retained their response to Agency deficiencies. The amendment is considered a minor amendment.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is satisfactory in CMC and may be approved with pending ~~acceptable~~ MV.

19. REVIEWER: DATE COMPLETED:

Sema Basaran, Ph.D. 12-19-2001/3-1-2002

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

Chem Review #2