CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S6

APPROVAL LETTER

FEB 19 1998

NDA 19-982/ S-006

Lederle Laboratories
c/o Wyeth-Ayerst Laboratories
Attention: Diane Mitrione
170 Radnor-Chester Drive
St. Davids, PA 19087

Dear Ms. Mitrione:

Please refer to your supplemental new drug application (NDA) dated January 13, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zebeta (bisoprolol fumarate) 5 mg and 10 mg Tablets.

The user fee goal date is July 14, 1998.

The supplemental application provides for new packaging components for Zebeta Tablets, in response to the Federal Register Notification of a Final Rule Action (Vol. 60, No. 140, p. 37710, July 21, 1995), which provided for amendments to the requirements for child-resistant closures for pharmaceutical products. The 30 count package will consist of a rectangular white HDPE bottle with a new CR cap with a tamper evident heat induction inner seal.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

/S/ 2/19/98

James H. Short, Ph.D.
Acting Chemistry Team Leader, DNDC I
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S6

CHEMISTRY REVIEW(S)

FEB 19 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-982
3. Name and Address of Applicant (City & State) Lederle Laboratories c/o Wyeth-Ayerst Laboratories 170 Radnor-Chester Road St. Davids, PA 19087		4. Supplement(s) Number(s) Date(s) SCP-006 1/13/98
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: New packaging components for Zebeta Tablets, 5 mg and 10 mg. This submission is in response to the Federal Register Notification of a Final Rule Action (vol. 60, No. 140, p. 37710, July 21, 1995), which provided for amendments to the requirements for child-resistant closures for pharmaceutical products.		
9. Pharmacological Category β_1-selective adrenoceptor blocking agent for treatment of hypertension	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 5 mg & 10 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No
16. Comments: Currently, the 30 count bottle packages of Zebeta Tablets have a child-resistant polypropylene Pop-Lock plug with a polypropylene outer cap. The applicant seeks approval of child-resistant polypropylene cap with a tamper evident heat induction inner seal (HIS). Note: 100 count bottle packages of Zebeta Tablets in both dosage strengths with a heat induction inner seal were approved in the original application.		
17. Conclusions and Recommendations: AP		
18. REVIEWER		
Name Danute G. Cunningham	Signature /S/	Date Completed February 11, 1998
Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO ☐ District		

19982S06.SUP

/S/ 2/19/98

JUN 6 1994

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-982
3. Name and Address of Applicant (City & State) Lederle Laboratories Division of American Cyanamid Company 401 N. Middletown Road Pearl River, NY 10965		4. Supplement(s) Number(s) Date(s)
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) - Dates R-001 10/27/93
7. Supplement Provides For: Annual report for the period 8/92 - 8/93.		
9. Pharmacological Category β_1-selective adrenoceptor blocking agent for treatment of hypertension	10. How Dispensed ☑ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 5 mg & 10 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Included in the report:
SUMMARY OF SIGNIFICANT NEW INFORMATION: None.
DISTRIBUTION DATA: 5 mg and 10 mg - 0.
LABELING: Container labels - no expiration date and lot number, probably applied at the time of the manufacture. Insert - 250M 2/93 Q44655 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.
NONCLINICAL LABORATORY STUDIES: Literature submitted.
CLINICAL DATA: Literature submitted.
CHEMISTRY, MANUFACTURING AND CONTROLS CHANGES: Drug substance - changed code numbers to reflect both the United States and International markets. Same bulk drug substance is being used both the United States and International markets.

17. Conclusions and Recommendations:

NAI. Expiration date - 24 months.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	June 1, 1994

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

19982Y01.ARP

6/3/94

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-982
3. Name and Address of Applicant (City & State) Lederle Laboratories Division of American Cyanamid Company 401 N. Middletown Road Pearl River, NY 10965		4. Supplement(s) Number(s) Date(s)
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) - Dates R-002 10/7/94
7. Supplement Provides For: Annual report for the period 8/93 - 8/94.		
9. Pharmacological Category β_1-selective adrenoceptor blocking agent for treatment of hypertension	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 5 mg & 10 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Included in the report:
SUMMARY OF SIGNIFICANT NEW INFORMATION: Summary is included.
DISTRIBUTION DATA: 5 mg tablets - 10 mg tablets -
LABELING: No changes. Container label (30s) - satisfactory. Insert - 22503-92 Rev. 12/92 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.
NONCLINICAL LABORATORY STUDIES: Included a report on Acute Toxicity of Bisoprolol Fumarate (CL 297,939) to Daphnia magna.
CLINICAL DATA: Bibliography included.
CHEMISTRY, MANUFACTURING AND CONTROLS CHANGES: Drug substance - updated Quality Control Monograph No. G1907H. The changes are editorial. No revisions were made to the specifications or test methods.

17. Conclusions and Recommendations:

NAI Expiration date - 5 years.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	November 22, 1994

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

19982Y02.ARP

11/29/94

MAR 4 1996

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-982
3. Name and Address of Applicant (City & State) Lederle Laboratories Division of American Cyanamid Company 401 N. Middletown Road Pearl River, NY 10965		4. Supplement(s) Number(s) Date(s)
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) - Dates Y-003 2/13/96
7. Supplement Provides For: Annual report for the period 8/94 - 8/95.		
9. Pharmacological Category β_1-selective adrenoceptor blocking agent for treatment of hypertension	10. How Dispensed ☐ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 5 mg & 10 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. **Comments:**

Included in the report:
SUMMARY OF SIGNIFICANT NEW INFORMATION: None.
DISTRIBUTION DATA: 5 mg tablets - tablets; 10 mg - tablets domestic. There was no foreign distribution.
LABELING: Container labels (30s) - satisfactory. Labels do not contain lot # and expiration date, probable applied at the time of the manufacture. Insert - 41530-94 Rev. 11/94 - satisfactory for DESCRIPTION and HOW SUPPLIED sections. Changes made include:

- Trademark on ZEBETA was changed from ™ to ®.
- Removed ADVANTUS PHARMACEUTICALS/ADVANTUS LOGO as an additional distributor for the product.
- Added bar code 128 for labeling verification.

NONCLINICAL LABORATORY STUDIES: Bibliography is included.
CLINICAL DATA: Bibliography is included.
CHEMISTRY, MANUFACTURING AND CONTROLS CHANGES: Stability data is included.

17. **Conclusions and Recommendations:**

NAI. Expiration date - 60 months.

18. **REVIEWER**

Name	Signature	Date Completed
Danute G. Cunningham	/S/	March 4, 1996

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

19982Y03.ARP

3/4/96

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS FOR HUMAN USE
(21 CFR 314.81)

DATE SUBMITTED: 02/13/96

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1997
See OMB Statement on Reverse of Part 1

NOTE: This report is required by law *(21 USC 355; 21 CFR 314.81). Failure to report can result in withdrawal of approval of the New Drug Application.*

INSTRUCTIONS

Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.

1. NDA OR ANDA NUMBER: N 19982

2. Report No. *(FDA Complete)*: Y- 003

APPLICANT NOTE
Reference NDA and Y numbers *(entered on Acknowledgement Copy)* in any subsequent correspondence regarding report.

4. APPLICANT: Lederle Laboratories, Pearl River, New York 10965

3. CFR SECTION NUMBER *(Antibiotic only)*:

5. DRUG NAME: ZEBETA (bisoprolol fumarate) Tablets, 5 mg and 10 mg

6. TYPE OF REPORT *(Check one)*: ☒ ANNUAL ☐ OTHER

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*:

8. PERIOD COVERED BY REPORT

FROM		TO	
YEAR	MONTH	YEAR	MONTH
94	8	95	8

Fold Line

REPORT INFORMATION REQUIRED *(See § 314.81 for description)*

9 *(Enter type of information attached under "Identification." If you have nothing to report, enter None.)*
(INFORMATION IN "9b" and "9c" IS ALWAYS REQUIRED.)

TYPE OF INFORMATION	IDENTIFICATION *(Volume No.(s)/Tab(s)/Page(s) of Report)*
a. SUMMARY OF SIGNIFICANT NEW INFORMATION	"Summary of Significant New Information" tab
b. DISTRIBUTION DATA	"Distribution Data" tab
c. LABELING *(Whether or not previously submitted)*	"Current Package Labeling" tab
d. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES	"Manufacturing and Control Changes" tab
e. NONCLINICAL LABORATORY STUDIES	"Nonclinical Laboratory Studies" tab
f. CLINICAL DATA	"Clinical Data" tab
g. STATUS REPORT POST-MARKETING STUDIES	None
h. STATUS OF OPEN REGULATORY BUSINESS *(Optional)*	None

Fold Line

TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Karel F. Bernady, Ph.D., Director, Marketed Products
U.S. Regulatory Affairs

SIGNATURE: Karel F. Bernady

FDA USE ONLY

10. REPORT FILED IN NDA NUMBER: N 19982

11. DATE OF RECEIPT

APPLICANTS RETURN ADDRESS *(Type within the window envelope tic marks)*

ORIGINAL

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-1245

Attn. Karel F. Bernady, Ph.D.

FORM FDA 2252 (6/92) PREVIOUS EDITION IS OBSOLETE

MAR 4 1997

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-982
3. Name and Address of Applicant (City & State) Lederle Laboratories Division of American Cyanamid Company 401 N. Middletown Road Pearl River, NY 10965		4. Supplement(s) Number(s) Date(s)
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) - Dates Y-004 12/26/96
7. Supplement Provides For: Annual report for the period 8/95 - 8/96.		
9. Pharmacological Category β_1-selective adrenoceptor blocking agent for treatment of hypertension	10. How Dispensed ☐ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 5 mg & 10 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. **Comments:**

Included in the report:
SUMMARY OF SIGNIFICANT NEW INFORMATION: None.
DISTRIBUTION DATA: - 5 mg tablets, - 10 mg tablets domestic distribution. No foreign distribution.
LABELING: There were no changes made. Labels (30's) - satisfactory. Labels do not contain lot # and expiration date, probably applied at the time of manufacture. Insert - 41530-94 Rev. 11/94 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.
NONCLINICAL LABORATORY STUDIES: Bibliography is included.
CLINICAL DATA: Bibliography is included.
CHEMISTRY, MANUFACTURING AND CONTROLS CHANGES: Stability data and other changes are included.

17. **Conclusions and Recommendations:**

NAI. Expiration date - 60 months in blisters or HDPE bottles. (Watch dissolution.)

18. **REVIEWER**

Name	Signature	Date Completed
Danute G. Cunningham	/S/	March 3, 1997

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

19982Y04.ARP

3/31/97

MAR 19 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-982
3. Name and Address of Applicant (City & State) Lederle Laboratories C/O Wyeth-Ayerst Laboratories P.O. Box 8299 Philadelphia, PA 19101-1245		4. Supplement(s) Number(s) Date(s)
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) - Dates Y-005 12/22/97
7. Supplement Provides For:		
9. Pharmacological Category β_1-selective adrenoceptor blocking agent for treatment of hypertension	10. How Dispensed ☐ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 5 mg & 10 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. **Comments:**

Annual report for the period 8/96 - 8/97.

SUMMARY OF SIGNIFICANT NEW INFORMATION: From 6/1/96 through 5/31/97. There have been 49 serious adverse drug events reported via the spontaneous world-wide reporting system.
DISTRIBUTION DATA: - 5 mg tablets and - 10 mg tablets domestic distribution.
LABELING: Container labels - satisfactory, lot number and expiration date probably applied during manufacture. Insert - Cl 4828-2 Revised May 22, 1997- satisfactory for DESCRIPTION and HOW SUPPLIED sections.
NONCLINICAL LABORATORY STUDIES: References are included.
CLINICAL DATA: References are included.
CHEMISTRY, MANUFACTURING AND CONTROLS CHANGES: Stability data and Index of Approved CMC Information, Version 3 are included.

17. **Conclusions and Recommendations:**

NAI. Expiration date - 36 months (approved 60 months)

18. **REVIEWER**

Name	Signature	Date Completed
Danute G. Cunningham	/S/	March 19, 1998

Distribution: ☑ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

19982Y05.ARP

/S/ Short
3-19-98

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS FOR HUMAN USE
(21 CFR 314.81)

DATE SUBMITTED: SEP 30 1999

Form Approved: OMB No. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Reverse of Page 1

NOTE: This report is required by law *(21 USC 355; 21 CFR 314.81). Failure to report can result in withdrawal of approval of the New Drug Application.*

INSTRUCTIONS

Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.

1. NDA OR ANDA NUMBER: N 19982

2. Report No. *(FDA Complete)*: Y- 007

APPLICANT NOTE
Reference NDA and Y numbers (entered on Acknowledgement Copy) in any subsequent correspondence regarding report

4. APPLICANT
Lederle Laboratories, Pearl River, New York 10965

3. CFR SECTION NUMBER *(Antibiotic only)*

5. DRUG NAME
ZEBETA (bisoprolol fumarate) Tablets, 5 mg and 10 mg

6. TYPE OF REPORT *(Check one)*
☒ ANNUAL ☐ OTHER

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*

8. PERIOD COVERED BY REPORT

FROM		TO	
YEAR	MONTH	YEAR	MONTH
98	8	99	9

REPORT INFORMATION REQUIRED *(See § 314.81 for description)*

9. *(Enter type of information attached under "Identification." If you have nothing to report, enter None.)*
(INFORMATION IN "9b" and "9c" IS ALWAYS REQUIRED.)

TYPE OF INFORMATION	IDENTIFICATION *(Volume No.(s)/Tab(s)/Page(s) of Report)*
a. SUMMARY OF SIGNIFICANT NEW INFORMATION	"Summary of Significant New Information" tab
b. DISTRIBUTION DATA	"Distribution Data" tab
c. LABELING *(Whether or not previously submitted)*	"Current Package Labeling" tab
d. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES	"Manufacturing and Control Changes" tab (SUPAC – IR change)
e. NONCLINICAL LABORATORY STUDIES	"Nonclinical Laboratory Studies" tab
f. CLINICAL DATA	"Clinical Data" tab
g. STATUS REPORT POST-MARKETING STUDIES	None
h. STATUS OF OPEN REGULATORY BUSINESS *(Optional)*	None

TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Karel F. Bernady, Ph.D., Director, Marketed Products
U.S. Regulatory Affairs

SIGNATURE: Karel F. Bernady ORIGINAL

APPLICANT'S RETURN ADDRESS *(Type within the window envelope tic marks)*

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299
Attn: Karel F. Bernady

FDA USE ONLY

10. REPORT FILED IN NDA NUMBER: N 19982

11. DATE OF RECEIPT

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT – 4 1999
HFD-110

FORM FDA 2252 (6/93) PREVIOUS EDITION IS OBSOLETE

☐Original Jacket ☐Duplicate Jacket ☐Acknowledgment ☐Applicant

NOV 22 1999

CHEMIST'S REVIEW	1.ORGANIZATION HFD-110	2. NDA Number 19-982
3. Name and Address of Applicant (City & State) Lederle Laboratories Division of American Cyanamid Company 401 N. Middletown Road Pearl River, NY 10965		4. Supplement(s) Number(s) Date(s)
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) Dates Y-007 9/30/99
7. Supplement Provides For:		
9. Pharmacological Category β_1-selective adrenoceptor blocking agent for treatment of hypertension	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 5 mg & 10 mg	
14. Chemical Name and Structure (±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol(*E*)-2-butenedioate (2:1) (salt)		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. **Comments:**

Annual report for the period 8/98-9/99.
SUMMARY OF SIGNIFICANT NEW INFORMATION: None.
DISTRIBUTION DATA: 5 mg tablets - tablets domestic, tablets foreign; 10 mg - tablets domestic, tablets foreign.
LABELING: No changes. Insert - Cl 5108-1 Issued July 7, 1998 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.
NONCLINICAL LABORATORY STUDIES: Bibliography is included.
CLINICAL DATA: Bibliography is included.
CHEMISTRY, MANUFACTURING AND CONTROLS CHANGES: Stability is updated. Other changes are reported.

17. **Conclusions and Recommendations:**

Expiration date - 36 months in HDPE bottles and blisters.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	November 16, 1999

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

19982Y07.ARP

/S/
11-22-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S6

ADMINISTRATIVE DOCUMENTS

DEC 22 1997

Minutes of a Telecon

Telecon Date:	December 19, 1997
Requested:	December 12, 1997
NDA:	19-982 Zebeta (bisoprolol fumarate) Tablets
Sponsor:	Wyeth-Ayerst Laboratories
Type of Telecon:	Change of Manufacturing Site
Meeting Chair:	Robert Wolters, Ph.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Diane Mitrione

FDA Participants:

Robert Wolters, Ph.D.	Team Leader, Chemistry, HFD-110
Zelda McDonald	RHPM, HFD-110

Wyeth-Ayerst Participants:

Karel Bernady, Ph.D.	Director, U.S. Regulatory Affairs
Ken Dilloway, Ph.D.	Director, Quality Assurance
Fred Eng, Ph.D.	Director, Technical Services
Lori Henning	Quality Assurance
Diane Mitrione	Director, U.S. Regulatory Affairs
Sol Motola, Ph.D.	Assistant Vice-President, Technical Affairs Div. Quality Assurance
Denise Papiernik	Technical Operations

Background:

The Firm is proposing to file a Special Supplement-Changes Being Effected to the approved Zebeta NDA for transferring the manufacturing, packaging, and release testing of the 5 mg and 10 mg Zebeta TAblets from the Cyanamid of Great Britain Ltd. (Cyanamid) campus in Gosport, England to the Ayerst-Wyeth Pharmaceuticals, Inc. (AWAPI) campus in Guayama, Puerto Rico. Both Cyanamid and Ayerst-Wyeth Pharmaceuticals, Inc. are affiliated companies of American Home Products Corporation. The Firm would like to effect this transfer under the SUPAC Immediate Release Solid Oral Dosage Forms Guidance.

Telecon:

Discussion Points/Agreements Reached

1. There are four compendial excipients that are tested to meet both EP and USP/NF requirements for which the Firm believes they no longer need to show comparability to the EP specifications : Microcrystalline cellulose, corn starch, magnesium stearate and purified water. The Firm has dissolution profile data comparing 3 lots each of the 5 and 10 mg strengths manufactured at Puerto Rico to 3 lots each of the 5 and 10 mg strengths manufactured at Gosport. The F_2 values meet the guidance document showing that the 2 strengths manufactured at Puerto Rico are equivalent to the 2 strengths manufactured at Gosport. The Firm agreed to verify this in the supplement.

DEC 22 1997

2. The Firm will be substituting equipment that is similar in physical and operating principles. The Firm was advised to consult the addendum to SUPAC IR guidance issued October 1997 regarding equipment changes and make sure they are clear on the subclasses and that their equipment is truly interchangeable.

3. Other than the above, the Agency agreed that the Firm's proposal is acceptable.

Signature minutes preparer: /S/ 12/22/97

Concurrence, Chair: /S/ 12/23/97

cc:
Orig. NDA
HFD-110
HFD-110/McDonald
HFD-110/Benton

Drafted 12/22/97 Finaled 12/22/97
RD:
Wolters 12/22/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S6

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 22 1993

Four Years from
the Date of this Letter NOV 22 2003

NDA 19-982
20-186

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Sullivan:

Reference is made to our December 23, 1998 written request for pediatric studies for Zebeta (bisoprolol) 5 and 10 mg Tablets and Ziac (bisoprolol/hydrochlorothiazide) 2.5/6.25 and 5/6.25 mg Tablets. We have recently reviewed that written request and have decided to amend the below listed sections of the Written Request. All other terms stated in our Written Request issued on December 23, 1998 remain the same.

Strategy

The requested data will provide guidance for the use of bisoprolol and bisoprolol fumarate/hydrochlorothiazide to reduce blood pressure in pediatric patients. These data will be derived from

- a dose-titration trial in hypertensive pediatric patients (bisoprolol fumarate/hydrochlorothiazide).
- safety data derived from the controlled trial, and an open treatment phase following the trial or other comparable database, with a summary of all available information on the safety of the drug in pediatric patients.

Pediatric Subgroups

Age groups

- school-age children (age 6-12 years or ≤ Tanner stage 3), preferred group for effectiveness study, and
- adolescents (> 12 years or > Tanner Stage 3 – 16 years).

Recruiting
If adolescents are included, at least one additional age group must also be included, and at least 50% of the patients in the trial should be 6-12 years old or ≤ Tanner Stage 3 or younger.

Dose-titration Trial

Trial Design

In addition to the trial designs outlined in the previous letter, a trial that would be considered responsive to this request is a double blind, multicenter, parallel, forced dose-escalation study, comparing different doses of bisoprolol fumarate/hydrochlorothiazide to placebo and a single dose of hydrochlorothiazide in the treatment of hypertension in patients 6 through 17 years of age, stratified into 2 age groups (<Tanner Stage 3, ≥ Tanner Stage 3). The study could consist of 3 phases: a 2 week screening and placebo-washout phase, a 10 week randomized treatment phase, and a 2 week dose tapering phase. The dose would be increased in all patients except those who could not tolerate higher doses because of adverse events.

The trial would be analyzed by some suitable non-linear, mixed effects model and would need to find a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose. If the slope of this line is not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show no effect), but it would be interpretable and, therefore, would be responsive to the written request. However, just finding a dose that is effective is not acceptable and such results would not be interpretable and would not be responsive to the written request.

Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format. You may submit this report with essential data in electronic form, with a case report form annotated with the names of the SAS variables.

Timeframe for submitting reports of the studies

Reports of the above studies must be submitted to the Agency on or before four years from the date of this letter. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above study to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS-PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, please contact:

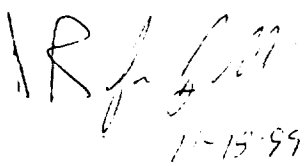
Ms. Zelda McDonald
Regulatory Heath Project Manager
(301) 594-5333

Sincerely yours,

/S/ 11/22/99

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA/IND 19-982
20,186
HFD-110/Division file
HFD-110/Project Manager
HFD-101/Office Director
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-2/TCrescenzi
Drafted by:zm /10/8/99
Initialed by:
Final: asb/11/15/99
filename: 19-982(ir)20,186.doc
PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)



ORIGINAL

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

January 13, 1998

NDA No. 19-982
Zebeta® Tablets

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products (HFD-110)
Center for Drug Evaluation and Research
Attn: Document Control Room, 16B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 19-982 REF. NO. 006
NDA SUPPL FOR SCP

Dear Dr. Lipicky:

Reference is made to Lederle Laboratories approved New Drug Application No. 19-982 for Zebeta® (bisoprolol fumarate) Tablets.

We are filing this supplement in accordance with 21 CFR 314.70(b)(2)(vii) to provide for new packaging components for Zebeta® Tablets, 5 mg and 10 mg. This submission is in response to the Federal Register Notification of a Final Rule Action (vol. 60, No. 140, p 37710, July 21, 1995), which provides for amendments to the requirements for child-resistant closures for pharmaceutical products.

Currently, the 30 count bottle packages of Zebeta® Tablets have a child-resistant polypropylene Pop-Lock plug with a polypropylene outer cap. We seek approval of a child-resistant polypropylene cap with a tamper evident heat induction inner seal (HIS). Please note that 100 count bottle packages of Zebeta® Tablets in both dosage strengths with a heat induction inner seal were approved in the original application. In addition, we also report a change in the shape of the bottle from the "classic" round design to a rectangular design. Finally, this supplement provides for various molders using different high density polyethylene resins for the bottles and alternative manufacturers of the child resistant closures and tamper evident inner seals.

In support of this supplement we provide the Purpose of this Supplement and the following:

Attachment I:	Comparison of Current and Proposed 30 Count Bottle Packages for Zebeta Tablets
Attachment II:	Updated Section II.E.2 - Method of Manufacture and Packaging - Container Closure System
Attachment III:	USP23 Chapter <661> Testing of New HDPE Bottles
Attachment IV:	Three Months Accelerated Stability Data for Zebeta Tablets Manufactured at AWPI and Packaged in the New 30 Count Bottle Package *(Note: A copy of the three months accelerated stability report for the same batches of Zebeta Tablets packaged in the currently approved container closure system is provided for comparison.)*

ORIGINAL

Attachment V: Certificates of Analysis for the Zebeta Tablet Stability Batches

Attachment VI: Post-Approval Stability Commitment, Expiration Dating Period, and Stability Protocol for Zebeta Tablets Packaged in the New 30 Count Bottles

In reference to the information submitted in this supplement, please note that Lederle Laboratories, Wyeth-Ayerst Laboratories, and Ayerst-Wyeth Pharmaceuticals Inc. (AWPI) are all corporate entities of American Home Products Corporation. Expiration dating for the products in the new packaging components is proposed to be thirty six months. Please note that supplement S-005 was submitted on December 22, 1997 to provide for manufacture of Zebeta® Tablets at the AWPI facilities. Tablets from the full-scale validation batches, which were made to support the site transfer supplement, were packaged in the components we are seeking approval in the submission. Thus, we have provided a copy of the stability report submitted in supplement S-005 for comparison purposes.

The effective date for implementation of the Final Rule is January 21, 1998. In the event that approval of this supplement may be later than the effective date, we intend to file for a stay of the enforcement of this Final Rule for Zebeta® Tablets as provided for in the Federal Register Notification.

As per 21 CFR 314.71(b) Wyeth-Ayerst Laboratories hereby certifies that a complete copy of this supplement has been forwarded as a field copy to the FDA District Office at the address below:

Mr. Samuel Jones, District Director
Food and Drug Administration
Southeast Region
P.O. Box 5719
Puerta de Tierra Station
San Juan, PR 00906-5719

We trust that you will find this supplement satisfactory and that it will be approved at your earliest convenience. If you have any questions, please contact the undersigned at (610) 902-3771.

Sincerely,

WYETH-AYERST LABORATORIES

Diane Mitrione

Diane Mitrione
Director, Marketed Products
U.S. Regulatory Affairs

(cover letter w/o attachments)
cc: Ms. Debra Pagano
Program Coordinator for Field Copy Submissions
Department of Health and Human Services
Food and Drug Administration
2nd and Chestnut Streets
Philadelphia, PA 19101-2973

DM/KFB/las:zebsuppa