CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S1

APPROVAL LETTER

S-001

NDA 19-982/S-001

Lederle Laboratories
A Division of American Cyanamid Company
Attention: David N. Ridge, Ph.D.
401 N. Middletown Road
Pearl River, NY 10965

JUN 11 1993

Dear Dr. Ridge:

Please refer to your May 20, 1993 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for ZEBETA (bisoprolol fumarate) Tablets.

The supplemental application provides for extension in expiration dating from three (3) to five (5) years for ZEBETA Tablets in all package styles.

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/ 6/11/93
Robert J. Wolters, Ph.D.
Supervisory Chemist
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFC-130/JAllen
HFD-110
HFD-110/CSO
HFD-83
HFD-232 (with labeling)
HFD-110/DCunningham/6/8/93 6/11/93
clb/6/10/93/N19982.S01
R/D init: RWolters/6/10/93

Approval Date: July 31, 1992

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S1

CHEMISTRY REVIEW(S)

JUN 11 1993

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) S-001 5/20/93 (CE)
5. Drug Name ZEBETA	6. Nonproprietary Name Bisoprolol fumarate	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Extension of the expiration dating from three to five years for bisoprolol fumarate tablets in all package styles.		
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 submission is stability data on two pilot batches and one production-scale batch of each strength stored in HDPE containers and PVC/foil blisters (update to amendment dated 11/11/91 to the NDA).

In addition, dissolution results on a larger sample (stability data) is included which demonstrate that the dissolution controls set at 75 rpm/Q= % at min at FDA request which were based on a very limited data is inappropriate for this product. (Supplement will be filed. Firm proposes/will propose 100 rpm/Q % at min).

17. Conclusions and Recommendations:
Data support 5 year expiration period. Approved.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	/S/	June 8, 1993

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

19982S01.SUP

6.10.93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S1

ADMINISTRATIVE DOCUMENTS

APR 1 1993

RECORD OF TELEPHONE MEETING

NDA/IND NUMBER	INITIATED BY	DATE
19-982	Lederle	March 26, 1993
PRODUCT NAME	FIRM NAME	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Bisoprolol	Lederle	David Ridge

Dr. Ridge called to inform me that about 25% of the tablets were failing stage one testing using 75 rpm, % after minutes. results were not much better. This results in going to stage two testing 95% of the time. We discussed several options i.e. longer time which would require testing after one hour, lower Q value about % or returning to the original requirements of % in minutes at 100 rpm. They will submit a supplement to provide for the original specifications. It will include the dissolution data and data comparing the production batches with the bio batch in several dissolution media. A separate copy will go to Bio.

/S/
Robert Wolters

SIGNATURE DIVISION HFD-110

cc: NDA-Orig.
HFD-110
HFD-110/CSO
HFD-110/Mittal
rjw

LEDERLE LABORATORIES

Lederle

A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 732-5000

March 3, 1993

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUPPL NEW CORRESP

Dear Doctor Lipicky:

Bisoprolol
Annual Reports
21 CFR 314.81 (b) (2)
21 CFR 312.33

Reference is made to 21 CFR 312.10(a)(2) and 21 CFR 314.90(a)(2) which permit a company (applicant) to waive applicable requirements under 21 CFR 312.33 and 21 CFR 314.81(b)(2). The regulation in both instances is exactly the same where it pertains to the submission of IND and NDA reports.

> "A description of an alternative submission or course of action that satisfies the purpose of the requirement"

Lederle Laboratories has one active NDA and three active INDs on the same product, Bisoprolol. When requesting material to be submitted for the annual reports, time and effort would be saved if all four annual reports were due in the same month. The NDA 19-982, Bisoprolol, was approved July 31, 1991, IND Bisoprolol/Hydrochlorothiazide, is reported in June and the remaining INDs both Bisoprolol, are reported in Septemeber.

The recommendation is that all four annual reports be reported in August, a logical halfway point.

I trust our proposal will be acceptable.

Truly yours,

Lydia Cerini

Lydia Cerini
Manager, Documentation
and Submissions

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982_S1

CORRESPONDENCE

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 735-5000

February 1 1993

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Dear Director:

Pursuant to 21 CFR 314.80, there are no Drug Experience Reports to submit in the Periodic Report for ZEBETA™ Bisoprolol Fumarate TABLETS, 5 AND 10 MG and no actions were taken.

NDA 19-982

The time period covered by this report is October 1, 1992 to December 31, 1992.

Sincerely yours,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

Attachments

ORIGINAL

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 732-5000

January 18, 1992

REPORTS

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857-1706

Re: NDA 19-982
ZEBETA®
(bisoprolol)

Gentlemen:

We submit herewith in duplicate a 15-Day Alert Report for the above referenced drug product.

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

92 JAN 26 AM 10:47

9300025.01
9300026.01

Attachment
AH/mh

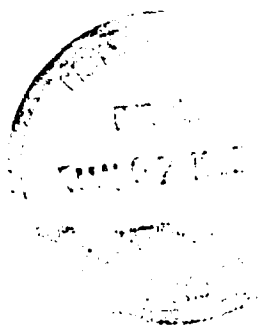
"15-DAY ALERT REPORT"

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 732-5000

December 28, 1992

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857-1706



ORIGINAL

Re: NDA 19-982
ZEBETA®
(bisoprolol)

Gentlemen:

We submit herewith in duplicate a 15-Day Alert Report for the above referenced drug product.

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

9204021.01

Attachment
AH/mh

"15-DAY ALERT REPORT"

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
401 N MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 732-5000

December 14, 1992

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857-1706

Re: NDA 19-982
ZEBETA®
(bisoprolol)

Gentlemen:

We submit herewith in duplicate a 15-Day Alert Report for the above referenced drug product.

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

9203923.01

Attachment
AH/mh

"15-DAY ALERT REPORT"

LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 735-5000

November 12, 1992

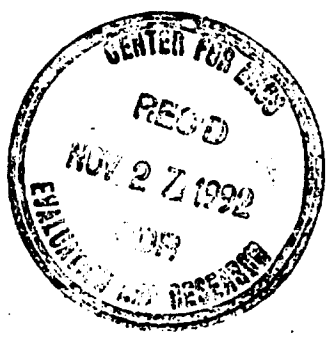
Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Dear Director:

Pursuant to 21 CFR 314.80, there are no Drug Experience Reports to submit in the Periodic Report for ZEBETA™ Bisoprolol Fumarate Tablets, 5 MG and 10 MG and no actions were taken.

NDA 19-982

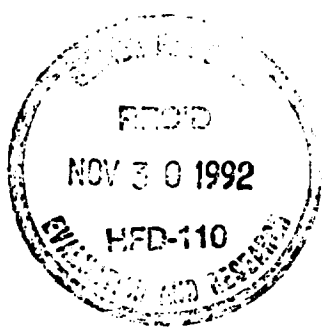
The time period covered by this report is July 1, 1992 to September 30, 1992.



Sincerely yours,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

Attachments



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LEDERLE LABORATORIES

A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 732-5000

October 13, 1992

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857-1706

Re: NDA 19-982
ZEBETA®
(bisoprolol)

Gentlemen:

We submit herewith in duplicate a 15-Day Alert Report for the above referenced drug product.

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

9203338.01
9203339.01

Attachment
AH/mh

"15-DAY ALERT REPORT"

LEDERLE LABORATORIES

Lederle

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 732-5000

May 20, 1993

NDA NO. 19-982 SEE NO. S-001
NDA SUBMISSION SCE

Dr. Raymond J. Lipicky, Director
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD 110, Room 16B-45
5600 Fishers Lane
Rockville, MD 20857

ZEBETA®
(bisoprolol fumarate) Tablets
NDA 19-982

Dear Dr. Lipicky:

We hereby submit this supplement to the subject NDA to propose an extension in expiration dating from three to five years for bisoprolol fumarate 5 and 10 mg tablets in all package styles.

The enclosed sixty-month stability report (Attachment 1) is an update of the report amended to the NDA on November 11, 1991. The data cover two pilot batches and one production-scale batch of each strength tablet and demonstrate good stability for up to sixty months in high density polyethylene bottles and in unit-dose PVC/foil blisters. Dissolution data remain steady over the period of this study.

Included as Attachment 2 is the latest product monograph, which was filed to the FDA on January 24, 1991. That monograph included dissolution testing at 100 rpm with a specification of Q % at minutes. In the July 31, 1992 NDA approval letter, the Agency requested that the dissolution controls be set at 75 rpm/Q % at minutes, the request being based upon a very limited data set obtained from the 5 and 10 mg biobatches. We have provided, as an addendum to the sixty-month stability report, (Attachment 3) dissolution test data at 75 rpm which demonstrate that testing under these conditions resulted in six specification failures out of 21 studies. Nine of the 21 studies required Stage II testing. Only six passed Stage I testing. We have also collected a much larger 75 rpm dissolution data set on samples representing a variety of batches, package styles and ages, and have seen similar results. Our conclusion is that the 75 rpm dissolution test is inappropriate for this product.

ORIGINAL

It is therefore our intention to file an additional supplement in the near future proposing a more suitable test and supported by the entire data set mentioned above. Within that supplement, we will likely propose a new specification of Q % at 100 rpm and minutes. Accordingly, we hereby present, as Attachment 4, a second addendum to the sixty-month stability report which demonstrates that all samples tested would pass this more appropriate specification.

We trust that the information contained herein will be sufficient for approval of an extension of expiration dating to five years for the subject product.. We currently have several validation batches of tablets on-hand which require additional dating in order to be commercially viable. We anticipate labeling this material during late-summer for our new product launch. Therefore, we would greatly appreciate an expeditious review of this supplement and offer our assistance in any way possible to achieve a timely approval.

Our thanks for your special consideration in this matter.

Sincerely,

David N. Ridge

David N. Ridge, Ph.D.
Associate Director
U.S. Technical Regulatory Affairs

Attachments
DNR:rk