

LEDERLE LABORATORIES

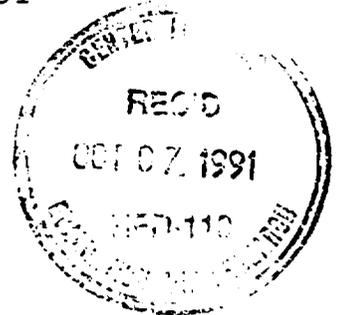
NEW CORRESPONDENCE



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

September 30, 1991

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



NDA 19-982
Bisoprolol (Hypertension)
RESPONSE TO FDA
REQUEST FOR INFORMATION

Dear Doctor Lipicky:

This letter is a further response to a request for information by Dr. Ganley, based on his review of the Bisoprolol Safety Update, submitted January 13, 1991.

An initial response on July 30, 1991, provided some details on Patient 90EMC0724002, but laboratory values for abnormal liver tests were not available at that time.

We have since received a facsimile (in French) from E. Merck containing the following information:

Patient 90EMC0724002 was a 54 year old woman treated with Bisoprolol and Practazin^R (altizide/spironolactone [diuretic combination]) for hypertension since October 1987 who also had abdominal pain since 1987. In November 1989, SGPT was increased (60 IU/L; Upper Limit of Normal:40 IU/L) and gamma GT was increased (54 IU/L; Upper Limit Normal:50 IU/L). Abdominal echography was normal. Bisoprolol was discontinued in December 1989 and abdominal pain disappeared.

If additional information becomes available, we will, of course, forward it to you.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:cf
#911122

ORIGINAL

NEW CORRESPONDENCE

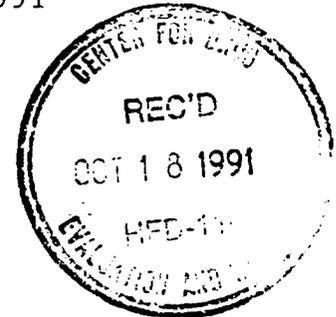
LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER NEW YORK 10965-1299
AREA CODE 914 7325000

October 17, 1991

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFB-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



NDA 19-982
Bisoprolol
monotherapy
SUMMARY BASIS OF APPROVAL

Dear Dr. Lipicky:

Enclosed is the revised Summary Basis of Approval for NDA 19-982 for Bisoprolol monotherapy. As you requested, we have incorporated the following information:

- "Tree" diagrams of the study design for the major trials: Figures 13, 15, 19, 20, and 21.
- "Intent-to-treat" analyses in the Efficacy section: Tables 36, 38, 43, and 44.
- Efficacy tables with "drug effect": Tables 35, 36, 39, 40, 43, 45, 48, and Figure 17.
- Systolic blood pressure data: Tables 39, 48; Figures 16, 18.
- Description of the Bisoprolol safety database: pp. 183-185; and possibly drug-related adverse experiences: pp. 197-201.

Minor corrections and format changes have been made throughout the document; in no case has a change altered the overall findings or conclusions of a table, figure, or text section.



Raymond J. Lipicky, M.D., Director
Page 2

The single correction we wish to note is a change in units from "mcg" to "ng" in Section IV.B. Pharmacokinetics, specifically, Tables 7 through 9 and 12 through 17. It is likely that the abbreviation "ng", as it appeared in the original reports, was incorrectly read as " μ g" and subsequently typed as "mcg" in the earlier draft of the SBA.

If I can be of further assistance, please do not hesitate to contact my office at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

CC: Ms. Zelda McDonald (cover letter only)

MHG:ccc-751
911153
ATT.

LEDERLE LABORATORIES

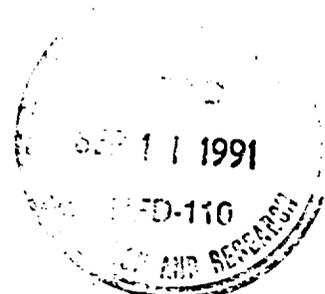
GENERAL CORRESPONDENCE



A Division of AMERICAN CYANAMID COMPANY
401 N MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
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September 10, 1991

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



NDA 19-982
Bisoprolol (Hypertension)
GENERAL CORRESPONDENCE

Dear Doctor Lipicky:

Enclosed is your 'cover memo' with your requested additions attached. Specifically, we are providing:

- p.11: pharmacokinetic values (plus reference table)
- p.15: diagram of Study 57-3 design (2 options)
- p.16: 'building plot' of Study 57-3 results (full scale and reduced)
- p.19: table of Study 57-1 results (full scale and reduced)

We respectfully suggest three changes for accuracy:

- p.10: first paragraph, "over" 65,000 patients should be "approximately" 65,000 patients
- p.12: third paragraph, "about 20X" should be "about 2-3 fold" (reference: PK Summary, NDA 19-982, vol 37 p 10; and PK reports 43-47, NDA 19-982, vols 46-47.)
- p.19: in the second paragraph, "supine" should be "sitting"

ORIGINAL



By way of clarification:

- p.20: While the only evidence for a dose-related increase in the incidence of diarrhea derives from Study 57-3, to a certain extent, our statistical testing for trend with bisoprolol dose attempts to dissect out the HCTZ contribution.
- p.24: Patient 11-440, enrolled in the open-label portion of Study 57-1, had elevated SGOT at the time of randomization. He had elevated liver tests throughout the course of the double-blind and open-label portions of the trial (highest SGOT; 132 IU/L), but withdrew because of GI complaints, not because of the liver test abnormalities. (Reference SBA Appendices, submitted January 18, 1991.)

If I can be of further assistance, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey
Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:cf-599

#

Enc.

CC: Ms. Zelda McDonald

LEDERLE LABORATORIES



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

NDA 19-982
(BP)

August 7, 1991



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

NDA 19-982
Bisoprolol
Response to FDA
Request for Information

Dear Dr. Lipicky:

Enclosed, as requested by Dr. Ernest Belair for his review of the repeat mouse carcinogenicity study, is information on tumor incidence data.

The repeat mouse carcinogenicity study was submitted to NDA 19-982 on March 27, 1991.

If I can be of further assistance, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:cf-478
#910964

CC: Dr. Ernest Belair
Ms. Zelda McDonald (memo only)

ORIGINAL

LEDERLE LABORATORIES SUPPLEMENTAL DATA



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

July 30, 1991

Raymond Lipicky, M.D., Director
Division of Anti-Infective
Drug Products
HFD-520, Room 12B-45
Office of Drug Evaluation II
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 19-982
Bisoprolol
Response to FDA
Request for Information

Dear Doctor Lipicky:

This letter is in response to a request by Dr. Ganley for additional information, based on his review of the bisoprolol Safety Update submitted January 13, 1991.

1) On page 46, under spontaneous reports, there was one laboratory abnormality noted but not identified. IDS# 12175 was a spontaneous report from France. This was a 52 year-old woman with hypertension who was started on bisoprolol (start date not provided). She also received tocopherol troxerutine for leg pain (dates not provided), nomegestrol for menstrual disorder (start date not provided; stopped December 27, 1989), and dihydroergotamine for migraine (start date not provided; stopped December 27, 1989). Because of liver abnormalities, she was started on silymarin on October 11, 1989 and stopped on December 27, 1989. The liver test abnormalities were reported as follows:

	<u>9/28/89</u>	<u>1/16/90</u>	<u>2/22/90</u>
SGOT (normal up to 35)	not reported	33	not reported
SGPT (normal up to 35)	19	127	"normal"
GGT (normal up to 25)	156	291	80

ORIGINAL



She was hospitalized and "still under treatment" at the time of the report. No further details were provided, but we will attempt to obtain additional information.

2) On page 62, under E. Merck spontaneous reports, there were two patients with liver test abnormalities and three with "circulatory collapse". Dr. Ganley asked if additional information is available.

Abnormal Liver Tests

a) 89EMD00192-01 - This was a 21 year-old woman treated with cyclosporin following renal transplantation in 1987. Liver test abnormalities (GGT 185 U/L, SGOT 86 U/L) were noted 2 months after initiation of bisoprolol 10 mg, while on concomitant prazosin and cyclosporin; baseline values were not provided. Liver enzymes remained elevated 3 months after discontinuation of bisoprolol and prazosin, although cyclosporin was continued. This case was included in the draft Summary Basis of Approval sent on January 18, 1991.

b) 90EMC0724002 - This was a 54 year-old woman receiving bisoprolol and Practazin^R (altizide/spironolactone [diuretic combination]) who developed abdominal pain and increased liver enzymes. Values were not provided but have been requested.

"Circulatory Collapse"

a) 90EMD00069-01 - This was a 43 year-old woman who received bisoprolol 5 mg daily, beginning August 9, 1988, for tachycardia (not further specified) and hypertension (160/100 mm Hg), especially during exercise (205 mm Hg systolic). She also had "swollen legs" of unknown etiology, was obese, and had a history of renal calculi. At the time she was started on bisoprolol, she was also put on a "strict diet". Around August 22, the bisoprolol dose was increased to 10 mg daily, and she began complaining of dizziness, increasing muscle weakness, and nocturia. She was seen by a urologist for her nocturia, but no information was provided. A neurologist saw her for her dizziness, and a diagnosis of "psychosomatic complaints" was made. On September 10, she



complained of severe dizziness, muscle weakness, and shortness of breath, at which point she went to bed. The next morning she "collapsed" after taking bisoprolol. She was seen by a "first-aid doctor"; her BP was 100/60 mm Hg, HR 60 bpm. Bisoprolol was discontinued, and she was started on Bayotensin^R (nitrendipine). After approximately 10 days, this was stopped, apparently because of hot flushes. Bisoprolol 2.5 mg daily was started. In early October, she went to another physician (internist) because of dizziness. Bisoprolol was again discontinued, and Effortil^R (etilefrine hydrochloride, a sympathomimetic agent), was started. She continued to complain of dizziness into early November. She stopped taking all medications, lost 7.5 kg, and the dizziness resolved.

b) 90EMD00058-01 - This was a 91 year-old woman who, since 1988, received bisoprolol (listed as 10 mg daily in one place, 2.5 mg in another place) for tachyarrhythmia. She also had hypertension. On September 27, 1989, she had a decrease in blood pressure and experienced a "tendency to collapse" about 1 hour after taking the medication (from a new package). The patient discontinued medication, and the remaining tablets were returned to E. Merck, but nothing abnormal was found.

c) 90EMD00058-02 - This was a 23 year-old woman who received bisoprolol 5 mg daily, beginning December 2, 1989, for paroxysmal tachycardia following a viral infection. Apparently beginning the first day of treatment and on each of 3 successive days, she experienced a syncopal episode, losing consciousness for approximately 1 minute, approximately 1 hour after taking medication. Bisoprolol was discontinued (apparently on December 6). The remaining tablets were returned to E. Merck, but nothing abnormal was found.

3) In 969 patients receiving bisoprolol in Japanese clinical trials (conducted by _____, abnormal laboratory values were reported in 28 patients. Included were abnormalities in SGOT (15 reports) and SGPT (13 reports). Dr. Ganley inquired if there is additional information on these abnormalities. We were not provided with any additional information, but we have requested that E. Merck provide us with further information.

4) Four new reports of traffic accidents were noted in the Safety Update: IDS# 10454 and # 10446, from a Phase IV trial in the U.K., IDS# 9406, from a Phase IV trial in Belgium, and IDS# 9887, a spontaneous report from Belgium. There is now information that IDS# 10446 was not involved a traffic accident. The physician has been contacted, but is unable to give us information about the cause or date of death, stating only that the death was unrelated to bisoprolol or the patient's hypertension. A copy of the Case Report Form (CRF) for IDS# 10454 is attached, as are the CRFs for IDS #'s 8152 and 9421, which you had previously asked about. For these three cases, we have been told that alcohol was involved. We have not yet received the CRF from IDS# 9406, from Belgium. We did receive a copy of a two-page CRF for IDS# 9401, one of the cases from Belgium you had previously asked about. The CRF is not in English and, therefore, is not attached. However, it does not appear that there is any information relevant to the traffic accident. We will check on this and try to send you a translated copy. We have not received any other information on any of these cases which has not already been sent to you.

If you have any other questions, do not hesitate to contact my office at (914) 732-2410.

Sincerely,

Maureen Garvey
Maureen Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:caf-420

#910932

CC: Dr. C. Ganley

Ms. Z. McDonald

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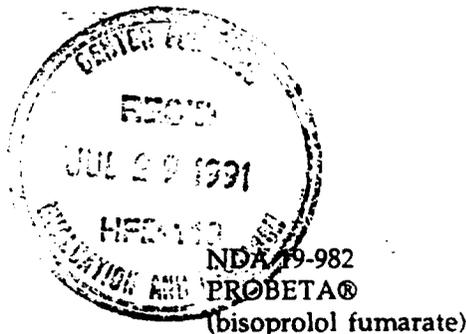


A DIVISION OF AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 732-5000

NDA ORIG AMENDMENT
(BC)

July 17, 1991

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
HFD 110-Document Control Room 16B/30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Lipicky:

We hereby amend the subject NDA with the proposal to introduce two new package styles for PROBETA (both 5 and 10mg tablets).

The first style will be a 7-tablet sample bottle and the other will be a 30-tablet trade bottle. For both of these presentations, the identical container/closure system will be utilized as has been described previously (NDA Vol. 4, p. 290) for bottles of 14 tablets (copy attached). The supportive specifications and DMF reference letters are in Vol. 4, p. 297-318 and the stability data to support all previously studied package styles are found in Vol. 5 pp 17-205. A revised packaging summary is also attached to this amendment. As previously filed, all primary packaging of these products will be done at our manufacturing site in

We commit to place the first three marketed batches in each of these new presentations into our stability program and test them accordingly to the protocol provided in Vol. 5 p. 12-15. We also commit to withdraw any batches which fail to meet specifications and to file the results of all marketed product stability studies in our Annual Reports.

As agreed to in conversations with Dr. Robert Wolters, revised draft labeling to cover these new package styles will be provided prior to NDA approval.

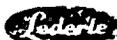
Sincerely,

David N. Ridge, Ph.D.
Director, Technical Services
Regulatory Affairs

DNR:sm

ORIGINAL

LEDERLE LABORATORIES



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

SUPPL. NEW CORRES

July 16, 1991

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



NDA 19-982
Bisoprolol/Hypertension
General Correspondence
Summary Basis of Approval

Dear Doctor Lipicky:

Enclosed, as we informed you at our meeting on July 10, 1991, are corrected and additional pages for insertion into the Summary Basis of Approval for bisoprolol, which was submitted on January 18, 1991.

Thank you for your attention.

Sincerely,

Maureen Garvey

Maureen Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:caf-405
#910853
cc: Ms. Zelda McDonald (Memo Only)

ORIGINAL

LEDERLE LABORATORIES



NEW CORRESPONDENCE

A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10968
AREA CODE 914 732-5000

June 11, 1991

Ernest J. Belair, Ph.D.
HFD 110 - Room 16B-19
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 19-982
Bisoprolol/Hypertension
Response to Request
for Information

Dear Doctor Belair:

Enclosed, as you requested for your review of the repeat mouse carcinogenicity study, are three copies of information on serum triglyceride changes with bisoprolol in toxicology studies.

Previous submissions related to the review of this study were made on May 1, 1991, May 22, 1991, and May 30, 1991. This information completes the response to your requests.

If I can be of further assistance, please call me at (914) 732-2410.

Sincerely,

Maureen Garvey
Maureen H. Garvey, Ph.D.
Assistant Director
U. S. Registration

MHG:cf-097

Enc.

#910720

cc: Dr. R. Lipicky
Ms. Z. McDonald

ORIGINAL

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER NEW YORK 10965-1299
AREA CODE 914 7325000

November 5, 1991

BT

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFD-110, Attention: Document Control Room 16B-30
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



NDA 19-982
Bisoprolol (Hypertension)
Response to FDA
Request for Information

Dear Dr. Lipicky:

As requested by Dr. Ernest Belair during a telephone conversation on September 5, 1991, with Dr. M. G. Riley and Mr. J. Schmuckler of American Cyanamid, we have reviewed and completed the incidence tables he prepared.

The tables are enclosed together with clarification of several items related to the historical control incidence table.

If we can be of further assistance please call Dr. Riley, Mr. Schmuckler or myself at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt-442
encs

cc: Dr. E. Belair (full copy)
Ms. Z. McDonald (letter only)

ORIGINAL

LEDERLE LABORATORIES **NEW CORRESPONDENCE**



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 73250

October 22, 1991

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFB-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



NDA 19-982
Bisoprolol fumarate
GENERAL CORRESPONDENCE

Dear Dr. Lipicky:

Enclosed is our response to FDA concerns regarding the carcinogenicity studies submitted in the referenced NDA.

The response, as described in the Introduction on page 1 of Volume 1, is followed by references in the remainder of Volume 1 and all of Volume 2.

I will call Ms. Zelda McDonald to arrange a meeting to discuss these FDA concerns and our response with you. In the meantime, if I can be of assistance, please call me at 914-732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt/375
Enclosures
#911172

cc: Ms. Z. McDonald

ORIGINAL

NEW CORRESPONDENCE

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

May 7, 1992



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

NDA 19-982
Bisoprolol
NDA 20-186
Bisoprolol/HCTZ
GENERAL CORRESPONDENCE

Dear Dr. Lipicky:

Thank you very much for taking the time to talk to me on Friday about the Bisoprolol and Bisoprolol/HCTZ NDAs. I appreciate your view that a meeting might not be profitable at this time since we are completely informed regarding the current status of the NDA reviews. However, your thoughts and projections were part of what we hoped to gain from a meeting, and our conversation was an informative and helpful substitute.

As we understand the status of the NDAs, it is possible that Bisoprolol will be approved in May, with the B/HCTZ combination approval a subsequent possibility in July. If Bisoprolol monotherapy is approved in June, approval of Bisoprolol/HCTZ is likely in August.

We are aware that the Bisoprolol NDA has been in Dr. Temple's office for some time. We would appreciate any assistance you could give us to ensure that it receives Dr. Temple's attention as soon as possible, so that the above target dates for approval can be met.

Thank you for your assistance.

Sincerely,

Maureen Garvey
Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt-1291

cc: Ms. Z. McDonald

ORIGINAL

LEDERLE LABORATORIES



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

January 30, 1992

Ernest J. Belair, Ph.D.
HFD 110-Room 16B-19
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-982
Bisoprolol/Hypertension
RESPONSE TO REQUEST
FOR INFORMATION

Dear Dr. Belair:

Enclosed, as discussed with Dr. DeFelice, are the toxicology and pharmacokinetics protocols for the mouse carcinogenicity study with bisoprolol which was conducted by Lederle Laboratories.

If I can be of further assistance, please call my office at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt-906
Event # 920098

cc: Ms. Z. McDonald (memo)
Dr. A. DeFelice (memo)
Dr. R. Lipicky (memo)



ORIGINAL

LEDERLE LABORATORIES NEW CORRESPONDENCE



A Division of AMERICAN CYANAMID COMPANY
ONE CYANAMID PLAZA, WAYNE, NEW JERSEY 07470

February 20, 1992

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



NDA 19-982
Bisoprolol fumarate
GENERAL CORRESPONDENCE

Dear Dr. Lipicky:

Enclosed are 3 copies of an amendment to the following nonclinical report submitted on March 27, 1991:

Burden, E.: Bisoprolol (CL# 297,939: a Beta Adrenergic Antagonist): Lifetime Drug-Diet Carcinogenicity Study in Mice (Study Nos. 87086 and 87201). Pages 1-1787 (1991), Pearl River.

The results presented in this amendment were previously submitted as part of the October 22, 1991 response to FDA concerns regarding this study.

If I can be of further assistance, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey
Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt-1051
Event #920181
cc: Ms. Z. McDonald

ORIGINAL

LEDERLE LABORATORIES

NDA ORIG AMENDMENT



(BP)

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

January 30, 1992

Ernest J. Belair, Ph.D.
HFD 110-Room 16B-19
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-982
Bisoprolol/Hypertension
RESPONSE TO REQUEST
FOR INFORMATION

Dear Dr. Belair:

Enclosed, as discussed with Dr. DeFelice, are the toxicology and pharmacokinetics protocols for the mouse carcinogenicity study with bisoprolol which was conducted by Lederle Laboratories.

If I can be of further assistance, please call my office at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt-906
Event # 920098

cc: Ms. Z. McDonald (memo)
Dr. A. DeFelice (memo)
Dr. R. Lipicky (memo)



ORIGINAL

LEDERLE LABORATORIES

NDA ORIG AMENDMENT



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

BC

December 20, 1991

Dr. Raymond Lipicky, Director
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
HFD 110-Document Control Room 16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

PROBETA (bisoprolol
fumarate) Tablets
NDA 19-982

Dear Dr. Lipicky:

Subsequent to your review of our recent three-year stability amendment, and upon the agreement with Review Chemist Donna Cunningham, we hereby commit that all post-approval marketed product stability batches of bisoprolol fumarate tablets will be stored at a target temperature of 25°C. Our Marketed Product Stability Protocol will be revised accordingly and filed to this NDA.

Sincerely yours,

David N. Ridge, Ph.D
Director Technical Services
Regulatory Affairs

DNR:lw

cc. Ms Donna Cunningham
Dr. Robert Wolters



ORIGINAL

LEDERLE LABORATORIES NDA ORIG AMENDMENT



A DIVISION OF AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

December 13, 1991

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFB-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



NDA: 19-982
Bisoprolol
RESPONSE TO FDA
REQUEST FOR INFORMATION

Dear Dr. Lipicky:

Enclosed are responses to comments raised by Dr. Mehul Mehta, FDA Division of Biopharmaceutics, in his review of the Biopharmaceutics package for the Bisoprolol NDA (19-982). The responses are presented in the same order as in the Summary of Comments section of the Biopharmaceutics review (Attachment I).

Also enclosed are the Hydrochlorothiazide assay validation and Bisoprolol discriminatory dissolution technical reports (Attachments II and III respectively).

If I can be of further assistance, please contact me at (914) 732-2410.

Sincerely,

Maureen Garvey
Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

cc: Dr. M. Mehta
Ms. Z. McDonald
Dr. R. Walters

MHG:dlt-633
911396

ORIGINAL

LEDERLE LABORATORIES



A DIVISION OF AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

NDA ORIG AMENDMENT
(BM)

December 12, 1991

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFB-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



NDA 19-982
Bisoprolol
Follow-up
Response to FDA
Request for Information

Dear Dr. Lipicky:

This letter provides additional information in response to a request by Dr. Ganley. Initial information on IDS #12175, a spontaneous report from France, was provided in a letter dated July 30, 1991.

This patient, a 52 year old woman with hypertension, receiving bisoprolol in addition to tocopherol troxerutine for leg pain (dates not indicated) norgestrel for menstrual disorder (start date not provided; stopped December 27, 1989), and dihydroergotamine for migraine (start date not provided; stopped December 27, 1989). Because of liver abnormalities, she was started on silymarin on October 11, 1989 and stopped on December 27, 1989. The liver test abnormalities reported are shown below:

ORIGINAL



Data from 1/91 and 4/91 are new to this correspondence.
Data from 9/89, 1/90, 2/90 were provided on 7/30/91.

	<u>9/28/89</u>	<u>1/16/90</u>	<u>2/22/90</u>	<u>1/91</u>	<u>4/91</u>
SGOT (N< 35)	**	33	**	36	**
SGPT (N< 35)	19	127	*	81	35
GGT (N< 25)	156	291	80	291	80

* Normal, numerical value not provided

** Not provided

If I can be of further assistance, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt-466
#911368

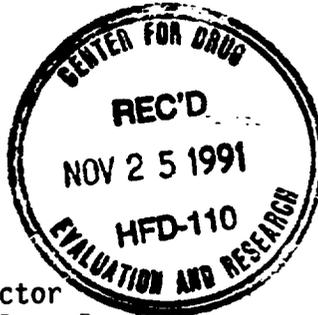
LEDERLE LABORATORIES

NDA DRUG AMENDMENT



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

bc



November 19, 1991

Dr. Raymond Lipicky, Director
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
HFD 110-Document Control Room 16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Bisoprolol fumarate
tablets
NDA 19-982

Dear Dr. Lipicky:

We hereby make a minor revision to our amendment of July 17, 1991 which provided for a new 7-tablet sample bottle and a 30-tablet trade presentation for bisoprolol fumarate, 5 and 10 mg. tablets. The 7-tablet sample package proposed in that amendment utilized an HDPE bottle with polypropylene POP-LOK[®] CRC closure and polypropylene screw cap. We now propose to replace that closure system with a polypropylene screw cap and a foil/polyethylene heat-induction seal. Stability studies have been conducted in this latter container-closure system in trade bottles of 100 and 500 tablets and have been reported in our original NDA filing as well as in our stability amendment of November 11, 1991. The specifications for the current sample as well as for the presentations filed in the original NDA are attached.

We hereby restate our commitment to place the first three batches manufactured in this package style on stability study according to our submitted protocol and to report the results periodically.

Sincerely yours,

David N. Ridge, Ph.D.
Director, Technical Services
Regulatory Affairs

ORIGINAL

U.S. REGULATORY AFFAIRS

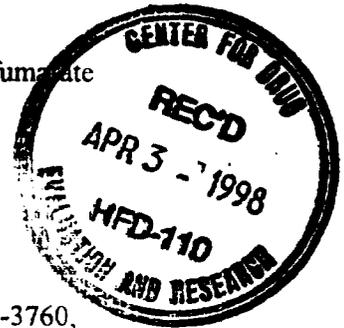
April 2, 1998

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the ADE Periodic Report for Zebeta® (bisoprolol fumarate tablets).



NDA No. 19-982.

The time period covered by this report is March 1, 1997 through February 28, 1998.

If you have any questions regarding this report, please contact the undersigned at (610) 902-3760, or Ms. Mary Alice Dankulich at (610) 902-3726.

Sincerely,

WYETH-AYERST LABORATORIES

Mary Alice Dankulich for KFB

Karel F. Bernady, Ph.D.
Director, Marketed Products
U.S. Regulatory Affairs

KFB/MAD/sb.ADE 19-982

ORIGINAL

Div. 110
P-015

110 —
110-17-702

**Bristol-Myers Squibb
Pharmaceutical Research Institute**

P.O. Box 5400 Princeton, NJ 08543-5400 609 818 5000

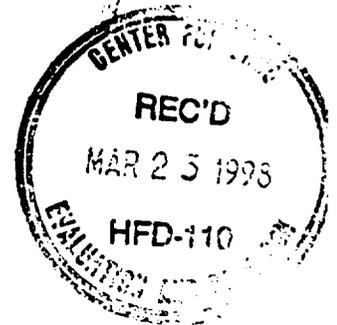
**ORIGINAL
REPORT**

March 10, 1998

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

Dear Sir/Madam:

Attached you will find a Facsimile Form FDA 3500A.



Sincerely yours,

Heide A. Cunning

Heide A. Cunning, B.S.
Manager
Worldwide Safety & Surveillance

HAC:lj
Attachment

ORIGINAL

WYETH-AYERST  RESEARCH

U.S. REGULATORY AFFAIRS

June 4, 1998

~~NDA No. 19-982~~
Zebeta (bisoprolol fumarate) Tablets

NDA No. 20-186
Ziac (bisoprolol fumarate and hydrochlorothiazide) Tablets

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
Attn: Document Control Room, HFD-110
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852



~~SUPP. WITH CORRESP~~
(SNC)

Dear Dr. Lipicky:

Reference is made to our approved New Drug Applications for Zebeta (bisoprolol fumarate) Tablets and Ziac (bisoprolol fumarate and hydrochlorothiazide) Tablets, NDAs 19-982 and 20-186, respectively. Additional reference is made to a May 20, 1998 Federal Register Notice announcing the availability of a list entitled "List of Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population." This list was published under the statutory requirements of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Under the statutory requirements of FDAMA, manufacturers may receive six months of market exclusivity for conducting pediatric clinical trials on drugs which are contained in the aforementioned list. Both bisoprolol and bisoprolol/hydrochlorothiazide are noted in the aforementioned list.

Submitted herewith, for Agency comment, are two draft protocols for study of Ziac and Zebeta in the pediatric population:

Protocol 0896A2-903, "A Double-Blind, Placebo-Controlled, Dose Escalation Safety and Efficacy Study of Ziac[®] (bisoprolol fumarate/hydrochlorothiazide) in Patients 8 to 18 Years of Age"

Protocol 0896A2-904, "An Open-label, Single-dose, Randomized Crossover Study to Determine the Pharmacokinetic Profiles of Ziac[®] (bisoprolol fumarate/hydrochlorothiazide) and Zebeta[®] (bisoprolol fumarate) in Patients, 8 to 18 Years of Age, with Stage I-Stage II Essential Hypertension"

We believe that the completion of both protocols will provide prescribers with appropriate information to guide therapy for both bisoprolol alone and in combination with hydrochlorothiazide in the pediatric patient population. These protocols are designed to provide information regarding the use of bisoprolol and bisoprolol/hydrochlorothiazide in pediatric patients with essential hypertension. Hypertensive patients under the age of eight frequently have elevated blood pressure secondary to other disease processes, therefore we have restricted the lower age for study participation in both protocols to eight years old. We also believe it is

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

ORIGINAL

NDA No. 19-982

Zebeta (bisoprolol fumarate) Tablets

NDA No. 20-186

Ziac (bisoprolol fumarate and hydrochlorothiazide) Tablets

June 4, 1998

Page 2

appropriate to generate dose titration, safety, efficacy and pharmacokinetic data on Ziac, while generating only pharmacokinetic data on bisoprolol, because the pharmacokinetic profile of bisoprolol in Ziac should be no different than bisoprolol alone (i.e., in Zebeta). Prescribers can therefore be assured of the safety of the single agent based on blood level data since both safety and efficacy data will be generated for the combination product in the pediatric population.

We request, in writing, the Agency's concurrence that completion of these studies and submission of the data (targeted for September 1999), will result in an additional six months of market exclusivity for both Ziac and Zebeta, in accordance with FDAMA provisions. Market exclusivity expires for both products on March 24, 2000. An extension of market exclusivity for conduct of pediatric studies would mean that the exclusivity would be granted for the period of time from March 24, 2000 through September 24, 2000.

In addition, we respectfully request the Agency promptly issue the written request for pediatric studies of bisoprolol and bisoprolol/hydrochlorothiazide, since market exclusivity expires in less than two years.

We intend to initiate Protocols 0896A2-903 and 0896A2-904 in September 1998, therefore Agency comments as soon as possible are appreciated. Please contact the undersigned at 610-902-3771 (fax 610-964-5972) if there are any questions regarding this submission.

Sincerely,

WYETH-AYERST LABORATORIES



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

DCM/drk.280.doc

cc: Desk Copy, Zelda McDonald

ORIGINAL

U.S. REGULATORY AFFAIRS

April 15, 1999

Food and Drug Administration
Central Document Room
Center for Drug Evaluation and Research
12229 Wilkins Avenue, Room 6B-45
Rockville, Maryland 20852-1833



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the ADE Periodic Report for Zebeta® (bisoprolol fumarate tablets).

NDA No. 19-982.

The time period covered by this report is March 1, 1998 through February 28, 1999.

If you have any questions regarding this report, please contact the undersigned at (610) 902-3760, or Ms. Mary Alice Dankulich at (610) 902-3726.

Sincerely,

WYETH-AYERST LABORATORIES



Karel F. Bernady
Karel F. Bernady, Ph.D.
Director, Marketed Products
U.S. Regulatory Affairs

KFB/MAD/sb ADE 19-982

ORIGINAL

ORIGINAL
Div 110
P-016

U.S. REGULATORY AFFAIRS

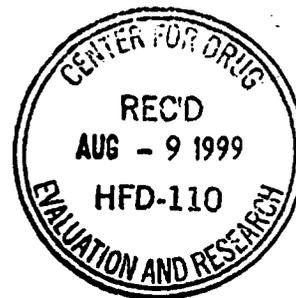
August 6, 1999

Zebeta® Tablets
NDA 19-982

SUPPL NEW CORRESP

SNR

Raymond J. Lipicky, M. D., Director
Division of Cardio-Renal Drug Products (HFD 110)
Office of Drug Evaluation I
Att.: Document Control Room 5002
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Correspondence Regarding Geriatric Use Labeling

Dear Dr. Lipicky:

Reference is made to the Lederle Laboratories approved New Drug Application 19-982 for Zebeta®, bisoprolol fumarate, Tablets.

We also refer to the Final Rule published in the **Federal Register** on Wednesday, August 27, 1997. This Final Rule amends CFR 201.57, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs", to provide for adding a "Geriatric Use" subsection to the **Precautions** section in the labeling.

In accord with Priority Implementation B. for Geriatric Use submissions in 1999, which includes new drugs approved from 1989 to the present, **we are affirming by this letter that the approved labeling for Zebeta Tablets does not require revision because it complies with the Final Rule under CFR 201.57 (f)(10)(vi) and provides sufficient information for the safe and effective use of the drug product in the elderly. We base our conclusion on the following reasons:**

The **Precautions** section of the labeling contains a "Use in Elderly Patients" subsection which has been present since approval of the NDA in 1992. This subsection reads as follows:

"Use in Elderly Patients: Zebeta has been used in elderly patients with hypertension. Response rates and mean decreases in systolic and diastolic blood pressure were similar to the decreases in younger patients in the U. S. Clinical studies. Although no dose response study was conducted in elderly patients, there was a tendency for older patients to be maintained on higher doses of bisoprolol fumarate.

Observed reductions in heart rate were slightly greater in the elderly than in the young and tended to increase with increasing dose. In general, no disparity in adverse experience reports or dropouts for safety reasons was observed between older and younger patients. Dose adjustment based on age is not necessary."

The **Dosage and Administration** section of the labeling contains information on dose adjustment in the elderly that has been present since NDA approval. The text in this section pertaining to the elderly reads as follows:

"Elderly Patients: It is not necessary to adjust the dose in the elderly, unless there is also significant renal or hepatic dysfunction (see above and **Use in Elderly patients in Precautions**)."

Note: The reference "see above" refers to text appearing immediately before the "Elderly Patients" subsection which discusses cautious dosing with Zebeta in patients with renal or hepatic impairment.

We believe that the current labeling for Zebeta® Tablets, detailed above, provides accurate, appropriate, and relevant information to prescribers to direct the use of the drug product by the elderly, and that the labeling requires no revision based on our experience with the drug to date.

If you have any questions regarding this letter, please contact me at (610) 902-3770 or Ms. Jean Lassen at (610) 902-3762.

Sincerely,

WYETH-AYERST LABORATORIES



Roberta R. Acchione
Associate Director
Marketed Products I
U. S. Regulatory Affairs

WYETH-AYERST  RESEARCH

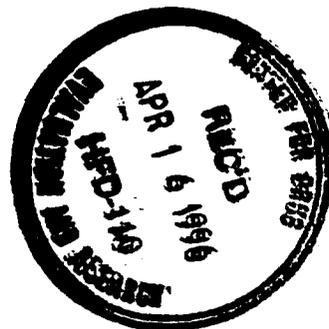
P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610)964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

April 12, 1996

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852



Dear Sir or Madam:

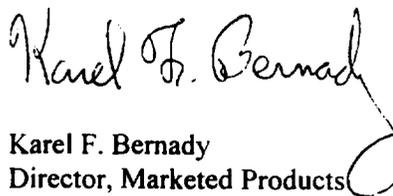
Pursuant to 21 CFR 314.80, enclosed is the 13th Quarterly ADE Periodic Report for Zebeta Tablets.

NDA No. 19-982.

The time period covered by this report is November 1, 1995 through February 29, 1996.

Sincerely,

WYETH-AYERST LABORATORIES



Karel F. Bernady
Director, Marketed Products
U.S. Regulatory Affairs



KFB/PFM/jcn:ADE 19-982

ORIGINAL
P-013
DIU-110

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

November 12, 1993

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

Re: NDA 19-982
ZEBETA™

Gentlemen:

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

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

9302363.01
9302364.01

Attachment
AH/mh

REPORT

NOV 17 1993

NOV 19 1993

"15 DAY ALERT REPORT"

ORIGINA

D

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

March 18, 1994

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

9400510.01

Attachment
AH/mh

"15-DAY ALERT REPORT"

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10965
AREA CODE 914 725-5000



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

Dear Director:

Pursuant to 21CFR314.80, 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 November 1, 1993 to January 31, 1994.

Sincerely yours,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

Attachments

REPORT

P-005
DIV 110
ORIGINAL

LEDERLE LABORATORIES

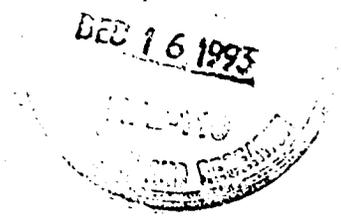


A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 732-5000

SUPPL NEW CORRESP

December 15, 1993

Dr. Edward Zimney
Division of Drug Marketing,
Advertising and Communications
HFD 240 - Room 11B-06
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



ZEBETA™
Bisoprolol Fumarate
NDA 19-982

Dear Dr. Zimney:

Enclosed for your review is our proposed introductory promotional material for the referenced NDA, along with the pertinent references and Prescribing Information.

A copy of this introductory material is also being sent to the Division of Cardio-Renal Drug Products.

Thank you for your prompt attention to this matter. If you have any questions, please do not hesitate to call me at (914) 732-4563.

Sincerely,

Madeleine M. Jester, R.N., J.D.
Associate Director
Marketed Products Support

MJ:ko
Encl.

cc: Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products

O.K.
RL 1/12/94

ORIGIN/

Copy of this page
sent to DDMAC
Jim 1/14/94

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY

PEARL RIVER, NEW YORK 10965

AREA CODE 914 785-8000

December 3, 1993

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



Dear Director:

Pursuant to **21CFR314.80**, 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 **August 1, 1993 to October 31, 1993.**



Sincerely yours,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

Attachments

REPORT
P. 004
Div 110
ORIGINAL

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

May 10, 1994

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



NDA 19-982
ZEBETA™
(bisoprolol fumarate)
GENERAL CORRESPONDENCE

SUPPL NEW CORRESP

Dear Doctor Lipicky,

We refer to your letter of January 13, 1994 in which you requested the addition of cutaneous vasculitis to the ADVERSE REACTION section of the ZEBETA (bisoprolol fumarate) labeling. We have thoughtfully considered your request and we will comply.

We have discussed this issue with E. Merck and reviewed our own safety database as well as the literature. We are confident that the case of cutaneous vasculitis reported in association with bisoprolol in the European Journal of Internal Medicine is an isolated case, albeit with a positive rechallenge. In addition, our review of the literature revealed that cutaneous vasculitis has been associated with the use of atenolol and acebutalol. (See attached references.)

In light of the published evidence, we respectfully suggest the following wording for all beta blocker drug labeling:

"[Bisoprolol], like other beta blockers, has been associated rarely with cutaneous vasculitis."

We await further notice from the Agency prior to taking action on this matter. In the meantime, we will monitor for any additional reports of this particular adverse event in the course of our continued monitoring of the safety profile of bisoprolol.

CONFIDENTIAL

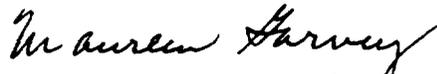
Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products

-2-

If you have any questions about this correspondence or wish to discuss this issue with persons from our Medical Development group, please call me at (914) 732-2410.

Thank you for your attention.

Sincerely ,



Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt
Event #940367

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

August 31, 1994

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 two 15-Day Alert Reports for the above referenced drug product.

Sincerely,

A handwritten signature in black ink, appearing to read "G. Warren McCarl".

G. Warren McCarl, MD
Director
Global Regulatory Operations

9401769.01
9401770.01

Attachment
GWMC/mh

"15-DAY ALERT REPORT"

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10968
AREA CODE 914 735-8000

August 29, 1994

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



Dear Director:

Pursuant to **21CFR314.80**, there are no Drug Experience Reports to submit in the Periodic Report for **ZEBETA™** Bisoprolol Fumarate Tablets, 5mg and 10mg, and no actions were taken.

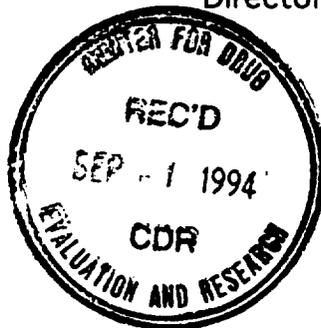
NDA 19-982

The time period covered by this report is May 1, 1994 to July 31, 1994.

Sincerely yours,

G. Warren McCarl, M.D.
Director, Global Regulatory Operations

/hk
Attachments



ORIGINAL

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

June 20, 1994

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:

54 JUN 24 AM 7:17

REPORT

ORIGINAL

Sincerely,

G. Warren McCarl, MD
Director
Global Regulatory Operations

9401253.01

Attachment
GWMC/mh

"15-DAY ALERT REPORT"

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY

PEARL RIVER, NEW YORK 10969

AREA CODE 914 783-8000



May 31, 1994

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

Dear Director:

Pursuant to 21CFR314.80, there are no Drug Experience Reports to submit in the Periodic Report for ZEBETA™ (Bisoprolol Fumarate) 5mg and 10mg Tablets, and no actions were taken.

NDA 19-982

The time period covered by this report is February 1, 1994 to April 30, 1994.

Sincerely yours,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance



Attachments

P-006
Div 110
ORIGINAL

LEDERLE LABORATORIES



A DIVISION OF AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

October 28, 1994

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
Food and Drug Administration
Woodmont 2 Building
1451 Rockville Pike, 5th Floor
Rockville, MD 20852



NDA 19-982
ZEBETA®
(bisoprolol fumarate)
NDA 20-186
ZIAC®
(bisoprolol fumarate/HCTZ)
General Correspondence

Dear Dr. Lipicky:

We refer to your September 22, 1994 request.

We hereby grant you permission to include data from NDA 19-982 for ZEBETA® (bisoprolol fumarate) and NDA 20-186 for ZIAC® (bisoprolol fumarate/ HCTZ) in a meta- analysis that will examine the safety of placebo-controlled trials of antihypertensive agents. We would be willing to supply you with any missing case report forms which you might require. It is our understanding, as you have stated it and as occurred in the anti-anginal analysis publication, that specific drugs will not be identified.

We have forwarded your letter to Ms. Sharon Hamm at Elan Pharmaceuticals, the holder of NDA 19-614 for Verelan® and Mr. Roger Foster at Mylan, the holder of NDA 19-129 for Maxide®.

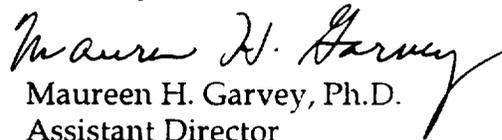
ORIGINAL

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products

-2-

If you have any further requests with respect to this project, please feel free to call me at (914) 732-2410.

Sincerely,

A handwritten signature in black ink that reads "Maureen H. Garvey". The signature is written in a cursive style with a long, sweeping tail on the letter "y".

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt
Event #940988/940989

LEDERLE LABORATORIES



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

October 3, 1994

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,

G. Warren McCarl, MD
Director
Global Regulatory Operations

RECEIVED

9402010.01

Attachment
GWMC/mh

ORIGINAL

"15-DAY ALERT REPORT"

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10995
AREA CODE 914 785-3000

November 28, 1994

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



Dear Director:

Pursuant to **21CFR314.80**, 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 **August 1, 1994 to October 31, 1994.**

Sincerely yours,

G. Warren McCarl, M.D.
Director, Global Regulatory Operations

/hk
Enclosures



ORIGINAL
DIV 110
P-008

WYETH-AYERST **W** 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

April 28, 1997



Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the ADE Periodic Report for Zebeta® (bisoprolol fumarate tablets).

NDA No. 19-982.

The time period covered by this report is March 1, 1996 through February 28, 1997.

If you have any questions regarding this report, please contact the undersigned at (610) 902-3760, or Ms. Mary Alice Dankulich at (610) 902-3726.

Sincerely,

WYETH-AYERST LABORATORIES

Mary Alice Dankulich for K

Karel F. Bernady, Ph.D.
Director, Marketed Products
U.S. Regulatory Affairs



KFB/PPM/cn.ADE 19-982

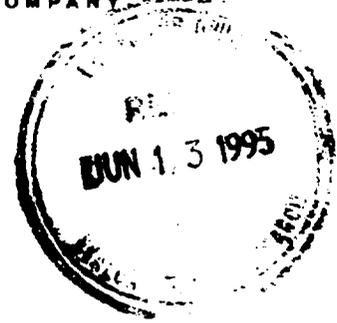
ORIGINAL

P-014
DEU-110

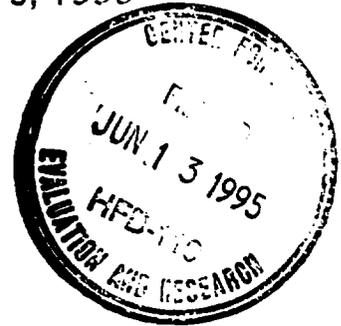
LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10968
AREA CODE 914 785-8000



June 5, 1995



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

Dear Director:

Pursuant to 21CFR314.80, there are no Drug Experience Reports to submit in the Periodic Report for ZEBETA™ (Bisoprolol Fumarate) 5mg and 10mg Tablets, and no actions were taken.

NDA 19-982

The time period covered by this report is February 1, 1995 to April 30, 1995.

Sincerely yours,

G. Warren McCarl, M.D.
Director, Global Regulatory Operations

/hk
Enclosures

ORIGINAL
PC10
D1110

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

March 27, 1995



Charles Ganley, M.D.
Division of Cardio-Renal Drug Products
1451 Rockville Pike 5th floor
Rockville, MD 20852

SUPPL NEW CORRESP

~~NDA 19-982~~
Bisoprolol fumarate
(hypertension)
NDA 20-186
Bisoprolol fumarate/HCTZ
(hypertension)
GENERAL CORRESPONDENCE

Dear Doctor Ganley:

We refer to your request for information on cancer diagnoses and patient exposures in the referenced NDAs. Although you were unable to state the exact reason for requesting this information, we respect the request and hereby provide:

Table 1: Summary of patient exposure in the major hypertension trials in NDA 19-982 and 20-186: Studies 57-1, 57-3, 57-29, and 57-500.

Table 2: Summary of patient exposure in all the major trials in NDA 19-982 and 20-186: Studies 57-1, 57-3, 57-4, 57-5, 57-29, and 57-500.

Table 3: Listing of patients diagnosed with cancer in all the major trials in NDA 19-982 and 20-186: Studies 57-1, 57-3, 57-4, 57-5, 57-29, and 57-500.

These tables have been prepared according to the sample tables you faxed to us. If you have any further questions, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt
Event #950174/950175

1000

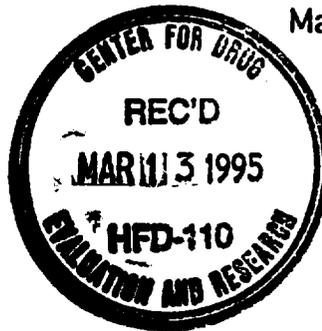
LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10908
AREA CODE 914 725-8000

March 7, 1995

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



Dear Director:

Pursuant to 21CFR314.80, 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 November 1, 1994 to January 31, 1995.

Sincerely yours,

G. Warren McCarl, M.D.
Director, Global Regulatory Operations

/hk
Attachments

ORIGINAL

P-009
DIV 110



WYETH-AYERST  LABORATORIES

P.O. BOX 8299, PHILADELPHIA, PA 19101 • (610) 341-2351 • FAX: (610) 989-4596 Division of American Home Products Corporation

VERN G. DEVRIES, Ph.D.
ASSISTANT VICE PRESIDENT
REGULATORY AFFAIRS

June 1, 1995



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

19-982
ZEBETA® Bisoprolol Fumarate
Tablets, 5 mg, 10 mg

SUPPL NEW ORDERED

Dear Dr. Lipicky:

Reference is made to NDA No. 19-982 held by Lederle Laboratories, for ZEBETA® Bisoprolol Fumarate Tablets.

Under separate cover you will be receiving a letter from Lederle Laboratories providing notification that effective June 1, 1995 Wyeth-Ayerst Laboratories has been appointed to be responsible for all regulatory communications concerning the above-referenced new drug application. A copy of the Lederle letter is attached. Please direct all future correspondence concerning this application to Wyeth-Ayerst at the following address:

Director, Marketed Products
US Regulatory Affairs
Wyeth-Ayerst Laboratories
PO Box 8299
Philadelphia, PA 19101

Sincerely yours,

Vern G. DeVries, Ph.D.

VGD:nd
Attachment

ORIGINAL

WYETH-AYERST  LABORATORIES

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 341-2239
FAX: (610) 989-4596

Division of American Home Products Corporation

REGULATORY AFFAIRS

November 30, 1995

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the 12th Quarterly ADE Periodic Report for Zebeta Tablets.

NDA No. 19-982.

The time period covered by this report is August 1, 1995 through October 31, 1995.

Sincerely,

WYETH-AYERST LABORATORIES

Patricia Fote Mann for

Karel F. Bernady
Director, Marketed Products
U.S. Regulatory Affairs

KFB/PPM/jcn: ADE 19-982

P-012
Div-110

WYETH-AYERST  LABORATORIES

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 341-2239
FAX: (610) 989-4596

Division of American Home Products Corporation

REGULATORY AFFAIRS

September 5, 1995

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the 11th Quarterly ADE Periodic Report for Zebeta Tablets.

NDA No. 19-982.

The time period covered by this report is May 1, 1995 through July 31, 1995.

Sincerely,

WYETH-AYERST LABORATORIES

Patricia Foti Mann for

Karel F. Bernady
Director, Marketed Products
Drug Regulatory Affairs

KFB/PEM/jen.ADE 19-982

ORIGINAL
P-011
Div-110

WYETH-AYERST **W** LABORATORIES

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 341-2239
FAX: (610) 989-4596

Division of American Home Products Corporation

REGULATORY AFFAIRS

July 20, 1995

NDA	12-489	19-032
19-982	12-796	19-561
20-186	18-238	

SUPPLY LIST COMPLETED

Ms. Natalia A. Morgenstern, Chief,
Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Ms. Morgenstern:

Reference is made to your July 17, 1995 letter concerning our correspondence of June 1, 1995 to Hydromox (quinethazone) Tablets NDA 19-982 and Ziac (bisoprolol fumarate/hydrochlorothiazide) Tablets NDA 20-186.

Our June 1, 1995 letter indicated that Wyeth-Ayerst will now be responsible for all regulatory communications concerning each of these drug applications. Although Wyeth-Ayerst will be responsible for regulatory communications, the sponsor or applicant for each of these NDAs remains unchanged. Lederle is still the sponsor of these applications and Wyeth-Ayerst is simply acting as a regulatory communications agent.

To avoid confusion Wyeth-Ayerst will include the name Lederle in the Name of Applicant box of the Form FDA 365h which accompanies submissions to each of these applications. We trust that this will eliminate any confusion.

Your July 7 letter also requested that we provide similar documentation clarifying ownership of the A.H. Robins applications in the Cardio-Renal Division. We wish to assure you that except for ISMO (isosorbide mononitrate) NDA 19-091, all of the A.H. Robins NDAs are still owned by A.H. Robins. Wyeth-Ayerst is acting as an agent for these A.H. Robins NDAs in exactly the same manner as we are acting as an agent for the Lederle NDAs. Although the ISMO NDA was originally submitted by A.H. Robins, it was transferred to Wyeth during the NDA review/approval process.

ORIGINAL

The A.H. Robins applications in the Cardio-Renal Division for which Wyeth-Ayerst is acting as a regulatory communications agent are as follows:

NDA	Product Name
12-489	Exna (benzthiazide) Tablets
12-769	Quinidex (quinidine sulfate) Extend Tabs
18-238	Micro-K (potassium chloride) LS
19-032	Tenex (guanfacine HCl) Tablets
19-561	Micro-K (potassium chloride) Capsules

We trust that this clarifies the relationship between Wyeth-Ayerst Laboratories and the NDAs still held by A.H. Robins and Lederle Laboratories.

If you have any questions please contact me at (610) 341-2242.

Sincerely,
WYETH-AYERST LABORATORIES



Joseph L. Morrison, Ph.D.
Director, Regulatory Affairs
Marketed Products

LEDERLE LABORATORIES



A DIVISION OF AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

October 21, 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

SUPPLEMENTAL

(SE-

NDA 19-982
ZEBETA™
(Bisoprolol/Fumarate)
SUMMARY BASIS OF APPROVAL

Dear Doctor Lipicky:

Enclosed is the Summary Basis of Approval for NDA 19-982, ZEBETA™ (bisoprolol fumarate), revised per your comments. The SBA is in two volumes: Volume 1 is the document itself, Volume 2 contains the appendices.

Also enclosed are two 3.5 inch diskettes containing Volume 1 of the SBA. Our word processing group has recommended that the disks be loaded onto a hard drive for use because of the size of the text file.

If you have any questions, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt
Event # 931023
cc: Ms. Z. McDonald



LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10985-1299
AREA CODE 914 7325000

NDA 19-982 (AL)



July 30, 1992

Robert J. Temple, M.D.
HFD-100 Room 14B-45
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-982
Bisoprolol fumarate
(hypertension)
Package Insert

ORIGINAL

Dear Doctor Temple:

We refer to your letter of June 11, 1992, to revised labeling, complete or partial, which was faxed to us on June 16, 1992, July 22, 1992 and July 27, 1992 and to telephone conversations with the Agency on June 19, 1992, June 26, 1992, July 9, 1992 and July 28, 1992.

Enclosed, as you requested, are twelve copies of the final printed labeling (Lederle Code 22016-92/PRD11) for ZEBETA™ bisoprolol fumarate which reflect your revisions and our discussions with the Agency. Changes to the version faxed to us (in addition to the changes requested by the Agency) on July 22, 1992 are itemized in the attached memo.

Final, printed, immediate container labels are being produced and will be submitted as soon as possible. Additionally, introductory promotional material has not yet been prepared. That material will be submitted as soon as it is available.

If you have any questions regarding this submission, please call me at (914) 732-2410.

Sincerely,

Maureen Garvey
Maureen H. Garvey, Ph.D.
Associate Director
U.S. Registration

MHG:dlt
Attachment
Event # 920997

cc: Dr. R. Lipicky
Ms. Z. McDonald

LEDERLE LABORATORIES



A DIVISION OF AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

July 8, 1992

Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFB-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

NDA 19-982
Bisoprolol
GENERAL CORRESPONDENCE

Dear Dr. Lipicky:

We refer to your letter faxed to us on June 16, 1992. As we indicated in our telephone conversation on June 26, 1992, we plan to submit final printed labeling for bisoprolol fumarate as soon as possible. Per your suggestion, we are faxing adverse experience tables for your consideration prior to submission of the complete Package Insert.

Introductory promotional material have not yet been developed. We will submit these materials as soon as they are available. If you have any questions, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey
Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt
Event # 920762

cc: Ms. Z. McDonald

ORIGINAL



LEDERLE LABORATORIES

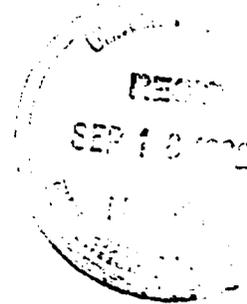


A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

(N-FA)

September 11, 1992

Raymond 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



NDA 19-982
ZEBETA™
Bisoprolol fumarate
FINAL PRINTED LABELING

Dear Doctor Lipicky:

We refer to your letter of July 31, 1992. Enclosed, as you requested, are twelve copies of the final printed labeling for ZEBETA™ bisoprolol fumarate, seven of which are mounted on heavy weight paper.

Also enclosed are twelve copies of the final printed immediate container labels, seven of which are mounted on heavy weight paper.

If you have any questions regarding this submission, please call me at (914) 732-2410.

Sincerely,

Maureen Garvey
Maureen H. Garvey, Ph.D.

MHG:dlt-Event #921229

cc: Ms. Z. McDonald

ORIGINAL

LEDERLE LABORATORIES



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

REPORTS

July 21, 1993

93 JUL 28 PM 11:05

UNIVERSITY OF MARYLAND
AND SUBSTITUTES

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:

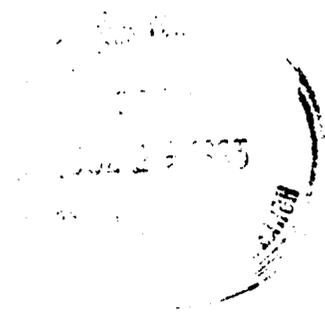
We submit herewith in duplicate a 15-Day Alert Report for the above referenced drug product.

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

9301554.01

Attachment
AH/mh



"15-DAY ALERT REPORT"

LEDERLE LABORATORIES



A Division of AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10908
AREA CODE 914 795-5000

June 14, 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, 5mg and 10mg, and no actions were taken.

NDA 19-982

The time period covered by this report is January 1, 1993 to April 30, 1993.

Sincerely yours,

Alan Hitchcock
Assistant Director
Global Regulatory Compliance

Attachments



D10
110

P-003
ORIGINAL

LEDERLE LABORATORIES

Lederle

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

(BC)

November 11, 1991

Raymond J. Lipicky, Director
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
HFD 110-Room 16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 19-982
PROBETA^R
(bisoprolol fumarate)

Dear Dr. Lipicky:

We hereby amend the subject NDA with updated 24, 36 and 48-month stability data for bisoprolol fumarate 5 and 10 mg tablets in all of the package styles presented in our original NDA filing. The updated package includes data generated at our Pearl River, NY laboratories on two pilot batches and one production-scale batch of each strength tablet and supplements the 12-month data presented in the original NDA (Vol. 5, pp. 35-809). The information contained herein does not include updates to the additional pilot batches which have been on study in our Gosport, U.K. facilities. The data contained in the attached report demonstrate bisoprolol fumarate tablets to have good long term stability in all package style studied. Accordingly, we hereby request three-year expiration dating for this product. We trust that you will find this information sufficiently supportive of our proposal.

Sincerely yours,

David N. Ridge

David N. Ridge, Ph.D.
Director, Technical Services
Regulatory Affairs

DNR:1w



ORIGINAL

LEDERLE LABORATORIES



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

October 8, 1993

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

Re: NDA 19-982
ZEBETA®
(bisoprolol)

93 OCT 14 11:11:11

Gentlemen:

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

Sincerely,

Allan Hitchcock
Assistant Director
Global Regulatory Compliance

9302073.01
9302077.01
9302078.01

Attachment
AH/mh

"15-DAY ALERT REPORT"



LEDERLE LABORATORIES

NDA ORIG AMENDMENT



A Division of AMERICAN CYANAMID COMPANY
401 N. MIDDLETOWN ROAD
PEARL RIVER, NEW YORK 10965-1299
AREA CODE 914 7325000

EM

March 13 1992



Raymond J. Lipicky, M.D.
Division of Cardio-Renal Drug Products
HFB-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

NDA 19-982
Bisoprolol
RESPONSE TO FDA
Request for information

Dear Dr. Lipicky:

This letter is a further response to a request for information by Dr. Ganley based on his review of the bisoprolol Safety Update submitted February 13, 1991. An initial response was submitted on July 30, 1991 followed by additional information on September 30, 1991.

The July 30, 1991 submission indicated occurrences of SGOT (15 reports) and SGPT (13 reports) abnormalities among 969 patients receiving bisoprolol in Japanese clinical trials

We were not provided with laboratory normal values, which varied from institution to institution.

Recently, we received the enclosed information on the 16 Japanese patients who experienced SGOT/SGPT abnormalities. (The 28 incidences in 16 patients were erroneously identified as having occurred in 28 patients in the July 30, 1991 submission.)

ORIGINAL

One patient withdrew because of the liver test abnormalities. SGOT and SGPT levels in this patient were highest at Week 29: 105 and 104 respectively, after which they decreased to 80 and 86 at Week 33 on continued bisoprolol therapy. SGOT and SGPT returned to pre-drug levels within two months after discontinuing bisoprolol.

If I can be of additional assistance, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Assistant Director
U.S. Registration

MHG:dlt-971
Event #920228

cc: Charles Ganley, M.D. (desk copy)
Ms. Z. McDonald (memo only)