CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Lederle Laboratories
A Division of American Cyanamid Company
Attention: Mr. Allan Hitchcock
401 N. Middletown Road
Pearl River, NY 10965-1299

OCT 7 1993

Ref: NDA 19-982
Product Name: Zebeta (bisoprolol fumarate) Tablets

Dear Mr. Hitchcock:

This letter concerns reporting requirements under section 505(k) of the Federal Food, Drug, and Cosmetic Act for drug products that have been approved in accordance with the provisions of section 505(b)(1) of the Act.

The new drug regulations section 314.81 sets forth requirements for reports that are to be submitted for each product covered by an approved new drug application (NDA), whether or not the drug is marketed. Our records indicate that the annual report that was due by September 30, 1993 has not been received for the above referenced drug product.

Failure to submit required reports is a ground for withdrawal of approval of the new drug application under section 505(e) of the Act. A copy of the required transmittal form FD-2252 (Transmittal of Periodic Reports for Drugs for Human Use) is enclosed for your convenience.

If you have ceased to market this drug product and you anticipate no further marketing of it in the future, you may, if you wish, request that the Food and Drug Administration withdraw approval of the new drug application. We would then proceed to publish in the Federal Register a notice withdrawing approval of the application, stating that marketing of the drug has been discontinued and the applicant has requested withdrawal of approval of the application under 21 CFR 314.150(c).

We are concerned about improving our management of NDAs during the review process. NDAs unnecessarily held in an active status overburden our document rooms and distort our workload assignment. We, therefore, hope for your cooperation.

If you choose neither to submit the required report nor to make such a request within 30 days of receipt of this letter, we will proceed to publish a notice of opportunity for hearing on a proposal to withdraw approval of the new drug application on the grounds of failure to report.

Please submit all communications regarding this NDA to the following specific address:

Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: DOCUMENT CONTROL ROOM #16B-30
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact:

Ms. Sandra Matthews
Application Examiner
Telephone: (301) 443-4730

Sincerely yours,

/S/ 10/7/93

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: FD Form 2252

OCT 2 8 1992

NDA 19-982

Lederle Laboratories
A Division of American Cyanamid Company
Attention: Maureen H. Garvey, Ph.D.
401 N. Middletown Road
Pearl River, NY 19065-1299

Dear Dr. Garvey:

We acknowledge the receipt of your September 11, 1992 submission containing final printed labeling in response to our July 31, 1992 letter approving your new drug application for Zebeta (bisoprolol fumarate) 5 and 10 mg Tablets.

We have reviewed the labeling that you have submitted in accordance with our July 31, 1992 letter, and we find it acceptable.

Sincerely yours,

10/28/92

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80
HFD-232 (with labeling)
HFD-110/ZMcDonald/9/23/92;9/24/92 Zm 10/23/92
sb/9/24/92;10/23/92
R/D: DCunningham/9/20/92
RWolters/9/25/92
EBelair/10/27/92
ADeFelice/10/21/92
CGanley/10/22/92
NMorgenstern/10/22/92

ACKNOWLEDGE AND RETAIN

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-982

JAN 19 1996

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Dear Dr. Bernady:

Please refer to your new drug application submitted under section 505(b) of the Food, Drug, and Cosmetic Act for Zebeta (bisoprolol fumarate) Tablets.

This letter concerns reporting requirements under section 505(k) of the Federal Food, Drug, and Cosmetic Act for drug products that have been approved in accordance with the provisions of section 505(b) of the Act.

The new drug regulations under 21 CFR 314.81 set forth requirements for reports that are to be submitted for each product covered by an approved new drug application (NDA), whether or not the drug is marketed. Our records indicate that the annual report that was due by September 31, 1995 has not been received for the above referenced drug product.

Failure to submit required reports is a ground for withdrawal of approval of the new drug application under section 505(e) of the Act. A copy of the required transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use) is enclosed for your convenience.

If you have ceased to market this drug product and you anticipate no further marketing of it in the future, you may, if you wish, request that the Food and Drug Administration withdraw approval of the new drug application. We would then proceed to publish in the Federal Register a notice withdrawing approval of the application, stating that marketing of the drug has been discontinued and the applicant has requested withdrawal of approval of the application under 21 CFR 314.150(c).

If you choose to request withdrawal of approval of the NDA, to avoid being billed under the Prescription Drug User Fee Act of 1992 (PDUFA) for a listed drug, we suggest that you notify the Product Information Management Branch to remove your product from the approved products list by October of this year. You may contact them at:

Food and Drug Administration
Product Information Management Branch, HFD-058
5600 Fishers Lane
Rockville, MD 20857
(301) 594-1086

We are concerned about improving our management of NDAs during the review process. NDAs unnecessarily held in an active status overburden our document rooms and distort our workload assignment. We, therefore, hope for your cooperation.

If you choose neither to submit the required report nor to make such a request within 30 days of receipt of this letter, we will proceed to publish a notice of opportunity for hearing on a proposal to withdraw approval of the new drug application on the grounds of failure to report.

Please submit all communications regarding this NDA to the following specific address:

Center for Drug Evaluation and Research
HFD-110
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
Telephone: (301) 594-5333

Sincerely yours,

/S/ 1/19/96

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: FD Form 2252

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

17.1

NDA
19-982
20-186

JUL - 7 1995

Wyeth-Ayerst Laboratories
Attention: Vern G. DeVries, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101

Dear Dr. DeVries:

Please refer to your new drug applications for Hydromox (quinethazone) Tablets (NDA , Zebeta (bisoprolol fumarate) Tablets (NDA 19-982) and Ziac (bisoprolol fumarate/hydrochlorothiazide) Tablets (NDA 20-186) and to your correspondence of June 1, 1995.

We are not able to determine, from the documentation submitted, just what the relationship is between Lederle and Wyeth-Ayerst Laboratories. Your letter indicates that Wyeth-Ayerst will be responsible "for all regulatory communications concerning the above referenced new drug applications." Does this mean that Lederle is still the sponsor of these applications, and that Wyeth-Ayerst will act as their agent? If a change of ownership is involved, please submit the following documentation for each application:

1. A new Form FDA 356h signed by an authorized agent or official of the company.

2. Evidence of the new ownership of the NDA. This may be in the form of a letter or other documentation from the former applicant to show that all rights have been assigned or transferred to the new owner. Patent or copyright ownership by the new firm is not acceptable evidence of ownership of the NDA.

3. Assurance that a complete copy of the previous owner's NDA has been provided to the new owner.

We also note that the same documentation clarifying ownership should be submitted to all applications in this Division formerly held by A.H. Robins.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

/S/ 7/7/95

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

IN CHIEF

DEPARTMENT OF HEALTH & HUMAN SERVICES N 19-982 Public Health Service

Food and Drug Administration
Rockville MD 20857

SENT

September 3, 1996

Wyeth-Ayerst
P.O. Box 8299
Philadelphia, PA 19101-8299
ATTENTION: Dr. Bernady

Dear Dr. Bernady:

This is in response to your May 31, 1996 FAX which you sent to me. Concerning your site change for the manufacture, packaging, testing and scale-down of Zebeta, NDA 19-982. bisoprolol fumarate, Tablets, we understand your issues as follows:

1) you indicate that the procedures will be essentially the same and that there will be minor changes in manufacture, for example blend time, and

2) there will be some equipment changes.

You think that your filing strategy should be a changes being effected supplement.

In answer to your inquiry:

1) With respect to changes in procedure, if the changes (e.g., blend times) are outside the validated range, we agree that it will require a Changes Being Effected supplement.

2) With respect to equipment:

The following refers to changes of equipment to similar equipment or equipment of the same design and operating principle as these words are used throughout the SUPAC IR guidance document.

The SUPAC IR guidance document (for immediate release solid oral tablets and capsules) allows a change to alternative equipment of the same design and operating principle of the same of differing capacity. A firm should present a brief justification, in the submission, that the equipment is the same design and operating principle. If the firm is unclear about whether the equipment is the same design and operating principle, they may be able to get some clarification from the FDA district office. The firm should be prepared to show validation data for the equipment and product specific verification data during the regularly scheduled Field inspection.

If you use the above information in a submission to the Agency, please accompany your submission with copies of your original communication to the Agency and this response letter.

If you have further questions, please contact us.

Sincerely,

/S/

Marilyn A. Apfel, Ph.D.

cc:
HFD-110/NDA 19-982
HFD-110/Cunningham

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

DATE SUBMITTED 12/26/96

Form Approved: OMB No. 0910-0001 Expiration Date: April 30, 1994 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.*

1. NDA OR ANDA NUMBER: N 19982

2. Report No *(FDA Complete)*: Y- 004

REPORTS

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.

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
95	8	96	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

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

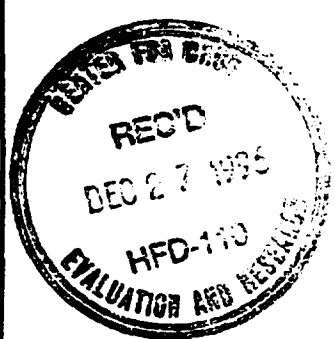
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-1245

Attn. Karel F. Bernady, Ph.D.

FDA USE ONLY

10. REPORT FILED IN NDA NUMBER: N 19982

11. DATE OF RECEIPT



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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

1711

NDA 19-982
20-186

OCT 19 1994

Lederle Laboratories
A Division of American Cyanamid Company
Attention: Maureen H. Garvey, Ph.D.
401 N. Middletown Road
Pearl River, NY 19065-1299

Dear Dr. Garvey:

Please refer to your new drug applications for Zebeta (bisoprolol fumarate) 5 and 10 mg Tablets (NDA 19-982) and Ziac (bisoprolol fumarate/hydrochlorothiazide) 2.5/6.25 and 10/6.25 mg Tablets (NDA 20-186) and to our letter dated January 13, 1994, requesting that you add "Cutaneous vasculitis (confirmed on rechallenge)" to the **ADVERSE REACTIONS** section of the labeling.

We also acknowledge receipt of your correspondence dated May 10, 1994 wherein you suggested the following wording for all beta blocker labeling:

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

Instead of your proposed wording, we ask that, "Cutaneous vasculitis" be added to the **ADVERSE REACTIONS/Skin** subsection of the labeling so as to furnish adequate information for the safe and effective use of these drugs.

Please submit final printed labeling in the form of a supplement to this application. Please incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

To each NDA, please submit fifteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If you have any questions, please contact:

Ms. Zelda McDonald
Consumer Safety Officer
Telephone: (301) 594-5300

Sincerely yours,

/S/ 11/19/94

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 22 1994

Lederle Laboratories
A Division of American Cyanamid Company
Attention: David N. Ridge, Ph.D.
401 N. Middletown Road
Pearl River, NY 10965-1299

RE: NDA 19-129 triamterene/hydrochlorothiazide (Maxzide-25)
NDA 19-614 verapamil (Verelan)
NDA 19-982 bisoprolol fumarate (Zebeta)
NDA 20-186 bisoprolol fumarate/hydrochlorothiazide (Zinc)

Dear Dr. Ridge:

The Division of Cardio-Renal Drug Products (DCRDP) is requesting your permission to include data from your NDAs, noted above, in a meta-analysis that will examine the safety of placebo-controlled trials of antihypertensive agents. DCRDP is planning to analyze data from all antihypertensive drugs submitted as NDAs or as supplements between January 1, 1978 and December 31, 1993.

You may recall that DCRDP conducted a similar analysis of the placebo-controlled trials of submitted anti-anginal agents (see enclosed article, *Glasser et. al.* Exposing Patients with Chronic, Stable, Exertional Angina to Placebo Periods in Drug Trials. JAMA.1991;265:1550-1554). Upon completion of the analysis of hypertensive agents, we will prepare a similar publication with the assistance of Dr. Stephen Glasser of the University of South Florida's Cardiovascular Unit for Research and Education (CURE) and Dr. Donna Arnett, an epidemiologist.

As you can see with the anti-anginal analysis publication, DCRDP does not intend to target specific drugs; however, distinctions may be made on the basis of drug class.

DCRDP is eager to complete this evaluation and subsequent publication and is awaiting your written permission to begin the process. As with the anti-anginal review, this analysis will entail reviewing case report forms for all patients who dropped out of the trials, regardless of reason. Therefore, as a part of your written agreement, please add that you would be willing to supply us with any missing case report forms that we may require. If necessary, assistance from us in gathering the needed case report forms may be provided in certain situations.

If you have any questions or comments, please contact:

Igor Cerny, Pharm D
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110

address for U.S. Mail:
5600 Fishers Lane,
Rockville, MD 20857

address for overnight couriers:
1451 Rockville Pike, 5th floor
Rockville, MD 20857

Phone: (301) 594-5382
FAX: (301) 594-5494

Thank you in advance for your cooperation and assistance.

Sincerely,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-982
20-186

JAN 13 1994

Lederle Laboratories
A Division of American Cyanamid Company
Attention: Maureen H. Garvey, Ph.D.
401 N. Middletown Road
Pearl River, NY 19065-1299

Dear Dr. Garvey:

Please refer to your new drug applications for Zebeta (bisoprolol fumarate) Tablets, 5 and 10 mg (NDA 19-982) and Ziac (bisoprolol fumarate/hydrochlorothiazide) 2.5/6.25, 5.0/6.25 and 10/6.25 mg Tablets (NDA 20-186).

We have reviewed your adverse reaction report dated November 12, 1993 that contained a report published in the European Journal of Internal Medicine concerning the case of a 45 year old man who developed leukocytoclastic vasculitis while on bisoprolol. The vasculitis recurred upon rechallenge. We recommend that, "Cutaneous vasculitis (confirmed on rechallenge)" be added to the **ADVERSE REACTIONS** section of the labeling so as to furnish adequate information for the safe and effective use of these drugs.

Please submit final printed labeling in the form of supplements to these applications. Please incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, please provide highlighted or marked-up copies that show the changes that are being made.

Please submit twelve copies of the printed labeling, seven of which are individually mounted on heavy weight paper or similar material to each application.

Sincerely yours,

/S/ 11/12/94

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 19-982
NDA 20-186

JUN 12 1996

Lederle Laboratories
Attention: Dr. David Ridge
401 N. Middletown Road
Pearl River, NY

Dear Dr. Ridge:

Please refer to your new drug applications (NDA) for Bisoprolol and for Ziac.

We are conducting a meta-analysis to determine the reason-specific rates of drop-out from all treatment groups in placebo-controlled trials of antihypertensive drugs (Hypertension Adverse Reaction Meta-Analysis or HARM). This information will be used to: (1) increase the power for assessing adverse event rates in placebo-treated subjects and within certain drug classes, and (2) provide data pertinent to consideration of the ethics of placebo-controlled trials in hypertension. To this end we are presently examining the case report forms for drop-outs for more than 90 NDAs including your NDAs 19-982 and 20-186 for which you have granted us permission.

In regard to NDA 19-982 and 20-186 we currently have the case report forms for all the post-randomization patient drop-outs due to adverse reactions of the following clinical trials: protocols 84-05, 57-1, 57-3, and 8404 (NDA 19-982); and protocol 57-29 (NDA 20-186).

We would appreciate it, however, if you could forward us copies of the case report forms for the above clinical trials in which there were post-randomization patient drop-outs for any reason other than for adverse reactions. This would include: unsatisfactory response, intercurrent medical problem, failure to follow appointment schedule, therapy refusal, administrative problems, or other reasons. (For NDA 19-982: 2, 4, 91, and 1 CRFs are needed from studies 8405, 57-1, 57-3, and 8404, respectively; for NDA 20-186: 25 additional CRFs are needed for study 57-29).

Thank you for your cooperation.

Sincerely yours,

/S/ 6/12/96

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

18-1

JUL - 1 1996

NDA 19-982
~~20-186~~

Wyeth-Ayerst Research Laboratories
Attention: Karel F. Bernardy, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Bernardy:

Please refer to your new drug applications (NDA) for Bisoprolol (19-982) and for Ziac (20-186).

We are conducting a meta-analysis to determine the reason-specific rates of drop-out from all treatment groups in placebo-controlled trials of antihypertensive drugs (Hypertension Adverse Reaction Meta-Analysis or HARM). This information will be used to: (1) increase the power for assessing adverse event rates in placebo-treated subjects and within certain drug classes, and (2) provide data pertinent to consideration of the ethics of placebo-controlled trials in hypertension. To this end we are presently examining the case report forms for drop-outs for more than 90 NDAs and request permission to include your NDAs 19-982 and 20-186. You have already granted us permission to use data from NDAs 18-553 (Inderal) and 18-587 (Wytensin)

In regard to NDA 19-982 and 20-186 we currently have the case report forms for all the post-randomization patient drop-outs due to adverse reactions of the following clinical trials: protocols 84-05, 57-1, 57-3, and 8404 (NDA 19-982); and protocol 57-29 (NDA 20-186).

We would appreciate it, however, if you could forward us copies of the case report forms for the above clinical trials in which there were post-randomization patient drop-outs for any reason other than for adverse reactions. This would include: unsatisfactory response, intercurrent medical problem, failure to follow appointment schedule, therapy refusal, administrative problems, or other reasons. (For NDA 19-982: 2, 4, 91, and 1 CRFs are needed from studies 8405, 57-1, 57-3, and 8404, respectively; for NDA 20-186: 25 additional CRFs are needed for study 57-29).

Thank you for your cooperation.

Sincerely yours,

/S/ 7.1.96

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 23 1998

Two Years from
the Date of this Letter DEC 23 2000

NDAs 19-982
20-186
INDs

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

Dear Dr. Sulllivan:

Please refer to your proposed pediatric study request for Zebeta (bisoprolol) 5 and 10 mg Tablets and Ziac (bisoprolol/hydrochlorothiazide) 2.5/6.25 and 5/6.25 mg Tablets, dated June 4, 1998 submitted to NDAs 19-982 and 20-186 and October 19, 1998 submitted to INDs

We have completed our review of your submission and conclude that your proposed pediatric study request is inadequate.

To obtain needed pediatric information on bisoprolol, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below.

Strategy

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

- a dose-ranging trial in hypertensive pediatric patients;
- pharmacokinetic trials in subjects from four pediatric age groups: infants and toddlers, pre-school children, school-age children, and adolescents; and
- safety data derived from the controlled trial and an open treatment phase following the trial, with a summary of all available information on the safety of the drug in pediatric patients.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of bisoprolol on the growth and development of pediatric patients, and we encourage you to perform an active control comparison with diuretic-based therapy.

Pediatric Subgroups

Age groups

The five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1-- 24 months),
- pre-school children (age 2-- 6 years),
- school-age children (age 6 --Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (Tanner Stage 3-- 16 years).

With respect to effectiveness, studies of antihypertensive drugs should be focused on, and include a reasonable proportion of, pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide "children" into "pre-school "and "school-age" children. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
- may tolerate doses similar to the smallest doses approved for adults, and
- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

Racial groups

Because response to some therapies in adult hypertension appears to be different in black and non-black populations, your recruitment scheme should be designed to assure a mixture of black and non-black patients.

Formulation Issues

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailablility compared to the marketed product.

Dose-ranging Trial

Trial Design

A trial that would be considered responsive to this request will entail randomized, double-blind observation of parallel dose groups, using a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The trial need not be successful (that is, it need not demonstrate that any particular regimen of bisoprolol is effective in pediatric patients), but it must be interpretable, as explained in the following discussion of possible study designs.

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of bisoprolol, with the doses chosen to give blood levels in a range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved adult dose.[1] After two weeks of treatment,[2] the trial would be analyzed by looking for a significantly

[1] Doses would usually be derived from adult doses scaled by body surface area, but there should be, from PK data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.

positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.[3] If the slope of this line were 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.

Although we believe that the hazard associated with two weeks of placebo treatment is likely to be small, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be similar to Trial A, but without the placebo arm.

If analysis of Trial B revealed a significantly positive slope to the dose-response line, the trial would be considered successful by the usual criteria. If, however, Trial B, shows no dose-response, i.e., if the dose-response line is horizontal, the trial will be considered uninterpretable, not merely unsuccessful.[4] In this case, Trial B would then be considered not responsive to this request.

To avoid this possibility, Trial B could be modified to include a randomized withdrawal phase (Trial C). Patients in Trial C would be recruited and treated like those in Trial B. At the end of the 2-week treatment period, patients would be rerandomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo, with close followup and withdrawal to open-label treatment at the discretion of their physicians. The analysis of Trial C would be a slope analysis for the first phase, but then (if the first phase revealed a flat dose-response curve) an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. This design would allow you to distinguish among a positive dose response (line not flat), doses too low or no effect for some other reason (line flat, withdrawal identical between active treatment and placebo), and doses too high (line flat, withdrawal slower on active treatment). Because this is essentially a placebo-controlled trial, it would be considered interpretable no matter what the outcome so long as the sample size for the withdrawal phase were adequate.

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of bisoprolol and then randomly withdrawn to lower doses (including placebo), with the same close followup, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

Recruiting

The trial should be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must also be included, and 50% of the patients in the trial should be Tanner Stage 3 or younger. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions likely to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be followed weekly, so that unacceptable increases in blood pressure can be detected promptly. Prior treatment with bisoprolol or other therapy should be neither required nor disqualifying.

Eligibility

A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or non-active treatment should pose no risk so long as patients are appropriately monitored.

---

[2] The study period might need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

[3] In general, there will be interest in the effect on both systolic and diastolic pressure. Usually, the best measure of blood pressure change will be mmHg, but if pressures vary widely, percent change could be used.

[4] When placebo is included (as in Trial A), a flat dose-response line means simply that all of the doses tested were too low, so they were ineffective, or that the drug does not work in children. Without placebo (as in Trial B), it is alternatively possible that all of the doses tested were too high, and that they were all equally effective.

You should take steps to attempt to obtain a reasonable distribution of age, race, and gender in the trial.

Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional (P= 0.05) statistical significance. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

Pharmacokinetic Trials

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from infants and toddlers, pre-school children, school-age children, and adolescents. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in the dose-response trial or from safety studies. Data should be collected with respect to bisoprolol and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the bioavailability (AUC), half-life, C_{max}, and t_{max} in pediatric subjects of the various age groups.

Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format; or, as an alternative, you may submit an abbreviated study report along with all data in electronic form, with a case report form annotated with the names of the SAS variables used for each blank on the form.

Labeling Changes

The results of the completed studies may be used in the labeling of your drug products to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population[5] that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your products are approved.

Timing of Submission of Reports

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

---

[5] For example, pediatric patients with hypertension secondary to advanced renal disease.

Please submit protocols for the above studies 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. Please 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 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:

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 to the pediatric population.

If you have any questions, please contact:

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

Sincerely yours,

/S/ 2/25/98

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

JUL 13 1998

NDA 19-982
20-186

Wyeth-Ayerst Research
Attention: Ms. Diane Mitrione
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your new drug applications (NDAs) for Zebeta (bisoprolol fumarate) Tablets (NDA 19-982) and Ziac (bisoprolol fumarate and hydrochlorothiazide) Tablets (NDA 20-186).

In reviewing your submission of June 4, 1998, our Biopharmaceutist has raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence.

We would appreciate your written response.

If you have any questions, please contact:

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

Sincerely yours,

/S/ 7/10/98

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 19-982
HFD-110/Div. Files
DISTRICT OFFICE
HFD-110/Z.McDonald;6/27/98 ZM 7/10/98
sb/6/30/98;7/9/98
Initialed by: EFadiran/6/30/98
MGordon/7/1/98
SChen/7/1/98
NMorgenstern/7/9/98
filename: N19982GC.WPD

GENERAL CORRESPONDENCE

AUG 19 1998

NDA 19-982
20-186

Wyeth-Ayerst Research
Attention: Ms. Diane Mitrione
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your new drug applications (NDAs) for Zebeta (bisoprolol fumarate) Tablets (NDA19-982) and Ziac (bisoprolol fumarate and hydrochlorothiazide) Tablets (NDA 20-186).

In reviewing your submission of June 4, 1998, our Statistician has raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence.

We would appreciate your written response.

If you have any questions, please contact:

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

Sincerely yours,

/S/ 8/19/98

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDAs 19-982 & 20-186
HFD-110/Div. Files
HFD-110/Z.McDonald zm 8/19/98
Drafted by: zm/August 14, 1998
Initialed by: W Nuri/8/17/98
K Mahjoob/8/17/98
N Morgenstern/8/17/98
final: sb/8/18/98
filename: 19982gc980818.doc

GENERAL CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDAs 19-982
20-186
INDs

MAR 17 1999

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

Dear Dr. Sullivan:

We refer to your correspondence dated February 23, 1999 that referenced our February 9, 1999 meeting and contained your minutes of that meeting. You also asked us to concur that your minutes reflect discussion that occurred during that meeting.

In general, your minutes and our minutes are in agreement, however, we wish to clarify the following points:

1. In your letter of February 23, 1999, you are correct regarding submission of completed study results. In addition to a documented electronic submission of all the data collected, there should be a short analytical description of the major findings.

2. There is need for pharmacokinetic information in children under age 6. We look forward to receipt of your new protocol and hope you can execute it within the required time frame.

If you have any questions, please contact:

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

Sincerely yours,

/S/ 3/17/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

SEP 25 199

Lederle Laboratories
A Division of American Cyanamid Company
Attention: Maureen H. Garvey, Ph.D.
401 N. Middleton Road
Pearl River, NY 10965-1299

Dear Dr. Garvey:

Just a quick note of thanks for helping the Division and the Cardiovascular and Renal Drugs Advisory Committee hold a successful meeting that evaluated the current status of left ventricular hypertrophy and the effects of antihypertensive therapy on left ventricular hypertrophy.

As you may be aware, the Advisory Committee concluded that, at present, there were no controlled clinical trial data that allowed any conclusion to be drawn regarding the effects of any single drug, or any class of drugs on left ventricular hypertrophy.

Take this letter as a gentle reminder that all promotion regarding the effects of any drug or any class of drugs on progression, regression or any other effect on left ventricular hypertrophy is expected to cease immediately.

Sincerely yours,

/S/ 9/25/91

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 19982
HFD-110
HFD-240
HFD-110/CSO
HFD-110/RLipicky
sb/9/18/91;9/20/91
R/D: DRoeder/8/21/91
ZMcDonald/8/21/91
NMorgenstern/8/21/91

RR 9-25-91
ZM 9/25/91

GENERAL CORRESPONDENCE

APR 9

NDA 19-982

Lederle Laboratories
A Division of American Cyanamid Company
Attention: Maureen H. Garvey, Ph.D.
Pearl River, NY 10965

Dear Dr. Garvey:

We acknowledge receipt on March 28, 1991 of your March 27, 1991 amendment to your supplemental new drug application for Bisoprolol Tablets.

We consider this amendment major under 21 CFR 314.60 of the regulations and we have determined that 90 additional days will be required for its review. The new due date is June 26, 1991.

If you have any questions, please contact:

Ms. Zelda McDonald
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

/S/ 4/9/91

Raymond G. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFC-130/JAllen
HFD-83
HFD-110
HFD-110/CSO
HFD-110/ZMcDonald
sb/4/5/91

REVIEW EXTENSION

NDA 19-982

AUG 15 1991

Lederle Laboratories
A Division of American Cyanamid Company
Attention: Maureen H. Garvey, Ph.D.
Pearl River, NY 10965

Dear Dr. Garvey:

Please refer to your new drug application for Probeta (bisoprolol) Tablets.

In reviewing your submission of July 28, 1989 and March 27, 1991, our statistician raised a number of questions that require your attention. Our concerns with your submissions are detailed as part of this correspondence (see enclosure).

We would appreciate your written response.

Sincerely yours,

/S/ 8/15/91

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFC-130/JAllen
HFD-80/DDIR
HFD-110
HFD-110/CSO
HFD-110/ZMcDonald;8/14/91 8/15/91
sb/8/14/91;8/15/91
R/D: NMorgenstern/8/14/91

GENERAL CORRESPONDENCE

DEC 12 1990

NDA 19-982

Lederle Laboratories
Attention: David N. Ridge, Ph.D.
Middletown Road
Pearl River, NY 10965

Dear Dr. Ridge:

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

We also refer to your amendment dated November 1, 1990.

We have completed our review of this amendment and have the following requests:

1. Please correct the typographical error on page 002 for the coloring. If the color is the same as in the original submission, it should read,

2. One of the recommendations included in the INTERLABORATORY CROSS-OVER STUDY ON DISSOLUTION ON MONOCOR TABLETS report (page 140) is to use freshly prepared standard solutions for any dissolution and assay tests and to assay dissolution samples and standard solutions within six hours of the preparation. Please incorporate these recommendations in the description of the methodology used for dissolution and assay and content uniformity.

3. Please specify the type of electrode used in the assay procedure for fumaric acid content (bulk drug substance).

We would appreciate your written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Ms. Zelda McDonald
Consumer Safety Officer
(301) 443-4730

cc:
BUF-DO
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/ZMcDonald/12/4/90;12/4/90
sb/12/4/90;12/7/90/0625Q
R/D: RWolters/12/5/90
CResnick/12/5/90
CGanley/12/6/90
NMorgenstern/12/6/90
INFORMATION REQUEST

zm 12/7/90

Sincerely yours,

12/12/90

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

LEDERLE LABORATORIES

Lederle

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

N ORIG 4 ORIG AMENDME

BC

December 27, 1989

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
MONOCOR[R]
Response to FDA Request

Dear Doctor Lipicky:

We refer to your letter of October 19, 1989 delineating requests and recommendations relative to the manufacturing/controls section of the referenced NDA which was submitted on July 28, 1989.

Attached is a point-by-point response to your requests.

Sincerely yours,

Dennis J. Foley, Ph.D.
Director
Regulatory Liaison

DJF:ps
#900002

CC: Ms. Z. MacDonald

ORIGINAL

LEDERLE LABORATORIES

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

NDA ORIG AMENDMENT
(EM)

November 22, 1989

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

Dear Doctor Lipicky:

Based on phone conversations between Dr. Charles Ganley, Medical Officer and Lederle staff on November 2 and November 13 the following information is provided to clarify questions raised by Dr. Ganley.

Attachment 1: Memo from Dr. B. Bryzinski to Dr. Ganley regarding patients who discontinued therapy in the 57-3 study. (This information was previously sent to Dr. Ganley on November 6, 1989).

Attachment 2: Information on all patients in study 57-3 who left the study early due to "lost-to-follow-up."

Sincerely,

/Dennis J. Foley

Dennis J. Foley, Ph.D.
Director
Regulatory Liaison

DJF:ps
#891719

ORIG NEW CORRES

LEDERLE LABORATORIES

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

November 16, 1989

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

Dear Doctor Lipicky:

Enclosed please find two floppy diskettes containing the tumor data from the following carcinogenicity studies which were submitted with the referenced NDA on July 28, 1989:

Diskette #87059 Mouse Carcinogenicity (Report #116, Volume 25)

Diskette #87058 Rat Carcinogenicity (Report #120, Volume 27)

These datasets have been created in accordance with the FDA guidelines dated April 19, 1989; a few exceptions are noted in the attached memo from Dr. D. Giltinan which also includes three appendices containing hard copies, (Appendix 1) Proc Contents (Appendix 2) and descriptive information (Appendix 3).

Sincerely,

Dennis J. Foley, Ph.D.
Assistant Director
Regulatory Liaison

DJF:ps

CC: Ms. Z. MacDonald

LEDERLE LABORATORIES

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

ORIG NEW CORRES

May 4, 1990

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

MONOCOR[R] (bisoprolol hemifumarate) Tablets
NDA 19-982

Dear Doctor Lipicky:

We hereby amend the referenced application to clarify the statement in Vol. 4, Page 231 of the NDA, which indicates the Manufacturer of the drug product.

Paragraph 3 states that the film coating process for the tablets was carried out at This was the case only for the two production-scale clinical lots for which Batch Records are presented in Section 3.B.V. However, we wish to inform you that the coating process will be carried out routinely only at the facilities.

Other than those two batches referenced above, numerous other stability and validation samples were manufactured and coated at and are presented in the NDA.

Attached herewith is a corrected Page 231 to clarify this point.

Sincerely yours,

Gordon R. Personeus, Director
Technical Services
Regulatory Affairs

GRP:drm
Enc.
D000028

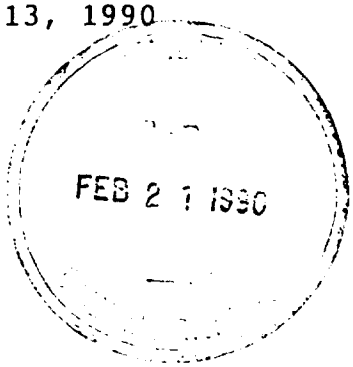
ORIGINAL

LEDERLE LABORATORIES NDA ORIG AMENDMENT

(BM)

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

February 13, 1990



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, MD 20857

NDA 19-982
MONOCOR^{R}
Bisoprolol Fumerate

Dear Doctor Lipicky:

Attached are the scatter plots from Study 57-3 as requested by Dr. Ganley on December 5, 1989. The plots, showing values at baseline vs. Week 12 (or last double-blind visit), are grouped by parameter (cholesterol, triglycerides, platelets), and for each test by treatment group (bisoprolol [all dose levels], bisoprolol + HCTZ [all dose levels], and placebo). It should be noted that for triglycerides, the plots are presented two ways: one set shows all patients, the other excludes patients with values greater than 700 mg/dL (so the scale can be spread out).

Based on this presentation of the data, there does not appear to be any substantial shift in serum cholesterol or platelets, while triglycerides increased with bisoprolol and bisoprolol + HCTZ. This is consistent with what was described in the 57-3 Study Report, except that in the report, a mean decrease from baseline with bisoprolol was reported for platelets.

Sincerely,

Dennis J. Foley, Ph.D.
Director
Regulatory Liaison

DJF:ps
#900146

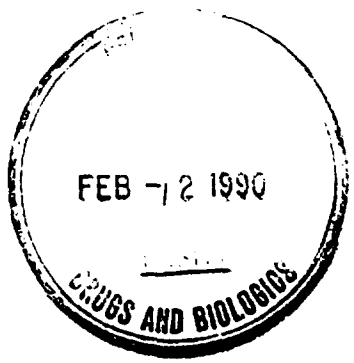
CC: Dr. C. Ganley (cover memo)
Ms. Z. MacDonald (cover memo)

ORIGINAL

LEDERLE LABORATORIES

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

ORIG NEW CORRES



February 6, 1990

Raymond J. Lipicky, M.D.
Acting Director
Div. of Cardio-Renal Drug Products
National Center for Drugs & Biologics
HFD-110 - Document Control Room 16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MONOCOR® (bisoprolol hemifumarate)
NDA 19-982

Dear Dr. Lipicky:

Attached are copies of letters addressed to Messrs. Drew and Hopes correcting a batch number within the validation sample package recently submitted to them. That package was actually dated January 30, 1990, not January 19, 1990, as the letters referenced.

Sincerely yours,

David N. Ridge
Assis. Director, Technical Services
Regulatory Affairs

ORIGINAL

Dr Lipicky # 2

LEDERLE LABORATORIES

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

ORIG NEW CORRES

January 30, 1990

2/8/90

Raymond J. Lipicky, M.D.
Acting Director
Div. of Cardio-Renal Drug Products
National Center for Drugs & Biologics
HFD 110 - Document Control Room 16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MONOCOR® (bisoprolol hemifumarate)
NDA 19-982

Dear Doctor Lipicky:

Attached herewith find copies of letters of transmittal and the attachments for the validation samples sent to Mr. Hopes and Mr. Drew at the FDA Laboratories.

Sincerely,

David N. Ridge /DNR

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

DNR:drm
34.15

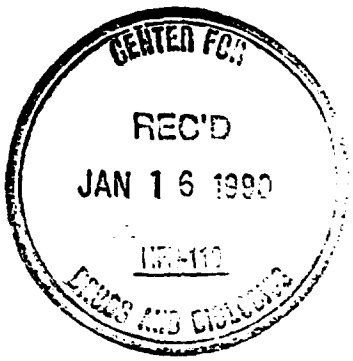
LEDERLE LABORATORIES

Lederle

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

January 11, 1990

Raymond J. Lipicky, Acting Director
Division of Cardio-Renal Drug Products
HFD 110-16B-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
MONOCOR® Bisprolol

Dear Dr. Lipicky:

We refer to Dr. Ganley's telephone contact of January 3, 1990 requesting copies of selective case record forms from the 57-3 multi-center clinical study.

With respect to the request for case records of patients who discontinued treatment due to clinical adverse experiences or laboratory abnormalities (as identified in Tables 27A and 27B of Volume 96 in the original NDA submission), these cases were included in the original filing. Specific cross references are provided in the attached Tables which were previously faxed to Dr. Ganley.

Also included in this submission are case records for patients from the 57-3 study listed as "lost to follow up" in our submission of November 22, 1989 as well as for patients 9-794, 8-811, 15-398 and 6-674 as requested.

Sincerely yours,

D.J. Foley, Ph.D.
Director Regulatory Liaison

DJF/lrm
Attachments
#900029

LEDERLE LABORATORIES

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

NDA ORIG AMENDMENT

February 7, 1990

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 Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 19-982
MONOCOR® Bisoprolol

Dear Dr. Lipicky:

Attached is the safety update for the subject NDA. Information is included on 6,600 patients not included with the original NDA filing of July 28, 1989 as well as full reports (involving 800 patients) of long term studies 57-1 (U.S.) and 57-500 which were conducted in Europe.

Sincerely yours,

for Dennis J. Foley, Ph.D.
Director
Regulatory Liaison

DJF:ko
Att.
900109

LEDERLE LABORATORIES

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

October 12, 1990

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

NDA 19-982
MONOCOR® Bisoprolol fumarate
Response to FDA Request

Dear Dr. Lipicky:

In response to a telephone request made by Dr. Charles Ganley to Dr. Gary Dukart on 10/5/90, and as discussed with Dr. Ganley, we are providing the following clarification and attachments:

1. The M4 metabolite was looked for in both plasma and urine of healthy volunteers. This metabolite was not detected in man. The NDA references for these studies are Volume 38, Report 3, and Volume 39, Report 26.

2. Graphs of concentration vs. time for bisoprolol and the M1 metabolite from the data on page 377 of Volume 39 of the NDA are attached. As agreed, the bisoprolol and M1 curves are plotted together against concentration using both a linear scale and a log scale.

3. A listing of patients withdrawn prematurely because of liver abnormalities.

Thank you for your attention.

Sincerely yours,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MHG:DK-552(KOC)
901097
cc: Dr. C. Ganley

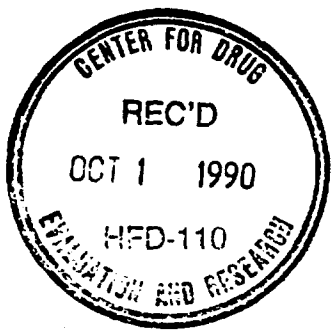
LEDERLE LABORATORIES

Lederle

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

September 28, 1990

NDA ORIG AMENDMENT
(BM)



Raymond J. Lipicky, M.D., Acting 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

NDA 19-982
MONOCOR® Bisoprolol fumarate
Follow-up Response to FDA Request

Dear Dr. Lipicky:

In a September 10, 1990 response to a request by Dr. C. Ganley, Medical Officer, we provided CRFs for six patients from Study 57-500 who stopped treatment prematurely because of "lost to follow-up" or "patient request". Parts of the CRF for Patient 2023 were very light, as was our copy from E. Merck.

Enclosed is a more legible copy of this CRF (3 modules) which we recently received from E. Merck.

Thank you for your attention.

Sincerely yours,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MHG/pas
#901044
cc: Dr. C. Ganley
Ms. Z. McDonald

ORIGINAL

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AREA CODE 914 732-5000

NDA ORIG AMD
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September 24, 1990

Raymond J. Lipicky, M.D., Acting 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

NDA 19-982
MONOCOR® Bisoprolol fumarate
NDA Safety Update-Follow-Up Information

Dear Dr. Lipicky:

As discussed with Dr. Charles Ganley on September 21, 1990, attached is the updated information regarding two patients who were incorrectly coded as deaths and five patient deaths which were reported without details in the NDA 19-982 Monocor Bisoprolol Safety Update Report, Vol. 1 p. 137

We apologize for the delay in forwarding this information to you. If we can be of further assistance, please let us know.

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MG/pas/36
#901034

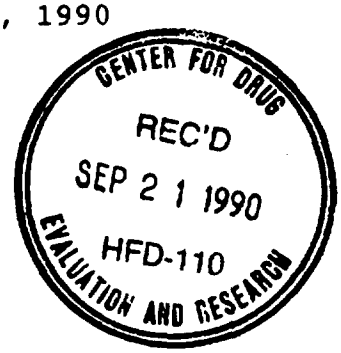
cc: Dr. C. Ganley
Ms. Z. McDonald

LEDERLE LABORATORIES NDA ORIG AMENDMENT

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

BP

September 19, 1990



Raymond J. Lipicky, M.D., Acting 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

NDA 19-982
MONOCOR® Bisoprolol fumarate
Response to FDA Request

Dear Dr. Lipicky:

As requested by Dr. E. Belair, Reviewing Pharmacologist, we are hereby providing supplemental histopathology tables for the 6 month-rat (NDA Reports 95 and 96, Volume 13) and dog (NDA Reports 101 and 102, Volumes 16 and 17, respectively) studies with bisoprolol, and the 6 month-rat (NDA Report 109, Volumes 21 and 22) and dog (NDA Report 110, Volume 23) studies with bisoprolol in combination with hydrochlorothiazide. Similar tables were filed to the NDA on August 28, 1990 for the one year rat and dog studies.

References and explanatory comments are also provided for the summary tables provided in the NDA for the mouse and rat carcinogenicity studies.

With this submission we have now provided all information requested by Dr. Belair at the FDA meeting on July 18. Based on a phone conversation with Dr. Belair on September 11, there was mutual agreement that summary tables would not be necessary for one month and range-finding studies. If we can be of further assistance, please let me know.

Sincerely yours,

Dennis J. Foley, Ph.D.
Director Regulatory Liaison

DJF/pas/22

cc: Dr. E. Belair
Ms. Z. McDonald

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NDA ORIG AMENDMENT BP

LEDERLE LABORATORIES

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PEARL RIVER, NEW YORK 10965
AREA CODE 914 732-5000

August 28, 1990

CENTER FOR DRUG
REC'D
AUG 3 0 1990
HFD-110
EVALUATION AND RESEARCH

Raymond J. Lipicky, M.D., Acting 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

NDA 19-982
MONOCOR® Bisoprolol fumarate
RESPONSE TO FDA REQUEST

Dear Dr.Lipicky :

We refer to discussions with Dr. E. Belair, Reviewing Pharmacologist, at an FDA meeting on July 18 and a subsequent phone conversation with Lederle staff on July 25.

Based on these discussions we hereby provide:

1) Supplemental histopathology summary tables for the chronic 12-month rat study (NDA Report 97, Volume 14) and the chronic 12-month dog study (NDA Report 104, Volume 18). Similar tables for other animal studies will be submitted in the near future.

2) Clarification of the footnote on the body-weight tables and use of asterisk symbols in the chronic 12-month rat study cited above.

Sincerely,

Dennis J. Foley, Ph.D.
Director
Regulatory Liaison

DF/lr
#900944
Enclosures
cc: Dr. E. Belair
Ms. Z. McDonald

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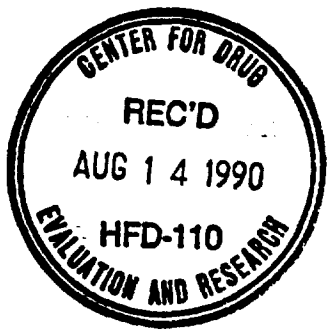
PEARL RIVER, NEW YORK 10965
AREA CODE 914 732-5000

NDA ORIG AMENDMENT

August 9, 1990



Raymond J. Lipicky, M.D., Acting 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

NDA 19-982
MONOCOR® Bisoprolol fumarate
RESPONSE TO FDA REQUEST

Dear Dr. Lipicky:

We refer to requests made by Dr. C. Ganley, Medical Officer, on June 28 relative to clarification of information provided in reports of clinical studies (#33 512-2036, -1054, -1008 and -2030/2) conducted by E. Merck.

Attached is a response to Dr. Ganley's questions from the E. Merck Clinical Department.

Sincerely,

Dennis J. Foley, Ph.D.
Director
Regulatory Liaison

DJF:ko
Attach.
#900875

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AREA CODE 914 732-5000

NDA ORIG AMENDMENT
(BM)

June 18, 1990

Raymond J. Lipicky, M.D., Acting 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

NDA #19-982
Bisoprolol

Dear Dr. Lipicky:

Information is hereby provided for patients #26 and #31 who dropped out of E. Merck study #1005 (NDA reference - Volume 85, Page 208 submitted July 28, 1989). This information was requested by Dr. C. Ganley on May 30, 1990.

It is not known why Patient #26 no longer returned. The last supine BP values were 140/90 and 150/90 mm HG (duplicate measurements), HR was 68 bpm. No adverse experiences were noted.

Patient #31 dropped out to go on "rehabilitation"/vacation. It was explained to me that in Germany, if people have certain chronic conditions, insurance pays for people to go to a spa. This patient, who was 46 years old when the study began, had a history of enucleation of one eye, CABG, gout, and hyperlipidemia. E. Merck does not know exactly what the patient went on rehabilitation for, but it was definitely not related to any adverse experiences (none were reported) or his level of blood pressure control (although his last supine BP values were 150/100 and 145/100 mm Hg, HR of 56 bpm). E. Merck indicated that we should think of the reason for early termination as being that the patient went on vacation.

Sincerely,

Dennis J. Foley, Ph.D.

Dennis J. Foley, Ph.D.
Director Regulatory Liaison

DJF:ko
#900698

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PEARL RIVER, NEW YORK 10965
AREA CODE 914 732-5000

NDA ORIG AMENDMENT
BP

June 18, 1990

Raymond J. Lipicky, M.D., Acting 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

NDA #19-982
Bisoprolol

Dear Dr. Lipicky:

We refer to a phone conversation on April 16 with Dr. E. Belair, Reviewing Pharmacologist, during which he requested:

1) Clarification on body weight calculations (per footnote on pages 1-10 of Volume 1.14 of NDA submitted July 28, 1989).

2) Tables of drug consumed in feeding studies.

This information is now being supplied in the attached materials.

If there are any questions regarding this submission, do not hesitate to contact our office.

Sincerely,

for Dennis J. Foley, Ph.D.
Director Regulatory Liaison

DJF:ko
Attach.
#900696

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Lederle

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

ORIG NEW CORRES

October 15, 1990

Charles Ganley, M.D., Medical Officer
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
HFD-110 - Rm 16B/45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-982
MONOCOR®
Response to FDA Request

Dear Doctor Ganley:

Enclosed are three copies of the E. Merck Study No.33512-4054 "Bisoprolol - Interaction with Warfarin," which you requested at our October 3, 1990 meeting to discuss the Bisoprolol SBA.

Thank you for your attention.

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MHG:DK - 87(PAS)
#901106
Enc.

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

HFD

NDA ORIG AMENDMENT

October 30, 1990

Raymond J. Lipicky, M.D., 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

HFD-110

NDA 19-982
MONOCOR® Bisoprolol fumarate
Response to FDA Request

Dear Dr. Lipicky:

The enclosed information is being provided in response to a request made by Dr. Charles Ganley to Dr. Libby Miller in a telephone conversation on October 19, 1990.

1) Dr. Ganley asked about 12 patients in Study 57-1 who had trough/peak assessments but were not included in the effectiveness analysis. Attachment 1 identifies these patients, along with the reason the patients were excluded (reason for ineligibility/inevaluability).

2) Dr. Ganley asked if any patients in Study 57-3 had SBP values $\leq$ 100 mm Hg. Attachment 2 identifies all patients and visits at which SBP was $\leq$ 100 mm Hg, in any position (sitting, supine, or standing). Attachment 3 provides the complete set of SBP values at each visit for each patient identified in Attachment 2.

3) Dr. Ganley asked if any patients in Study 57-3 had a change from baseline SBP $\geq$ 30 mm Hg at any time on study. Attachment 4 identifies all patients and visits with change from baseline SBP $\geq$ 30 mm Hg at any time on study. Attachment 5 provides the complete set of SBP values at each visit for each patient identified in Attachment 4.

   Please note for Attachments 2-5, "Change" refers to change from baseline. Baseline is based on the average of the values at the last three visits during the run-in period. In these attachments, this baseline value can be obtained by adding the "change" value to the visit value provided.

ORIGINAL

In Attachments 3 and 5, multiple baseline values are provided under "Visit". These correspond to the different run-in visits.

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MHG/pas/139
#901134

LEDERLE LABORATORIES

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

NEW CORRESPONDENCE

October 30, 1990

Raymond J. Lipicky, M.D., 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

NDA 19-982
MONOCOR® Bisoprolol fumarate
Response to FDA Request

Dear Dr. Lipicky:

As was discussed in a telephone conversation with Dr. Charles Ganley on October 16, 1990, this communication provides capsules on the four patients who died as a result of traffic accidents and the single patient who was involved in a non-fatal traffic accident. With regard to the four patients who died: no details were provided about each patient's condition at the time of the accident or whether each was a driver or a passenger in the vehicle.

Patient ID #8152, a 42 year-old male smoker with hypertension, began receiving bisoprolol 10 mg daily in November 5, 1988. On November 16, after almost 2 weeks on therapy, he was killed in a road traffic accident. The investigator considered his death to be remotely related to bisoprolol.
(Reported in NDA 19-982 vol. 145, p. 186.)

Patient ID #9401, a 34 year-old man with hypertension, began receiving bisoprolol 10 mg daily on June 1, 1989 and continued at least through June 26 (his last clinic visit). Some time in July, he died as a result of a traffic accident. The investigator considered this remotely related to bisoprolol.
(Repoted in NDA 19-982 Safety Update vol. 1, pp. 104 and 138.)

Patient ID #9421, a 49 year-old male smoker with hypertension and angina pectoris, began receiving bisoprolol 10 mg daily on December 16, 1988. He was asked to reduce his smoking and alcohol intake. On March 4, 1989, he was reportedly seen because of high alcohol consumption. On April 4, he was involved in a traffic accident and died of his injuries. The investigator considered this remotely related to bisoprolol. No information was provided on whether alcohol was a factor in the accident.
(Reported in NDA 19-982 Safety Update vol. 1, pp. 104 and 138.)

ORIGINAL

Patient ID #9406, a 40 year-old woman with hypertension began bisoprolol treatment February 2, 1988 and discontinued treatment after Visit 3 (April 6, 1988). Reason for discontinuation was not reported. The patient died in a car accident some time during 1988. Despite a request for additional information, the exact date of death is not available. The investigator considered this patient's death remotely related to bisoprolol.
(Reported in NDA 19-982 Safety Update vol. 1, p 138 and September 24, 1990 NDA Safety Update Follow-up Information Communication.)

Patient ID #9887, a 36 year-old man with hypertension, received bisoprolol 5 mg (one-half of a 10 mg tablet) daily beginning September 18, 1989. On September 19, he complained of vertigo, fatigue, dyspnea, diarrhea, paresthesia, and pruritus. On September 23, the patient, who is a taxi driver, "blacked out" and was involved in a traffic accident, resulting in hospitalization. Bisoprolol was stopped and he recovered. No assessment was provided for the syncopal episode, but the investigator considered the other adverse experiences definitely related to bisoprolol.
(Reported in IND (Hypertension) Annual Report (to be filed).

Thank you for your attention.

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph. D.
Manager
Regulatory Liaison

MHG/pas/128
#901132

LEDERLE LABORATORIES

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

NDA ORIG AMENDMENT
(BM)

September 10, 1990

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 Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 19-982
MONOCOR® Bisoprolol fumarate
Response to FDA Request

Dear Doctor Lipicky:

The following information is provided in response to phone requests by Dr. C. Ganley, Medical Officer:

1) Request of July 20, 1990 to redo graphs from E. Merck study #1005 (page 30, Volume 130) and to generate tables for treatment duration of all patients in clinical studies.

   Graphs showing 24-hour blood pressure profiles from study #1005 are provided for evaluable and non-evaluable patients in Attachments 1A and 1B, respectively. The supporting raw data are provided in Attachment 1C.

   Attachment 2 is a list of clinical studies for which information from E. Merck was requested. This list includes studies for which we had received study reports, as well as trials listed in the 2-year safety report to the BGA under studies completed but not yet reported to the BGA. In responding, E. Merck provided distribution information for all of these trials except Study 2041; although some adverse experience information from this trial was included in their 2-year safety report, they did not yet have data on duration of exposure. They also provided this information for one trial not included in the list, Study 4037. This was included in the NDA as a publication (Reference 52: Joubert

ORIGINAL

PH, Verter CP, Wellstein A. Ethnic differences in response to beta-blockade: Fact or artifact? A study with bisoprolol and propranolol. Eur J Clin Pharmacol 1988; 34:363-368). There were only 16 subjects in that study; they received intravenous doses of bisoprolol (or propranolol or saline).

Attachment 3 is a listing of Cyanamid-sponsored clinical trials for which distribution information is being provided. [Please note that this information is not available for either the Cyanamid or E. Merck Phase IV/Post-Marketing Studies.]

The distribution information from these clinical trials is as follows:

	No. Patients		
	E. Merck	American Cyanamid	Total
Single Dose*			
IV	110	0	110
PO	361	118	479
2-7 Days	417	91	508
8-30 Days	547	119	666
31-90 Days	866	475	1341
91-180 Days	207	133	340
>180 Days	1053	519	1572
	3561	1455	5016

* Includes single-dose crossover trials.

2) Request of July 26, 1990 for additional statistical analyses for open-label study 57-1.

Tables summarizing distribution by maximum dose, efficacy, and termination reasons by sex, race, age and baseline SiDBP are provided in Attachment 4.

Similar information on efficacy is also provided for study 57-500 in Attachment 5. The clinical report for this study was included in the NDA Safety Update submitted on February 7, 1990. A corrected summary table (Table 16) from that report is provided in Attachment 6 showing response rates by time and treatment (Volume 10 of Safety Update). The table in the original report incorrectly based response rates only on SuDBP $\leq$ 90 mm Hg, not SuDBP $\leq$ 90 mm Hg or decrease from baseline $\geq$ 10 mm Hg (despite the wording in the footnote). Corrected text tables from Volume 9 of the Safety Update, along with the original pages indicating the changes, are

also included in Attachment 6.

3) Request of August 14, 1990 for CRFs on patients from study 57-500 who stopped treatment prematurely because of "lost to follow-up" or "patient request".

CRFs for the following six patients involved are provided in Attachment 7:

- Patient 1060: "Patient request." The CRF states that the patient did not want to continue in the trial or with the treatment. There was no indication of adverse experiences as the reason for withdrawal.

- Patient 2023: "Lost to follow-up." This patient moved to another part of Sweden. Last SuBP was 142/88 mm Hg. The only AE was mild vivid dreams.

- Patient 3006: "Patient request." This patient was not actually listed in the CRF as having stopped prematurely; the patient completed 6 months of open-label treatment (end of Study 1051) but did not continue with the additional year of open-label treatment (Study 1065). This patient has no history of CAD, but developed dyspnea and angina in March, 1986, and was felt to have had a probable AMI (not drug-related). The patient then stopped treatment at the end of April. In response to a request for clarification, information from the E. Merck monitor is simply that the patient did not want to continue in the study for another year.

- Patient 3019: "Patient request." This patient was not actually listed in the CRF as having stopped prematurely; the patient completed 6 months of open-label treatment but did not continue with the additional year of open-label treatment. Last SuBP was 140/97 mm Hg on bisoprolol + HCTZ, a response rated moderate by the investigator. In response to a request for clarification, the E. Merck monitor indicated that the investigator decided that this was not the optimal treatment for this patient, so the patient did not continue for the additional year.

- Patient 4023: "Lost to follow-up." This patient failed to return after June 26, 1986 (AIL Week 12 as recorded in CRF, O-L Week 26 based on our conventions relating to actual date). SuBP at the time was 158/104 mm Hg, and HCTZ was to be added.

Patient 4025: "Lost to follow-up." The patient moved to another part of the UK. His last SuBP assessment after 9 months of O-L treatment was 136/94 mm Hg. No AE's were reported.

In response to Dr. Ganley's request for clarification concerning the 10 patients in 57-500 listed as not completing because of "Other" reasons (administrative error), these patients completed the double-blind phase and 6 months of open-label treatment under Study 1051, but the one-year open-label continuation protocol (Study 1065) had not yet been established. Therefore, these patients did not actually discontinue treatment prematurely.

4) Request of August 23, 1990 to resolve discrepancy in the number of evaluable patients stated in E. Merck report #1032 (Volume 137 of NDA).

The correct numbers of evaluable patients are as follows:

132 patients up to the end of the 8 week titration phase.
126 patients between end of titration phase and 1 year.
106 patients at the end of 1 year.

The Cyanamid synopsis is, therefore, incorrect.

5) Request of August 24, 1990 to clarify the distinction between Phase IV and post-marketing studies in Volume 140 of NDA.

Information on "Other Studies" includes separate information on international Cyanamid and E. Merck Phase IV trials. E. Merck also makes a distinction between Phase IV trials and post-marketing ("observational" studies), the latter being large seeding-type studies which Cyanamid includes under the broad Phase IV heading.

Spontaneous reports, which are adverse reports from patients receiving marketed products, are provided separately for Cyanamid and E. Merck. Since each company provides information on adverse reports to the other company, there can be some duplication of reporting (such as the one patient who died of LV failure).

The "Other Studies" section in the NDA (Volume 140, page 170) included the E. Merck 2-year safety report to the BGA. This report included data from some clinical trials (Phase I-III) previously unreported to the BGA, as well as serious AE's reported to the BGA. Whenever possible, if we had already included some of these studies elsewhere in the NDA, we tried to note that.

Pages 30 and 31 of Volume 140 contained information on additional serious AE's from E. Merck clinical trials which we became aware of after the cutoff for the NDA.

6) Request of August 31, 1990 to clarify if all patients from centers in Study 57-1 for whom there were peak/trough assessment actually had such assessments.

Trough/peak assessments were not part of the original protocol; they were added as an amendment. In order to determine if all patients had these assessments after the implementation of this amendment, our Department of Statistical Analysis checked the first date of peak measurements at each site, and then looked at each site for patients with a Week 3 Visit (the visit for trough/peak measurements) but not a peak assessment after that date. There were nine such patients from four sites:

Site	Patient No.	Date of Wk. 3 Visit	Date of First Peak Measurement at Site
2	246	11/24/87	11/13/87
7	331	10/05/87	09/01/87
	504	11/19/87	
	506	11/27/87	
	508	01/26/88	
8	390	06/23/87	06/12/87
	391	07/21/87	
13	459	09/16/87	09/08/87
	465	09/23/87	

It should be noted that 4/9 patients had their Week 3 Visits within three weeks of when their sites began obtaining trough/peak measurements.

The number of patients that did have trough/peak assessments at these four sites were as follows: two at Site 2, eight at Site 7, ten at Site 8, and 17 at Site 13.

To the best of our knowledge we have now responded to all of Dr. Ganley's outstanding questions, please let me know if we can be of further assistance.

Sincerely,

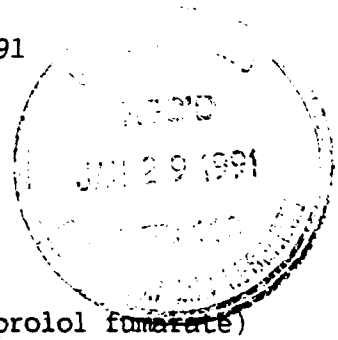
Dennis J. Foley, Ph. D.
Director Regulatory Liaison

DF/pas
cc: Dr. C. Ganley
Ms. Z. McDonald

LEDERLE LABORATORIES

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

January 24, 1991



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

NDA 19-982
MONOCOR® (bisoprolol fumarate)

Dear Dr. Lipicky:

We reference your letter of December 12, 1990 to the subject NDA (Attachment 1) and hereby provide the requested information.

1. The coating colors and codes remain as they were in the original submission. The listing of Opadry Pink YS/1/7003 on page 002 of the November 1, 1990 amendment was indeed a typographical error and should have read Opadry Pink YS/1/1252. A corrected page 002 is enclosed (Attachment 2).

2. We have revised our drug product monograph to incorporate the recommendations that freshly prepared standard and test solutions be prepared and used within six hours for dissolution, assay and content uniformity. This new monograph (G1970G) is provided in Attachment 3.

3. The electrode currently utilized in the potentiometric titration for fumaric acid content in bulk drug is a combined glass electrode f.e. type. It is supplied by and is available in the U.S., if required.

We wish to point out an additional change that has been made to product Monograph G1970G (Attachment 3, referenced above). This change is in the 10 mg tablet description. The amendment of November 1, 1990 had inadvertently contained an outdated monograph (G1970E) which had described the 10 mg tablet as scored on both sides. A change to an unscored 10 mg tablet had been made prior to the manufacture of full-scale validation batches and this change has been supported in the November 1, submission with 12- tablet comparative dissolution profiles for those batches. Therefore, the new Monograph 1970G reflecting the correct description for that tablet is provided. Revised Certificates of Analysis of the 5 and 10 mg validation batches which now reference the corrected monograph, are also being provided in Attachment 4. The description of the 5 mg tablet remains unchanged. The draft package insert has been revised to incorporate the one description change and is available upon request.

ORIGINAL

We trust that this information will now satisfy all outstanding chemistry, manufacturing and control issues for this NDA.

Sincerely,

David N. Ridge

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

DNR:lw

Attachments

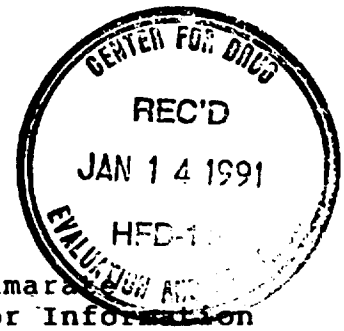
NDA ORIG AMENDMENT
(B2)

LEDERLE LABORATORIES

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

January 7, 1991 (1) 1/14/91

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 Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 19-982
MONOCOR® Bisoprolol/fumarate
Response to Request for Information

Dear Doctor Lipicky:

The following enclosures are being sent in response to a request by Dr. Charles Ganley:

1. Revised listing of all deaths among patients receiving bisoprolol, along with cause of death and duration of bisoprolol therapy. Attached is a second copy which indicates the minor corrections made to the draft listing sent on November 28, 1990.

2. For Studies 57-1 D-B and O-L, 57-3, and 57-500: a table of patients with normal baseline SGOT and SGPT and subsequent concurrent abnormalities in SGOT and SGPT.

3. For Studies 57-1 D-B and O-L, 57-3, and 57-500: a table of patients with normal baseline liver tests and subsequent abnormalities in more than one liver test at any time on study.

If I can be of further assistance, please call me at (914) 735-2410.

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph.D. Manager
Regulatory Liaison

MHG:ko-671
Enc.
#910007

cc: Dr. C. Ganley
Dr. K. Mahjoob
Ms. Z. McDonald

ORIGINAL

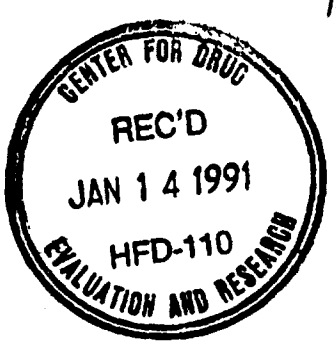
LEDERLE LABORATORIES

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

(B2)

January 7, 1991

10/4/91



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 Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 19-982
MONOCOR® Bisoprolol/fumarate
Response to Request for Information

Dear Doctor Lipicky:

Enclosed is the summary of the response surface analysis results on the 57-3 bisoprolol/HCTZ combination therapy which was requested by Dr. Mahjoob through Dr. Ganley on January 3, 1991.

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

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MHG:ko-670
Enc.
#910006

cc: Dr. C. Ganley
Dr. K. Mahjoob
Ms. Z. McDonald

ORIGINAL

LEDERLE LABORATORIES

Lederle

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

December 3, 1990

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

NDA 19-982
MONOCOR® Bisoprolol fumarate
Request for Information

Dear Dr. Lipicky:

Enclosed are the following items which were requested by Dr. Charles Ganley.

1. Draft lising of patients on bisoprolol who died, along with cause of death and duration of bisoprolol therapy. In cases where death occurred after treatment had been stopped, timing since end of therapy is also indicated. Please note that this includes information currently being prepared for the new Safety Update, which involved treatment with bisoprolol or bisoprolol + HCTZ of approximately 30,000 patients not previously included in the NDA or February Safety Update. We will be re-checking the information and will let you know if any discrepancies are found.

2. Copies of references on the use of glucagon in cases of beta-blocker overdose.

3. Copy of the table in Volume 110, p. 99 of the NDA. Some of the same information can also be found in Volume 110, pp 260-262.

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

Sincerely,

Maureen Garvey

Maureen H.Garvey, Ph.D.
Manager
Regulatory Liaison

MHG:DK(pas-195)
Enc.
#901204
cc: Dr. C. Ganley

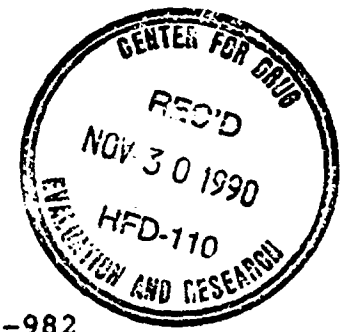
LEDERLE LABORATORIES

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

NDA ORIG AMENDMENT
(BM)

November 26, 1990

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 Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 19-982
MONOCOR® Bisoprolol fumarate
Response to FDA Request

Dear Doctor Lipicky:

Enclosed are hard copies of the capsule summaries which were faxed to Dr. Charles Ganley on November 20, 1990. These capsules are for patients with increased liver tests and one patient with increased bleeding time.

The other part of his request, for patients who died, was to provide a table of time from initiation of therapy until death. This will be sent as a separate listing.

If there are any further questions, please call me at (914) 732-2410.

Sincerely,

Maureen H. Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MHG:DK(KOC-601)
Enc.
#901191

ORIGINAL

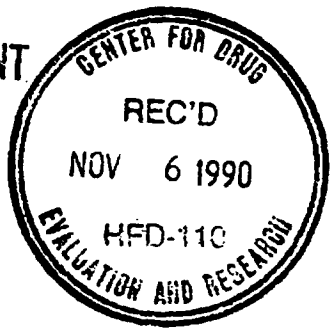
LEDERLE LABORATORIES

Lederle

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

November 1, 1990

NDA ORIG AMENDMENT
(BC)



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
MONOCOR® (bisoprolol fumarate)

Dear Dr. Lipicky:

We are hereby submitting an amendment to the subject NDA to provide for changes in the Chemistry, Manufacturing and Control Section. The modifications presented herein are only minor changes in the manufacturing process for, and resulting from, the first full-scale validation runs. Revisions also reflect minor changes in operating instructions consistent with standard practice and documentation format for the production operation at
Batches prepared during the full-scale validation runs are documented herein. Dissolution profiles were completed on these batches as well as on the same reference batches as had been submitted for FDA method validation in January 1990. All profiles indicate that dissolution properties have remained unchanged.

We also propose to conduct certain secondary packaging activities at specified facilities in the United States, subsequent to packaging in primary containers in the as provided in the original NDA.

We trust that sufficient documentation has been provided to complete the Chemistry/Pharmacy review of this application. Please contact us as soon as possible if any further clarifications are needed.

Sincerely,

David N. Ridge

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

ORIGINAL

1.45

LEDERLE LABORATORIES

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

NDA 54

February 13, 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
SAFETY UPDATE

Dear Doctor Lipicky:

As requested by you at our meeting on October 3, 1990, we hereby submit the Safety Update for Bisoprolol.

In addition, as indicated to Ms. Zelda McDonald in a telephone call on February 12, 1991, we are submitting a Summary of the repeat mouse carcinogenicity study. The final report for this study will be filed to the bisoprolol/hypertension IND in the near future.

Sincerely,

Maureen Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

914-732-2410

MHG:koc-772
Enc.
#910246

ORIGINAL

LEDERLE LABORATORIES

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

NDA ORIG AMENDMENT

March 27, 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
RESPONSE TO REQUEST FOR INFORMATION

Dear Doctor Lipicky:

As requested by Dr. Ernest Belair, we hereby submit the mouse carcinogenicity study which was filed to IND on February 27, 1991.

We wish to affirm that the study, referred to in the 1988, 1989 and 1990 IND Annual Reports, was a repeat study; there were no new findings, and, as with the other carcinogenicity studies, the results were negative. Our intention in submitting the Study Summary with the NDA Safety Update was to apprise the reviewers of the completion and results of the study.

In consideration of the above, we respectfully request that the NDA review time not be formally extended by this amendment. We would welcome the opportunity to present the study data and meet with Dr. Belair if this would be of assistance.

Thank you for your attention.

Sincerely,

Maureen Garvey

Maureen H. Garvey, Ph.D.
Manager
Regulatory Liaison

MHG:ko-894
Enc.
#910425

ORIGINAL

LEDERLE LABORATORIES

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

May 14, 1991

Mr. Dave Roeder
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
NDA 20-186
Bisoprolol/Hydrochlorothiazide
INFORMATION FOR
ADVISORY COMMITTEE

Dear Mr. Roeder:

We will present data in support of bisoprolol as monotherapy and bisoprolol/hydrochlorothiazide as combination therapy for hypertension at the June 6, 1991 Cardio-Renal Advisory Committee meeting. Enclosed, for your review, are the following materials related to our presentation:

Volume 1
- Overview
- Draft SBA for Bisoprolol
- Proposed Monotherapy and Combination Therapy Package Inserts
- Summary of Ambulatory Blood Pressure Monitoring Results

Volume 2
- Integrated Summary of Effectiveness, submitted in Bisoprolol/Hydrochlorothiazide NDA
- Integrated Summary of Safety, submitted in Bisoprolol/ Hydrochlorothiazide NDA

Volume 3
- Clinical Report for Study 57-3, adequate and well-controlled trial (multifactorial study) submitted in support of Bisoprolol (NDA 19-982) and Bisoprolol/ Hydrochlorothiazide (NDA to be submitted, May, 1991)

ORIGINAL

Lederle

Mr. Dave Roeder May 14, 1991

Volume 4
- Statistical Appendices for Study 57-3 Clinical Report

Volume 5
- Clinical Report for Study 57-29, adequate and well-controlled trial (confirmatory trial) submitted in support of Bisoprolol/Hydrochlorothiazide
- Statistical Appendices for Study 57-29 Clinical Report

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

Sincerely,

for Maureen Garvey

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

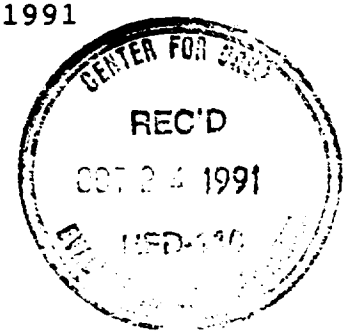
MHG:ko-1074
Enc.

LEDERLE LABORATORIES

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

NEW CORRESPONDENCE

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, as requested by Dr. Charles Ganley, are examples of bisoprolol labeling currently in use outside the United States:

-United Kingdom: Monocor* Data Sheet from the ABPI
-France: Soprol* Package Insert (with translation)
-Denmark: Monocor* Package Insert (with translation)
-Belgium: Isoten* Package Insert (with translation)

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

Sincerely,

Maureen Garvey

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

MHG:dlt-369
#911159
Enclosures

cc: Dr. Charles Ganley
Ms. Zelda McDonald