

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**19982**

**ADMINISTRATIVE DOCUMENTS**

CSO Review of Final Printed Labeling  
NDA 19-982

OCT 28 1992

Date of Submission: September 11, 1992  
Date of Review: September 22, 1992  
Applicant Name: Lederle Laboratories  
Product Name: Zebeta (bisoprolol fumarate) Tablets, 5 & 10 mg

**Evaluation:**

This submission provides for final printed labeling in accordance with our approval letter, based on draft labeling, dated July 31, 1992. The final labeling is exactly like the draft labeling except that the type size is larger as requested in the approval letter, and the subheading "Pregnancy: Teratogenic Effects" under PRECAUTIONS has been removed. Dr. DeFelice agreed that it should be removed because no teratogenic effects are reported. The subheading "Pregnancy Category C" remains.

In a September 21, 1992 telephone conversation, Dr. Garvey informed me that this submission does not contain cartons because they will not be using them. The bottles will be "bundled" together in shipping boxes that will be delivered directly to pharmacies.

**Recommendation:**

An acknowledge and retain letter should issue for this submission in accordance with 21 CFR 314.105 (b) [approval on the basis of draft labeling].

**/S/**  
Zelda McDonald, CSO

cc: Orig. NDA  
HFD-110  
HFD-111/McDonald  
HFD-111/Benton

**RECORD OF MEETING**

<u>NDA/IND NUMBER</u>	<u>INITIATED BY</u>	<u>DATE</u>
NDA 19-982	Lederle	November 14, 1991
<u>PRODUCT NAME</u>	<u>FIRM NAME</u>	<u>NAME AND TITLE OF PERSON WITH WHOM CONSERVATION WAS HELD</u>
Probeta (bisoprolol fumarate)	Lederle	David Ridge

Discussed the new amendment that he delivered to the Document room. It contained stability data to support a 36 month expiry date. The new time points are 18, 24, 36, and 48 months. The only problem I saw after a cursory review was the room temperature data were at 10 C and not . They should add a commitment to tests the first three production batches at 10 C to assure that the higher temperature will not affect the stability.

Their physician sample of 7 is in the same bottle as their marketed package of 100 tablets. Our guidelines do not require stability data in this case. However it does not have a child-resistant closure. He said that their interpretation of the CPSC regulations did not require one for containers of 10 or less. I said that this Division required one since patients usually get several samples and there is the chance of an accidental over dose if many bottles are consumed. I would check and see if we have a policy. (I checked with Dr. K. and he said that there is a policy statement from CPSC that does not require a child-resistant safety closure for physician samples. I called Dr. Ridge and inform him of this.

Lederle is completing the response to the deficiencies found by Biopharmaceutics. I said that I wanted a desk copy since it concerned the dissolution method.

SIGNATURE R. J. Wolters

/S/

DIVISION HFD-110

cc: NDA Orig  
HFD-110  
HFD-110/CSO  
HFD-110/Cunningham

UPDATE  
CSO overview of NDA 19-982  
Probeta (bisoprolol fumarate) Tablets  
October 30, 1991

JUN 11 1992

## Medical Review

This NDA was submitted on August 3, 1989 for mild to moderate hypertension, 5 to 20 mg once a day dosing. In his review dated January 8, 1991, Dr. Ganley recommended that bisoprolol be approved for mild to moderate hypertension, but he believed the initial starting dose should be 2.5 mg. He also made labeling suggestions and comments in appendix F of his review.

Lederle submitted a response to a request for any information concerning possible interactions between bisoprolol and anti-coagulant therapy on October 18, 1990. In his review of this submission dated October 22, 1990, Dr. Ganley concluded bisoprolol does not change the prothrombin time in patients on warfarin therapy.

## Cardiovascular and Renal Drugs Advisory Committee

Bisoprolol was presented before the Advisory Committee on June 6, 1991. The Committee unanimously recommended that bisoprolol be approved for hypertension.

## Statistical Review

In his review dated April 12, 1991, Dr. Mahjoub concluded there is strong evidence to support the efficacy and safety of bisoprolol. Study 57-3 demonstrated that bisoprolol is effective at doses of 2.5, 10 and 40 mg once-a-day for all patients. There is a significant dose-response relationship. The blood pressure response may have plateaued around 30 mg Q.D. There is no significant treatment-by-race interaction, although the data suggest that bisoprolol may be slightly less effective for black compared to non-black patients.

## Biopharmaceutical Review

In his review dated February 15, 1991, Dr. Mehta concluded that the biopharmaceutical section of this NDA is approvable. The dissolution specifications are not finalized, however, and additional dissolution results as outlined in his comment # 7 should be submitted within 30 days post approval of the NDA. Dr. Mehta recommended that Lederle's proposed specifications be considered Interim Specifications. Lederle has been provided with a copy of Dr. Mehta's review so they are aware of his dissolution recommendation.

## Pharmacology Reviews

### Dr. Belair

In his review dated October 29, 1991, Dr. Belair was of the opinion that Bisoprolol is a tumorigen. He recommended that all of the slides be re-read blind, and in the case of the second mouse study, the remaining tissues should be processed and read in the same manner. In addition a 90-day dose-ranging study, including a parallel toxicokinetic study, should be initiated as soon as possible using the same mouse strain and supplier as used in the second mouse study. If the sponsor cannot agree this course of action, or if statistically significant

tumor incidences persist after blinding, Dr. Belair recommended that this drug be treated as is appropriate for a drug with carcinogenic potential.

#### Dr. DeFelice

In his supervisory review dated August 28, 1991, Dr. DeFelice concluded that tumorigenicity had been adequately assessed and is not evident from the data provided, given the irreproducibility of the results across and within species and use of statistical analyses able to distinguish among very low absolute incidences.

#### **Chemistry Review**

There are no outstanding chemistry issues. The methods have been validated, see Review #4 of Ms. Cunningham's review.

The establishment inspections have been completed and found acceptable as follows:

Acceptable on February 2, 1991 - manufacturer, packager of drug product:

Acceptable on February 12, 1991- Labeling trade bottles, attachment of package insert, shrink-wrapping of "bundled" trade bottles, repacking of "bundles" in shipping containers:

American Cyanamid  
Lederle Lab. Division  
Middletown Road  
Pearl River, NY 19065

#### **CSO Summary**

1. In his memo to Dr. Temple dated October 18, 1991, Dr. Lipicky was of the opinion that neither carcinogenicity study found a signal that can be reasonably be suspected to raise a question about the tumorigenic potential of bisoprolol up to several thousand times the doses anticipated for use in man and concluded that the results not only have no bearing on approvability but should not appear in the labeling.

Bisoprolol is scheduled for discussion at the Carcinogenicity Assessment Committee meeting on November 19, 1991.

2. Lederle responded on July 30, 1991 to the questions in Dr. Ganley's safety update review. (Their correspondence is with Dr. Ganley's review.) The only request that is still outstanding is the information on the Japanese clinical trials conducted by Tanabe for E. Merck. I called Dr. Maureen Garvey today (10/30/91) and asked that they follow-up on trying to get that information. She said she would.

3. Dr. Lipicky included Dr. Ganley's and Dr. Mehta's labeling suggestions (where appropriate) in the marked-up labeling.

4. Mr. Gary Buehler thinks that the tradename, Probeta, is too much like that of the oral hypoglycemic, Diabeta (glyburide) and could be prescribed by mistake especially given the fact that both will be available in the same strengths, 2.5 and 5.0 mgs. Mr. Buehler brought this to Dr. Lipicky's attention, and Dr. Lipicky said he would have to think about it. (In their review dated April 9, 1991, the labeling committee stated, " A review did not reveal names which look or sound like the proposed name.")

5. On October 28, 1991, Dr. Wolters asked Ms. Linda Carter to submit the final update request to compliance.

Other than those listed above, to my knowledge, there are no other issues that might prevent action on this NDA.

*/S/*  
Zelda McDonald, CSO

cc: Orig. NDA  
HFD-110

DEPARTMENT OF HEALTH & HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Public Health Service

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Memorandum

DATE : OCT 18 1991

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approvable status of NDA 19-982, Bisoprolol fumarate (Probeta®),  
Lederle Laboratories

TO : Director, Office of Drug Evaluation I, HFD-100

This memorandum and attached materials constitute the Division's recommendation that bisoprolol is approvable. Following submission of final printed labeling, barring unforeseen circumstances, we anticipate forwarding an approval recommendation.

Other than a carcinogenicity study issue, there are no known unresolved issues. A fresh draft package insert is attached for your markup, as well as an approvable letter for your signature, should you agree with the Division's assessment of this NDA. The Division does not think the results of the carcinogenicity studies bar approval. The Carcinogenicity Assessment Committee will make a recommendation with respect to labeling. The most recent safety update is dated February 19, 1991, and we think no further safety updates are required.

**UNRESOLVED ISSUES**

The results of carcinogenicity testing are somewhat unresolved at the moment. A meeting of the Carcinogenicity Assessment Committee has been scheduled and should have met prior to completion of your review. I do not think the issues raised by these results are relevant to your considerations regarding approval, else I would not have forwarded this application as approvable. I am not sure the results even belong in labeling. The following summarizes my thoughts. Dr. DeFelice's comments (the supervisory pharmacologist) can be found in the review package.

### One Rat Study

The one rat study conducted and reported was a drug-fed-in-diet study. Two control groups (50/sex group) received an ordinary diet. Three other groups received 5, 25, or 125 mg/kg/day bisoprolol (50/sex group) for a grand total of 500 rats studied. If there is an issue here, out of the 500 rats studied, observations made in two males and four females raise the controversy.

*In toto*, nobody found anything, although our statistical group claims a finding for adrenal cortical carcinoma ( $p = 0.0449$  from the exact permutation trend test) in male rats only, and the sponsor found pancreatic islet cell adenoma ( $p = 0.03$  by the Peto trend test) in female rats, but our statistical group found a  $p$  of 0.060 (please note the third decimal of precision) from the EXACT permutation trend test. Otherwise, everything was clean, including mortality (so one can question the maximally tolerated dose).

For overall adrenal tumor incidence in male rats, the following numbers were reported in the submission, 7/100, 4/50, 4/50 and 4/50 (tumor-bearing animals/number in the group) for the control, 5, 25 and 125 mg/kg/day groups, respectively. The diskette submitted by the sponsor had 8/100, 4/50, 4/50, and 4/50. So there is a minor discrepancy (probably a typo or error in proofreading). Nothing in overall tumors of the adrenal gland, however, is even remotely to be suspected as a signal in this study. For females the equivalent numbers are 7/100, 2/50, 4/50, and 3/50. So in this regard (i.e., total tumors of the adrenal gland), there seems to be neither an advantage nor disadvantage to being a female rat.

In male rats the incidence of adrenal cortical carcinoma (the statistically significant finding) was 0/100, 0/50, 0/50, and 2/50 for the control, 5, 25, and 125 mg/kg/day groups, respectively. The two tumors noted were at terminal sacrifice and were a histological diagnosis without obvious tumor mass at necropsy (I think).

The incidence rates for islet cell adenoma were 1/100, 1/50, 3/50, and 3/50 for the control, 5, 25, and 125 mg/kg/day groups. Hardly something I would call looking like a dose-response, and the exact permutation trend test confirms my biological interpretation, so this is just a plain non-finding (in spite of the Peto trend test being "statistically significant").

Since there was no increased incidence of adrenal tumors detected in either species, and because the study was not powered to provide any kind of statistical significance to things that have an incidence of 2/500 (0.4%), that is two tumors out of 500 animals studied, I reject this observation as having any validity. The  $p$  value computed for this retrospective subgroup, in my judgment, has no inferential

value. Obviously, it can be computed. However, one should make no inference from the value regardless of its largeness or smallness.

So, I think the rat study is devoid of any biologically relevant finding. I think the results should not be a factor in deciding about approval and, moreover, should not appear in labeling. The study found nothing.

Clearly then, the carcinogenicity study found no drug related histopathology (including tumors) and did not statistically significantly affect survival (if anything it protected against dying). So one is in the usual dilemma of whether the study conditions reasonably approach the Maximally Tolerated Dose (MTD).

The high dose (125 mg/kg/day) is, on a body weight basis, 2,500 times the minimum recommended dose of 0.05 mg/kg/day in man and 156 times the maximum recommended dose of 0.8 mg/kg/day in man. So, if one were to make literal extrapolations to man (on a body weight basis) there is a "safety margin" of from two to three orders of magnitude. That is pretty big, in my judgment, and is somewhat analogous to comparing 1 inch ripples in a pond to 200-foot tidal waves during a typhoon. I recognize that on a meters squared basis the comparison is less dramatic. But, I am not at all concerned about the "closeness" to MTD.

Nonetheless, the 125 mg/kg/day diet-fed study was "close." Based on the 6-month chronic study, doses above 200 mg/kg/day seem reasonably to predict that the rats' survival may have been adversely affected at only a multiple of two. So I don't care whether the projection to man is safe at 2000 or 4000 times or 125 or 250 times. Any extrapolation to man one cares to make is in orders of magnitude. The precise number one puts for the most significant digit (e.g., 2 or 4 in the thousands place) seems totally irrelevant to me.

### Two Mouse Studies

*The first study* involved 500 mice (250 male and 250 female) that were randomized to control (two groups of 50/sex/group) or drug (50/sex group) at dose levels of 10, 50, and 250 mg/kg/day in feed. In female mice, bisoprolol tended to prolong survival as a function of dose ( $p = 0.01$ ), but a similar statistically significant finding was present between the two control groups. So, although one could not claim bisoprolol decreases mortality in mice, one certainly cannot use the carcinogenicity study to defend being at maximally tolerated dose.

Our statistical analysis showed statistically significant findings for metastatic carcinoma of the lungs ( $p = 0.03471$  by the exact permutation trend test in female mice, ovarian cystadenoma ( $p = 0.00893$  by the exact permutation trend test),

abdominal lymph node hemangioma ( $p = 0.0485$  by the exact permutation trend test) in male mice, and granulocytic leukemia ( $p = 0.0397$  by exact permutation trend test).

For metastatic adenocarcinoma, the results expect me to infer that an incidence of 0/100, 0/50, 0/50 and 2/50 for the control, 10, 50, and 250 mg/kg/day groups, respectively, prove that there were carcinomas of other organs that were more severe in the high dose group (i.e., metastasized) when there was no malignant adenoma, produced by bisoprolol, seen in any organ of the body and no others observed in the particular two animals that had a metastasis. This, I submit, is a total non-finding and the  $p$  value calculated should not lead one to speculate about, on its face, a biologically irrelevant and implausible finding. Note the 0.03  $p$  is by trend test, a very weak (or should I say not precise, perhaps suspect, or perhaps nonsense when applied post-hoc to subgroup analysis) flag of a biological signal.

The abdominal lymph node hemangioma finding came from incidences of 0/100, 1/50, 0/50 and 2/49 for the control, 10, 50, and 250 mg/kg/day groups, respectively. Hardly what I would regard a convincing dose-response relationship, but when the statistics are 3 out of 149 on drug and 0 out of 100 in control, ordered by dose, what else can the statistics say? Again, I throw this away as having any form of biological relevance. The finding, therefore, has no implication with respect to risk to man, let alone that this high dose group represents between 311 to 5000 times the maximal and minimal recommended dose in man, respectively (on a body weight basis). I shall defer repetition of my ripple to tidal wave analogy, except by reference.

For granulocytic leukemia, the score goes 6/150 vs. 2/100 for drug vs. control groups, respectively. This is derived from incidences of 2/100, 0/50, 3/50, and 3/50 for the control, 10, 50, and 250 mg/kg/day groups, respectively. Again, I am not at all convinced that this looks like a dose-response but can readily understand a statistically significant numerical calculation. At the risk of sounding like a broken record, nonsense. It is another non-finding.

Obviously, the above two arguments go for the ovarian cystadenoma where the findings were 3/100, 0/50, 3/50, and 6/50 for the control, 10, 50, and 250 mg/kg/day groups, respectively.

So, I see no signal worth bothering about (except for purposes of "debunking") in the mouse study and cannot, even remotely, infer from the results that any tumorigenic potential of bisoprolol has been suggested. Instead, I see a lot of fishing expeditions that, I think, we should discourage when evaluating this form of bioassay.

*The second mouse study* evaluated two groups, 50/group/sex for control and 50/group/sex at 200 mg/kg/day is a diet-fed life-time mouse study. The dose was

only 80% of the 250 mg/kg/day used in the first study. So, it is at a lower dose than the first. Two other dosage groups were studied (8 and 40 mg/kg/day) but were not subjected to histological evaluation.

None of the "statistically significant" findings of the first study were replicated. So much for the findings of the first study; also, so much for the inference one should take from the numerical values of the p calculated from the results of first study. They were "noise." The second study did not replicate any of them.

Rather, the second study found new "statistically significant" tumors. Namely, bronchiolo-alveolar adenomas in treated females ( $p = 0.0253$ ) as well as grouped lung tumors ( $p = 0.02$ ) and salivary gland malignant lymphoma ( $p = 0.01349$ ) but only a marginal significance for thymus gland malignant lymphoma ( $p = 0.06013$ ).

Instead of taking this second study item by item, I simply point out what I think is self-evident. Neither study found a signal that can be reasonably (although I recognize that some persons could) be suspected to raise a question about the tumorigenic potential of bisoprolol up to several thousand times (on a body weight basis) the doses anticipated for use in man. The two mouse studies have no implication whatsoever that bisoprolol poses a risk in man. There may be risk in man, but the results of the two mouse studies do not suggest there is a risk. The two mouse studies are best interpreted, in my judgment, as having found nothing worth conveying to anybody. Thus, the results not only have no bearing on approvability, they should not appear in labeling.

I choose not to address the MTD in the mouse. My arguments would be much like those of the rat; the dose studied is big. I consider this a non-issue.

### BACKGROUND

As summarized in the attached SBA, there are over 300 clinical trials (including post-marketing studies) and data that represent study type information and/or post-marketing experience from over 65,000 patients. Rather an overwhelming total database.

I assert that the major support of efficacy can be derived simply from two clinical trials (Studies 57-1 and 57-3), both conducted by Lederle in the United States. All of the other clinical trial information has been examined to look for inconsistency with respect to the results of Studies 57-1 and 57-3. No inconsistencies have been found. Consequently, the descriptions of the antihypertensive effects found in Studies 57-1 and 57-3 can be taken as representative of all studies.

A similar selective, extensive look at adverse effects has been taken looking for inconsistencies in the much larger database available. For safety, the algorithm is a bit more complex, but the SBA presents the data fairly well. As is frequently the case (even when there are less than 65,000 patients represented), as one includes more and more data, denominators become hard to track explicitly.

At a meeting of the Cardiovascular and Renal Drugs Advisory Committee (June 6, 1991), a detailed discussion of the data contained within the NDA led to a unanimous vote that bisoprolol should be approved.

A safety update has been submitted (cut off date for analysis being December 1990 and receipt date was February 19, 1991). It has been reviewed and no new phenomenology discovered. There is no need for any further safety updates.

### CLINICAL PHARMACOLOGY

Bisoprolol is a beta<sub>1</sub>-selective, beta-blocking agent that exists in the to-be-marketed formulation as a racemic mixture (the R(+) form is relatively inactive compared to the S(-) form where most of the beta-blocking comes from). In man, over a dose range of 5 to 40 mg, the R(+) and S(-) forms are equivalent in plasma with respect to AUC (R-Isomer: 159.4 to 1097.1 ng/hr/ml; S-Isomer: 153.5 to 1203.6 ng/hr/ml), C<sub>max</sub> (R-Isomer: 9.2 to 82.5 ng/ml; S-Isomer: 9.3 to 85.8 ng/ml), and elimination half-life (R-Isomer: 12.4 to 9.4 hours; S-Isomer: 10.9 to 9.5 hours). The relationships to dose are shown in the following table. Most of the plasma measurements in the NDA, except where stereoselective assays were specifically performed, are the results of non-stereoselective assays (i.e., total bisoprolol [R(+) plus S(-)]).

Table 1

Summary of Mean (CV%) Pharmacokinetic Results for the Bisoprolol Enantiomers (R and S) in 8 Healthy Subjects (Study 57-12)

Dose (mg)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>0-∞</sub> (ng·hr/mL)	t <sub>1/2</sub> (hr)
5				
(R-Isomer)	9.2(26)	3.1(70)	159.4(24)*	12.4(23)*
(S-Isomer)	9.3(17)	4.2(64)	153.5(19)*	10.9(30)*
10				
(R-Isomer)	19.7(22)	3.5(83)	257.9(23)*	9.3(27)*
(S-Isomer)	19.3(18)	2.6(46)	296.2(22)*	10.2(25)*
20 (2x10)				
(R-Isomer)	39.7(16)	2.4(42)	546.7(27)*	8.6(21)*
(S-Isomer)	40.3(15)	2.2(47)	597.0(26)*	9.6(27)*
40 (4x10)				
(R-Isomer)	82.5(18)	1.3(63)	1097.1(21)*	9.4(19)*
(S-Isomer)	85.8(19)	1.3(60)	1203.6(20)*	9.5(17)*

\* = PK parameters calculated by model-independent method.

Pharmacokinetically, bisoprolol is well described and shows less than a 20% first-pass (liver or intestinal wall) effect, with doses of less than 5 mg saturating this process since the AUCs are nicely linear from doses of 5 through 40 mg at steady-state on a multiple dosing (once-a-day) regimen. At steady-state, peak concentrations are \_\_\_\_\_ fold greater than at single dose. This is consistent with a linear pharmacokinetic model having a terminal elimination half-life of 11 to 12 hours.

Although clearly metabolized, metabolites have been detected only in urine (8 of them). Gross figures of 42 to 60% unchanged drug and 15 to 20% of metabolite M1 have been recovered in urine following single 20 and 60 mg oral doses. The M1 metabolite is known to be inactive, so 57 to 80% of administered drug is recovered as parent plus an inactive metabolite. Both hepatic and renal impairment lead to a longer half-life (about 20 x) of total bisoprolol in plasma. There are no age related effects on bisoprolol pharmacokinetics, nor does debrisoquine or a number of other commonly used drugs affect bisoprolol pharmacokinetics. For some reason, rifampin does decrease bisoprolol  $C_{max}$ , AUC, and  $t_{1/2}$ .

Bisoprolol clearly blunts increases in exercise heart rate over a dose range from 2.5 mg through 40 mg, and with respect to this effect it is 10 times more potent than metoprolol and 5 times more potent than propranolol. A modicum of plasma-concentration-effect analyses were conducted but were inconclusive and not well pursued by either Lederle or us.

Hemodynamically (invasive and non-invasive following oral and IV doses, with measurements at peak effect), as could be expected, filling pressures rose a little, cardiac output fell at rest and during exercise, total peripheral resistance increased and heart rate, systolic and diastolic blood pressures fell. Nothing of note here. Additionally, it is clear that bisoprolol decreases peripheral renin levels.

From extensive studies evaluating pulmonary function (among other parameters), bisoprolol compared favorably with metoprolol and atenolol and could be differentiated from propranolol. Thus, it need not be contraindicated in bronchial asthma and can be used (as a last resort) in patients with chronic obstructive lung disease. Again, no particular distinguishing characteristics here.

ANTIHYPERTENSIVE EFFICACY

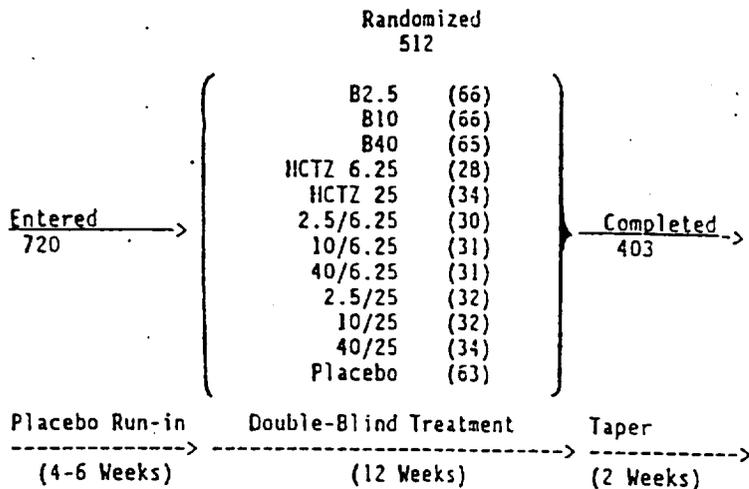
The only indication sought in this NDA is hypertension. I will dwell, momentarily, on only two of the studies submitted. The five volumes accompanying this memorandum deal with the rest.

Study 57-3

Study 57-3 will also be used to support another NDA that is a fixed dose combination of bisoprolol plus hydrochlorothiazide. Consequently, more than usual attention needs to be paid to this single study. Also, it obviously supports the approval of bisoprolol alone. The study was a 3 x 4 factorial design as indicated in the following table. Numbers in the cells are numbers that produced analyzable data.

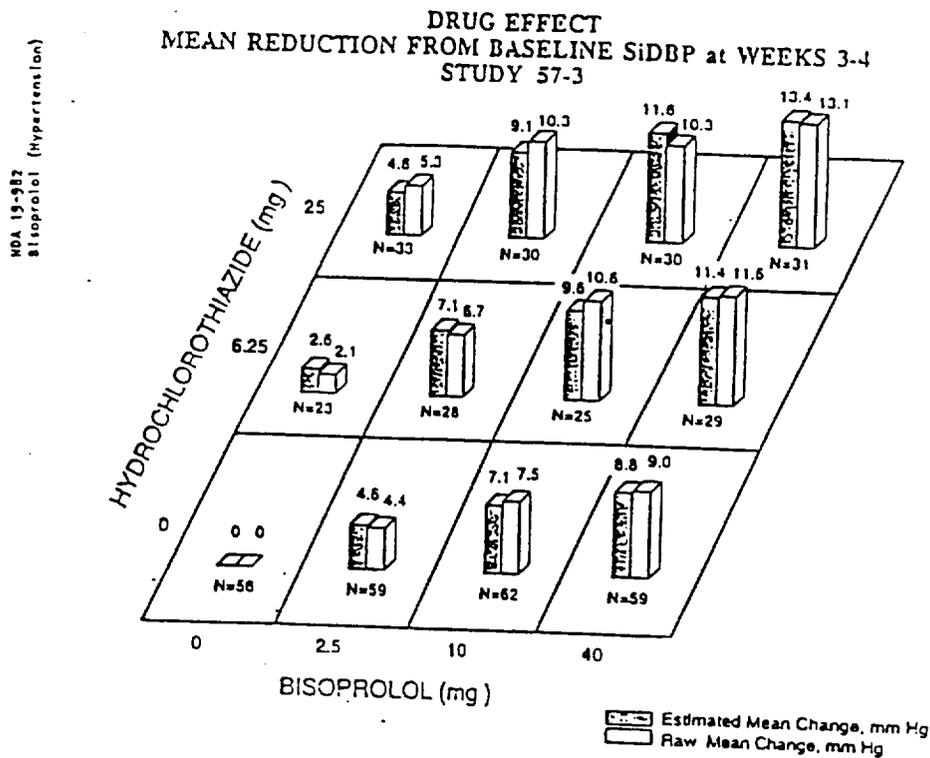
		<u>Bisoprolol</u>			
		<u>0</u>	<u>2.5 mg</u>	<u>10 mg</u>	<u>40 mg</u>
H	0	56	59	62	59
C	6.25 mg	23	28	25	29
T	25 mg	33	30	30	31
Z					

The trial was executed as a randomized, parallel-group, placebo-controlled, dose-ranging trial that is analogous to the following diagram. Numbers are patients randomized and patient completed.



The results of the trial are rather straightforwardly presented in the reviews and the SBA. The straightforwardness largely derives from the fact that the results were able to be handled by standard ANOVA. Each dose of single entity (except for the 10 and 40 mg bisoprolol groups, where the difference between groups had a p of only 0.07) was readily differentiable not only from placebo, but one dose from another dose by conventional criteria and with total disregard for monotonicity, direction or magnitude of change as a function of dose. The same was true for each combination component (an occasional p of 0.06 or 0.08). Pretty impressive, on a whole. There is no question as to whether I believe the individual numbers. Each is real (in a statistically significant sense) and consequently, is a reasonable estimate of the magnitude of effect.

The single graph that I think is the best representation of results, follows. It shows drug effect (placebo subtracted) for measurements taken just before dosing at weeks 3 and 4 of the study. Both bisoprolol and HCTZ were administered orally, once-a-day in the morning.



In my judgment, the following are of major importance when the overall antihypertensive response is examined:

a) The antihypertensive response increases with an increasing dose of not only each single entity but as the dose of each entity is increased in combination. That is, the greatest effect (i.e., decrease in blood pressure) is at a dose of 25 mg HCTZ in combination with 40 mg bisoprolol.

Of course, one should ignore the quadratic model (i.e., not look at the numerical values that come from the fitted model). The quadratic form dictates that response must fall as dose increases. It is a biologically inappropriate model (only in rare cases would one expect anything other than a monotonically increasing effect as a function of dose, but eventually reaching a maximum effect), and the model obviously does not fit the data (as shown in Diagrams VI and VII of Dr. Smith's statistical review). Although numerical analysis says the fit of a quadratic model is "good," Dr. Smith has not shown fits from any other model. I reject the quadratic model on simple common sense grounds. It is not a sensible model to have chosen.

The sponsor "model" dependent analysis is an "additive model," well described by the sponsor, and it does not have the defect of requiring that the response decrease as dose increases. The additive model "fits" the data well also. I think the numbers that come from the additive model are the best estimates of treatment effect.

b) The added contribution of HCTZ is most obvious at the 6.25 mg dose. That is to say, when 6.25 mg of HCTZ are added to any dose of bisoprolol, something material is gained (2 to 3 mm Hg) for each dose of bisoprolol, and bisoprolol still exhibits its dose-response. Of course, the same is true when 25 mg of HCTZ are added to any dose of bisoprolol, however, potassium balance in the body becomes noticeably affected.

c) Bisoprolol has no effect upon potassium balance of the body; it is well known that HCTZ does. The following presents the numbers of patients who developed serum potassium less than 3.5 mEq/L at some time during the study. The numerator is number of subjects, the denominator is number of

subjects randomized to a dose of HCTZ (intent-to-treat), the number in parenthesis is a %. This is across all doses of bisoprolol.

0 mg HCTZ 4/252 (2%)	6.25 mg HCTZ 7/118 (6%)	25 mg HCTZ 16/128 (13%)
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More about this when the combination product is sent to you.

So Study 57-3 is strong support for the antihypertensive efficacy of bisoprolol, not only alone but also in combination with hydrochlorothiazide. It not only clearly beats placebo but the magnitude of drug effect (about 11 mm Hg for sitting diastolic blood pressure with bisoprolol alone) is entirely respectable.

Study 57-1

The second study is a straightforward randomized, placebo-controlled, parallel group, dose ranging trial with 276 randomized patients (about half the size of 57-3) designed to study bisoprolol monotherapy, with measurement of blood pressure at trough. The drug effect (placebo subtracted trough data) on supine diastolic blood pressure at 3-4 weeks of double blind treatment in mm Hg decrease are shown in the following table.

Table 2

Mean Change from Baseline SiDBP and Drug Effect  
at Week 3-4 Primary Analysis Patients (N=240)  
Study 57-1

Parameter	Placebo	B5	B10	B20
N	60	59	60	61
Raw Mean Change	-3.4	-8.3	-10.8	-11.9
Drug Effect**	N/A	-4.0	-7.4	-8.5
Adj Mean Change (mmHg)*	-1.6	-6.3	-8.8	-10.0
Adj Drug Effect**	N/A	-4.7	-7.2	-8.4

\* Adjusted for center

\*\* Drug Effect = Treatment mean change from baseline minus placebo mean change

Each of these doses were differentiable from placebo (p less than 0.01 in each case) by standard statistical tests. Ordinarily, I would have interpreted these data as showing that an effective (i.e., differentiable from placebo) dose would be below 5 mg and that more than 20 mg would have a greater effect. Indeed, Study 57-3 (which came after 57-1 and used the results of 57-1 for selecting doses to study) confirms such a prediction. The usable dose range of bisoprolol is at least from as low as 2.5 mg to as high as 40 mg once-a-day orally. Each increment in dose between those ranges can be expected to produce a greater effect (and there are statistically significant empirical results to support that statement). Parenthetically, this is the second beta-blocker (I can remember) where there were clear dose-related effects on blood pressure (betaxolol being the first). I think that all appropriately designed and/or analyzed trials of beta-blockers would find the same thing.

#### Other Studies

The reviews and SBA adequately address other studies that were submitted. There is nothing contradictory to the conclusion one can draw from Studies 57-1 and 57-3. Bisoprolol is an effective antihypertensive drug.

#### SAFETY

Overall, there is nothing remarkable in the safety analysis. The only dose-related adverse effect appears to be diarrhea, however, the only evidence for that is derived from the factorial trial, and hydrochlorothiazide cannot be dissected from that finding. There was an increased number of dropouts, as a function of dose, from U.S. conducted trials. But the reasons for dropping out are a mixed bag. Nothing was consistent as a function of dose, except for diarrhea. Of course, bradycardia increases as dose increases; bisoprolol is a beta-blocker.

Within the analyzed clinical trial experience, it is clear that 40 mg of bisoprolol is more effective than 20 mg, and it is not clear that there are any dose related, clinically meaningful, rate-limiting side effects. It is entirely reasonable to think that doses significantly in excess of 40 mg could have been studied. Consequently, a limit of 40 mg as the upper dose for Dosing and Administration can be recommended without any hesitation whatsoever.

The SBA probably contains the most succinct consolidation of the overall serious and non-serious events seen not only in clinical trials but also in post-marketing experience. In your perusal of this document it is important to bear in mind the outline of the Table of Contents and to read the heading of each table. The analysis, like that of efficacy, is principally concerned with the U.S. trial experience. Deaths

and serious events contain all events, including post-marketing experience. I gave a whirl at organizing this section better, but failed.

### Deaths

Although the SBA cites 124 known deaths it is important to note that of the 1010 patients involved in U.S. clinical trials (4 to 12 weeks in duration) there were no deaths, and no deaths occurred during the double-blind phase among 366 patients enrolled in the Lederle U.S. anti-anginal (an indication not being sought at this time) trials. The distribution of deaths can be accounted for as follows:

- 1 - occurred 11 months after participation in a Lederle sponsored controlled hypertension trial,
- 2 - occurred in E. Merck sponsored controlled hypertension trials,
- 13 - occurred in E. Merck sponsored uncontrolled clinical (hypertension or angina) trials,
- 1 - occurred in Lederle sponsored uncontrolled angina trials, and
- 107 - occurred in E. Merck sponsored post-marketing trials or from spontaneous reports.

Two of the 124 deaths occurred in controlled hypertension (1 in placebo controlled and 1 in atenolol controlled) trials sponsored by E. Merck, neither of which were, in my judgment, even remotely related to drug. The deaths in post-marketing studies are basically from open-label, long-term exposure and cannot be reasonably evaluated. I have read through the capsular summaries of each of the deaths (Appendix II of the SBA) and cannot ascribe a drug-related cause to any of them.

The reports make interesting reading and with some amusement I note investigators attributing infectious disease, stroke, and myocardial infarction as possibly related to bisoprolol, but I found no investigator judgment that could possibly relate bisoprolol to the development of congestive heart failure. So much for investigator cause-specific mortality assessments, no wonder we insist on all-cause mortality.

### Dropouts

There is a case summary of all dropouts that occurred in U.S. Clinical Trials as Appendix II to the SBA. I have read through them and cannot say I discovered

anything. Only one patient (patient 1-177 from Study 57-18) had diarrhea (as one of the other symptoms that led to dropping out). Amazing, since diarrhea pops out as the only dose-related side effect of bisoprolol. The most unusual things of note are "loosening of teeth" and fractured femurs.

Several patients (e.g., patient 4-186 [Study 57-3], patient 11-440 [Study 57-1], patient 7-507 [Study 57-1]) were dropped for SGOT/SGPT abnormalities. The case histories do not implicate drug. Moreover, an overall analysis of all data leads one to conclude that bisoprolol decreases the SGOT/SGPT. There is no signal with regard to liver troubles that I can see. Dr. Ganley points out that Study 57-3 and SGOT/SGPT is a worry. During the 13 weeks of double-blind 13/337 (3.9%) of patients receiving bisoprolol (alone or in combination) had normal transaminases at baseline, but had both SGOT and SGPT elevated concomitantly at least once, while 0/58 (0%) of patients receiving placebo had such an event.

The one case of hematology abnormalities, thrombocytopenia patient 8-382 [Study 57-1], was thrombocytopenic before and after bisoprolol.

Etc., etc., I found nothing worthy of comment except for one case of putative labyrinthitis which had a negative rechallenge. This case was very perceptively handled.

#### Post-Marketing experience

The post-marketing adverse experiences are most easily examined by looking in the attached Integrated Safety Summary. There is nothing I see in that report that contradicts anything in the more detailed analyses contained within the SBA and Dr. Ganley's review.

#### Overall

It is difficult, in fact, to discern what, if any, of a plethora of side effects one would directly ascribe to bisoprolol (outside of bradycardia). Those I would pick are fatigue and diarrhea. Among the most commonly reported adverse events, I would exclude headache, edema and URI as being related to drug. On a whole, a pretty "safe" appearing beta-blocker.

CONCLUSION

So, bisoprolol is safe and effective for use as an antihypertensive. My suggestions have been incorporated into the clean draft package insert. We recommend you sign the attached approvable letter.

*/s/ 10/18/91*

Raymond J. Lipicky, M.D.

cc: Orig NDA  
HFD-110  
HFD-110/CSO  
HFD-110/RLipicky  
ef:8/9/91;8/12/91;8/23/91  
10/7/91;10/9/91

*/s/ 10/19/91*

JUN 11 1992

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: JUN 15 1992

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Bisoprolol (Probeta, NDA 19-982)

TO: Raymond Lipicky, M.D., Director  
Division of Cardio-Renal Drug Products, HFD-120

Bisoprolol appears to be a well-worked up (dose-response, large exposure) cardioselective beta-blocker with no suggestions of unusual toxicity. I agree with the Division's conclusion, uniformly shared, as I understand it, that the various positive trend tests are not persuasive and that bisoprolol does not, on the basis of the 3 carcinogenicity studies done, have a carcinogenic potential. I reviewed the deaths and adverse drop-outs and see nothing unusual.

There are a few dose-related side effects, I believe, including diarrhea (SBA, p 198 shows this is true for monotherapy) and sinusitis. I suspect that bradycardia, somnolence, aesthemia and various GI complaints are also and have asked for these to be shown in labeling and in the SBA (better than now). There seems little doubt that a positive ANA titer can develop, about 15% in long-term use.

I have marked up labeling a fair amount. If you concur, issue the letter; if not, let's discuss.

/S/

Robert Temple, M.D. )

cc:

(Orig. NDA 19-982  
HFD-100/Chron File  
HFD-100/NDA File  
HFD-110  
HFD-110/CSO  
HFD-100/Carter  
HFD-101/Botstein  
RT:jp:6/15/92  
Revised:RT:jp:6/15/92(2)



	81	82	83	84	85	86	87	88	89
captopril	346	1141	2102	3040	4976	8545	11572	12983	7946
enalapril						2546	8109	11888	8297
lisinopril								1329	2390

Spontaneous reporting cannot produce incidence rates. However, some crude measure of the relative frequency of reporting reactions indicating renal toxicity can be made by calculating a reporting rate using the number of ADRs as the numerator and an estimate of prescriptions dispensed as the denominator. Below is the reporting rate per 100,000 prescriptions dispensed over the period 1981-89.

	81	82	83	84	85	86	87	88	89
captopril	1.2	4.7	1.4	1.3	0.2	0.7	0.5	0.3	0.3
enalapril						2.2	1.2	0.6	0.3
lisinopril								1.7	1.5

Since reporting is almost always more frequent during the first two years of marketing, one should never compare rates between newly approved drugs and drugs that have been on the market for awhile. Thus, one must compare rates for each drug by its year of marketing. The table which follows makes this comparison for renal ADRs over the first three years of marketing.

	Reporting rate/100,000 Rxs (unadjusted)		
	MY1	MY2	MY3
captopril	1.2	4.7	1.4
enalapril	2.2	1.2	0.6
lisinopril	1.7	1.5	-

One further adjustment is necessary. Since overall reporting to FDA's spontaneous reporting system increased substantially after 1981 affecting all drugs, one must account for this increase in the secular trend of reporting to the system. Using a method previously described<sup>1</sup>, the table below presents the adjusted rates of renal reactions over the first three years of marketing for the ACE-inhibitors.

	Reporting rate/100,000 Rxs (adjusted)		
	MY1	MY2	MY3
captopril	1.2	4.7	1.4
enalapril	0.9	0.8	0.5
lisinopril	0.7	-	-

These rates, with the exception of captopril's second marketing year, are generally quite comparable given the nature of the data

from which they were derived. However, there is no ready explanation in these data for captopril's apparent rate excess in year two; nonetheless, captopril's rates have generally remained stable (as well as comparable to enalapril's rates) in marketing years 4 through 8 varying between 0.3 and 1.3 reports/100,000 Rxs.

Reports coded as kidney failure represent one of the most potentially serious of the renal ADRs listed in the reactions that were examined. Below is a table presenting the number of cases of kidney failure, the proportion that was serious (ie, resulted in hospitalization, disablement or death) and the total number of deaths reported in these cases.

	Kidney Failure	Serious	Deaths
captopril	119	71	23
enalapril	138	100	11
lisinopril	31	26	1

When one compares the reporting rates for kidney failure among these three ACE-inhibitors over their marketing lifetimes, the adjusted rates for captopril, enalapril and lisinopril were 0.23, 0.38 and 0.64 per 100,000 Rxs dispensed respectively. The apparent disparity between those associated with captopril and enalapril compared to that of lisinopril may be due to the fact lisinopril's rate is based on a single year which also happens to be its first marketing year. For example, comparing enalapril's first year to lisinopril, one sees that enalapril actually had a slightly higher rate of kidney failure reports (0.94) than those associated with lisinopril (0.64).

The apparent difference between captopril and enalapril/lisinopril in the proportion of serious to all reports of kidney failure probably has no real clinical significance but is likely due to differences in the quality as well as completeness of acquiring/reporting this information between the manufacturers involved. The rates of death associated with individuals who experienced kidney failure in this series of reported cases were low (ie, between .027 and .044 per 100,000 prescriptions dispensed) and do not appear to be reflect noteworthy differences between any of the three drugs. It should be further understood that not all the reported deaths were necessarily associated directly with the occurrence of kidney failure and the use of ACE-inhibitors in these individuals.

In order to develop a better perspective as to the actual occurrence of kidney failure in association with the use of one of the ACE-inhibitors (enalapril), information is available from the Prescription-event monitoring program. Over 13,000 patients were monitored and the percentage of patients experiencing renal failure during the first month of treatment was 0.7%. It was determined that this represented an excess rate of 0.2 cases per 1000 patients

in this population<sup>2</sup>. In followup to this study, Speirs and his colleagues<sup>3</sup> found that 75 of 1098 patients who had died with kidney failure showed a greater than 50% rise in creatinine or urea concentrations. Enalapril was believed to have contributed to deteriorating renal function and subsequent death in only 10 of this patients. However, they failed to find a single instance of a patient with mild to moderate uncomplicated hypertension who died of renal failure as a result of taking enalapril.

Packer and his associates<sup>4</sup> studied the hemodynamic effects of captopril and enalapril in 42 patients with severe chronic heart failure. They determined that the two drugs produced hemodynamic and symptomatic improvement but had different effects on renal function. They speculated that the more prolonged action of enalapril increased the risk of hypotension which may also explain the differences in risk between the two drugs with regard to its adverse effect on creatinine clearance and potassium homeostasis. Unfortunately, we were unable to examine whether any differences in renal toxicity may exist in patients being treated for CHF with ACE-inhibitors using FDA's data base because it would have entailed an individual review of all 624 reports in our system, a task clearly beyond our resource capabilities at this time.

If I may be of further assistance, please do not hesitate to contact me.

/S/ 

Allen C. Rossi, DDS, MS

/S/

Concur:

Lynn Bosco, MD, MPH, Team Leader, HFD-733

/S/

Bruce Stadel, MD, MPH, Branch Chief, HFD-733

cc:

NDA

Drug 1.7 Captopril, Enalapril, Lisinopril

Kathleen Bongiovanni, HFD-110

GFaich HFD-700

CAnello HFD-701

BStadel HFD-733

LBosco HFD-733

References

1. Rossi AC, Hsu JP, Faich GA. Ulcerogenicity of piroxicam: an analysis of spontaneously reported data. Br Med J 1987; 294: 147-150
2. Inman WH et al. Postmarketing surveillance of enalapril. I: results of prescription-event monitoring. Br Med J 1988; 297: 826-829
3. Speirs CJ et al. Postmarketing surveillance of enalapril. II: investigation of the potential role of enalapril in deaths with renal failure. Br Med J 1988; 297: 830-832
4. Packer M et al. Comparison of captopril and enalapril in patients with severe chronic heart failure. NEJM 1986; 315: 847-853

## RECORD OF TELEPHONE MEETING

<u>NDA/IND NUMBER</u> 19-982	<u>INITIATED BY</u> Lederle	<u>DATE</u> July 23, 1990
<u>PRODUCT NAME</u> Monocor Bisoprolol Fumarate	<u>FIRM NAME</u> Lederle Labs	<u>NAME AND TITLE OF PERSON WITH WHOM CONSERVATION WAS HELD</u> David Ridge, Ph.D. Assistant Director, Technical Services Regulatory Affairs
<u>TELEPHONE NUMBER</u> 814-732-3655		

The following was discussed.

Lederle is rewriting the SOI to change from development to production. The scale would not be changed. This would not present a problem, but they should specify all changes that were made.

The SOI only stated that the granulation is press without a further description of the press. Lederle did not want to specify the press size. Would this be a problem? I stated that they should "fine tune" the description of the press that will be used, but did not have to specify any size.

Currently Lederle is planning to use a Pelagreeny coating pan which would permit them to coat two batches in one coating operation. They would have to validate at least one batch prior to submission with a commitment to validate two additional batches, and include the standard stability commitment.

During the manufacture of the heart shape tablets there were some embossing problems. They need to modify the tablet punch. This change would need a supplement to be supported with comparative dissolution data and a stability commitment.

Plans are being formulated to increase the scale to tablets. They would combine the granulation from batches. The current production record states that adjustment of the excipients is performed after granulation. When they increase the size to million, they will delete the adjustment as they have not had to adjust any batches.

Since Lederle is packaging the tablets in propylene rather than HDPE for their European production, they want to include bottles made of propylene to be

package in Ireland for US sales until Pearl River is ready for repackaging. They have 2 years at 20° C and 2 years at "accelerated condition" of 30° C and 75% RH. This would be acceptable for a two year expiration date, but they should not refer to this as accelerated data.

They would not need any additional stability data if the tablets are repackaged in Pearl River provided they submit stability data on the bulk package. The NDA already includes stability data in HDPE bottles and the resin would not change.

RJ Wolters

SIGNATURE           /S/          7125190           DIVISION           HFD-110          

cc: (NDA orig)  
HFD-110  
HFD-110/CSO  
HFD-110/Cunningham  
HFD-110/Wolters

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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Date: 5/9/91

From: HFD-110 / Raymond Lipicky, M.D., Charles J. Ganley, M.D.

Subject: Reporting of adverse laboratory results in bisoprolol studies NDA #19-982

To: HFD-344 / Antoine El Hage

This memo is a response to your concerns about the conduct of clinical protocols 57-1 and 57-3 involving bisoprolol fumarate by the American Cyanamid Company. The main concern involved the failure of investigators to record laboratory values outside the central lab normal limits in the C.R.F and whether some patients did not fulfill inclusion/exclusion criteria based on laboratory results (specifically with regard to elevated blood sugars and the diagnosis of "uncontrolled" diabetes mellitus). In addition, there was a failure to report a cerebral vascular accident to the I.R.B. Please see attached document of an inspection at one investigator site.

I have reviewed the protocol specifically addressing inclusion / exclusion criteria and the reporting of adverse laboratory results. I have attached copies of pertinent portions of the protocol for clarification.

Concerning the failure to report lab results outside the central lab normal limits in the C.R.F.:

The protocol states that only values outside the Cyanamid safety limits or felt to be clinically significant by the investigator will be noted and recorded [see attached page from vol. 1.98, p. 229]. In the C.R.F., the reporting sheet for adverse laboratory results states that "clinically significant adverse changes and/or outside cyanamid safety limits" are to be recorded [see attached page from vol. 1.98, p. 273]. Thus, the sponsor stated up-front that only values outside their own safety limits were to be recorded in the C.R.F. Unfortunately, these values were not included in the original protocol. I spoke with the company concerning this and they responded that all labs were included in the C.R.F on a central lab sheet with the abnormal values flagged. The sponsor also received a copy of the central lab sheet. All flagged values were reviewed by the sponsor and investigator and the clinical significance was determined. The reason for this is to prevent transcription errors from the central lab sheet to the C.R.F.

In the NDA, the sponsor reported the abnormal laboratory results based on concern thresholds and not based on their safety limits. I have attached a copy of the concern thresholds.

Concerning the failure to exclude patients with abnormal lab results at baseline:

The only laboratory exclusion criteria were patients with baseline creatinine, SGOT or SGPT > 1.5 times the upper limit of normal and potassium < 3.2 mEq/L. Blood sugars that demonstrate uncontrolled diabetes mellitus are left open for interpretation and as such the sponsor and investigator have a lot of flexibility as to who can be included. As far as SGOT and SGPT are concerned, I reviewed the data of 57-3 again and there were 42 patients with an abnormal SGOT or SGPT (value > 50) at baseline (last value obtained). Of these 42, 15 had a SGOT or SGPT value > 75 (1.5 times the upper limit) and only 1 had a value > 100 (patient 021-00709: SGPT = 107). These 15 represent 2.7% of the total randomized patients. In this instance, the sponsor should have not included these patients in the trial. However, in view of the small number of patients involved and the unlikely event that their exclusion would dramatically change the efficacy results, I do not feel that the sponsor needs to reanalyze the data with these patients excluded.

Failure of investigator to report a cerebral vascular accident to the I.R.B.:

In the N.D.A, the report for study 57-3 lists a patient (#9-790) who suffered a stroke. The sponsor is checking to see if these are the same adverse clinical events. *Note: They were the same. cb.*

**Conclusions:**

- 1) The sponsor and investigator reported adverse lab results on the C.R.F. as they had outlined in the protocol. Thus, the investigator did follow the protocol by using Cyanamid safety limits rather than those supplied by the central lab. The attached report on Dr. Nicholas Vlachakis should be amended to show this. If the sponsor plans to use these limits in reporting adverse lab results, these limits should be included in the protocol.
- 2) The diagnosis of uncontrolled diabetes mellitus is left open for interpretation by the protocol.
- 3) There were some patients included that should have been excluded by the lab exclusion criteria. The number of patients is small and their exclusion is unlikely to change the overall results of the study. However, the sponsor should be made aware of this problem in order to prevent similar occurrences in future trials.

*/S/*  
\_\_\_\_\_  
Charles J. Ganley, M.D.

*/S/*  
\_\_\_\_\_  
Raymond Lipicky, M.D. ✓

cc: orig  
HFD-110  
HFD-110 / cso/ c.ganley  
HFD-344 / a. el hage

RECORD OF TELEPHONE CONVERSATION

AUG 21 1991

Date: August 20, 1991  
NDA#: 19-982  
Product: Probeta (bisoprolol fumarate) Tablets  
Firm: Lederle  
Contact: Maureen Garvey, Ph.D.  
Phone#: 914-732-2410

I called Dr. Garvey, per Dr. Ganley's review dated August 12, 1991, and requested that any phase IV trials performed under Lederle's supervision have a mechanism to follow-up serious adverse events promptly and completely. Dr. Garvey thought that there already was a mechanism, however, she would convey our request formally and check to make sure.

*IS/*  
Zelda McDonald, CSO  
HFD-110

Meeting Minutes  
Lederle & FDA  
August 9, 1991

AUG 20 1991

NDA: 19-982 Probeta (bisoprolol fumarate) Tablets

Purpose: To discuss mouse carcinogenicity studies and the Summary Basis of Approval (SBA).

FDA Participants:

Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Albert DeFelice, Ph.D.	Supervisory Pharmacologist, HFD-110
Ernest Belair, Ph.D.	Pharmacologist, HFD-110
Zelda McDonald	CSO, HFD-111

Lederle Participants:

Brian Bryzinski, M.D.	Director, Clinical Research
Maureen Garvey, Ph.D.	Manager, Regulatory Liaison
Dale Johnson, Pharm. D., Ph.D.	Director, Toxicology Research
Kenneth Koury, Ph.D.	Head, Statistical Design & Analysis
M. Gary Riley, Mvsc., Ph.D.	Dept. Head, Experimental Pathology

Background:

The mouse carcinogenicity studies reported in the original submission dated July 28, 1989 and those submitted in the amendment dated March 27, 1991 were found to have statistically significant incidences of several rare tumors. In addition, the rat studies reported in the original submission were not clean. Dr. Lipicky requested this meeting to inform Lederle of the findings reported in the FDA pharmacology and statistical reviews and to discuss problems with the SBA.

Meeting:

Animal Carcinogenicity Issues

Dr. Lipicky began by stating that the animal carcinogenicity findings were an approvability issue. He questioned whether another beta-blocker should be approved for hypertension when it possibly causes tumors. Dr. Lin emphasized the importance of the fact that even though some of the tumors were rare (i.e., less than 5 per organ), a statistical analysis had to be done; this was not done by Lederle statisticians. Dr. Lipicky said Lederle will have to address this issue and said we would provide Lederle with copies of the statistical reviews. He suggested the following two ways of approaching the issue:

1. If Lederle really believes the findings, they could address the biological relevance of the findings and whether or not the numbers were computed correctly.

2. If Lederle does not believe the findings, they could conclude the bioassay is not very good and repeat the readings of the slides and the analyses in a blinded fashion.

3. A less desirable third alternative would be to reread only the specific tissues in question and the controls.

If Lederle produces a rebuttal that is accepted then we can proceed with the approval process. If Lederle ends up having to re-read the slides, that will take a period of time, therefore, we would ask Lederle to withdraw the NDA until the reread and analyses are completed. In addition, we may need a vote from the Carcinogenicity Assessment Committee as to whether the tumor information needs to be put in the labeling.

Dr. DeFelice asked if Lederle has any better historical control information, because the only information he has is that from the company who supplies the rats and mice and that of the contract laboratory. Lederle stated they did not have vast historical control information but would respond with more documentation and a presentation if that were acceptable to us. Dr. Belair asked if the documentation could precede the presentation by two weeks, and Lederle agreed.

Dr. Belair said he was a little disturbed by the chosen mouse maximum tolerated dose (MTD). In their three month dose-ranging study Lederle used a high dose of 640 mg/kg/day that did not seem to cause any serious toxicity. He did not see why Lederle used a dose of 250 mg/kg/day instead of one close to 640 mg/kg/day and requested more information justifying their choice. Dr. Lipicky said that if we come to the conclusion Lederle could have studied higher doses then there will be an MTD problem.

#### SBA

Dr. Lipicky said the following was missing:

1. In the major controlled clinical trials, there were no tree diagrams configured in such a way as to track the numbers of patients right on the tree.

2. For the major controlled clinical trials, only the diastolic blood pressure is listed. In light of the Shepp trials, we would like to see the systolic changes.

Lederle asked if they will be able to include the systolic information in the package insert, and Dr. Lipicky said probably, yes.

3. In general, for all the controlled trials, none of the tables and figures have drug effect as opposed to placebo response.

4. Because of the very large adverse experience data base, Dr. Lipicky had trouble wending his way through it and had trouble making the numbers add up.

Lederle said the numbers will agree if they split them out by trial, bisoprolol and placebo treated patient. They will expand table 67.

Dr. Lipicky said he could not find an analysis of dose related adverse effects and he was especially interested in incidence rates. Lederle said they will supply the table from the Advisory Committee Meeting presentation. In addition, Dr. Lipicky said he had not found information on what limits the upper dose of bisoprolol or information on intent-to-treat analysis. Lederle came to the conclusion they would revise the SBA and resubmit it.

Zelda McDonald, CSO

cc: Orig. NDA

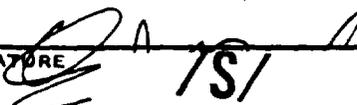
HFD-110

HFD-111/McDonald

HFD-111/Benton

RD: HFD-110/DeFelice 8/19/91

HFD-110/Belair 8/19/91

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE 7/11/91		
<p>Dr. Pool was advised that we have reservations about the alleged nonsignificance of the lung (females) and renal cell (males) tumors incidences in the second mouse carcinogenicity study. It was suggested that prompt intermediate dose histopathology evaluation of the subject organs would be desirable. It was also suggested that similar steps be initiated for any organs showing a large increase in treated group (200 mg/kg) incidence compared with control.</p>	NDA NUMBER 19-982		
	IND NUMBER		
	TELECON/MEETING		
	INITIATED BY <input type="checkbox"/> APPLICANT/ SPONSOR <input checked="" type="checkbox"/> FDA	MADE BY <input checked="" type="checkbox"/> BY TELE- PHONE <input type="checkbox"/> IN PERSON	
	PRODUCT NAME  Monacor (Bisoprolol)		
	FIRM NAME  Lederle Laboratories		
	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD  William Pool, Ph.D., Director, Safety Assessment  TELEPHONE NO.  (914) 732-4380  cc: Orig HFD-110 ✓ HFD-110/CSO HFD-110/ADeFelice HFD-110/EBelair		
SIGNATURE  Ernest Belair, Ph.D.	DIVISION  DCRDP/HFD-110		

11/1  
01/6

Meeting Minutes  
Lederle & FDA  
July 10, 1991

JUL 16 1991

NDA: 19-982 Probeta (bisoprolol fumarate) Tablets  
20-186 bisoprolol fumarate/hydrochlorothiazide

Purpose: To discuss how to proceed since there are changes as a result of the June 1991  
Advisory Committee Meeting

FDA Participants:

Raymond Lipicky, M.D. Director, Div. of Cardio-Renal Drug Products, HFD-110  
Charles Ganley, M.D. Medical Officer, HFD-110 (Reviewer for Bisoprolol)  
Zelda McDonald CSO, HFD-110

Lederle Participants:

Brian Bryzinski, M.D. Director, Cardiovascular Clinical Research  
Robert Desjardins, M.D. Vice President, Clinical Research  
Libby Miller, Ph.D. Project Director  
Maureen Garvey, Ph.D. Manager, Regulatory Liaison

Bisoprolol - Advisory Committee issues

Dr. Desjardins asked if there would be any dramatic wording in the labeling with regard to diarrhea since it was discussed at the Advisory Committee meeting as an adverse event for bisoprolol. He went on to say that because of the power of the study where diarrhea was seen, they saw a lot of other dose related side effects. Dr. Desjardins said the analysis of that study is available and asked if they should submit it to the NDA. Dr. Lipicky said Lederle should submit the analysis because the issue will have to be addressed, but he did not see it as a big problem. It would probably go in the list of adverse events.

Dr. Desjardins said, at the Advisory Committee meeting, Dr. Brater asked for information on metabolites in urine regarding slow and rapid metabolizers of debrisoquin. Dr. Desjardins asked if Lederle should submit the table they had with that data. Dr. Lipicky said they should submit it so that there will be no loose ends.

Bisoprolol/hydrochlorothiazide (HCTZ) - low dose

In their original submission, Lederle proposed doses of 5/6.25 and 10/6.25 bisoprolol/HCTZ but as a result of the recommendation of the Advisory Committee, agreed to market the lower dose of 2.5/6.25 as their initial therapy starting dose.

Dr. Desjardins said Lederle currently does not have a commercial formulation for the 2.5 mg/6.25 mg (low) dose and asked for clarification about when Dr. Lipicky planned to take an action on the combination NDA (NDA 20-186). Dr. Lipicky said he planned to take an action around November, 1991. He might recommend an approvable letter for the original strengths (5/6.25 and 10/6.25) but then he might wait. It would all depend on timing.

Dr. Desjardins asked if Lederle could work out the labeling for the 2.5/6.25 before the commercial formulation is completed. Dr. Lipicky said yes, but stability studies would have to be done. The Regulations say Lederle could ask for a waiver of the bioequivalence studies if the formulation is compositionally proportional. Dr. Lipicky is not comfortable with that idea, however, and has already asked one company to make an argument as to why they think it is acceptable to not do bio studies even though no human will have taken that formulation before it is marketed. Lederle said there are minor differences in the formulation so they are planning to do a bio study and asked what a reasonable usage study would be. If the old formulation is not within specs, would it be o.k. to do a dose proportionality study? Dr. Lipicky said they would be best off using the studied formulation, but if they can not, the dose proportionality study would suffice. Dr. Desjardins asked if they needed to do a food interactions study at the lower dose. Dr. Lipicky said it was not a necessity.

#### SBA for bisoprolol/HCTZ

Dr. Garvey stated that Lederle was aware they would need to prepare an SBA for the bisoprolol/HCTZ application because they would be the first to get an initial therapy indication for a combination product. She asked what they would need to stress and pointed out that pre-clinical studies had not been done on the 2.5/6.25 dose. Dr. Lipicky said he had not thought about the SBA. Not having the pre-clinical studies presented a problem, but Lederle could handle it any way they wished to. Because the application may be approved before the 2.5/6.25 dose is ready, Dr. Desjardins asked if they should write the SBA to include the 2.5/6.25 dose. Dr. Lipicky said they should write it for the 2.5/6.25 dose and put a paragraph at the end stating they do not know how to make it yet. That would be the only paragraph that would need to be deleted.

Dr. Desjardins said they plan to submit the SBA in October, 1991 and asked if they could meet with us after that to discuss the labeling. Dr. Lipicky emphasized that Lederle will not know what the final labeling will be until after Dr. Temple has seen it. Lederle will have an opportunity to discuss Dr. Lipicky's marked-up labeling with him before the package leaves our Division.

*JS*  
Zelda McDonald, CSO

cc: Orig. NDAs

HFD-110

HFD-111/McDonald

HFD-111/Benton

RD: HFD-110/Ganley 7/16/91

Drafted 7/11/91

NDA 19-982

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 20, 1992

TO: Albert DeFelice, Ph.D., Supervisory Pharmacologist

FROM: Ernest J. Belair, Ph.D.

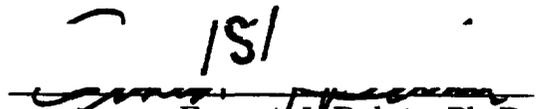
SUBJECT: Review of Latest Amendments to Monacor (Bisorprolol Fumarate) Submission, NDA 19-982

As requested, the amendments to NDA 19-982 (GENERAL CORRESPONDENCE) of January 30, 1992 and February 20, 1992 have been reviewed. The former dealt with the complete protocols for the mouse carcinogenicity and pharmacokinetics studies, and the latter provided the lung tumor data for all the treated female mice, i.e., the low and middle doses as well as the high dose and the control dose (Group 1).

The protocol amendment was needed to determine if the selective evaluation of the high and Group 1 control dose groups was planned from the onset, or if it was a serendipitous, last minute decision. The protocol indicated that it had been properly planned.

The lung tumor data amendment demonstrated that, even with the additional data from the mid and low dose groups, the incidence of lung tumors was not statistically significant.

The above listed data further contribute to the approvability of Monacor, as outlined in my memorandum of January 30, 1992 to Dr. A. DeFelice.

  
Ernest J. Belair, Ph.D.

cc:  
Orig. NDA  
HFD-110  
HFD-110/CSO  
HFD-110/EBelair  
19-982.APP

NDA 19-982

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 30, 1992 *ALJ 4/3/92*  
TO: Dr. Albert DeFelice  
FROM: Dr. Ernest J. Belair  
SUBJECT: Preclinical Approvability of Monacor (Bisoprolol Fumarate), and Recommended Labeling Changes.

On November 1, 1991, I expressed my wish to defer signing off on the preclinical approval of Monacor (bisoprolol fumarate), a  $\beta$ -1-adrenoceptor antagonist sponsored by American Cyanamid, Lederle Pharmaceutical Co., until the evidence for carcinogenicity had been reviewed by the Carcinogenicity Advisory Committee (CAC). The CAC met on November 19, 1991, and the pharmacological and toxicological data were presented, along with the statistical evaluation by the agency statistician.

Dr. Weissinger's Draft Report of the CAC meeting minutes issued on January 15, 1992; the report and its conclusions were then critiqued based on consultations and literature searches accomplished in the interim time since the CAC meeting. My critique and recommendations issued as a report on January 28, 1992. I have recommended that Monacor (bisoprolol fumarate) be considered approvable, relative to preclinical issues; the issues related to carcinogenic potential have been resolved to my satisfaction.

I have also recommended that the lung slides from the second mouse study be completed, including the second control group, and that the individual data and summary data be submitted to complete our files on this issue. I am confident that the additional data will have no effect on our overall conclusions.

Attached you will find the last section of the preclinical NDA Review, the LABELING section, which was completed with the accomplishment of the prerequisite steps described above.

/S/

~~Ernest J. Belair, Ph.D.~~

ATTACHMENT

cc:

Orig. NDA

HFD-110

HFD-110/CSO

HFD-110/EBelair

19-982.APP

A. N. F.  
2/3/92

## ATTACHMENT

## LABELING (Preclinical)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two long-term studies in mice (20 and 24 months) and one in rats (26 months) were conducted with bisoprolol. No evidence of significant carcinogenic potential was seen in mice given oral doses up to approximately 250 mg/kg/day, which is 313 times the daily maximum recommended human dose (MRHD) of 0.8 mg/kg (calculated on the basis of 50 Kg subjects), or in rats given oral doses up to approximately 125 mg/kg/day, which is 157 times the daily MRHD. Calculating the doses on the basis of body surface area, mice were administered doses of 800 mg/M<sup>2</sup> and rats doses of 875 mg/M<sup>2</sup>; these were 30 and 32 times the daily MRHD of 27.2 mg/M<sup>2</sup>, respectively. Bisoprolol was devoid of mutagenic or clastogenic potential when evaluated in in vivo and in vitro assays.

Reproduction studies in rats did not show any impairment of fertility at doses up to 150 mg/kg/day, or up to 188 and 39 times, respectively, the daily MRHD of 0.8 mg/kg and 27.2 mg/M<sup>2</sup>.

USAGE IN PREGNANCYPregnancy category C

Bisoprolol was not teratogenic in rats at doses up to 150 mg/kg/day, which is 188 times (or 39 times on a M<sup>2</sup> basis) the daily MRHD. Bisoprolol was fetotoxic (increased late resorptions) at 50 mg/kg/day (325 mg/M<sup>2</sup>) and maternotoxic (decreased food intake and body weight gain) at 150 mg/kg/day (1050 mg/M<sup>2</sup>). Bisoprolol was not teratogenic in rabbits at daily doses of up to 12.5 mg/kg (157.5 mg/M<sup>2</sup>) which is 16 times the daily MRHD (6 times on the basis of dose/body surface area), but was embryolethal (increased early resorptions) at daily doses of 12.5 mg/kg (157.5 mg/M<sup>2</sup>).

There are no adequate and well controlled studies in pregnant women. Monacor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

JUL 31 1992

UPDATE  
CSO overview of NDA 19-982  
ZEBETA (bisoprolol fumarate) Tablets  
July 30, 1992

**Medical Review**

This NDA was submitted on August 3, 1989 for mild to moderate hypertension, 5 to 20 mg once a day dosing. In his review dated January 8, 1991, Dr. Ganley recommended that bisoprolol be approved for mild to moderate hypertension, but he believed the initial starting dose should be 2.5 mg. He also made labeling suggestions and comments in appendix F of his review.

Lederle submitted a response to a request for any information concerning possible interactions between bisoprolol and anti-coagulant therapy on October 18, 1990. In his review of this submission dated October 22, 1990, Dr. Ganley concluded bisoprolol does not change the prothrombin time in patients on warfarin therapy.

Cardiovascular and Renal Drugs Advisory Committee

Bisoprolol was presented before the Advisory Committee on June 6, 1991. The Committee unanimously recommended that bisoprolol be approved for hypertension.

**Statistical Review**

In his review dated April 12, 1991, Dr. Mahjoo concluded there is strong evidence to support the efficacy and safety of bisoprolol. Study 57-3 demonstrated that bisoprolol is effective at doses of 2.5, 10 and 40 mg once-a-day for all patients. There is a significant dose-response relationship. The blood pressure response may have plateaued around 30 mg Q.D. There is no significant treatment-by-race interaction, although the data suggest that bisoprolol may be slightly less effective for black compared to non-black patients.

**Biopharmaceutical Review**

In his review dated February 15, 1991, Dr. Mehta concluded that the biopharmaceutical section of this NDA is approvable. The dissolution specifications are not finalized, however, and additional dissolution results as outlined in his comment # 7 should be submitted within 30 days post approval of the NDA. Dr. Mehta recommended that Lederle's proposed specifications be considered Interim Specifications. Lederle has been provided with a copy of Dr. Mehta's review so they are aware of his dissolution recommendation.

In her review dated June 15, 1992, Dr. Kaus stated that the firm has satisfactorily responded to comments raised by Dr. Mehul Meta in his review of the original NDA 19-982. She recommended the following dissolution specifications:

Apparatus type: USP method #2  
Medium: Deaerated Water, 900 mL  
Speed of Rotation: 75 rpm  
Sampling time: minutes  
Q value: %

She also listed labeling comments (see her review, page 6) Dr. Lipicky said her comments would be taken into consideration at the time the labeling is marked-up for approval. There is no need to send them to the firm.

### **Pharmacology Reviews**

#### **Dr. Belair**

In his review dated October 29, 1991, Dr. Belair was of the opinion that Bisoprolol is a tumorigen. He recommended that all of the slides be re-read blind, and in the case of the second mouse study, the remaining tissues should be processed and read in the same manner. In addition a 90-day dose-ranging study, including a parallel toxicokinetic study, should be initiated as soon as possible using the same mouse strain and supplier as used in the second mouse study. If the sponsor cannot agree this course of action, or if statistically significant tumor incidences persist after blinding, Dr. Belair recommended that this drug be treated as is appropriate for a drug with carcinogenic potential.

#### **Dr. DeFelice**

In his supervisory review dated August 28, 1991, Dr. DeFelice concluded that tumorigenicity had been adequately assessed and is not evident from the data provided, given the irreproducibility of the results across and within species and use of statistical analyses able to distinguish among very low absolute incidences.

### **Chemistry Review**

There are no outstanding chemistry issues. The methods have been validated, see Review #4 of Ms. Cunningham's review.

The establishment inspections have been completed and found acceptable as follows:

Acceptable on February 2, 1991 - manufacturer, packager of drug product:

Acceptable on February 12, 1991- Labeling trade bottles, attachment of package insert, shrink-wrapping of "bundled" trade bottles, repacking of "bundles" in shipping containers:

American Cyanamid  
Lederle Lab. Division  
Middletown Road  
Pearl River, NY 19065

Acceptable on November 8, 1990 - Manufacture of new drug substance

FUR of all three of the above found acceptable on June 15, 1992

Lederle has elected to change the trade name from "Probeta" to "ZEBETA". In his E-mail to Dr. Wolters dated July 28, 1992, Mr. Kent Johnson stated that he and Yana Mille had found no look-alike or sound-alike problems during their limited review of ZEBETA.

### CSO Summary

1. In his memo to Dr. Temple dated October 18, 1991, Dr. Lipicky was of the opinion that neither carcinogenicity study found a signal that can be reasonably be suspected to raise a question about the tumorigenic potential of bisoprolol up to several thousand times the doses anticipated for use in man and concluded that the results not only have no bearing on approvability but should not appear in the labeling.
2. Dr. Lipicky included Dr. Ganley's, Dr. Mehta's and Dr. Kaus' labeling suggestions (where appropriate) in the marked-up labeling.
3. An approvable letter issued on June 11, 1992. The final labeling submitted July 31, 1992 which we will call draft (because they have not submitted the carton and container labels) contains all the requested changes.

To my knowledge, there are no issues that might prevent action on this NDA.

/S/

Zelda McDonald, CSO

cc: Orig. NDA  
HFD-110

Record of Meeting  
GAO & FDA  
June 29, 1992

SEP 18 1992

*Reg*

NDA #: 19-982 Zebeta (Bisoprolol fumarate) Tablets

General Accounting Office (GAO) participants:

George Silberman                      Assistant Director, Program Evaluation & Methodology Division  
Michele Orza, Sc.D.                      Program Evaluation & Methodology Division

FDA Participants:

Robert Temple, M.D.                      Director, Office of Drug Evaluation I, HFD-100  
David Rosen, Esq.                      Acting Special Assistant to the Director, HFD-110  
Robert O'Neill, Ph.D.                      Director, Division of Biometrics, HFD-710  
Raymond Lipicky, M.D.                      Director, Div. of Cardio-Renal Drug Products, HFD-110  
Charles Ganley, M.D.                      Medical Officer, HFD-110  
Al DeFelice, Ph.D.                      Supervisory Pharmacologist, HFD-110  
Robert Wolters, Ph.D.                      Supervisory Chemist, HFD-110  
Preet Gill-Kumar, Ph.D.                      Pharmacologist, HFD-110  
Mehul Mehta, Ph.D.                      Biopharmaceutist, HFD-420  
George Chi, Ph.D.                      Supervisory Statistician, Div. of Biometrics, HFD-713  
Kooros Mahjoob, Ph.D.                      Statistician, HFD-713  
Zelda McDonald                      CSO, HFD-111 *zgm 9/18/92*  
Gary Buehler                      CSO, HFD-111

Background:

Dr. Orza is engaged in a GAO project wherein she is looking at the quality of NDA submissions. Instead of looking at all NDAs, she has targeted, for her sample, all NDAs for NMEs submitted in 1989 (There are 26 in all) . Her protocol requires that she discuss each application first with the FDA reviewers and then with the applicant. The purpose of this meeting was to discuss the perceived strengths and weaknesses of the bisoprolol fumarate application with the reviewer in each discipline.

Meeting:

Mr. Silberman began the meeting by stating that their Division was the "statistical" division of the GAO. They have decided to detail the major steps in the process of reviewing an NDA and obtain from FDA the most significant limitations in reviewing each NDA. They will then obtain Industry's viewpoint.

Dr. Temple asked if the GAO would be reporting about specific companies because he was of the opinion that generalizing is not useful. Mr. Silberman said they would have to talk with their attorneys to see how specific they can be in the reporting. They are not quite sure at this point who they should talk with at the companies; the vice president or, say, a chemist and whether the companies would want that person's statements to be official. Dr. Temple asked if they would be presenting their findings in considerable detail, and Mr. Silberman said yes. Dr. Orza said that they will write up the Zebeta case and run it by us.

NOV 1 1991

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 1, 1991

FROM: Ernest J. Belair, Ph.D.

SUBJECT: NDA 19-982, bisoprolol fumarate (CL 287,939)

TO: Albert F. DeFelice, Ph.D.  
Supervisory Pharmacologist, HFD-110

I wish to defer signing-off on NDA 19-982, bisoprolol fumarate (Lederle Laboratories, Division of American Cyanamid) until the evidence for tumorigenicity in mice and rats is discussed with the Carcinogenicity Advisory Committee.

/S/

Ernest J. Belair, Ph.D.  
November 1, 1991

cc:  
Orig. NDA  
HFD-110  
HFD-110/CSO  
HFD-110/EBelair  
clb/11/4/91  
N19982.MEM

NOV 13 1991

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 13, 1991

FROM: Ernest J. Belair, Ph.D.  
Division of Cardio-Renal Drug Products

SUBJECT: ADDENDUM #1 TO NDA REVIEW OF BISOPROLOL HEMIFUMARATE  
NDA 19-982 11/13/91

TO: See cc: Below

Attached are replacement pages for the original review of NDA 19-982 to correct and/or update some data.

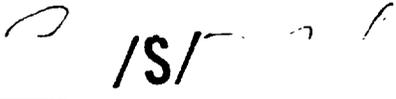
page 65: The graphs for males and females were accidentally switched.

page 67: Last sentence of the first paragraph, "in the evaluation section" has been replaced by "ATTACHMENT E and in the evaluation section."

First sentence of the second paragraph, "E" of Attachment I.E. was replaced by "F".

page 143: Line 8 of the first paragraph, "0-0.3%" was originally a typographical error based on my rough draft of ATTACHMENT I.E. (see below); some of these pages were manually corrected. The revised version of ATTACHMENT I.E. indicated that 0-0.3% was indeed correct; it has been changed to so conform.

ATTACHMENT I.E.: Sponsor's historical control data (ATTACHMENT I.E.) was reorganized to conform with control data. The meaning of some of the data was difficult to interpret, consequently, the rough draft of the table was faxed to sponsor for verification and correction of 9/5/91; the revisions were received on 11/06/91, after the NDA review issued.

  
Ernest J. Belair, Ph.D.

cc: Orig.  
HFD-110  
HFD-102/JWeissinger  
HFD-345/GJames  
HFD-110/CSO  
HFD-110/ADeFelice  
HFD-110/EBelair  
sh/11/13/91:0308H

Figure 9.

Body Weight (g) Effects of Bisoprolol on Male Mice in an 87-Week Carcinogenicity Study

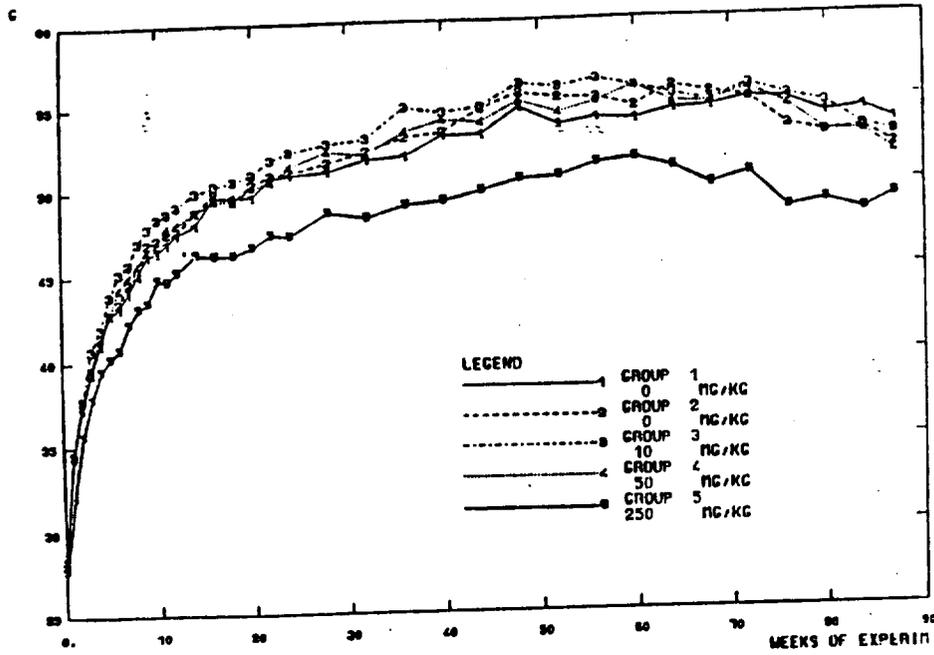
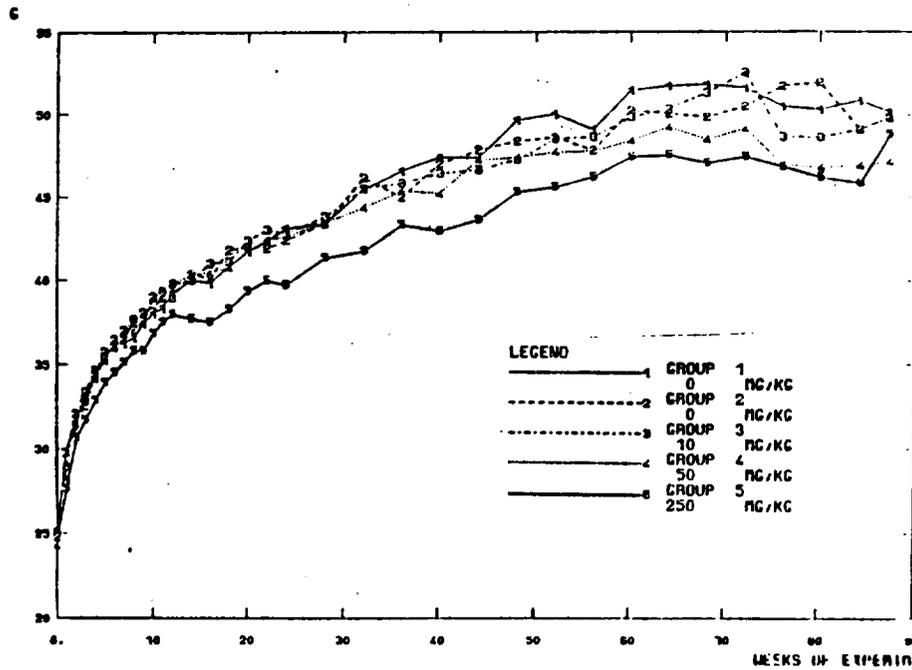


Figure 10.

Body Weight (g) Effects of Bisoprolol on Female Mice in an 87-Week Carcinogenicity Study



N.B. Ordinate is "Animal Body Weight in Grams", abscissa is "Weeks of Drug Administration" in Figures 9 and 10..

Attachment I. D., sponsor's summary of the historical incidence of spontaneous tumors in untreated NMRI mice, is not in a format which lends itself readily for comparison of study tumor incidence. These data will be reorganized and presented ATTACHMENT E and in the evaluation section.

Attachment I. F. presents the incidence, by organ, of nonneoplastic histopathological organ lesions found in the bisoprolol-treated mice compared with control groups of animals. Examination of the data in Attachment I. E. revealed that there were three lesions which might be interpreted as showing dose-related trends of increasing incidence: the lung (emphysema, focal), liver (single cell necrosis), and uterus (glandular, cystic hyperplasia).

In summary, Sponsor's statistical team maintains that "the data analyzed in this study do not provide evidence for an increase in tumor prevalence due to treatment with bisoprolol". We consider that the high dose used in this study was probably not at the MTD, that segments of the data escaped evaluation (tumor incidence of 5 or less animals per group), and that sufficient attention was not paid to the significant p-value of the test for heterogeneity of ovarian adenoma incidence.

Toxicokinetics: Satellite groups were not provided for correlation of bisoprolol ADME with carcinogenicity study results. A study of plasma concentrations resulting from administration of 10, 50, and 250 mg/kg/day bisoprolol in the feed for 14 days was summarized in report 119, and the mean plasma concentrations are shown below:

Sponsor notes that there was considerable variation in the blood concentrations of bisoprolol, suggesting "that the time of maximum food intake and /or the amount of food taken by the animals was quite different". Mean blood levels of bisoprolol were higher in males than in females. Blood levels were proportional to the dose following 10 and 50 mg/kg/day on days 2 and 14, but were 2 to 3 times the levels proportional to the lower doses after 250 mg/kg/day. However, sponsor notes that plasma concentrations were lower than those obtained after oral administration (by gavage) of comparable doses to mice by factors of 50 to 100; see Table 8 where doses of 10, 100, and 250 mg/kg, by gavage result in  $C_{max}$  values of 0.60, 8.36, and 13.80 ug/ml, respectively. This led sponsor to conclude that blood sampling times had been chosen too late in the drug elimination phase. We conclude that this study is of little utility, since we cannot be sure as to exactly what caused the relatively low blood levels. This study does point out, however, that there is a good probability that the blood levels expected on the basis of the previous pharmacokinetic studies will not occur; should evidence for carcinogenicity be observed, the drug will have to be considered to have a greater potency than indicated by the target doses.

Table 13  
Tumor Incidence Rates  
Male Mice, Lymph Nodes Hemangioma-abdominal Lymph Node

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	17	0	7	0	5	0	8
51-70	0	27	0	11	0	14	1	7
71-86	0	27	1	18	0	17	0	17
Terminal	0	29	0	14	0	14	1	17
Total	0	100	1	50	0	50	2	49

The FDA statistician, Dr. Lin, also reported that sponsor submitted combined granulocytic leukemia data for females which showed a significant dose-response relationship for all organs ( $p=0.04$ ) by the exact permutation trend test. The data for this tumor can be seen in the table below which is Table 14 of Dr. Lin's report. Historical control data from the E. Merck

Table 14  
Tumor Incidence Rates  
Female Mice, All Organs, Granulocytic Leukemia

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	14	0	8	1	6	0	2
51-70	1	27	0	12	0	12	2	11
71-86	1	37	0	20	2	17	1	18
Terminal	0	22	0	10	0	15	0	19
Total	2	100	0	50	3	50	3	50

Notes: T: Number of necropsies with the above tumor.  
N: Number of necropsies.

Laboratories (attachment I. D.) recalculated by this reviewer showed that the control incidence of granulocytic leukemia in 20-24 month studies had a mean of 0.6% with a range of 0-0.3% (Attachment I. E., Table 4.); thus, this neoplasm is rare and its incidence is significant at 0.05%. Moreover, it should be observed that the mean incidences of the mid and high dose groups were 5 and 10 times, respectively, the mean historical incidence for this neoplasm.

Dr. Lin combined all tumors in the same organ for various organs and tumor types (excluding the combined granulocytic leukemia) and found that none of the combinations was significant. However, there is evidence that unwarranted combinations may have been made, and the combinations need to be reexamined before they are used as supporting data.

In summary, there are significant dose-related trends of tumor incidence in female mice (lungs metastatic adenocarcinoma-B, ovaries cystadenoma, and granulocytic leukemia) and male mice (lymph nodes hemangioma of the abdominal

Table 1.  
Summary of Neoplastic Lesions in Two Groups of Control  
Male NMRI Mice (E. Merck): 18 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<b>MALIGNANT LYMPHOMA AND MYELOSIS</b>				
<u>numerous organs</u>	200			
malignant lymphoma				
Hodgkin				
granulocytic leukemia				
<u>hematopoietic system and lymphatic system</u>	200			
malignant lymphoma		20	10.0	6-14
Hodgkin				
plasmacytoma				
histiocytic sarcoma		7	3.5	3-4
<u>bone marrow</u>	200			
malignant lymphoma				
granulocytic leukemia				
<u>lymph nodes</u>	200			
malignant lymphoma				
<u>thymus</u>	200			
malignant lymphoma				
<b><u>TUMORS</u></b>				
<u>skin/subcutis</u>	200			
squamous papilloma				
keratoacanthoma				
lipoma (hibernoma)				
hemangioma				
fibrosarcoma/sarcoma, nos				
osteosarcoma				
hemangioendothelioma				
sebaceous adenoma		1	0.5	0-1
<u>mammary gland</u>	200			
solid carcinoma				
cylindro-adenocarcinoma				
papillary adenocarcinoma				
<u>spleen/lymph nodes</u>	200			
hemangioma				
hemangioendothelioma				

Table 1: (continued)  
 Summary of Neoplastic Lesions in Two Groups of Control  
 Male NMRI Mice (E. Merck): 18 Month Studies

2/16

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>bone</u>	200			
osteoma				
osteosarcoma				
<u>pelvic connective tissue</u>	200			
fibrosarcoma				
<u>lung</u>	200			
adenoma				
adenoma (malignant degeneration)				
adenomatosis				
adenocarcinoma				
alveologenic carcinoma		31	15.5	10-21
<u>salivary gland</u>	200			
adenoma				
undifferentiated carcinoma				
<u>liver</u>	200			
neoplastic nodule		3	1.5	1-2
hepatoma, benign				
hepatocellular carcinoma		1	0.5	0-1
cholangioma				
cholangiocarcinoma		1	0.5	0-1
hemangioendothelioma		2	1.0	1-1
hemangioma		1	0.5	0-1
<u>gallbladder</u>	200			
adenocarcinoma				
<u>pancreas (except islets)</u>	200			
eccrine adenoma				
liposarcoma				
<u>stomach</u>	200			
adenocarcinoma		1	0.5	0-1
squamous carcinoma				
<u>forestomach</u>	200			
papilloma				
metastasising anaplastic carcinoma				
squamous cell carcinoma				

Table 1: (continued)  
Summary of Neoplastic Lesions in Two Groups of Control  
Male NMRI Mice (E. Merck): 18 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>intestine</u>	200			
polyp				
leiomyosarcoma				
<u>kidney</u>	200			
cortical carcinoma				
cortical tumor/adenoma		2	1.0	1-1
lipoma				
adenomyosarcoma (Hilms' tumor)				
<u>urinary bladder</u>	200			
papilloma				
ganglioneuroma				
carcinoma				
pleomorphic carcinoma				
carcinosarcoma				
leiomyosarcoma		3	1.5	1-2
<u>testis</u>	200			
Leydig cell tumor		1	0.5	0-1
hemangioendothelioma				
<u>epididymis</u>	200			
adenoma		1	0.5	0-1
<u>uterus</u>	—			
mucosal polyp				
stromal polyp				
fibroma				
neurilemoma				
hemangioma				
leiomyoma				
mixed mesenchymal tumor				
hemangioendothelioma				
leiomyosarcoma				
adenocarcinoma				
carcinosarcoma				
stromal sarcoma				
fibrosarcoma				
<u>ovary</u>	—			
gonadal stromal tumor				
luteoma				
granulosa/theca cell tumor				
arrhenoblastoma				
interstitial cell tumor				
papillary cystadenoma				
hemangioma				

Table 1: (continued)  
**Summary of Neoplastic Lesions in Two Groups of Control**  
**Male NMRI Mice (E. Merck): 18 Month Studies**

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
carcinoma, nos				
granulosa cell carcinoma				
fibrosarcoma				
hemangioendothelioma				
<u>pituitary gland</u>	200			
adenoma				
malignant adenoma				
<u>adrenal gland</u>	200			
adrenocortical adenoma/cortical		13	6.5	5-8
phaeochromocytoma		2	1.0	0-2
<u>thyroid gland</u>	200			
cystadenoma				
follicular adenoma		1	0.5	0-1
undiff. adenocarcinoma				
C-cell tumor				
<u>islet of Langerhans</u>	200			
islet cell tumor		1	0.5	0-1
<u>brain</u>	200			
mixed glioma				
<u>orbit</u>	200			
pleomorphic sarcoma				
<u>lacrimal gland</u>	200			
cystadenoma				
adenocarcinoma, nos				
<u>Harder's gland</u>	200			
papillary cystadenoma/adenoma		2	1.0	1-1
adenocarcinoma		1	0.5	0-1
<u>abdominal cavity</u>	200			
hemangioendothelioma		1	0.5	0-1
<b><u>METASTATIC TUMORS</u></b>				
numerous organs	200			
lymph nodes	200			
lung	200			
peritoneum	200			
primary site unknown (fibrosarcoma)	200	1	0.5	0-1

**N.B.**

nos - Not otherwise specified.  
 Total # Animals - Total number of animals.  
 # Tumor-Bearing Animals - Total number of tumor-bearing animals.  
 Percent - Mean percent of tumor-bearing animals.  
 Range - The lowest and highest percent of tumor-bearing animals found  
 in the study groups.  
 No Numbers - No reported tumors.

Table 2.  
 Summary of Neoplastic Lesions in Two groups of Control  
 Female NMRI Mice (E. Merck): 18 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<b>MALIGNANT LYMPHOMA AND MYELOSIS</b>				
<u>numerous organs</u>	200			
malignant lymphoma				
Hodgkin				
granulocytic leukemia				
<u>hematopoietic system and lymphatic system</u>	200			
malignant lymphoma		51	25.5	21-30
Hodgkin				
plasmacytoma				
histiocytic sarcoma		4	2.0	1-3
<u>bone marrow</u>	200			
malignant lymphoma				
granulocytic leukemia				
<u>lymph nodes</u>	200			
malignant lymphoma				
<u>thymus</u>	200			
malignant lymphoma				
<b>TUMORS</b>				
<u>skin/subcutis</u>	200			
squamous papilloma		1	0.5	0-1
keratoacanthoma				
lipoma (hibernoma)				
hemangioma				
fibrosarcoma/sarcoma, nos				
osteosarcoma				
hemangioendothelioma		1	0.5	0-1
sebaceous adenoma				
<u>mammary gland</u>	200			
solid carcinoma				
cylindro-adenocarcinoma				
papillary adenocarcinoma				
<u>spleen/lymph nodes</u>	200			
hemangioma				
hemangioendothelioma				

Table 2: (continued)  
 Summary of Neoplastic Lesions in Two groups of Control  
 Female NMRI Mice (E. Merck): 18 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>bone</u>	200			
osteoma				
osteosarcoma		1	0.5	0-1
<u>pelvic connective tissue</u>	200			
fibrosarcoma				
<u>lung</u>	200			
adenoma				
adenoma (malignant degeneration)				
adenomatosis				
adenocarcinoma				
alveologenic carcinoma		19	9.5	8-11
<u>salivary gland</u>	200			
adenoma				
undifferentiated carcinoma				
<u>liver</u>	200			
neoplastic nodule		2	1.0	1-1
hepatoma, benign				
hepatocellular carcinoma				
cholangioma				
cholangiocarcinoma				
hemangioendothelioma				
hemangioma				
<u>galbladder</u>	200			
adenocarcinoma				
<u>pancreas (except islets)</u>	200			
eccrine adenoma				
liposarcoma				
<u>stomach</u>	200			
adenocarcinoma				
squamous carcinoma				
<u>forestomach</u>	200			
papilloma				
metastasising anaplastic carcinoma				
squamous cell carcinoma				

Table 2: (continued)  
 Summary of Neoplastic Lesions in Two groups of Control  
 Female NMRI Mice (E. Merck): 18 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>intestine</u>	200			
polyp				
leiomyosarcoma				
<u>kidney</u>	200			
cortical carcinoma				
cortical tumor/adenoma				
lipoma				
adenomyosarcoma (Wilms' tumor)				
<u>urinary bladder</u>	200			
papilloma				
ganglioneuroma				
carcinoma				
pleomorphic carcinoma				
carcinosarcoma				
leiomyosarcoma				
<u>testis</u>	—			
Leydig cell tumor				
hemangioendothelioma				
<u>epididymis</u>	—			
adenoma				
<u>uterus</u>	200			
mucosal polyp		11	5.5	5-6
stromal polyp		1	0.5	0-1
fibroma				
neurilemoma		1	0.5	0-1
hemangioma				
leiomyoma		2	1	0-2
mixed mesenchymal tumor				
hemangioendothelioma				
leiomyosarcoma		2	1.0	0-1
adenocarcinoma				
carcinosarcoma				
stromal sarcoma				
fibrosarcoma		1	0.5	0-1
<u>ovary</u>	200			
gonadal stromal tumor		16	8.0	6-10
luteoma				
granulosa/theca cell tumor				
arrhenoblastoma				
interstitial cell tumor				
papillary cystadenoma		2	1	0-2
hemangioma				

Table 2: (continued)  
Summary of Neoplastic Lesions in Two groups of Control  
Female NMRI Mice (E. Merck): 18 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
carcinoma, nos				
granulosa cell carcinoma				
fibrosarcoma				
hemangioendothelioma				
<u>pituitary gland</u>	200			
adenoma		1	0.5	0-1
malignant adenoma				
<u>adrenal gland</u>	200			
adrenocortical adenoma/cortical		1	0.5	0-1
phaeochromocytoma		3	1.5	1-2
<u>thyroid gland</u>	200			
cystadenoma				
follicular adenoma				
undiff. adenocarcinoma				
C-cell tumor		2	1.0	0-2
<u>islet of Langerhans</u>	200			
islet cell tumor				
<u>brain</u>	200			
mixed glioma				
<u>orbit</u>	200			
pleomorphic sarcoma				
<u>lacrimal gland</u>	200			
cystadenoma				
adenocarcinoma, nos				
<u>Harder's gland</u>	200			
papillary cystadenoma/adenoma		4	2.0	1-3
adenocarcinoma				
<u>abdominal cavity</u>	200			
hemangioendothelioma				
<b><u>METASTATIC TUMORS</u></b>				
numerous organs	200			
lymph nodes	200			
lung	200			
peritoneum	200			
primary site unknown (fibrosarcoma)	200			

**N.B.**

nos - Not otherwise specified.

Total # Animals - Total number of animals.

# Tumor-Bearing Animals - Total number of tumor-bearing animals.

Percent - Mean percent of tumor-bearing animals.

Range - The lowest and highest percent of tumor-bearing animals found  
in the study groups.

No Numbers - No reported tumors.

**Table 3.**  
**Summary of Neoplastic Lesions in Five Groups of Control**  
**Male NMRI Mice (E. Merck): 20-24 Month Studies**

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL</u> <u># ANIMALS</u>	<u># TUMOR-</u> <u>BEARING</u> <u>ANIMALS</u>	<u>MEAN</u> <u>PERCENT</u>	<u>RANGE OF</u> <u>PERCENTS</u>
<b>MALIGNANT LYMPHOMA AND MYELOSIS</b>				
<u>numerous organs</u>	340			
malignant lymphoma		21	6.2	0-18
Hodgkin				
granulocytic leukemia		4	1.2	0-5
<u>hematopoietic system and</u> <u>lymphatic system</u>	340			
malignant lymphoma		36	10.6	0-20
Hodgkin		1	0.3	0-3
plasmacytoma				
histiocytic sarcoma		6	1.8	0-8
<u>bone marrow</u>	300 <sup>a</sup>			
malignant lymphoma				
granulocytic leukemia				
<u>lymph nodes</u>	340			
malignant lymphoma		3	0.9	0-3
<u>thymus</u>	340			
malignant lymphoma				
<b>TUMORS</b>				
<u>skin/subcutis</u>	340			
squamous papilloma				
keratoacanthoma				
lipoma (hibernoma)		1	0.3	0-2
hemangioma				
fibrosarcoma/sarcoma, nos		1	0.3	0-1
osteosarcoma				
hemangioendothelioma		1	0.3	0-1
sebaceous adenoma				
<u>mammary gland</u>	340			
solid carcinoma				
cylindro-adenocarcinoma				
papillary adenocarcinoma				
<u>spleen/lymph nodes</u>	340			
hemangioma		1	0.3	0-1
hemangioendothelioma		1	0.3	0-1

<sup>a</sup>One study (T4047) was not included due to the small number of bone marrow samples examined.

Table 3: (continued)  
Summary of Neoplastic Lesions in Five Groups of Control  
Male NMRI Mice (E. Merck): 20-24 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>bone</u>	340			
osteoma				
osteosarcoma				
<u>pelvic connective tissue</u>	340			
fibrosarcoma				
<u>lung</u>	340			
adenoma		28	8.2	0-21
adenoma (malignant degeneration)		1	0.3	0-1
adenomatosis				
adenocarcinoma				
alveologenic carcinoma		65	19.1	0-38
<u>salivary gland</u>	340			
adenoma				
undifferentiated carcinoma				
<u>liver</u>	340			
neoplastic nodule		7	2.1	0-6
hepatoma, benign		1	0.3	0-1
hepatocellular carcinoma		3	0.9	0-4
cholangioma		1	0.3	0-2
cholangiocarcinoma				
hemangioendothelioma		7	2.1	0-8
hemangioma		5	1.5	0-8
<u>gallbladder</u>	340			
adenocarcinoma		1	0.3	0-1
<u>pancreas (except islets)</u>	340			
eccrine adenoma				
liposarcoma				
<u>stomach</u>	340			
adenocarcinoma		2	0.6	0-4
squamous carcinoma		1	0.3	0-1
<u>forestomach</u>	340			
papilloma		2	0.6	0-2
metastasising anaplastic carcinoma				
squamous cell carcinoma				

Table 3: (continued)  
 Summary of Neoplastic Lesions in Five Groups of Control  
 Male NMRI Mice (E. Merck): 20-24 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>intestine</u>	340			
polyp				
leiomyosarcoma				
<u>kidney</u>	340			
cortical carcinoma		1	0.3	0-2
cortical tumor/adenoma				
lipoma		1	0.3	0-1
adenomyosarcoma (Hilms' tumor)				
<u>urinary bladder</u>	340			
papilloma		3	0.9	0-3
ganglioneuroma		1	0.3	0-1
carcinoma				
pleomorphic carcinoma		1	0.3	0-1
carcinosarcoma		1	0.3	0-2
leiomyosarcoma		1	0.3	0-2
<u>testis</u>	340			
Leydig cell tumor		15	4.4	0-8
hemangioendothelioma		1	0.3	0-1
<u>epididymis</u>	340			
adenoma				
<u>uterus</u>	---			
mucosal polyp				
stromal polyp				
fibroma				
neurilemoma				
hemangioma				
leiomyoma				
mixed mesenchymal tumor				
hemangioendothelioma				
leiomyosarcoma				
adenocarcinoma				
carcinosarcoma				
stromal sarcoma				
fibrosarcoma				
<u>Ovary</u>	---			
gonadal stromal tumor				
luteoma				
granulosa/theca cell tumor				
arrhenoblastoma				
interstitial cell tumor				
papillary cystadenoma				
hemangioma				

Table 3: (continued)  
 Summary of Neoplastic Lesions in Five Groups of Control  
 Male NMRI Mice (E. Merck): 20-24 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
carcinoma, nos				
granulosa cell carcinoma				
fibrosarcoma				
hemangioendothelioma				
<u>pituitary gland</u>	340			
adenoma				
malignant adenoma				
<u>adrenal gland</u>	340			
adrenocortical adenoma/cortical		10	2.9	0-12
phaeochromocytoma				
<u>thyroid gland</u>	340			
cystadenoma		1	0.3	0-1
follicular adenoma		1	0.3	0-2
undiff. adenocarcinoma				
C-cell tumor				
<u>islet of Langerhans</u>	340			
islet cell tumor		1	0.3	0-2
<u>brain</u>	340			
mixed glioma		1	0.3	0-2
<u>orbit</u>	340			
pleomorphic sarcoma		1	0.3	0-2
<u>lacrimal gland</u>	340			
cystadenoma				
adenocarcinoma, nos		1	0.3	0-1
<u>Harder's gland</u>	340			
papillary cystadenoma/adenoma		11	3.2	0-12
adenocarcinoma				
<u>abdominal cavity</u>	340			
hemangioendothelioma				
<b><u>METASTATIC TUMORS</u></b>				
numerous organs	340			
lymph nodes	340			
lung	340			
peritoneum	340			
primary site unknown (fibrosarcoma)	340			

N.B.

nos - Not otherwise specified.

Total # Animals - Total number of animals.

# Tumor-Bearing Animals - Total number of tumor-bearing animals.

Percent - Mean percent of tumor-bearing animals.

Range - The lowest and highest percent of tumor-bearing animals found  
 in the study groups.

No Numbers - No reported tumors.

Table 4.  
Summary of Neoplastic Lesions in Five Groups of Control  
Female NMRI Mice (E. Merck): 20-24 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<b>MALIGNANT LYMPHOMA AND MYELOSIS</b>				
<u>numerous organs</u>	340			
malignant lymphoma		30	8.8	0-25
Hodgkin		4	1.2	0-4
granulocytic leukemia		2	0.6	0-3
<u>hematopoietic system and lymphatic system</u>	340			
malignant lymphoma		78	22.9	2-42
Hodgkin				
plasmacytoma		1	0.3	0-1
histiocytic sarcoma		3	0.9	0-2
<u>bone marrow</u>	300 <sup>a</sup>			
malignant lymphoma				
granulocytic leukemia				
<u>lymph nodes</u>	340			
malignant lymphoma		3	0.9	0-3
<u>thymus</u>	340			
malignant lymphoma		1	0.3	0-1
<b>TUMORS</b>				
<u>skin/subcutis</u>	340			
squamous papilloma		1	0.3	0-1
keratoacanthoma		1	0.3	0-2
lipoma (hibernoma)				
hemangioma		1	0.3	0-1
fibrosarcoma/sarcoma, nos		5	1.5	0-2
osteosarcoma		1	0.3	0-1
hemangioendothelioma				
sebaceous adenoma				
<u>mammary gland</u>	340			
solid carcinoma		1	0.3	0-1
cylindro-adenocarcinoma		1	0.3	0-1
papillary adenocarcinoma		1	0.3	0-1
<u>spleen/lymph nodes</u>	340			
hemangioma				
hemangioendothelioma				

<sup>a</sup>One study (T4047) was not included due to the small number of bone marrow samples examined.

Table 4: (continued) Page 2  
 Summary of Neoplastic Lesions in Five Groups of Control  
 Female NMRI Mice (E. Merck): 20-24 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>bone</u>	340			
osteoma		2	0.6	0-2
osteosarcoma				
<u>pelvic connective tissue</u>	340			
fibrosarcoma		1	0.3	0-1
<u>lung</u>	340			
adenoma		30	8.8	0-23
adenoma (malignant degeneration)		1	0.3	0-1
adenomatosis		1	0.3	0-1
adenocarcinoma		1	0.3	0-3
alveologenic carcinoma		29	8.5	0-22
<u>salivary gland</u>	340			
adenoma		1	0.3	0-1
undifferentiated carcinoma		1	0.3	0-1
<u>liver</u>	340			
neoplastic nodule		3	0.9	0-3
hepatoma, benign		1	0.3	0-1
hepatocellular carcinoma				
cholangioma				
cholangiocarcinoma				
hemangioendothelioma		4	1.2	0-2
hemangioma				
<u>gallbladder</u>	340			
adenocarcinoma				
<u>pancreas (except islets)</u>	340			
eccrine adenoma		1	0.3	0-2
liposarcoma		1	0.3	0-1
<u>stomach</u>	340			
adenocarcinoma				
squamous carcinoma				
<u>forestomach</u>	340			
papilloma		2	0.6	0-2
metastasising anaplastic carcinoma		1	0.3	0-1
squamous cell carcinoma		1	0.3	0-1

Table 4: (continued) Page 3  
Summary of Neoplastic Lesions in Five Groups of Control  
Female NMRI Mice (E. Merck): 20-24 Month Studies

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
<u>intestine</u>	340			
polyp		1	0.3	0-1
leiomyosarcoma		1	0.3	0-2
<u>kidney</u>	340			
cortical carcinoma		2	0.6	0-2
cortical tumor/adenoma				
lipoma				
adenomyosarcoma (Wilms' tumor)		1	0.3	0-1
<u>urinary bladder</u>	340			
papilloma				
ganglioneuroma				
carcinoma		1	0.3	0-1
pleomorphic carcinoma				
carcinosarcoma				
leiomyosarcoma				
<u>testis</u>	—			
Leydig cell tumor				
hemangioendothelioma				
<u>epididymis</u>	—			
adenoma				
<u>uterus</u>	340			
mucosal polyp		1	0.3	0-2
stromal polyp		3	0.9	0-4
fibroma		1	0.3	0-2
neurilenoma		1	0.3	0-2
hemangioma		1	0.3	0-1
leiomyoma		3	0.9	0-3
mixed mesenchymal tumor		1	0.3	0-2
hemangioendothelioma		1	0.3	0-2
leiomyosarcoma		1	0.3	0-1
adenocarcinoma		3	0.9	0-2
carcinosarcoma		1	0.3	0-1
stromal sarcoma		1	0.3	0-1
fibrosarcoma		2	0.6	0-2
<u>OVARY</u>	340			
gonadal stromal tumor		14	4.1	0-12
luteoma		1	0.3	0-1
granulosa/theca cell tumor		17	5.0	0-17
arrhenoblastoma		3	0.9	0-3
interstitial cell tumor		1	0.3	0-1
papillary cystadenoma		5	1.5	0-6
hemangioma		2	0.6	0-2

Page 4

**Table 4: (continued)**  
**Summary of Neoplastic Lesions in Five Groups of Control**  
**Female NMRI Mice (E. Merck): 20-24 Month Studies**

<u>LOCATION &amp; TUMOR</u>	<u>TOTAL # ANIMALS</u>	<u># TUMOR- BEARING ANIMALS</u>	<u>MEAN PERCENT</u>	<u>RANGE OF PERCENTS</u>
carcinoma, nos		1	0.3	0-3
granulosa cell carcinoma		1	0.3	0-1
fibrosarcoma		1	0.3	0-1
hemangioendothelioma		1	0.3	0-1
<u>pituitary gland</u>	340			
adenoma		4	1.2	0-2
malignant adenoma		1	0.3	0-1
<u>adrenal gland</u>	340			
adrenocortical adenoma/cortical phaeochromocytoma		2	0.6	0-4
<u>thyroid gland</u>	340			
cystadenoma				
follicular adenoma				
undiff. adenocarcinoma		1	0.3	0-1
C-cell tumor				
<u>islet of Langerhans</u>	340			
islet cell tumor		1	0.3	0-2
<u>brain</u>	340			
mixed glioma				
<u>orbit</u>	340			
pleomorphic sarcoma				
<u>lacrimal gland</u>	340			
cystadenoma		2	0.6	0-2
adenocarcinoma, nos				
<u>Harder's gland</u>	340			
papillary cystadenoma/adenoma		4	1.2	0-4
adenocarcinoma				
<u>abdominal cavity</u>	340			
hemangioendothelioma				
<b><u>METASTATIC TUMORS</u></b>				
numerous organs	340	1	0.3	0-1
lymph nodes	340	2	0.6	0-2
lung	340	1	0.3	0-1
peritoneum	340	1	0.3	0-1
primary site unknown (fibrosarcoma)	340			

**N.B.**  
 nos - Not otherwise specified.  
 Total # Animals - Total number of animals.  
 # Tumor-Bearing Animals - Total number of tumor-bearing animals.  
 Percent - Mean percent of tumor-bearing animals.  
 Range - The lowest and highest percent of tumor-bearing animals found  
 in the study groups.  
 No Numbers - No reported tumors.