CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982

MEDICAL REVIEW

OCT 22 1990

Medical Officer Review

NDA #: 19-982/C
Drug: bisoprolol (Monocor)
Sponsor: Lederle Labs
Date Received: 10/18/90
Date Reviewed: 10/19/90
Type of Submission: Response to FDA request
Medical Officer: 11-D

This submission was in response to a request for any information concerning possible interactions between bisoprolol and anti-coagulant therapy.

In study 4054 (submitted 10/18/90), 12 healthy male subjects entered a 2 week stabilization period during which time the dose of warfarin was adjusted until the prothrombin time increased to times the control value. Once the warfarin dose was stable for 5 days, bisoprolol 10 mg once daily was given concurrently with warfarin therapy for 10 days. After bisoprolol therapy was stopped, warfarin was continued for 5 days. The results show that bisoprolol does not change the prothrombin time in patients on warfarin therapy.

/S/

Charles J. Ganley, M.D.

cc: orig
HFD-110
HFD-110/cso
HFD-110/c. ganley

concurred /S/ 10/22/90

14.1
9-11-92 (FA)

MEDICAL OFFICER REVIEW

SEP 25 1992

IND #: 19-982/N-FA
DRUG NAME: bisoprolol
SPONSOR: lederle
TYPE OF DOCUMENT: final printed labeling
DATE RECEIVED: 9/18/92
DATE REVIEW COMPLETED: 9/25/92
MEDICAL OFFICER: Charles J. Ganley, M.D.

This submission contains the final printed labeling for bisoprolol. Upon reviewing the labeling, all information appears to conform to what we had agreed upon previously. However, there is a statement concerning the effect of bisoprolol on HDL cholesterol that, in retrospect, may not be correct. The statement is, "HDL- cholesterol changes averaged -0.1% for bisoprolol fumarate treated patients and 0.7% for placebo". This seems to imply that bisoprolol has no effect on HDL cholesterol. This in actuality may not be the case. In my review of the NDA, I made a general statement that HDL cholesterol mean values seem to decrease by % in patients treated with 5 - 20 mg of bisoprolol based on looks at the data from studies 1051, 57-1, 1031 and 4026. My impression is that none of these results individually was statistically significant due to the size of the trials. In the SBA, 2 long term open label trials (not placebo controlled) suggest that 12.8% of patients with normal baseline HDL-cholesterol levels at baseline had greater than one post-baseline value change by > 15% (study 57-1 OL) and 40% of patients with normal baseline HDL-cholesterol levels at baseline had greater than one post-baseline value change by > 15% (study 57-500).

Conclusion:

The sponsor needs to do the following:

1) Provide information on how they arrived at the percentages used in the labeling;
2) Provide HDL values for the following trials - 1051, 57-1, 1031, 4030 and 4026. It should include -> mean values at baseline and during follow-up and the number of patients with decreases or increases greater than 15% of baseline(in patients with normal baseline HDL).

At this time if possible, it may be reasonable to omit the sentence in dispute until this issue is resolved, so that this statement is not used in advertising.

/S/

Charles J. Ganley, M.D.

cc: orig.
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MEDICAL OFFICER REVIEW

SEP - 6 1994

NDA #: 19-982/SNC
NDA Volume: 17.1
DRUG NAME: bisoprolol
SPONSOR: Lederle
TYPE OF DOCUMENT: General Correspondence
DATE RECEIVED: 5/16/94
DATE REVIEW COMPLETED: 9/2/94
MEDICAL OFFICER: Charles J. Ganley, M.D.

The Cardio-Renal division sent a letter to Lederle on 1/13/94 requesting that cutaneous vasculitis be added to the adverse events section of the labeling. This was based on the report of a case of vasculitis with positive rechallenge. Lederle responds to this request by suggesting the following labeling for all beta blockers.

[Name of beta blocker], like other beta blockers, has been associated rarely with cutaneous vasculitis.

They support this by providing 2 case reports from the literature of possible atenolol and acebutalol induced vasculitis.

Conclusion:

The incidence of vasculitis is probably quite rare in bisoprolol treated patients. Thus, it may not warrant a sentence describing the adverse event. A word listing in the adverse events section would suffice. The original proposed labeling change needs review.

Although vasculitis may be reported with other beta blockers, it is not clear that this should be class labeling. As often is the case, it is sometimes difficult to attribute an adverse event to a drug. In the case reported for bisoprolol, since there was a positive rechallenge with bisoprolol, this is highly suggestive that bisoprolol was causative in this case. Other beta blockers need reviewed on a case by case basis.
Each beta blocker should be addressed on an individual basis.

/S/

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / S.CHEN

OCT 28 1991

MEDICAL OFFICER REVIEW

NDA#: 19-982/NC
DRUG NAME: bisoprolol
SPONSOR: Lederle
TYPE OF DOCUMENT: information amendment
DATE RECEIVED: 10/24/91
DATE REVIEW COMPLETED: 10/28/91
MEDICAL OFFICER: Charles J. Ganley, M.D.

Content:

The sponsor submits foreign labeling for bisoprolol. There is no additional information in this labeling that requires inclusion in U.S. labeling.

/S/

Charles J. Ganley, M.D.

cc: orig.
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MEDICAL OFFICER REVIEW

NDA#: 19-982/SU
DRUG NAME: bisoprolol
SPONSOR: Lederle
TYPE OF DOCUMENT: safety update
DATE RECEIVED: 2/19/91
DATE REVIEW COMPLETED: 7/2/91
MEDICAL OFFICER: CHARLES J. GANLEY, M.D.

This submission covers the adverse experience information received prior to 10/1/90 which was not included in the NDA or previous safety update. The patients included in this update are presented in the following chart.

Patients Included in This Safety Update
(Does Not Include Patients in NDA or Safety Update of February, 1990)

Study No.	No. Bisop. Pts.*	No. B/HCTZ Pts.	Total No. Pts.#
57-29	158	160	547
57-22	25	-	33
47 378-1002 (D-B)	72	69	215
47 378-1003 (D-B)	66	69	199
47 478-1002 (O-L)	-	207++	207++
47 378-1003 (O-L)	-	191++	191++
47 378-005	18	18	18
4054	12	-	12
U.S. Ph. IV Trials	203+	-	406
Cyanamid Int. Ph. IV/PM Trials	18,538+	-	18,700
Cyanamid Spontaneous Reports***	24	-	24
E. Merck Compl. Clin. Trials**	134+	-	242
E. Merck Clin. Trials Not Yet Rpted.**	149+	-	175
E. Merck Ph. IV Trials**	41+	-	87
E. Merck Post-Marketing Trials**	4,432	-	4,432
E. Merck Compl. PM Trials Not Yet Analyzed/Reported	5,442	-	5,442
E. Merck Spontaneous Reports**	108***	-	108***
Japanese Clinical Trials**	969	-	969
Total	30,391	590##	31,609

* Includes patients in which treatment is still blinded
** From E. Merck five-year report to the BG.
*** Based on no. events, not necessarily no. pts.
\+ Estimated where still blinded
++ Pts. previously in D-B study
\# Includes patients on other agents
Including 14 patients who received B/HCTZ in 47 378-1002 and 47 378-1003 D-B (4 and 10 pts., respectively) but did not enter the O-L trials, where all pts. received B/HCTZ

Only adverse events that may be of clinical significance will be presented.

In study 47 378-1002, one patient receiving bisoprolol + HCTZ therapy experienced a decline in neutrophil count from 3.91 to 1.12 x 10^9/L.

In study 47 378-1003, one patient receiving bisoprolol + HCTZ therapy and concomitant tiaprofenic acid had end of study increases in alkaline phosphatase (136 IU/L), SGOT (67 IU/L), SGPT (84 IU/L) and GGT (164 IU/L).

In study 47 378-1002, one patient on bisoprolol + HCTZ therapy experienced a decline in neutrophil count from 3.73 x 10^9/L to .76 x 10^9/L. This patient remained on therapy and a repeat neutrophil count at the end of study was 2.09 x 10^9/L.

Other laboratory abnormalities of significance are listed in the following chart.

Study	Treatment	Lab Abnormality
47 378-1003	bisoprolol + HCTZ	Alk. Phos: 81 --> 204 (Nl: 30 - 115 IU/L) SGOT: 16 --> 41 (Nl: <42 IU/L) SGPT: 12 --> 83 (Nl: < 46 IU/L) GGT: 19 --> 217 (Nl: < 65 IU/L)
47 378-1003	bisoprolol + HCTZ	SGPT: 26 --> 151 IU/L SGOT: 30 -->51 IU/L GGT: 39 --> 94 IU/L Alk. Phos.: 98 --> 142 IU/L
47 378-1003	bisoprolol + HCTZ	SGPT: 11 --> 43 --> 105 IU/L GGT: 4 --> 12 --> 75 IU/L

The following table lists the deaths during phase IV trials that were not reported in the NDA and previous safety update. It is difficult to determine whether bisoprolol was a contributing factor in any of these deaths.

Causes of Death in Bisoprolol-Treated Patients*

Cause	No. of Cases
Cardiac	28 (2≠)
(AMI- 17)	
(CHF- 7 [1≠])	
(Cardiac arrest- 1)	
(Ruptured aortic aneurysm- 1≠)	
(CVA- 2)	
Traffic accident	3 (1≠)
Cancer	2 (1≠)
Pneumonia	1+
Peritonitis	1
Suicide (by hanging)	1
Unknown Cause	3 (1≠)
Insufficient Information	29

* Cases not previously included in NDA or Safety Update of February, 1990, unless new information now available.

+ Note: one of the cases of CHF and one of the cases of CVA also had pneumonia/pulmonary infection.

≠ Previously identified, but no details available in Safety Update of February, 1990.

Spontaneous Reports (to Lederle)

There is one report of a taxi driver "blacking out" while receiving bisoprolol (5 mg) which resulted in a traffic accident .

There is a report of a 19 year old male who ingested 140 mg of bisoprolol and subsequently developed bradycardia (42 bpm). The patient responded to atropine and survived.

E. Merck Trials

Completed trials enrolled 904 patients. There were 4 cases of hypogeusia.

Spontaneous Reports (to E. Merck)

These reports encompass the time 9/1/88 - 8/21/90. There are 108 reports not previously filed. Of interest are 2 reports of increased liver function tests, 3 cases of "circulatory collapse" and 1 case of overdose. The case of overdose involved a 25 year old man who ingested 200 10 mg tablets. The patient developed bradycardia but responded to treatment (not specified).

Japanese Clinical Trials (969 patients)

There are abnormal lab results reported in 28 patients (no individual data provided). Thirteen of the cases involve increases in SGPT.

Traffic Accidents

In addition to the traffic accident listed above, there were 3 additional reports of fatal traffic accidents. There is no information provided on these events. It is not known whether the victims were the driver or passengers in the vehicle.

Conclusions:

In all the clinical trials listed, the dropout rate due to adverse experience was < 7%. There were no significant new reports that have not been reported in the past. The liver function abnormalities noted in the spontaneous reports to E. Merck need further investigation as well as the cases of "circulatory collapse". The reports of decreased neutrophil count in trials 47 378-1002 and 47 378-1003 will be reviewed further in the combination NDA. More information on the abnormal liver function tests reported in the Japanese study should be provided. Previously, there were 6 reports of traffic accidents in patients receiving bisoprolol. In this submission, there are four additional reports of traffic accidents involving patients receiving bisoprolol (3 fatal, 1 non-fatal). Unfortunately, there is scant information on these individuals. Additional information should be provided if these patients were involved in phase IV trials.

Regulatory Action:

Additional information as listed in the conclusions needs to be provided. Requested 7/2/91 by phone to DR. GANLEY.

/S/

CHARLES J. GANLEY, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / S.CHEN

Concurred 7/2/91

AUG 12 1991

MEDICAL OFFICER REVIEW

NDA#: 19-982/C
DRUG NAME: Bisoprolol
SPONSOR: Lederle
TYPE OF DOCUMENT: information amendment
DATE RECEIVED: 8/6/91
DATE REVIEW COMPLETED: 8/12/91
MEDICAL OFFICER: Charles J. Ganley, M.D.

Content:

The sponsor provides additional information on several patients with adverse laboratory results that were described in the SBA. In addition, they provide the CRFs for three patients involved in auto accidents while receiving bisoprolol in phase IV trials. Unfortunately, there is a paucity of helpful information describing the adverse experiences.

Conclusion:

Little additional information can be obtained from the CRFs. It is unfortunate that we obtain more information from 1639 adverse events reports then from CRFs submitted for these phase IV studies. Lederle may not be to blame because I believe the phase IV trials in Europe were performed under the supervision of E. Merck. If this is a sample of the type of follow-up and accountability that we can expect in future phase IV trials, then phase IV trials are a waste of time, effort and money.

Regulatory Action:

Tell Lederle that any phase IV trials performed under their supervision should have a mechanism to follow-up serious adverse events promptly and completely.

/S/

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / S.CHEN

MEDICAL OFFICER REVIEW

NDA #: 19-982/BM
DRUG NAME: bisoprolol
SPONSOR: Lederle
TYPE OF DOCUMENT: information amendment
DATE RECEIVED: 3/16/92
DATE REVIEW COMPLETED: 3/20/92
MEDICAL OFFICER: Charles J. Ganley, M.D.

Upon request from the this division, the sponsor submits additional information on patients with liver function abnormalities from Japanese trials. For the most part, liver function tests are mildly abnormal. The highest values are not greater than 3 times the upper limit of normal. Patients # 1, 4, 6, 8, 9, 14, 15 and 16 may be related to bisoprolol use. Patient #14 was the only one with clinical symptoms that may be attributable to the liver function abnormalities. The number of patients exposed to bisoprolol in these trials was 969. Thus, the incidence of subclinical liver function abnormalities is less than 2%.

Conclusion:

This information does not change my opinion about the relationship between liver function abnormalities and bisoprolol that was expressed in the review of the original NDA. That is that bisoprolol is capable of causing changes in liver function tests but there are few cases of clinical hepatitis reported.

/S/
Charles J. Ganley, M.D.

cc: orig.
HFD-110
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3/20/92

3 pages Attached

MCDONALD

NDA #: 19-982/D
DRUG NAME: bisoprolol
SPONSOR: Lederle
TYPE OF DOCUMENT: 1639
DATE RECEIVED: 11/17/93
DATE REVIEW COMPLETED: 11/29/93
MEDICAL OFFICER: Charles J. Ganley, M.D.

NOV 29 1993

This submission contains a report published in the European Journal of Internal Medicine (1992;3:275) concerning the case of a 45 year old man who developed leukocytoclastic vasculitis while on bisoprolol. The vasculitis recurred on rechallenge.
Regulatory Action:
Cutaneous vasculitis (confirmed on rechallenge) should be included in the adverse reactions section.

/S/
Charles J. Ganley, M.D.

cc: orig
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O.K
RL
12/2/93

NOV 2 - 1998

Medical Review

NDA#19,982
Drug name: bisoprolol/ hydrochlorothiazide (Ziac)
Type of Document: 2 draft protocols
Date Submitted 6-4-98.

IND Vol: 22.1
Sponsor: Wyeth-Ayerst
Date Completed:

Protocol 0896A-903 "A double-blind, placebo controlled, dose escalation safety and efficacy study of bisoprolol fumate/hydrocholorthiazide in patients 8 to 18 years of age."

Protocol design: randomized, double-blind, placebo controlled
Objective: safety and efficacy of Ziac in hypertensive children 8 to 18 years of age
Duration of trial: 3 week screening and washout phase, 12 week treatment phase, 2 week tapering phase for a total of 17 weeks.
Dose and dosing schedule: Ziac 2.5, 5, 10 mg, placebo (drug product contains bisoprolol and 6.25 mg hydrocholorthiazide). If sitting diastolic or systolic BP is >95th percentile for the dose will be increased to the next highest dose
Number of subjects: 105 total (70 Ziac and 35 placebo, 2:1 randomization)
Inclusion criteria: between 8 and 18 years of age inclusive, documented diagnosis of hypertension (average sitting diastolic and/or systolic BP > 95th percentile for age, sex, and height at each of the last 2 visit of placebo washout
Background medications: none
Primary endpoints: 2 primary endpoints 1) reduction in sitting systolic BP and 2) reduction in diastolic BP at week 12.
Pharmacokinetics: Population pharmacokinetics

Protocol 0896A-904 "An open label, single dose, randomized, crossover study to determine the pharmacokinetic profiles of Ziac and Zebeta in patients 8 to 18 years of age with stage I-stage II essential hypertension"
Protocol design: randomized, open label, cross over
Objective: pharmacokinetic profiles of Ziac (bisoprolol/ hydrocholorthiazide) and Zebeta (bisoprolol) in hypertensive children 8 to 18 years of age
Study procedures: single dose day 1 with vital signs and blood sampling at 0, 2, 3, 4, 8, 22, and 24 hours after dose. Seven days later the patient will return to receive the other drug and undergo the same procedures.
Dose and dosing schedule: Ziac mg, Zebeta 5 mg (drug product contains bisoprolol and 6.25 mg hydrocholorthiazide). If sitting diastolic or systolic BP is >95th percentile the dose will be increased to next highest dose
Number of subjects: 12
Inclusion criteria: between 8 and 18 years of age inclusive, documented diagnosis of hypertension (average sitting diastolic and/or systolic BP > 95th percentile for age, sex, and height at each of the last 2 visit of placebo washout

Background medications: none

Questions and comments:

Protocol 0896A-903
-sponsor should define how p value will be allocated for the 2 primary endpoints;
-ensure that endpoint is last visit instead of visit 12 to allow for drop outs;
-recommend parallel dose groups instead of dose titration
-need to perform pregnancy testing in appropriate patients throughout treatment phase

Protocol 0896A-904
-need to perform pregnancy testing in appropriate patients prior to each active treatment phase.
-dose of Ziac is unclear in protocol
-conflicting schedules for vital signs and blood sampling (4 hours data point is missing from section 3).

/S/ 11-2-98

Maryann Gordon, MD

cc
Orig.
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