CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982

CHEMISTRY REVIEW(S)

JAN 10 1990

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #2

A. 1. NDA 19-982 Date Completed: January 12, 1990

Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
[Dennis Foley, Ph.D. (914)-732-3478]

AF#: 14-731

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297.939 (American Cyanamid Co.)
EMD 33 512 (E. Merck)
CAS - 104344-23-2
CAS - 66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
Pursuant to Section 505(b) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant's attorney herein makes the following certification based on his information, advise and belief:

(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any U.S. Letters Patent would be infringed by the manufacture or sale of the above product.

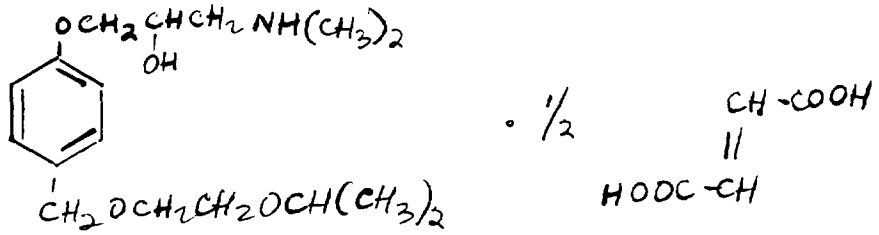
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):
(±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl) amino]-2-propranol(E)-2-butenedioate (2:1)(salt) (CA approved name).

(±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)-2-propanol hemifumarate

2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (E)-2-butenedioate (2:1)(salt)

Molecular Formula: $C_{18}H_{31}NO_4.1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate salt)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989 - response to information request letter.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

IND
IND

4. Related Documents (INDs, NDAs, etc.):

DMF
DMF
DMF
DMF
DMF
DMF

DMF
DMF
DMF
DMF
DMF
DMF
DMF

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by

(DMF

Coating for the production batches of 5 mg (batch No. R682-184) and 10 mg (batch No. R682-188) tablets was conducted by

Medicines Licence, GMP statement are included. The last inspection of the facility was on February 1988 (by DHSS).

C. Remarks:

Foreign marketing history for E. Merck and for American Cyanamid and registration approval dates are included. E. Merck markets include Germany, Switzerland, France, Belgium, Austria, United Kingdom, Ireland, Luxembourg, Netherlands, Spain, Italy, Greece, Denmark, Guatemala, Chile, Colombia, Hong Kong, Singapore, and Thailand. American Cyanamid markets include United Kingdom, Belgium, Netherlands, France, Taiwan, and Denmark.

Bisoprolol is a racemic mixture. It has been reported that the pharmacologic activity of bisoprolol is predominantly from the S(-) enantiomer (EMD 38 342). The S(-) stereoisomer (EMD 38 342) possesses 15-40 times greater activity than the R(+) enantiomer (EMD 38 341). Plasma concentration vs time profiles for the R(+) and S(-) enantiomers of bisoprolol after oral 5, 10, 20 and 40 mg bisoprolol (racemate) were similar, indicating that disposition is not stereospecific, a finding in contrast to that for other ß-blockers including propranolol, pindolol and metoprolol. Dose-proportionality in plasma C_{max} and AUC was observed for each enantiomer through the 5 to 40 mg dose range. Urinary excretion profiles for R(+)- and S(-)- bisoprolol were essentially 1:1 after a 20 mg oral dose supporting the absence of stereoselective elimination of bisoprolol enantiomers.

MONOCOR - name does not appear in conflict with any existing names. Monochlor, which is 80% monochloracetic acid, is the only name that is close to proposed name of MONOCOR.

EI of the facilities listed under Facilities was requested on August 11, 1989.

Samples will be sent to FDA laboratories for methods validation.

December 27, 1989 - response to the information request letter.

D. Conclusions and/or Recommendations:

Responses to the deficiencies are satisfactory. No action indicated.

Methods validation will be performed by NY District Laboratory and by Division of Drug Analysis in St. Louis, MO. The firm expects to send sample by the end of January or beginning of February, 1990. Samples are coming from England.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Altdorf, Switzerland, are included.

/S/
Danute G. Cunningham

1-18-90

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
Doc. # 0415

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #3

NDA 19-982 Date Completed: November 29, 1990

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

AF#: 14-731

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets

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CONCOR (for E. Merck in Europe)

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
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(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

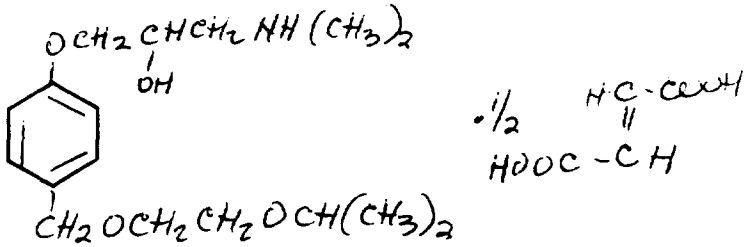
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):

(±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propranol(E)-2-butenedioate (2:1) (salt) (CA approved name)

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Molecular Formula: $C_{18}H_{31}NO_4 \cdot 1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989	response to deficiencies.
November 1, 1990	minor changes in chemistry, manufacture and controls.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
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DMF

DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

Coating for the production batches of 5 mg (batch No. R682-184) and 10 mg (batch No. R682-188) tablets was conducted by

Medicines License, GMP statement are included. The last inspection of the facility was on February 1988 (by DHSS).

(The above was used only to make the above lots and will not be used during the manufacture. Coating will be performed at facility).

C. Remarks:

Foreign marketing history for E. Merck and for American Cyanamid and registration approval dates are included. E. Merck markets include Germany, Switzerland, France, Belgium, Austria, United Kingdom, Ireland, Luxembourg, Netherlands, Spain, Italy, Greece, Denmark, Guatemala, Chile, Colombia, Hong Kong, Singapore, and Thailand. American Cyanamid markets include United Kingdom, Belgium Netherlands, France, Taiwan, And Denmark.

Bisoprolol is a racemic mixture. It has been reported that the pharmacologic activity of bisoprolol is predominantly from the S(-) enantiomer (EMD 38 342). The S(-) stereoisomer (EMD 38 342) possesses 15-40 times greater activity than the R(+) enantiomer (EMD 38 341). Plasma concentration vs time profiles for the R(+) and S(-) enantiomers of bisoprolol after oral 5, 10, 20 and 40 mg bisoprolol (racemate) were similar, indicating that disposition is not stereospecific, a finding in contrast to that for other β-blockers including propranolol, pindolol and metoprolol. Dose-proportionality in plasma C_{max} and AUC was observed for each enantiomer through the 5 to 40 mg dose range. Urinary excretion profiles for R(+)- and S(-)-bisoprolol were essentially 1:1 after a 20 mg oral dose supporting the absence of stereoselective elimination of bisoprolol enantiomers.

MONOCOR - name was assessed by CDER Labeling and Nomenclature Committee (9/18/90):

While the committee is not concerned about the similarity between Monopril and Monocor, there are several other look-alike/sound-alike names:

Monocid (cefonicid) - antibacterial
Monocortin (paramethasone 21-acetate) - a glucocorticoid (Germany)
Manticor (hydrocortisone) - (Canada)
Monopar (stilbazium iodide) - antihemintic
Minocin (minocycline HCl) - antibacterial
Mono-Kay (phytonadione) - prothrombogenic
Monochlor (monoacetic acid) - verruca cauterant

While Monoclor has some similarity to the proposed name, the committee do not believe it is a drug which is prescribed, rather it is used in the doctor's office. Therefore, they are far less concerned about the potential for medication errors in this case. Manticor is a Canadian drug; if this drug were marketed in the U.S. we would expect it to be marketed under a different name.

The committee is concerned in that "mono" may imply that this is a sole therapy type drug. Is it likely that Monopril will be the sole drug therapy in the treatment of hypertensive patients? If not, then the proposed tradename is far more objectional than if the product were used as single-drug therapy for hypertension.

Careful consideration of the committee's remarks is suggested.

EI of the facilities listed under Facilities, requested on August 11, 1989, was acceptable on 8/15/89. Reinspection of the plants was requested on July 13, 1990. Report was not received as of 11/27/90.

Additional EI requested for the facilities included in November 1, 1990 amendment. Request was made on November 29, 1990.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

December 27, 1989 amendment - response to deficiencies.

November 1, 1990 amendment - minor changes in the chemistry, manufacturing and controls information.

D. Conclusions and/or Recommendations:

Responses to deficiencies for Review #1 were satisfactory. Additional information requested after review of November 1, 1990 amendment.

/S/

Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N19982R3

11/29/90

8.1

JAN 23 1991

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #4

NDA 19-982 Date Completed: January 22, 1991

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

AF#: 14-731

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
Pursuant to Section 505(b) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant's attorney herein makes the following certification based on his information, advise and belief:

(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

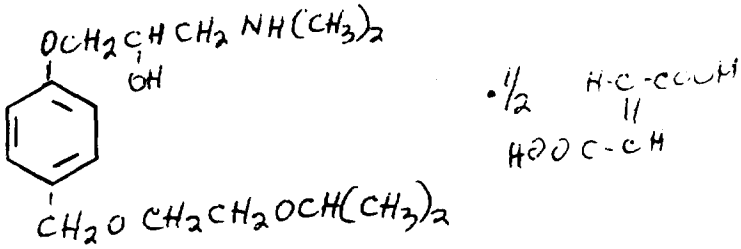
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):

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Molecular Formula: $C_{18}H_{31}NO_4 . 1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989	response to deficiencies.
November 1, 1990	minor changes in chemistry, manufacture and controls.
January 18, 1991	SBA

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
DMF
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DMF
DMF
DMF

DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

Coating for the production batches of 5 mg (batch No. R682-184) and 10 mg (batch No. R682-188) tablets was conducted by

Medicines License, GMP statement are included. The last inspection of the facility was on February 1988 (by DHSS).

(The above was used only to make the above lots and will not be used during the manufacture. Coating will be performed at facility).

C. Remarks:

Foreign marketing history for E. Merck and for American Cyanamid and registration approval dates are included. E. Merck markets include Germany, Switzerland, France, Belgium, Austria, United Kingdom, Ireland, Luxembourg, Netherlands, Spain, Italy, Greece, Denmark, Guatemala, Chile, Colombia, Hong Kong, Singapore, and Thailand. American Cyanamid markets include United Kingdom, Belgium Netherlands, France, Taiwan, And Denmark.

Bisoprolol is a racemic mixture. It has been reported that the pharmacologic activity of bisoprolol is predominantly from the S(-) enantiomer (EMD 38 342). The S(-) stereoisomer (EMD 38 342) possesses 15-40 times greater activity than the R(+) enantiomer (EMD 38 341). Plasma concentration vs time profiles for the R(+) and S(-) enantiomers of bisoprolol after oral 5, 10, 20 and 40 mg bisoprolol (racemate) were similar, indicating that disposition is not stereospecific, a finding in contrast to that for other β-blockers including propranolol, pindolol and metoprolol. Dose-proportionality in plasma C_{max} and AUC was observed for each enantiomer through the 5 to 40 mg dose range. Urinary excretion profiles for R(+)- and S(-)-bisoprolol were essentially 1:1 after a 20 mg oral dose supporting the absence of stereoselective elimination of bisoprolol enantiomers.

MONOCOR - name was assessed by CDER Labeling and Nomenclature Committee (9/18/90):

While the committee is not concerned about the similarity between Monopril and Monocor, there are several other look-alike/sound-alike names:

Monocid (cefonicid) - antibacterial
Monocortin (paramethasone 21-acetate) - a glucocorticoid (Germany)
Manticor (hydrocortisone) - (Canada)
Monopar (stilbazium iodide) - antihemintic
Minocin (minocycline HCl) - antibacterial
Mono-Kay (phytonadione) - prothrombogenic
Monochlor (monoacetic acid) - verruca cauterant

While Monochlor has some similarity to the proposed name, the committee do not believe it is a drug which is prescribed, rather it is used in the doctor's office. Therefore, the are far less concerned about the potential for medication errors in this case. Manticor is a Canadian drug; if this drug were marketed in the U.S. we would expect it to be marketed under a different name.

The committee is concerned in that "mono" may imply that this is a sole therapy type drug. Is it likely that Monopril will be the sole drug therapy in the treatment of hypertensive patients? If not, then the proposed tradename is far more objectional than if the product were used as single-drug therapy for hypertension.

After careful consideration we do not expect this to be a problem since a combination product if requested will have a different trade name.

EI of the facilities listed under Facilities, requested on August 11, 1989, was acceptable on 8/15/89. Reinspection of the plants was requested on July 13, 1990. Report was not received as of 1/22/91.

Additional EI requested for the facilities included in November 1, 1990 amendment. Request was made on November 29, 1990. Report was not received as of 1/22/91.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

December 27, 1989 amendment - response to deficiencies.

November 1, 1990 amendment - minor changes in the chemistry, manufacturing and controls information.

January 18, 1991 amendment - summary basis of approval. Generic name should be Bisoprolol Fumarate, not just Bisoprolol as written.

D. Conclusions and/or Recommendations:

Responses to deficiencies for Review #1 were satisfactory. Additional information requested after review of November 1, 1990 amendment. Report(s) on establishment inspections have not been received as of 1/22/91. Peter Smith advised me (1/22/91, telephone conversation) that an acceptable recommendation was made for Cyanamid of Great Britain, Gosport, U.K. facility.

/S/

Danute G. Cunningham

cc:
Orig
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N19982R4

1-23-91

7.1

JAN 30 1991

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #5

NDA 19-982 Date Completed: January 30, 1991

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

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USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

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(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

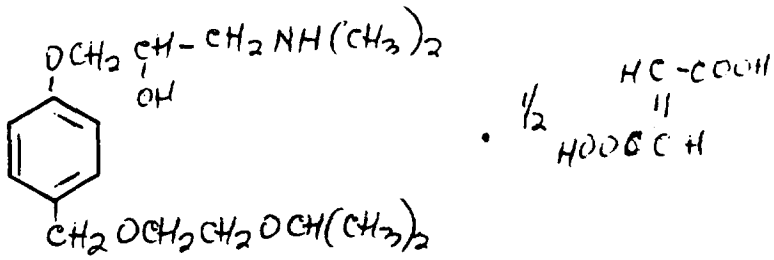
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



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B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989	response to deficiencies.
November 1, 1990	minor changes in chemistry, manufacture and controls.
January 18, 1991	SBA
January 24, 1991	Response to information requested after review of 11/1/90 amendment.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
DMF
DMF
DMF

DMF
DMF
DMF
DMF
DMF

DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

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Foreign marketing history for E. Merck and for American Cyanamid and registration approval dates are included. E. Merck markets include Germany, Switzerland, France, Belgium, Austria, United Kingdom, Ireland, Luxembourg, Netherlands, Spain, Italy, Greece, Denmark, Guatemala, Chile, Colombia, Hong Kong, Singapore, and Thailand. American Cyanamid markets include United Kingdom, Belgium Netherlands, France, Taiwan, And Denmark.

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Monopar (stilbazium iodide) - antihemintic
Minocin (minocycline HCl) - antibacterial
Mono-Kay (phytonadione) - prothrombogenic
Monochlor (monoacetic acid) - verruca cauterant

While Monochlor has some similarity to the proposed name, the committee do not believe it is a drug which is prescribed, rather it is used in the doctor's office. Therefore, the are far less concerned about the potential for medication errors in this case. Manticor is a Canadian drug; if this drug were marketed in the U.S. we would expect it to be marketed under a different name.

The committee is concerned in that "mono" may imply that this is a sole therapy type drug. Is it likely that Monopril will be the sole drug therapy in the treatment of hypertensive patients? If not, then the proposed tradename is far more objectional than if the product were used as single-drug therapy for hypertension.

After careful consideration we do not expect this to be a problem since a combination product if requested will have a different trade name.

EI of the facilities listed under Facilities, requested on August 11, 1989, was acceptable on 8/15/89. Reinspection of the plants was requested on July 13, 1990. Report was not received as of 1/30/91.

Additional EI requested for the facilities included in November 1, 1990 amendment. Request was made on November 29, 1990. Report was not received as of 1/30/91.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

D. Conclusions and/or Recommendations:

Responses to deficiencies for Reviews #1 and 3 were satisfactory.

Report(s) on establishment inspections have not been received as of 1/30/91. Peter Smith advised me (1/22/91, telephone conversation) that an acceptable recommendation was made for Cyanamid of Great Britain, Gosport, U.K. facility.

/S/

Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N19982R5

1/30/91

AUG 21 1991

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #6

NDA 19-982 Date Completed: August 14, 1991

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets
7/17/91 amendment: PROBETA

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)
7/17/91 amendment - PROBETA

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
Pursuant to Section 505(b) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant's attorney herein makes the following certification based on his information, advise and belief:

(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

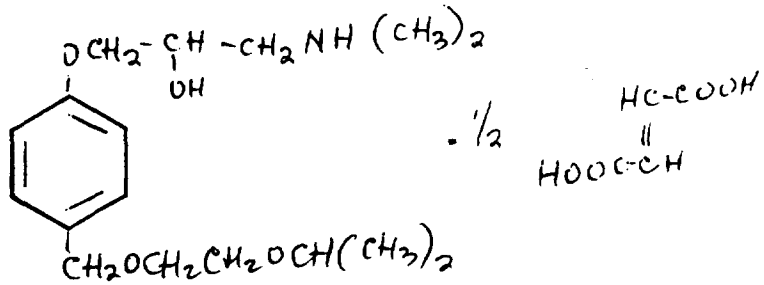
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):

(±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propranol(E)-2-butenedioate (2:1) (salt) (CA approved name)

(±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)-2-propanol hemifumarate

2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (E)-2-butenedioate (2:1) salt

Molecular Formula: $C_{18}H_{31}NO_4 . 1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989	response to deficiencies.
November 1, 1990	minor changes in chemistry, manufacture and controls.
January 18, 1991	SBA
January 24, 1991	Response to information requested after review of 11/1/90 amendment.
July 17, 1991	Two new package styles, name change

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
DMF
DMF
DMF

DMF
DMF
DMF
DMF
DMF

DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

C. Remarks:

Foreign marketing history for E. Merck and for American Cyanamid and registration approval dates are included. E. Merck markets include Germany, Switzerland, France, Belgium, Austria, United Kingdom, Ireland, Luxembourg, Netherlands, Spain, Italy, Greece, Denmark, Guatemala, Chile, Colombia, Hong Kong, Singapore, and Thailand. American Cyanamid markets include United Kingdom, Belgium Netherlands, France, Taiwan, And Denmark.

Bisoprolol is a racemic mixture. It has been reported that the pharmacologic activity of bisoprolol is predominantly from the S(-) enantiomer (EMD 38 342). The S(-) stereoisomer (EMD 38 342) possesses 15-40 times greater activity than the R(+) enantiomer (EMD 38 341). Plasma concentration vs time profiles for the R(+) and S(-) enantiomers of bisoprolol after oral 5, 10, 20 and 40 mg bisoprolol (racemate) were similar, indicating that disposition is not stereospecific, a finding in contrast to that for other β-blockers including propranolol, pindolol and metoprolol. Dose-proportionality in plasma C_{max} and AUC was observed for each enantiomer through the 5 to 40 mg dose range. Urinary excretion profiles for R(+)- and S(-)-bisoprolol were essentially 1:1 after a 20 mg oral dose supporting the absence of stereoselective elimination of bisoprolol enantiomers.

Product name was changed from originally proposed MONOCOR to PROBETA.

EI of the facilities listed under Facilities, requested on August 11, 1989, was acceptable on 8/15/89. Reinspection of the plants was requested on July 13, 1990. Acceptable on 2/8/91.

Additional EI requested for the facilities included in November 1, 1990 amendment. Request was made on November 29, 1990. Acceptable on 2/12/91.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

D. Conclusions and/or Recommendations:

Responses to deficiencies for Reviews #1 and 3 were satisfactory.

4-15-91

/S/
Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N19982R6

NOV 21 1991

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #7

NDA 19-982 Date Completed: November 20, 1991

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets
7/17/91 amendment: PROBETA

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)
7/17/91 amendment - PROBETA

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
Pursuant to Section 505(b) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant's attorney herein makes the following certification based on his information, advise and belief:

(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

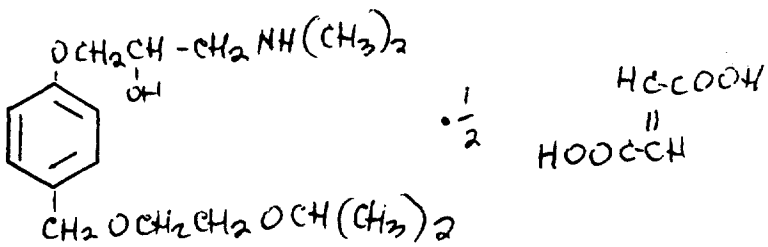
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):

(±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propranol(E)-2-butenedioate (2:1) (salt) (CA approved name)

(±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)-2-propanol hemifumarate

2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (E)-2-butenedioate (2:1) salt

Molecular Formula: $C_{18}H_{31}NO_4.1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989	response to deficiencies.
November 1, 1990	minor changes in chemistry, manufacture and controls.
January 18, 1991	SBA
January 24, 1991	Response to information requested after review of 11/1/90 amendment.

July 17, 1991	Two new package styles, name change
November 11, 1991	Update of stability - data generated at Pearl River, NY site.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
DMF
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DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

C. Remarks:

Foreign marketing history for E. Merck and for American Cyanamid and registration approval dates are included. E. Merck markets include Germany, Switzerland, France, Belgium, Austria, United Kingdom, Ireland, Luxembourg, Netherlands, Spain, Italy, Greece, Denmark, Guatemala, Chile, Colombia, Hong Kong, Singapore, and Thailand. American Cyanamid markets include United Kingdom, Belgium Netherlands, France, Taiwan, And Denmark.

Bisoprolol is a racemic mixture. It has been reported that the pharmacologic activity of bisoprolol is predominantly from the S(-) enantiomer (EMD 38 342). The S(-) stereoisomer (EMD 38 342) possesses 15-40 times greater activity than the R(+) enantiomer (EMD 38 341). Plasma concentration vs time profiles for the R(+) and S(-) enantiomers of bisoprolol after oral 5, 10, 20 and 40 mg bisoprolol (racemate) were similar, indicating that disposition is not stereospecific, a finding in contrast to that for other β-blockers including propranolol, pindolol and metoprolol. Dose-proportionality in plasma C_{max} and AUC was observed for each enantiomer through the 5 to 40 mg dose range. Urinary excretion profiles for R(+)- and S(-)-bisoprolol were essentially 1:1 after a 20 mg oral dose supporting the absence of stereoselective elimination of bisoprolol enantiomers.

Product name was changed from originally proposed MONOCOR to PROBETA.

EER final update was requested on 10/28/91 and has not been completed as of 11/20/91.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

November 11, 1991 amendment - update of stability. Applicant requests three year (36 months) expiration dating. The submitted stability data support the requested expiration date.

For the reported batches in the stability studies, the RT storage conditions were 23°C. In the post-approval stability studies, the RT storage temperature should be 30°C.

D. Conclusions and/or Recommendations:

Chemistry, manufacturing and controls information are satisfactory.

/S/
Danute G. Cunningham

11/21/91

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N19982R7

MAY 5 1992

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #8

NDA 19-982 Date Completed: May 4, 1992

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets
7/17/91 amendment: PROBETA

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)
7/17/91 amendment - PROBETA

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
Pursuant to Section 505(b) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant's attorney herein makes the following certification based on his information, advise and belief:

(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

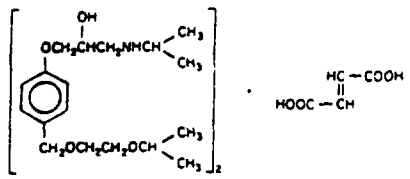
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):

(±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propranol(E)-2-butenedioate (2:1) (salt) (CA approved name)

(±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)-2-propanol hemifumarate

2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (E)-2-butenedioate (2:1) salt

Molecular Formula: $C_{18}H_{31}NO_4.1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989	response to deficiencies.
November 1, 1990	minor changes in chemistry, manufacture and controls.
January 18, 1991	SBA
January 24, 1991	Response to information requested after review of 11/1/90 amendment.

July 17, 1991	Two new package styles, name change
November 11, 1991	Update of stability - data generated at Pearl River, NY site.
November 19, 1991	New container sizes.
December 20, 1991	Stability information.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
DMF
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DMF

DMF
DMF
DMF
DMF
DMF

DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

C. Remarks:

Product name was changed from originally proposed MONOCOR to PROBETA.

EER final update was requested on 10/28/91 and has not been completed as yet.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

November 11, 1991 amendment - update of stability. Applicant requests three year (36 months) expiration dating. The submitted stability data support the requested expiration date. (Storage temperature was 23°C).

November 19, 1991 amendment - container

December 20, 1991 amendment - commitment was included that post-approval marketed product stability batches of PROBETA Tablets will be stored at target temperature of 25°C. (36 months stability data was included in 11/11/91 amendment for product stored at 23°C, their usual storage temperature in Europe).

D. Conclusions and/or Recommendations:

Chemistry, manufacturing and controls information are satisfactory.

/S/

Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
N19982R8

5-5-92

JUN 26 1992

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #9
ADDENDUM

NDA 19-982 Date Completed: June 26, 1992

1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets
7/17/91 amendment: PROBETA

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)
7/17/91 amendment - PROBETA

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

December 13, 1991 amendment - responses to Div. of Biopharmaceutics request for information.

Dissolution of Probeta (bisoprolol hemifumarate) film coated tablets in deaerated water or simulated gastric fluid without enzymes using apparatus II (paddle) at 50, 75, and 100 rpm

Dissolution - the following specifications are proposed by Division of Biopharmaceutics:

	Biopharm	Firm
Apparatus type:	USP, #2	USP, #2 (paddle)
Medium:	Water, 900 mL	Water, 900 mL
Speed of rotation:	75 rpm	100 rpm
Sampling time:	min	min
Q value:	%	%

Dissolution data in deaerated water at 50, 75 and 100 rpm paddle speeds:

	5 mg tablets (R1013-6)			10 mg tablets (R1013-7)		
	min	min	min	min	min	min
Paddle speed - 50 rpm						
High						
Low						
Ave (12)	82.8	90.7	94.1	76.8	82.6	85.1
SD	7.2	4.6	3.5	15.7	13.0	12.2
Paddle speed - 75 rpm						
High						
Low						
Ave (6)	86.3	92.7	92.2	82.3	90.4	91.8
SD	2.3	2.4	1.2	8.8	3.9	2.3
Paddle speed - 100 rpm						
High						
Low						
Ave	94.5(12)	98.0(12)	97.8(12)	86.3(6)	91.3(6)	93.7(6)
SD	2.7	1.7	2.2	3.8	5.2	4.6

C. Remarks:

EER final update was requested on 10/28/91. Acceptable 6/15/92.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

Expiration date - 36 months for the product, 5 years for the drug substance.

Dissolution data based on the results of one lot each strength supports the dissolution specifications as proposed by Biopharm.

D. Conclusions and/or Recommendations:

Chemistry, manufacturing and controls information are acceptable. The applicant should be informed of the proposed specifications.

/S/

Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
19982R9A.AMD

JUN 22 1992

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #9

NDA 19-982 Date Completed: June 19, 1992

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets
7/17/91 amendment: PROBETA

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)
7/17/91 amendment - PROBETA

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
Pursuant to Section 505(b) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant's attorney herein makes the following certification based on his information, advise and belief:

(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

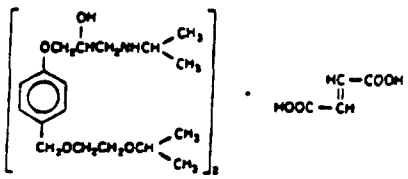
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):

(±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propranol(E)-2-butenedioate (2:1) (salt) (CA approved name)

(±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)-2-propanol hemifumarate

2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (E)-2-butenedioate (2:1) salt

Molecular Formula: $C_{18}H_{31}NO_4.1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

December 27, 1989	response to deficiencies.
November 1, 1990	minor changes in chemistry, manufacture and controls.
January 18, 1991	SBA

January 24, 1991	Response to information requested after review of 11/1/90 amendment.
July 17, 1991	Two new package styles, name change
November 11, 1991	Update of stability - data generated at Pearl River, NY site.
November 19, 1991	New container sizes.
December 20, 1991	Stability information.

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
DMF
DMF
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DMF
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DMF
DMF

DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

C. Remarks:

Product name was changed from originally proposed MONOCOR to PROBETA.

EER final update was requested on 10/28/91. Acceptable 6/15/92.

Methods validation was performed by St. Louis and NY District laboratories. Methods are satisfactory for regulatory purposes.

Both drug substance and drug product will be manufactured outside the United States. Statements that processes meet environmental requirements in Gosport, England and in Althof, Switzerland are included.

Expiration date - 36 months for the product, 5 years for the drug substance.

Dissolution - there is a difference in the specifications proposed by the firm's and those set by Biopharm. Tentatively the firm's specifications will be acceptable, but will request to generate and submit data using the parameters proposed by Biopharm.

D. Conclusions and/or Recommendations:

Chemistry, manufacturing and controls information are acceptable. Will request additional stability data either to support or reject dissolution specifications as suggested by Biopharm.

/S/

Danute G. Cunningham

cc:
Orig.
~~HFD-110~~
HFD-110/CSO
HFD-110/DGCunningham
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19-982
15.1

NOV 23 1993

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #10

NDA 19-982 Date Completed: Novewmber 24, 1993

A. 1. Applicant: American Cyanamid Company
Lederle Laboratories Division
Middletown Road
Pearl River, NY 10965
(Dennis Foley, Ph.D. 914-732-3478
David N. Ridge, Ph.D. 914-732-3655)

2. Product Name (s): MONOCOR (bisoprolol fumarate) Tablets
7/17/91 amendment: PROBETA
11/16/92 ZEBETA

Proprietary: MONOCOR (for American Cyanamid in Europe and U.S.)
CONCOR (for E. Merck in Europe)
7/17/91 amendment - PROBETA
11/16/92 - ZEBETA

Nonproprietary: Bisoprolol hemifumarate

USAN: Bisoprolol fumarate

Compendium: Not yet assigned.

Code Name and/or Number: CL 297,939 (American Cyanamid)
EMD 33 512 (E. Merck)
CAS-104344-23-2
CAS-66722-44-9 (bisoprolol)

Patent Certification:

Applicant: Lederle Laboratories Division
American Cyanamid Company
Pearl River, NY 10965

Certification:
Pursuant to Section 505(b) of the "Drug Price Competition and Patent Term Restoration Act of 1984", Applicant's attorney herein makes the following certification based on his information, advise and belief:

(i) Bisoprolol was the subject of U.S. Patents No. 4,171,370 expiring October 16, 1996 and 4,258,062 expiring March 24, 1998, both assigned to E. Merck of West Germany, which contain claims to the drug per se, pharmaceutical compositions containing the drug and methods of using the drug to affect the heart rate or blood pressure of a mammal.

(ii) Since the applicant has a license under the aforesaid patents from E. Merck, it is not believed that any S.S. Letters Patent would be infringed by the manufacture or sale of the above product.

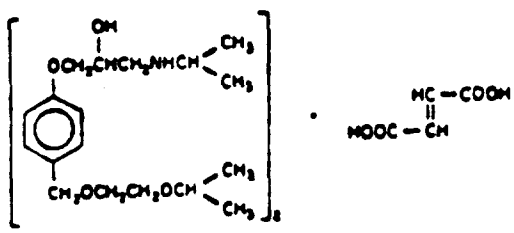
3. Dosage Form and Route of Administration:

Tablets, 5 mg and 10 mg, for oral administration.

4. Pharmacological Category and/or Principal Indications:

β_1-selective adrenoceptor blocking agent for treatment of hypertension.

5. Structural Formula and Chemical Name:



Chemical Name (s):

(±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propranol(E)-2-butenedioate (2:1) (salt) (CA approved name)

(±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)-2-propanol hemifumarate

2-Propanol, 1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (E)-2-butenedioate (2:1) salt

Molecular Formula: $C_{18}H_{31}NO_4.1/2\ C_4H_4O_4$

Molecular Weight: 383.49 (hemifumarate)
325.45 (free base)

MP: 100-103°C

B. 1. Initial Submission:

Date Submitted: July 28, 1989

Date Received: August 1, 1989

Date to Chemist: August 7, 1989

2. Amendments:

10/21/93 Summary Basis of Approval

3. Supporting INDs, NDAs, DMFs and Letters of Authorization:

DMF
DMF
DMF
DMF
DMF
DMF

DMF
DMF
DMF
DMF
DMF

DMF
DMF

IND
IND

4. Related Documents (INDs, NDAs, etc.):

None.

5. Facilities (Operation, Firm and Address):

Drug substance:

Manufacturer:

(DMF

Formerly bisoprolol fumarate (2:1) was manufactured at

DMF

Drug product:

Manufactured, packaged, and controlled by:

(DMF

C. Remarks:

Product name was changed from originally proposed MONOCOR to PROBETA and finally to ZEBETA.

10/21/93 - Summary Basis of Approval.

This NDA was approved on July 31, 1992.

D. Conclusions and/or Recommendations:

Chemistry, manufacturing and controls information section of SBA is acceptable.

/S/

Danute G. Cunningham

cc:
Orig.
HFD-110
HFD-110/CSO
HFD-110/DGCunningham
District
19982R10.NDA

11.27.93