CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-742

CHEMISTRY REVIEW(S)

NDA 21-742

Bystolic
(Nebivolol) Tablets

Mylan Bertek Pharmaceuticals Inc.

Ramsharan D. Mittal

Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Chemistry Review Data Sheet

1. NDA 21-742

2. REVIEW #: 6

3. REVIEW DATE: 10-DEC-2007

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N000(BC)	01-NOV-2007
N000(AM) resubmission	30-MAY-2007
N000(BZ)	27-APR-2007
N000(BC)	08-APR-2005
N000(BC)	03-FEB-2005
N000(BL)	15-DEC-2004
N000	30-APR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N000(BC)	05-DEC-2007
N000(BC)	04-DEC-2007
N000(BC)	02-DEC-2007

6. NAME & ADDRESS OF APPLICANT:

Mylan Bertek Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name Bystolic
b) Non-Proprietary Name (USAN) Nebivolol Hydrochloride
c) Code Numbers R067555 (dl-Nebivolol Hydrochloride)
R067138 (d-Nebivolol Hydrochloride)
R067145 (l-Nebivolol Hydrochloride)
d) Chem. Type/Submission Priority (ONDC only):
- Chem Type **1**
- Submission Priority **S**

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGIC CATEGORY:

Nebivolol is a highly beta1-selective (cardio selective) adrenoreceptor blocker for oral administration that also induces an endothelium-dependent vasodilation associated with the activation of the L-arginine-nitric oxide pathway. Nebivolol has no intrinsic sympathomimetic activity or membrane-stabilizing properties within the therapeutic dosing range.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2.5mg, 5mg and 10mg

13. ROUTE OF ADMINISTRATION: Oral

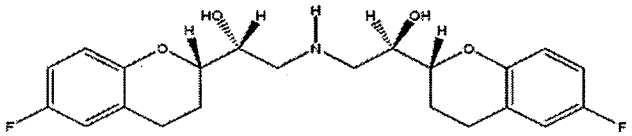
14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

____ SPOTS product – Form Completed
_x_ Not a SPOTS product

1. **CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:**

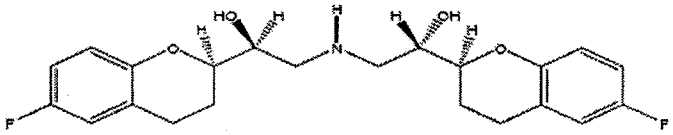
Chemical Name: (1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride and enantiomer
Molecular Weight: 441.90 (Nebivolol Hydrochloride)
Molecular Formula: $C_{22}H_{25}F_2NO_4 \cdot HCl$ (Nebivolol Hydrochloride)
Structural Formula:



• **HCl**

SRRR – or d-nebivilol hydrochloride

+



• **HCl**

RSSS – or l-nebivilol hydrochloride

A. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
	III			3, 4	Adequate	April 30, 2002 April 15, 2003	Reviewed By B. Rogers and S. Markofsky
	III			4	Adequate	-	30 and 100 tablets meet USP <661> and <671> acceptance criteria
	III			3 and 4	Adequate	April 22, 2002	Reviewed by Dr. Raymond P. Frankewich
	III			4	Adequate	-	
	III			3 and 4	Adequate	Sept. 22, 1999	Not Reviewed for updates
	III			4	Adequate	-	-
	III			3 and 4	Adequate	March 17, 2000	30 and 100 tablets
	III			3 and 4	Adequate	June 26, 2002	
	III			3 and 4	Adequate	September 07, 2001	
	III			4	Adequate	-	-
	III			3 and 4	Adequate	April 20, 2002	-
	III			3 and 4	Adequate	August 10, 1999	-
	III			3 and 4	Adequate	December 5, 2002	
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
15,417	II	Jannsen Pharmaceutica NV	Nebivilol Hydrochloride	1	Adequate	December 12, 2007	Drug Substance DMF been updated Adequate to support this NDA .
—	II	—	—	3	Adequate	July 7, 1999	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

17. RELATED/SUPPORTING DOCUMENTS:

IND 33,060

18. STATUS::

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No CMC Consults	-	-
EES	ACCEPTABLE	December 10, 2007	CMC Review # 6
Pharm/Tox	No CMC Consults	-	-
Biopharm	No CMC Consults	-	-
LNC	No CMC Consults	-	-
Methods Validation	Not Needed	-	This Review
DMETS	Proprietary name Cirmaxen Not Acceptable	October 18, 2007	Diane Smith
EA	Categorical Exclusion Acceptable	-	CMC Review # 2
Microbiology	N/A	-	-

The Chemistry Review for NDA 21-742

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An acceptable cGMP status of all facilities has been received from the Office of Compliance. All other pending CMC issues have been resolved. The application may be approved from a chemistry standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug substance, Nebivolol Hydrochloride is white to almost white powder, melts between [redacted] and is non hygroscopic. Nebivolol Hydrochloride is soluble in methanol, dimethylsulfoxide, N,N- Dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

[redacted]

No indication of polymorphism for Nebivolol Hydrochloride has been detected [redacted]

[redacted]

Mylan has established and validated analytical procedures for Assay, Chromatographic Purity, Stereoisomeric Purity, Residual Solvents, Particle Size and Specific Surface Area.

The drug product Nebivolol Hydrochloride immediate release tablets for the management of hypertension are presented in 3 different dose-strengths 2.5 mg, 5 mg and 10 mg. These formulations contain Nebivolol Hydrochloride equivalent to labeled quantity of free base as follows: 2.5 mg, 5 mg and 10 mg. Nebivolol Tablets are manufactured . The following inactive ingredients are used in the manufacture of the finished dosage form: Hypromellose; Polysorbate 80; Lactose Monohydrate; Pregelatinized Starch; Microcrystalline Cellulose; Croscarmellose Sodium; FD&C Blue #2; D&C Red #27; FD&C Yellow #6; Magnesium Stearate/Sodium Lauryl Sulfate ; and Colloidal Silicon Dioxide.

The Nebivolol Hydrochloride tablets are triangular shaped biconvex and come in three colors, 2.5 mg tablets are light blue, 5 mg tablets are beige and 10 mg tablets are pinkish-purple, 5 and 10 mg tablets weigh 230 mg and 2.5 mg tablets weigh 115 mg each. The changes have been made to provide for a tablet imprint to reflect Forest as the marketing partner, and to provide Forest Laboratories as an alternate packaging and analytical testing site. Nebivolol Hydrochloride tablets are changed to deboss with "FL" on one side and respective strength (2 ½ , 5, and 10) on the other side. Color and debossing differentiate the strengths of tablets from one another.

Nebivolol, 2.5mg Tablets are packaged in bottle sizes of 30 and 100 tablets . Nebivolol 5mg and 10mg Tablets are packaged in bottle sizes of 30 and 100 tablets

Mylan has evaluated the long term stability of Nebivolol 2.5mg, 5mg and 10mg Tablets, by performing stability studies at the ICH recommended conditions on the proposed market formulations packaged in the equivalent container/closure systems. Stability data for three batches of each strength of the market formulations are provided for product stored in the following configurations and test conditions:

- Bottles: 5mg and 10mg tablets, six months of accelerated storage conditions and forty eight months of long-term storage conditions
- Unit dose : 5mg and 10mg tablets, six months of accelerated storage conditions (40°C/75% R.H) and thirty six months long-term storage conditions
- Bottles: 2.5mg tablets, six months of accelerated and thirty six months of long-term storage conditions.

Mylan proposes a 36 month expiration date for Nebivolol 2.5mg, 5mg and 10mg Tablets.

Taking into consideration the submitted stability data and the ICH Guidance for Industry, Q1E Evaluation of Stability Data, June 2004 recommendations for long-term and accelerated data showing little or no change over time and little or no variability, an expiration date of 36 months is acceptable for the Nebivolol 2.5 mg, 5 mg and 10 mg tablets packaged in all proposed container/closure configurations.

B. Description of How the Drug Product is intended to be used

Nebivolol Tablets are indicated for use in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Nebivolol Hydrochloride is formulated as a once a day tablet for oral use in three dose strengths: 2.5 mg, 5 mg and 10 mg of nebivolol. The recommended doses in adults are up to 20 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has withdrawn the drug substance manufacturing and testing site at Janssen Pharmaceutica N V, Beerse, BE. The drug substance manufacturing will only be done at Janssen Pharmaceutica N V, Geel, Belgium site. An acceptable cGMP status of all facilities has been received from the Office of Compliance. All other pending CMC issues have been resolved. The application is recommended approval from a chemistry standpoint.

16 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

6 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Ramsharan Mittal
12/12/2007 03:58:04 PM
CHEMIST

Ramesh Sood
12/13/2007 02:24:23 PM
CHEMIST

Chemistry Review Data Sheet

1. NDA 21-742

2. REVIEW #: 5

3. REVIEW DATE: 29-NOV-2007

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N000(BC) Telephone Amendment	01-NOV-2007
N000(AM) resubmission	30-MAY-2007
N000(BZ)	27-APR-2007
N000(BC)	08-APR-2005
N000(BC)	03-FEB-2005
N000(BL)	15-DEC-2004
N000	30-APR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
e-mail correspondence from Dan Brun	28-NOV-2007

6. NAME & ADDRESS OF APPLICANT:

Mylan Bertek Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name — To be established
b) Non-Proprietary Name (USAN) — Nebivolol Hydrochloride
c) Code Numbers — R067555 (dl-Nebivolol Hydrochloride)
R067138 (d-Nebivolol Hydrochloride)
R067145 (l-Nebivolol Hydrochloride)
d) Chem. Type/Submission Priority (ONDC only):
- Chem Type 1
- Submission Priority S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGIC CATEGORY:

Nebivolol is a highly beta1-selective (cardio selective) adrenoreceptor blocker for oral administration that also induces an endothelium-dependent vasodilation associated with the activation of the L-arginine-nitric oxide pathway. Nebivolol has no intrinsic sympathomimetic activity or membrane-stabilizing properties within the therapeutic dosing range.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2.5mg, 5mg and 10mg

13. ROUTE OF ADMINISTRATION: Oral

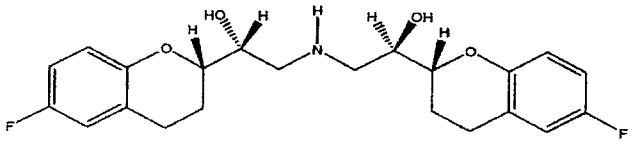
14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

____ SPOTS product – Form Completed
_x_ Not a SPOTS product

1. **CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:**

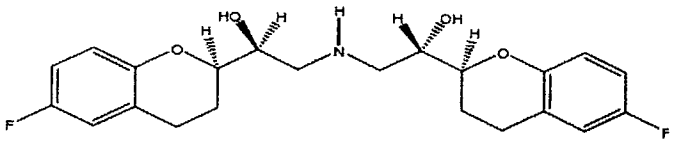
Chemical Name: (1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride and enantiomer
Molecular Weight: 441.90 (Nebivolol Hydrochloride)
Molecular Formula: $C_{22}H_{25}F_2NO_4 \cdot HCl$ (Nebivolol Hydrochloride)
Structural Formula:



• HCl

SRRR – or d-nebivilol hydrochloride

+



• HCl

RSSS – or l-nebivilol hydrochloride

A. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
	III			3, 4	Adequate	April 30, 2002 April 15, 2003	Reviewed By B. Rogers and S. Markofsky
	III			4	Adequate	-	30 and 100 tablets meet USP <661> and <671> acceptance criteria
	III			3 and 4	Adequate	April 22, 2002	Reviewed by Dr. Raymond P. Frankewich
	III			4	Adequate	-	
	III			3 and 4	Adequate	Sept. 22, 1999	Not Reviewed for updates
	III			4	Adequate	-	-
	III			3 and 4	Adequate	March 17, 2000	30 and 100 tablets
	III			3 and 4	Adequate	June 26, 2002	
	III			3 and 4	Adequate	September 07, 2001	
	III			4	Adequate	-	-
	III			3 and 4	Adequate	April 20, 2002	-
	III			3 and 4	Adequate	August 10, 1999	-
	III			3 and 4	Adequate	December 5, 2002	
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
15,417	II	Jannsen Pharmaceutica NV	Nebivilol Hydrochloride	4, 7	Adequate	Not Completed	Drug Substance DMF been updated Adequate to support this NDA - written review under progress. Sufficient information in the NDA review # 1.
[redacted]	II	[redacted]	[redacted]	3	Adequate	July 7, 1999	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

17. RELATED/SUPPORTING DOCUMENTS:

IND 33,060

18. STATUS::

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No CMC Consults	-	-
EES	WITHHOLD	-	This Review
Pharm/Tox	No CMC Consults	-	-
Biopharm	No CMC Consults	-	-
LNC	No CMC Consults	-	-
Methods Validation	Not Needed	-	This Review
DMETS	Proprietary name Cirmaxen Not Acceptable	October 18, 2007	Diane Smith
EA	Categorical Exclusion Acceptable	-	Mittal Review # 2
Microbiology	N/A	-	-

The Chemistry Review for NDA 21-742

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE from CMC perspective. Because of the withhold status of drug substance manufacturing site at Janssen Pharmaceutica N V, Beerse, BE, a final Approval recommendation of Nebivolol Tablets can not be given at this time since an overall recommendation from the Office of Compliance is WITHHOLD.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug substance, Nebivolol Hydrochloride is white to almost white powder, melts and is non hygroscopic. Nebivolol Hydrochloride is soluble in methanol, dimethylsulfoxide, N,N- Dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

Janssen Pharmaceutica supplies the drug substance, Nebivolol Hydrochloride to Mylan.

No indication of polymorphism for Nebivolol Hydrochloride has been detected

Mylan has established and validated analytical procedures for Assay, Chromatographic Purity, Stereoisomeric Purity, Residual Solvents, Particle Size and Specific Surface Area.

The drug product Nebivolol Hydrochloride immediate release tablets for the management of hypertension are presented in 3 different dose-strengths 2.5 mg, 5 mg and 10 mg. These formulations contain Nebivolol Hydrochloride equivalent to labeled quantity of follows: 2.5 mg, 5 mg and 10 mg.

The following inactive ingredients are used in the manufacture of the finished dosage form: Hypromellose; Polysorbate 80; Lactose Monohydrate; Pregelatinized Starch; Microcrystalline Cellulose; Croscarmellose Sodium; FD&C Blue #2; D&C Red #27; FD&C Yellow #6; Magnesium Stearate/Sodium Lauryl Sulfate ; and Colloidal Silicon Dioxide.

The Nebivolol Hydrochloride tablets are triangular shaped biconvex and come in three colors, 2.5 mg tablets are light blue, 5 mg tablets are beige and 10 mg tablets are pinkish-purple, 5 and 10 mg tablets weigh 230 mg and 2.5 mg tablets weigh 115 mg each. The changes have been made to provide for a tablet imprint to reflect Forest as the marketing partner, and to provide Forest Laboratories as an alternate packaging and analytical testing site. Nebivolol Hydrochloride tablets are changed to deboss with "FL" on one side and respective strength (2 ½ , 5, and 10) on the other side. Color and debossing differentiate the strengths of tablets from one another.

Nebivolol, 2.5mg Tablets are packaged in bottle sizes of (30 and 100 tablets), . Nebivolol 5mg and 10mg Tablets are packaged in bottle sizes of . 30 and 100 tablets

Mylan has evaluated the long term stability of Nebivolol 2.5mg, 5mg and 10mg Tablets, by performing stability studies at the ICH recommended conditions on the proposed market formulations packaged in the equivalent container/closure systems. Stability data for three batches of each strength of the market formulations are provided for product stored in the following configurations and test conditions:

- Bottles: 5mg and 10mg tablets, six months of accelerated storage conditions and forty eight months of long-term storage conditions
- Unit dose : 5mg and 10mg tablets, six months of accelerated storage conditions (40°C/75% R.H) and thirty six months long-term storage conditions
- Bottles: 2.5mg tablets, six months of accelerated and thirty six months of long-term storage conditions.

Mylan proposes a 36 month expiration date for Nebivolol 2.5mg, 5mg and 10mg Tablets.

Taking into consideration the submitted stability data and the ICH Guidance for Industry, Q1E Evaluation of Stability Data, June 2004 recommendations for long-term and accelerated data showing little or no change over time and little or no variability, an expiration date of 36 months is acceptable for the Nebivolol 2.5 mg, 5 mg and 10 mg tablets packaged in all proposed container/closure configurations.

B. Description of How the Drug Product is intended to be used

Nebivolol Tablets are indicated for use in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Nebivolol Hydrochloride is formulated as a once a day tablet for oral use in three dose strengths: 2.5 mg, 5 mg and 10 mg of nebivolol. The recommended doses in adults are up to 20 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The application is APPROVABLE from CMC perspective. Because of the withhold status of drug substance manufacturing site at Janssen Pharmaceutica N V, Beerse, BE, a final Approval recommendation of Nebivolol Tablets can not be given at this time since an overall recommendation from the Office of Compliance is WITHHOLD.

4 Page(s) Withheld

2 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-*_____

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/s/

Ramsharan Mittal
11/30/2007 12:06:45 PM
CHEMIST

Ramesh Sood
11/30/2007 01:33:45 PM
CHEMIST

TRADENAME
(Nebivolol Hydrochloride)
Tablets

NDA 21-742

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Mylan Bertek Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Indication: Treatment of hypertension

Presentation: Immediate release, triangular-shaped, biconvex tablet debossed with respective strength on one side and FL on the other.

2.5 mg Tablet: Light blue, [redacted] tablet, debossed with 2 ½, containing 2.5 mg of Nebivolol, packaged in: unit dose [redacted] of 10 tablets; [redacted] 30 and 100 count [redacted] bottle, [redacted].

5 mg Tablet: Beige, [redacted] tablet, debossed with 5, containing 5 mg of Nebivolol, packaged in: unit dose [redacted] of 10 tablets; [redacted], 30 and 100 count, [redacted] bottle, [redacted]

10 mg Tablet: Pinkish-purple, [redacted] debossed with 10, containing 10 mg of Nebivolol, packaged in: unit dose [redacted] of 10 tablets; [redacted] 30 and 100 [redacted] bottle, [redacted].

EER Status: **Pending**

Consults: EA – Acceptable – 10-MAR-2005
Methods Validation – Acceptable – 1-NOV-2007

Original Submission: 30-APR-2004
Resubmission: 27-APR-2007

Post-Approval Agreements: None

Drug Substance:

The drug substance, Nebivolol Hydrochloride, is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_{22}H_{25}F_2NO_4 \cdot HCl$, a molecular weight of 441.90, and a pKa of 8.4. Known chemically as (1RS,1'RS)-1,1'-[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride,

The drug substance is a white to almost white powder, melts and is non hygroscopic. The drug substance is practically insoluble It is soluble in methanol, dimethylsulfoxide, N,N- Dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

Nebivolol Hydrochloride is manufactured by Janssen Pharmaceutica, N.V., of Beerse, Belgium, and the data and information related to the manufacture of the drug substance are described in Drug Master File (DMF) . This DMF has been reviewed and found adequate to support this NDA (21-742). No indication of polymorphism has been detected and the manufacturing process consistently produces a single crystalline form of the racemic drug substance.

The structure of Nebivolol Hydrochloride was elucidated by ultraviolet-visible spectrophotometry, infrared spectrophotometry, proton and carbon (^1H and ^{13}C) nuclear magnetic resonance spectroscopy, chemical ionization mass spectrometry, high resolution mass spectrometry, elemental analysis, specific optical rotation, and single crystal X-ray diffraction. The applicant stated that all data presented in the DMF confirm that the chemical structure of Nebivolol Hydrochloride produced from Janssen's manufacturing process is consistent with the proposed structure. A primary reference standard was prepared and serves as the purest form of Nebivolol Hydrochloride to be used in the qualification of working reference standards.

The proposed release specification for Nebivolol Hydrochloride includes appearance, identification by infrared spectroscopy and high performance liquid chromatography , stereoisomeric identification by chiral HPLC, assay by ion pair HPLC and acid titration, purity by HPLC, impurities by HPLC, loss on drying, residue on ignition, heavy metals, specific surface area by gas adsorption, residual solvents, and particle size by laser diffraction.

Adequate stability data was provided in DMF [redacted] to support a retest date of [redacted] months for bulk drug substance, [redacted], stored at controlled room temperature, 68°-77°F (20°-25°C).

Conclusion: Drug substance is acceptable.

Drug Product:

TRADENAME is available for oral administration as an immediate release, triangular, biconvex tablet in an individual color and strength of Nebivolol: light blue at 2.5 mg ([redacted] mg as the hydrochloride), beige at 5 mg ([redacted] as the hydrochloride), and pinkish-purple at 10 mg ([redacted] as the hydrochloride).

In addition to the drug substance, each 2.5 mg strength tablet contains hypromellose USP [redacted] polysorbate 80 NF [redacted], lactose monohydrate USP [redacted] pregelatinized starch USP NF [redacted], croscarmellose sodium NF [redacted], microcrystalline cellulose NF [redacted] colloidal silicon dioxide NF [redacted], magnesium stearate/sodium lauryl stearate [redacted] and food dye (FD&C Blue #2; FD&C Red #27; FD&C Yellow #6) for a total tablet weight of 115 mg. The 5.0 mg strength tablet is dose-proportional for a total tablet weight of 230 mg. The 10.0 mg strength tablet [redacted] weight at 230 mg.

Specification of the drug product includes: appearance and description, identification by [redacted] HPLC and ultraviolet spectrophotometry, dissolution, content uniformity by [redacted] HPLC, impurities and related compounds by [redacted] HPLC and comparison with reference standard, assay by [redacted] HPLC, and water content by the Karl Fischer method. Reference standard for Nebivolol Hydrochloride is the same as that for drug substance. All test methods have been appropriately validated for their intended purpose.

Stability data indicate that there were no significant changes in chemical and physical properties for three batches of drug product, at each strength, stored in the proposed container/closure configurations, under accelerated and long-term storage conditions.

Adequate stability data were provided to support the proposed expiration dating of 36 months at room temperature, 68°-77°F (20°-25°C), for the drug product packaged in the proposed container/closure configurations.

Conclusion: Drug product is satisfactory.

Additional Items:

Review of the original application resulted in an Approvable letter, which did not contain CMC deficiencies. One CMC-related deficiency concerned the acceptance criterion for dissolution. In the resubmission, the applicant made several CMC changes to the drug

product manufacturing that resulted in new tablet appearance, quality, stability, and container/closure configurations.

As the analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the pharmaceutical industry, revalidation by Agency laboratories will not be requested.

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**, pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
11/6/2007 05:33:29 AM
CHEMIST

Chemistry Review Data Sheet

1. NDA 21-742

2. REVIEW #: 4

3. REVIEW DATE: 01-NOV-2007

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N000(BC)	08-APR-2005
N000(BC)	03-FEB-2005
N000(BL)	15-DEC-2004
N000	30-APR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	01-NOV-2007
N000(AM) resubmission	30-MAY-2007
N000(BZ)	27-APR-2007

6. NAME & ADDRESS OF APPLICANT:

Mylan Bertek Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name — To be established
b) Non-Proprietary Name (USAN) — Nebivolol Hydrochloride
c) Code Numbers — R067555 (dl-Nebivolol Hydrochloride)
R067138 (d-Nebivolol Hydrochloride)
R067145 (l-Nebivolol Hydrochloride)
d) Chem. Type/Submission Priority (ONDC only):

- Chem Type **1**
- Submission Priority **S**
-

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGIC CATEGORY:

Nebivolol is a highly beta1-selective (cardio selective) adrenoreceptor blocker for oral administration that also induces an endothelium-dependent vasodilation associated with the activation of the L-arginine-nitric oxide pathway. Nebivolol has no intrinsic sympathomimetic activity or membrane-stabilizing properties within the therapeutic dosing range.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2.5mg, 5mg and 10mg

13. ROUTE OF ADMINISTRATION: Oral

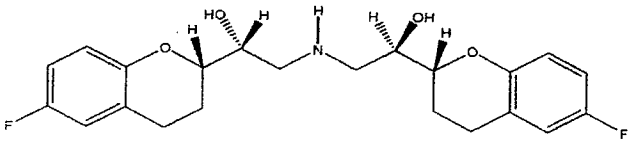
14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

____ SPOTS product – Form Completed
_x_ Not a SPOTS product

1. **CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:**

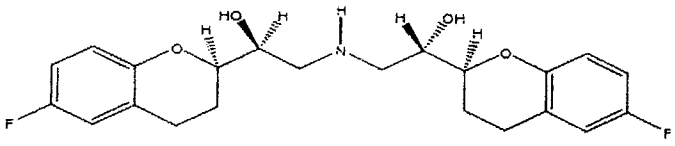
Chemical Name: (1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride and enantiomer
Molecular Weight: 441.90 (Nebivolol Hydrochloride)
Molecular Formula: $C_{22}H_{25}F_2NO_4 \cdot HCl$ (Nebivolol Hydrochloride)
Structural Formula:



• HCl

SRRR – or d-nebivilol hydrochloride

+



• HCl

RSSS – or l-nebivilol hydrochloride

A. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
	III			3, 4	Adequate	April 30, 2002 April 15, 2003	Reviewed By B. Rogers and S. Markofsky
	III			4	Adequate	-	30 and 100 tablets meet USP <661> and <671> acceptance criteria
	III			3 and 4	Adequate	April 22, 2002	Reviewed by Dr. Raymond P. Frankewich
	III			4	Adequate	-	
	III			3 and 4	Adequate	Sept. 22, 1999	Not Reviewed for updates
	III			4	Adequate	-	-
	III			3 and 4	Adequate	March 17, 2000	30 and 100 tablets
	III			3 and 4	Adequate	June 26, 2002	child- resistant properties
	III			3 and 4	Adequate	September 07, 2001	
	III			4	Adequate	-	-
	III			3 and 4	Adequate	April 20, 2002	-
	III			3 and 4	Adequate	August 10, 1999	-
	III			3 and 4	Adequate	December 5, 2002	
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-
	III			4	Adequate	This review	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
15,417	II	Jannsen Pharmaceutica NV	Nebivilol Hydrochloride	4, 7	Adequate	Not Completed	Drug Substance DMF been updated Adequate to support this NDA - written review under progress. Sufficient information in the NDA review # 1.
[redacted]	II	[redacted]	[redacted]	3	Adequate	July 7, 1999	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

17. RELATED/SUPPORTING DOCUMENTS:

IND 33,060

18. STATUS::

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No CMC Consults	-	-
EES	PENDING	-	This Review
Pharm/Tox	No CMC Consults	-	-
Biopharm	No CMC Consults	-	-
LNC	No CMC Consults	-	-
Methods Validation	Not Needed	-	This Review
DMETS	Proprietary name Cirmaxen Not Acceptable	October 18, 2007	Diane Smith
EA	Categorical Exclusion Acceptable	-	Mittal Review # 2
Microbiology	N/A	-	-

The Chemistry Review for NDA 21-742

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The cGMP inspection of the drug substance manufacturing facility (Jansen Pharmaceuticals) is pending.

The application is approvable from CMC perspective. A final Approval recommendation of Nebivolol Hydrochloride Tablets can not be given at this time since an overall recommendation from the Office of Compliance is pending. Regarding comments on the format of the container labels, please refer to section II.C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug substance, Nebivolol Hydrochloride is white to almost white powder, melts _____ and is non hygroscopic. Nebivolol Hydrochloride is soluble in methanol, dimethylsulfoxide, N,N- Dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

No indication of polymorphism for Nebivolol Hydrochloride has been detected

Mylan has established and validated analytical procedures for Assay, Chromatographic Purity, Stereoisomeric Purity, Residual Solvents, Particle Size and Specific Surface Area.

The drug product Nebivolol Hydrochloride immediate release tablets for the management of hypertension are presented in 3 different dose-strengths 2.5 mg, 5 mg and 10 mg. These formulations contain Nebivolol Hydrochloride equivalent to labeled quantity of free base as follows: 2.5 mg, 5 mg and 10 mg. Nebivolol Tablets are manufactured . The following inactive ingredients are used in the manufacture of the finished dosage form: Hypromellose; Polysorbate 80; Lactose Monohydrate; Pregelatinized Starch; Microcrystalline Cellulose; Croscarmellose Sodium; FD&C Blue #2; D&C Red #27; FD&C Yellow #6; Magnesium Stearate/Sodium Lauryl Sulfate ; and Colloidal Silicon Dioxide.

The Nebivolol Hydrochloride tablets are triangular shaped biconvex and come in three colors, 2.5 mg tablets are light blue, 5 mg tablets are beige and 10 mg tablets are pinkish-purple, 5 and 10 mg tablets weigh 230 mg and 2.5 mg tablets weigh 115 mg each. The changes have been made to provide for a tablet imprint to reflect Forest as the marketing partner, and to provide Forest Laboratories as an alternate packaging and analytical testing site. Nebivolol Hydrochloride tablets are changed to deboss with "FL" on one side and respective strength (2 ½ , 5, and 10) on the other side. Color and debossing differentiate the strengths of tablets from one another.

Nebivolol, 2.5mg Tablets are packaged in bottle sizes of 30 and 100 tablets . Nebivolol 5mg and 10mg Tablets are packaged in bottle sizes 30 and 100 tablets

Mylan has evaluated the long term stability of Nebivolol 2.5mg, 5mg and 10mg Tablets, by performing stability studies at the ICH recommended conditions on the proposed market formulations packaged in the equivalent container/closure systems. Stability data for three batches of each strength of the market formulations are provided for product stored in the following configurations and test conditions:

- Bottles: 5mg and 10mg tablets, six months of accelerated storage conditions and forty eight months of long-term storage conditions
- Unit dose : 5mg and 10mg tablets, six months of accelerated storage conditions (40°C/75% R.H) and thirty six months long-term storage conditions

- Bottles: 2.5mg tablets, six months of accelerated and thirty six months of long-term storage conditions.

Mylan proposes a 36 month expiration date for Nebivolol 2.5mg, 5mg and 10mg Tablets.

Taking into consideration the submitted stability data and the ICH Guidance for Industry, Q1E Evaluation of Stability Data, June 2004 recommendations for long-term and accelerated data showing little or no change over time and little or no variability, an expiration date of 36 months is acceptable for the Nebivolol 2.5 mg, 5 mg and 10 mg tablets packaged in all proposed container/closure configurations.

B. Description of How the Drug Product is intended to be used

Nebivolol Tablets are indicated for use in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Nebivolol Hydrochloride is formulated as a once a day tablet for oral use in three dose strengths: 2.5 mg, 5 mg and 10 mg of nebivolol. The recommended doses in adults are up to 20 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

The format of the labeling suggested by Mylan on the basis of the marketed products is not acceptable. The following format should be used:

TRADENAME
(establised name) Tablets
X mg

The amount "X" should be the amount of the established name moiety. The statements similar to "Each tablet contains: nebivolol hydrochloride equivalent to 2.5 mg [or 5 mg or 10 mg] nebivolol." are not acceptable.

FDA recommended changes described above should be included in marked up labeling.

The cGMP inspections of the drug substance manufacturing facility (Jansen Pharmaceuticals) is pending.

The application is approvable from CMC perspective. A final Approval recommendation of Nebivolol Hydrochloride Tablets can not be given at this time since an overall recommendation from the Office of Compliance is pending.

16 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

3 Page(s) Withheld

_____ Trade Secret / Confidential

8 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Ramsharan Mittal
11/2/2007 02:07:55 PM
CHEMIST

Ramesh Sood
11/2/2007 03:05:24 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	21-742
Applicant:	Mylan Bertek Pharmaceuticals
Letter Date:	30 May 2007
Stamp Date:	31 May 2007
PDUFA Date:	30 Nov 2007 (resubmission)
Tradename:	Cirmaxen
Established Name:	Nebivolol
Dosage Form:	Tablets, 2.5, 5 and 10 mg
Route of Administration:	Oral
Indication:	Treatment of hypertension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes -- Complete Response

Summary

NDA 21-742 was issued an Approvable letter on 31 May 2005 listing a number of deficiencies. The major deficiencies cited in the letter relate to safety; however, there was one CMC related issue concerning the acceptance criterion for dissolution. Mylan has responded to these deficiencies in the submissions dated April 27 and 30 May, 2007. In addition, Mylan has made several CMC changes, which they characterize as minor, since the Approvable action in 2005. Some of these are listed below:

- Addition of several Forest Laboratories packaging and testing sites
- Change in tablet imprinting
- Change in water content regulatory limits for the drug product
- Reduction in batch size for the 10 mg strength
- Change in container/closure systems for the drug product
- Additional stability data

The CMC review of the original NDA was done by Dr. Ramsharan Mittal. His Review #3, dated 29 April 2005, concludes that all CMC deficiencies have been satisfactorily addressed.

Comments and Recommendations

The Applicant has submitted a complete response to the dissolution specification deficiency identified in the AE letter. Although this was based on the OCPB reviewer recommendation, the response needs to be reviewed by the ONDQA chemist in keeping with current policy for immediate release tablets. It should be noted that the AE letter stated the acceptance criterion for

dissolution as —— in 30 min which the Applicant has interpreted as Q= —— in 30 min. This is contrary to the OCPB reviewer's expectation that Q=—— in 30 min (see review by E. Mishina dated 11 May 2005). The reviewer should critically evaluate all the CMC revisions, changes and updates included in this resubmission. Since more than 2 years have elapsed since the last overall recommendation from the Office of Compliance, all initial facilities have been resubmitted to EES and the new Forest Laboratories packaging and testing sites have been added. The reviewer should verify that this list is complete. There are a number of labeling issues that need to be addressed – mismatch of established name and strength in the PI and container labels (this was correct in the original NDA), chemical name different from the one in USAN. The USAN structures for both nebivolol and the hydrochloride salt do not clearly show that this is a racemate.

Kasturi Srinivasachar Pharmaceutical Assessment Lead	Aug 21, 2007 Date
Ramesh Sood, Ph.D. Branch Chief	Aug 21, 2007 Date

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/s/

Kasturi Srinivasachar
8/21/2007 12:52:48 PM
CHEMIST

Ramesh Sood
8/21/2007 01:49:36 PM
CHEMIST

CHEM III

NDA 21-742

Nebivolol Tablets

Bertek Pharmaceuticals Inc.

Ramsharan D. Mittal
Division of Cardio-Renal Drug Products

Chemistry Review Data Sheet

1. NDA 21-742

2. REVIEW #: 3

3. REVIEW DATE: 29-APR-2005

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N000(BC)	03-FEB-2005
N000(BL)	15-DEC-2004
N000	30-APR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N000(BC)	08-APR-2005

6. NAME & ADDRESS OF APPLICANT:

Bertek Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name — To be established
b) Non-Proprietary Name (USAN) — Nebivolol Hydrochloride
c) Code Numbers — R067555 (dl-Nebivolol Hydrochloride)
R067138 (d-Nebivolol Hydrochloride)
R067145 (l-Nebivolol Hydrochloride)
d) Chem. Type/Submission Priority (ONDC only):
- Chem Type **1**
- Submission Priority **S**

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGIC CATEGORY:

Nebivolol is a highly beta1-selective (cardio selective) adrenoreceptor blocker for oral administration that also induces an endothelium-dependent vasodilation associated with the activation of the L-arginine-nitric oxide pathway. Nebivolol has no intrinsic sympathomimetic activity or membrane-stabilizing properties within the therapeutic dosing range.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: **2.5mg, 5mg and 10mg**

13. ROUTE OF ADMINISTRATION: Oral

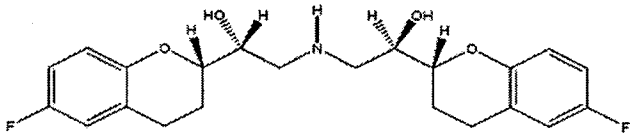
14. Rx/OTC DISPENSED: x Rx ___ OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

____ SPOTS product – Form Completed
x Not a SPOTS product

16. **CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:**

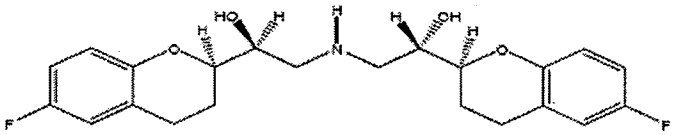
Chemical Name: (1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride
Molecular Weight 441.90 (Nebivolol Hydrochloride)
Molecular Formula C22H25F2NO4·HCl (Nebivolol Hydrochloride)
Structural Formula:



• **HCl**

SRRR – or d-nebivolol hydrochloride

+



• **HCl**

RSSS – or l-nebivolol hydrochloride

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
15,417	II	Jannsen Pharmaceutica NV	Nebovilol Hydrochloride	7	Adequate	Not Completed	Drug Substance DMF is Adequate to support this NDA - written review under progress
[redacted]	II	[redacted]	[redacted]	3	Adequate	July 7, 1999	-

B. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	April 30, 2002 April 15, 2003	Reviewed By B. Rogers and S. Markofsky
[redacted]	III	[redacted]	[redacted]	4	Adequate	-	[redacted] 30 and 100 tablets meet USP <661> and <671> acceptance criteria
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	April 22, 2002	Reviewed by Dr. Raymond P. Frankewich
[redacted]	III	[redacted]	[redacted]	4	Adequate	-	[redacted]
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	September 22, 1999	Not Reviewed for updates
[redacted]	III	[redacted]	[redacted]	4	Adequate	-	[redacted] 30 & 100 tablets
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	March 17, 2000	[redacted] 30 and 100 tablets
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	June 26, 2002	[redacted] child- resistant properties
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	September 07, 2001	[redacted]
[redacted]	III	[redacted]	[redacted]	4	Adequate	-	[redacted]
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	April 20, 2002	-
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	August 10, 1999	-
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	December 5, 2002	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

17. RELATED/SUPPORTING DOCUMENTS:

IND 33,060

18. STATUS::

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	ACCEPTABLE	February 23, 2005	
Pharm/Tox (Impurity Qualification)	ACCEPTABLE	March 24, 2005	Elizabeth Hausner
Biopharm*	Pending for Dissolution specifications	-	Elena Mishina
LNC	N/A	-	
Methods Validation	To be submitted after NDA approval	-	Mittal/Review # 2
DMETS	Proprietary name Betanox Not Acceptable	December 28, 2004	Debi Tran
EA	Categorical Exclusion Acceptable	-	Mittal/Review # 2
Microbiology	N/A	-	-

* The Office of Clinical Pharmacology and Biopharmaceutics has recommended following dissolution specifications:
Dissolution Medium: 0.01N Hydrochloric acid,
USP Apparatus
Paddle Speed 50 rpm
Volume 900 mL
Specification ___ in 30 minutes

OCPB review is PENDING.

The Chemistry Review for NDA 21-742

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of — months is acceptable for Nebivolol Tablets

The deficiencies noted in earlier CMC reviews have been addressed satisfactorily. The application may be approved from chemistry perspective.

The applicant should be informed to use the following recently approved nebivolol hydrochloride USAN chemical name in the package insert, which should be included in marked up labeling:

1*RS*,1'*RS*)-1,1'-[(2*RS*,2'*SR*)-bis(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug substance, Nebivolol Hydrochloride is white to almost white powder, melts and is non hygroscopic. Nebivolol Hydrochloride is soluble in methanol, dimethylsulfoxide, N,N- Dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

Janssen Pharmaceutica supplies the drug substance, Nebivolol Hydrochloride to Mylan.

No indication of polymorphism for Nebivolol Hydrochloride has been detected

Mylan has established and validated analytical procedures for Assay, Chromatographic Purity, Stereoisomeric Purity, Residual Solvents, Particle Size and Specific Surface Area.

The drug product Nebivolol Hydrochloride immediate release tablets for the management of hypertension are presented in 3 different dose-strengths 2.5 mg, 5 mg and 10 mg. These formulations contain Nebivolol Hydrochloride equivalent to labeled quantity of free base as follows: 2.5 mg, 5 mg and 10 mg. Nebivolol Tablets are manufactured via [redacted] process. The following inactive ingredients are used in the manufacture of the finished dosage form: Hypromellose; Polysorbate 80; Lactose Monohydrate; Pregelatinized Starch; Microcrystalline Cellulose; Croscarmellose Sodium; FD&C Blue #2; D&C Red #27; FD&C Yellow #6; Magnesium Stearate/Sodium Lauryl Sulfate : and Colloidal Silicon Dioxide.

The Nebivolol Hydrochloride tablets are triangular shaped biconvex and come in three colors, 2.5 mg tablets are light blue, 5 mg tablets are beige and 10 mg tablets are pinkish-purple, 5 and 10 mg tablets weigh 230 mg and 2.5 mg tablets weigh 115 mg each. Nebivolol Hydrochloride tablets are debossed with "BERTEK" on one side and respective strength (2 ½ , 5, and 10) on the other side. Color and debossing differentiate the strengths of tablets from one another.

The market formulations of Nebivolol 5mg and 10mg Tablets were derived directly from the formulations used in the pivotal clinical studies. The market formulations deviate from the corresponding clinical formulations only in the addition of colorants (to aid in product identification) and for the addition of colorants for maintaining a total tablet weight of 230mg.

The 2.5mg clinical tablets were formulated to be the same tablet weight (230mg) as the higher strength tablets in order to match the placebo tablets. For the market tablets, the formulations were modified such that the 2.5mg tablet is compositionally proportional to the 5mg tablet

The equipment used to manufacture the clinical and pilot batches of Nebivolol Tablets is of the same design and operating principles as the equipment that is intended for use in the production scale batches with the only difference being the size of the equipment. In

addition, the clinical and pilot batches were produced at the same site as that intended for future production batches. Executed batch records and associated Certificates of Analysis (for active and inactive ingredients, packaging components, and finished product) are provided for representative stability and clinical batches.

Nebivolol, 2.5mg Tablets are packaged in bottle sizes of [redacted] 30 and 100 tablets, [redacted]. Nebivolol 5mg and 10mg Tablets are packaged in bottle sizes of [redacted] 30 and 100 tablets, [redacted]

Mylan has evaluated the long term stability of Nebivolol 2.5mg, 5mg and 10mg Tablets, by performing stability studies at the ICH recommended conditions on the proposed market formulations packaged in the intended marketing container/closure systems. Stability data for three batches of each strength of the market formulations are provided for product stored in the following configurations and test conditions:

- Bottles: 5mg and 10mg tablets, six months of accelerated storage conditions and twenty four months of ongoing long-term storage conditions
- Unit dose [redacted] 5mg and 10mg tablets, six months of accelerated storage conditions (40°C/75% R.H) and up to twelve and eighteen months respectively of ongoing long-term storage conditions
- Bottles: 2.5mg tablets, six months of accelerated and twelve months of intermediate storage conditions, and twelve months of ongoing long-term storage conditions.

Mylan proposes a [redacted] month expiration date for Nebivolol 2.5mg, 5mg and 10mg Tablets.

Taking into consideration the submitted stability data and the ICH Guidance for Industry, Q1E Evaluation of Stability Data, June 2004 recommendations for long-term and accelerated data showing little or no change over time and little or no variability, an expiration date of [redacted] months is acceptable for the Nebivolol 5 mg and 10 mg tablets packaged in all proposed container/closure configurations.

Based on the 12 months long term data for 2.5 mg tablets and its compositional similarity to 5 mg tablets an expiration date of [redacted] months is also acceptable for the Nebivolol 2.5 mg tablets packaged in all proposed container/closure configurations.

B. Description of How the Drug Product is intended to be used

Nebivolol Tablets are indicated for use in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Nebivolol Hydrochloride is

formulated as a once a day tablet for oral use in three dose strengths: 2.5 mg, 5 mg and 10 mg of nebivolol. The recommended doses in adults are up to 20 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

An acceptable cGMP status of all facilities (attached at the end of this review) has been received from the Office of Compliance. Pending CMC issues have been addressed by the applicant. The application may be approved from chemistry perspective.

10 Page(s) Withheld

10 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ramsharan Mittal
4/29/05 02:42:20 PM
CHEMIST

Kasturi Srinivasachar
4/29/05 03:01:59 PM
CHEMIST

Chemistry Review Data Sheet

1. NDA 21-742

2. REVIEW #: 2

3. REVIEW DATE: 10-MAR-2005

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
N000(BC)	03-FEB-2004
N000(BL)	15-DEC-2004
N000	30-APR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N000	30-APR-2004

6. **NAME & ADDRESS OF APPLICANT:**

Bertek Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To Be established
b) Non-Proprietary Name (USAN): Nebivolol
c) Code Name/#: R067555; R067138 (d-Nebivolol) ; R067145 (l-Nebivolol)
d) Chem. Type/Submission Priority (ONDC only):
- Chem Type **1**
- Submission Priority **S**

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGIC CATEGORY:

Nebivolol is a highly beta1-selective (cardio selective) adrenoreceptor blocker for oral administration that also induces an endothelium-dependent vasodilation associated with the activation of the L-arginine-nitric oxide pathway. Nebivolol has no intrinsic sympathomimetic activity or membrane-stabilizing properties within the therapeutic dosing range.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: **2.5mg, 5mg and 10mg**

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

_____SPOTS product – Form Completed
_x_Not a SPOTS product

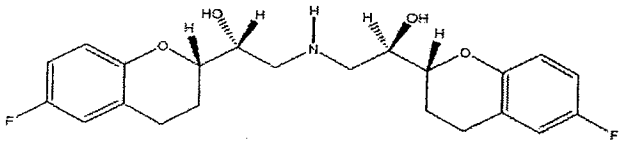
16. **CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:**

Chemical Name: (±)-[2R*[R*[R*(S*)]]]- α,α'-[iminobis-(methylene)] bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride

Molecular Weight 441.90 (Nebivolol Hydrochloride)

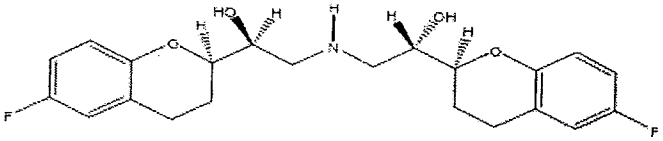
Molecular Formula C22H25F2NO4·HCl (Nebivolol Hydrochloride)

Structural Formula:



• HCl

SRRR – or d-nebivolol hydrochloride



• HCl

RSSS – or l-nebivolol hydrochloride

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
15,417	II	Jannsen Pharmaceutica NV	Nebovilol Hydrochloride	7	Adequate	January 24, 2005	Drug Substance DMF is Adequate to support this NDA - written review under progress
[redacted]	II	[redacted]	[redacted]	3	Adequate	July 7, 1999	-

B. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
[redacted]	III	[redacted]	[redacted]	3 and 4	Adequate	April 30, 2002 April 15, 2003	Reviewed By B. Roggers and S. Markofsky
	III			4	Adequate	-	[redacted] 30 and 100 tablets meet USP <661> and <671> acceptance criteria
	III			3 and 4	Adequate	April 22, 2002	Reviewed by Dr. Raymond P. Frankewich
	III			4	Adequate	-	[redacted]
	III			3 and 4	Adequate	September 22, 1999	Not Reviewed for updates
	III			4	Adequate	May 15, 1996	[redacted]
	III			3 and 4	Adequate	March 17, 2000	[redacted] 30 and 100 tablets
	III			3 and 4	Adequate	June 26, 2002	[redacted] child- resistant properties
	III			3 and 4	Adequate	September 07, 2001	[redacted]
	III			4	Adequate	-	-
	III			3 and 4	Adequate	April 20, 2002	-
	III			3 and 4	Adequate	August 10, 1999	-
	III			3 and 4	Adequate	December 5, 2002	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

17. RELATED/SUPPORTING DOCUMENTS:

IND 33,060

18. STATUS::

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	ACCEPTABLE	February 23, 2005	
Pharm/Tox + (Impurity Qualification)	PENDING		Elizabeth Hausner
Biopharm*	Approval	January 28, 2005	Elena Mishina
LNC	N/A	-	
Methods Validation	To be submitted after NDA approval	-	This Review
DMETS	Proprietary name Betanox Not Acceptable	December 28, 2004	Debi Tran
EA	Categorical Exclusion Acceptable	-	This Review
Microbiology	N/A	-	-

+ Dr. Elizabeth Hausner has been requested to review information related to the qualification of drug substance impurities described in N000(BC), 03-FEB-2004.

* The Office of Clinical Pharmacology and Biopharmaceutics have recommended following dissolution specifications:

Dissolution Medium: 0.01N Hydrochloric acid,
USP Apparatus
Paddle Speed 50 rpm
Volume 900 mL
Specification —— in 15 minutes

The Chemistry Review for NDA 21-742

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An acceptable cGMP status of all facilities has been received from the Office of Compliance. Based on the submitted stability data, an expiration date of — months is acceptable for Nebivolol Tablets packaged in — bottles of — 30, 100 — tablets and unit-dose —

The chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the Nebivolol 2.5 mg, 5 mg and 10 mg Tablets. The deficiencies as noted on pages 10-11 should be communicated to the applicant. The application is approvable from chemistry perspective pending resolution of these deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug substance, Nebivolol Hydrochloride is white to almost white powder, melts — and is non hygroscopic. Nebivolol Hydrochloride is soluble in methanol, dimethylsulfoxide, N,N- Dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

The drug substance Nebivolol hydrochloride, or (±)-[2R*[R*[R*(S*)]]]- α,α'-[iminobis-(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride, has

Janssen Pharmaceutica supplies the drug substance, Nebivolol Hydrochloride to Mylan. The

No indication of polymorphism for Nebivolol Hydrochloride has been detected

Mylan has established and validated analytical procedures for Assay, Chromatographic Purity, Stereoisomeric Purity, Residual Solvents, Particle Size and Specific Surface Area.

The drug product Nebivolol Hydrochloride immediate release tablets for the management of hypertension are presented in 3 different dose-strengths 2.5 mg, 5 mg and 10 mg. These formulations contain Nebivolol Hydrochloride equivalent to labeled quantity of free base as follows: 2.5 mg, 5 mg and 10 mg. Nebivolol Tablets are manufactured The following inactive ingredients are used in the manufacture of the finished dosage form: Hypromellose; Polysorbate 80; Lactose Monohydrate; Pregelatinized Starch; Microcrystalline Cellulose; Croscarmellose Sodium; FD&C Blue #2; D&C Red #27; FD&C Yellow #6; Magnesium Stearate/Sodium Lauryl Sulfate ; and Colloidal Silicon Dioxide.

The Nebivolol Hydrochloride tablets are triangular shaped biconvex and come in three colors, 2.5 mg tablets are light blue, 5 mg tablets are beige and 10 mg tablets are pinkish-purple, 5 and 10 mg tablets weigh 230 mg and 2.5 mg tablets weigh 115 mg each. Nebivolol Hydrochloride tablets are debossed with "BERTEK" on one side and respective strength (2 ½ , 5, and 10) on the other side. Color and debossing differentiate the strengths of tablets from one another.

The market formulations of Nebivolol 5mg and 10mg Tablets were derived directly from the formulations used in the pivotal clinical studies. The market formulations deviate from the corresponding clinical formulations only in the addition of colorants (to aid in product identification) and the addition of colorants for maintaining a total tablet weight of 230mg.

The 2.5mg clinical tablets were formulated to be the same tablet weight (230mg) as the higher strength tablets in order to match the placebo tablets. For the market tablets, the formulations were modified such that the 2.5mg tablet is compositionally proportional to the 5mg tablet

The equipment used to manufacture the clinical and pilot batches of Nebivolol Tablets is of the same design and operating principles as the equipment that is intended for use in the production scale batches with the only difference being the size of the equipment. In

addition, the clinical and pilot batches were produced at the same site as that intended for future production batches. Executed batch records and associated Certificates of Analysis (for active and inactive ingredients, packaging components, and finished product) are provided for representative stability and clinical batches.

Nebivolol, 2.5mg Tablets are packaged in bottle sizes of — 30 and 100 tablets, —. Nebivolol 5mg and 10mg Tablets are packaged in bottle sizes of — 30 and 100 tablets —

Mylan has evaluated the long term stability of Nebivolol 2.5mg, 5mg and 10mg Tablets, by performing stability studies at the ICH recommended conditions on the proposed market formulations packaged in the intended marketing container/closure systems. Stability data for three batches of each strength of the market formulations are provided for product stored in the following configurations and test conditions:

- Bottles: 5mg and 10mg tablets, six months of accelerated storage conditions and twenty four months of ongoing long-term storage conditions
- Unit dose — 5mg and 10mg tablets, six months of accelerated storage conditions (40°C/75% R.H) and up to twelve and eighteen months respectively of ongoing long-term storage conditions
- Bottles: 2.5mg tablets, six months of accelerated and twelve months of intermediate storage conditions, and twelve months of ongoing long-term storage conditions.

Mylan proposes a — month expiration date for Nebivolol 2.5mg, 5mg and 10mg Tablets.

Taking into consideration the submitted stability data and the ICH Guidance for Industry, Q1E Evaluation of Stability Data, June 2004 recommendations for long-term and accelerated data showing little or no change over time and little or no variability, an expiration date of — months is acceptable for the Nebivolol 5 mg and 10 mg tablets packaged in all proposed container/closure configurations.

Based on the 12 months long term data for 2.5 mg tablets and its compositional similarity to 5 mg tablets an expiration date of — months is also acceptable for the Nebivolol 2.5 mg tablets packaged in all proposed container/closure configurations.

B. Description of How the Drug Product is intended to be used

Nebivolol Tablets are indicated for use in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Nebivolol Hydrochloride is formulated as a once a day tablet for oral use in three dose strengths: 2.5 mg, 5 mg and 10 mg of nebivolol. The recommended doses in adults are up to 20 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

An acceptable cGMP status of all facilities (attached at the end of this review) has been received from the Office of Compliance Pending CMC issues listed on pages 10-11 of this review need to be communicated to the applicant. The application is approvable from chemistry perspective pending resolution of these CMC issues.

III. Administrative

A. Reviewer's Signature
B. Endorsement Block
C. CC Block

4 Page(s) Withheld

0 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Ramsharan Mittal
3/11/05 03:07:13 PM
CHEMIST

Kasturi Srinivasachar
3/11/05 03:43:38 PM
CHEMIST

Chemistry Review Data Sheet

1. NDA 21-742

2. REVIEW #: 1

3. REVIEW DATE: 14-FEB-2005

4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N000(BC)	03-FEB-2004
N000(BL)	15-DEC-2004
N000	30-APR-2004

6. NAME & ADDRESS OF APPLICANT:

Bertek Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name To Be established
b) Non-Proprietary Name (USAN): Nebivolol
c) Code Name/# R067555; R067138 (d-Nebivolol) ; R067145 (l-Nebivolol)
d) Chem. Type/Submission Priority (ONDC only):
- Chem Type **1**
- Submission Priority **S**

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGIC CATEGORY:

Nebivolol is a highly beta1-selective (cardio selective) adrenoreceptor blocker for oral administration that also induces an endothelium-dependent vasodilation associated with the activation of the L-arginine-nitric oxide pathway. Nebivolol has no intrinsic sympathomimetic activity or membrane-stabilizing properties within the therapeutic dosing range.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: **2.5mg, 5mg and 10mg**

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) :

_____SPOTS product – Form Completed
__x__Not a SPOTS product

16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

Chemical Name: (±)-[2R*[R*[R*(S*)]]]- α,α'-[iminobis-(methylene)] bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride

Molecular Weight 441.90 (Nebivolol Hydrochloride)

Molecular Formula C22H25F2NO4·HCl (Nebivolol Hydrochloride)

Structural Formula:

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS
15,417	II	Jannsen Pharmaceutica NV	Nebovilol Hydrochloride	7	Adequate	January 24, 2005	Drug Substance DMF is Adequate to support this NDA - written review under progress
—	II	—	—	1	Adequate	July 7, 1999	-

B. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW DATE	COMMENTS

	III		1 and 4	Adequate	April 30, 2002 April 15, 2003	Reviewed By B. Roggers and S. Markofsky
	III		4	Adequate	-	30 and 100 tablets meet USP <661> and <671> acceptance criteria
	III		1 and 4	Adequate	April 22, 2002	Reviewed by Dr. Raymond P. Frankewich
	III		4	Adequate	-	
	III		1 and 4	Adequate	September 22, 1999	Not Reviewed for updates
	III		4	Adequate	May 15, 1996	
	III		1 and 4	Adequate	March 17, 2000	30 and 100 tablets
	III		1 and 4	Adequate	June 26, 2002	
	III		1 and 4	Adequate	September 07, 2001	child- resistant properties
	III		4	Adequate	-	-
	III		1 and 4	Adequate	April 20, 2002	-
	III		1 and 4	Adequate	August 10, 1999	-
	III		1 and 4	Adequate	December 5, 2002	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

17. RELATED/SUPPORTING DOCUMENTS:

None.

18. STATUS::

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES+	Pending	January 31, 2005	
Pharm/Tox	N/A - No CMC Consults	November 18, 2004 December 21, 2004	Elizabeth Hausner
Biopharm*	Approval	January 28, 2005	Elena Mishina
LNC	N/A	-	
Methods Validation	To be submitted after NDA approval	-	This Review
DMETS*	Proprietary name Betanox Not Acceptable	December 28, 2004	Debi Tran
EA	Categorical Exclusion Acceptable	-	This Review
Microbiology	N/A	-	-

+ Inspection is due to be completed on February 16, 2005

* The Office of Clinical Pharmacology and Biopharmaceutics have recommended following dissolution specifications:
Dissolution Medium: 0.01N Hydrochloric acid,
USP Apparatus
Paddle Speed 50 rpm
Volume 900 mL
Specification [redacted] in 15 minutes

The Chemistry Review for NDA 21-742

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is deficient in some areas of manufacturing and controls such as specifications (water content) and stability protocols for the Nebivolol 2.5 mg, 5 mg and 10 mg Tablets. The deficiencies as noted on pages 85-86 of this review should be included in the action letter to the applicant. Based on the submitted stability data, an expiration date of — months is acceptable for Nebovilol Tablets packaged in — bottles of— 30, 100 — .

The Chemistry Manufacturing and Controls information in this application was provided for different dose strengths — 2.5 mg, 5 mg , 10 mg —. The applicant is marketing only three dose strengths 2.5 mg, 5 mg and 10 mg.

A final recommendation on approvability of Nebivolol Hydrochloride 2.5 mg, 5 mg and 10 mg Tablets can not be given at this time since an overall recommendation from the Office of Compliance is pending because cGMP inspection of the drug substance manufacturing facilities (Jansen Pharmaceuticals) has not been completed and the facilities are scheduled to be inspected between February 6 – 16, 2005.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug substance, Nebivolol Hydrochloride is white to almost white powder, melts — and is non hygroscopic. Nebivolol Hydrochloride is soluble in methanol, dimethylsulfoxide, N,N- Dimethylformamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

The drug substance Nebivolol hydrochloride, or (±)-[2R*[R*[R*(S*)]]]- α,α'-[iminobis-(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride, has

Janssen Pharmaceutica supplies the drug substance, Nebivolol Hydrochloride to Mylan. The

No indication of polymorphism for Nebivolol Hydrochloride has been detected

Mylan has established and validated analytical procedures for Assay, Chromatographic Purity, Stereoisomeric Purity, Residual Solvents, Particle Size and Specific Surface Area.

The drug product Nebivolol Hydrochloride immediate release tablets for the management of hypertension are presented in 3 different dose-strengths 2.5 mg, 5 mg and 10 mg. These formulations contain Nebivolol Hydrochloride equivalent to labeled quantity of free base as follows: 2.5 mg, 5 mg and 10 mg. Nebivolol Tablets are manufactured process. The following inactive ingredients are used in the manufacture of the finished dosage form: Hypromellose; Polysorbate 80; Lactose Monohydrate; Pregelatinized Starch; Microcrystalline Cellulose; Croscarmellose Sodium; FD&C Blue #2; D&C Red #27; FD&C Yellow #6; Magnesium Stearate/Sodium Lauryl Sulfate ; and Colloidal Silicon Dioxide.

The Nebivolol Hydrochloride tablets are triangular shaped biconvex and come in three colors, 2.5 mg tablets are light blue, 5 mg tablets are beige and 10 mg tablets are pinkish-purple, 5 and 10 mg tablets weigh 230 mg and 2.5 mg tablets weigh 115 mg each. Nebivolol Hydrochloride tablets are debossed with "BERTEK" on one side and respective strength (2 ½ , 5, and 10) on the other side. Color and debossing differentiate the strengths of tablets from one another.

The market formulations of Nebivolol 5mg and 10mg Tablets were derived directly from the formulations used in the pivotal clinical studies. The market formulations deviate from the corresponding clinical formulations only in the addition of colorants (to aid in product identification) and for the addition of colorants for maintaining a total tablet weight of 230mg.

The 2.5mg clinical tablets were formulated to be the same tablet weight (230mg) as the higher strength tablets in order to match the placebo tablets. For the market tablets, the formulations were modified such that the 2.5mg tablet is compositionally proportional to the 5mg tablet

The equipment used to manufacture the clinical and pilot batches of Nebivolol Tablets is of the same design and operating principles as the equipment that is intended for use in the production scale batches with the only difference being the size of the equipment. In addition, the clinical and pilot batches were produced at the same site as that intended for future production batches. Executed batch records and associated Certificates of Analysis (for active and inactive ingredients, packaging components, and finished product) are provided for representative stability and clinical batches.

Nebivolol, 2.5mg Tablets are packaged in bottle sizes of 30 and 100 tablets Nebivolol 5mg and 10mg Tablets are packaged in bottle sizes of 30 and 100 tablets

Mylan has evaluated the long term stability of Nebivolol 2.5mg, 5mg and 10mg Tablets, by performing stability studies at the ICH recommended conditions on the proposed market formulations packaged in the intended marketing container/closure systems. Stability data for three batches of each strength of the market formulations are provided for product stored in the following configurations and test conditions:

- Bottles: 5mg and 10mg tablets, six months of accelerated storage conditions and twenty four months of ongoing long-term storage conditions
- Unit dose 5mg and 10mg tablets, six months of accelerated storage conditions (40°C/75% R.H) and up to twelve and eighteen months respectively of ongoing long-term storage conditions
- Bottles: 2.5mg tablets, six months of accelerated and twelve months of intermediate storage conditions, and twelve months of ongoing long-term storage conditions.

Mylan proposes a month expiration date for Nebivolol 2.5mg, 5mg and 10mg Tablets.

was proposed as the trade name for this product and DMETS (December 28, 2004) found this name "Not Acceptable".

B. Description of How the Drug Product is intended to be used

Nebivolol Tablets are indicated for use in the management of hypertension. It may be used alone or in combination with other antihypertensive agents. Nebivolol Hydrochloride is formulated as a once a day tablet for oral use in three dose strengths: 2.5 mg, 5 mg and 10 mg of nebivolol. The recommended doses in adults are up to 20 mg/day.

C. Basis for Approvability or Not-Approval Recommendation

Pending CMC issues listed on pages 85-86 of this review need to be included in the action letter to the applicant. A final recommendation from the Chemistry perspective can not be given at this time since an overall recommendation from the Office of Compliance is still pending.

III. Administrative

A. Reviewer's Signature
B. Endorsement Block
C. CC Block

77 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Ramsharan Mittal
2/14/05 06:56:10 PM
CHEMIST

Kasturi Srinivasachar
2/15/05 08:23:59 AM
CHEMIST