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Edward Fromm
4/28/05 01:57:54 PM

3/18/05

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

DISCIPLINE REVIEW LETTER

Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea B. Miller, R.Ph., Esq
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your April 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (nebivolol) Tablets.

We also refer to your submissions dated December 15, 2004 and February 3, 2005.

A chemistry review of your submission is complete, and we have the following comments. Chemistry, Manufacturing, and Controls information was provided for — different dose strengths (—, 2.5, 5, 10, —— 20 mg). Since you plan to market———dose strengths (2.5, 5, and 10 mg) ———

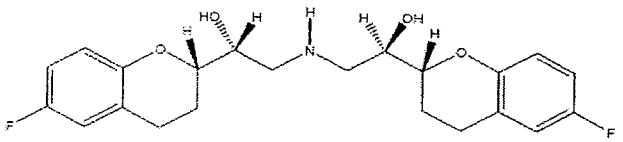
1. The primary and supportive stability data of all batches, strengths and packaging configurations show that there were only a few time points where moisture values were about —— The proposed limit for water content of — is too high and should be tightened to not more than —. For the identification test by UV, please provide the specific wavelength of the maxima.

2. Please note that mere generation of acceptable data from a number of batches will not be considered sufficient justification for deletion of in-process blend uniformity testing.

3. Please clarify if you will market unit dose , ——for Nebivolol 5 and 10 mg Tablets. If so, these should be described in the "How Supplied" section of the package insert.

4. The post-approval stability protocols for each strength state that the first three production lots will be packaged and placed in the long-term stability studies for the largest and smallest size of each bottle container/closure system to be marketed. From the protocols, it is not clear which specific bottle/number of tablets per strength will be placed on a post-approval stability protocol. The physician sample bottle is a promotional size, which should not be included among the marketed configurations but it should be placed on stability protocol in addition to the marketed sizes. Please revise the post-approval stability protocols specifying the bottle size/number of tablets/strength of nebivolol tablets.

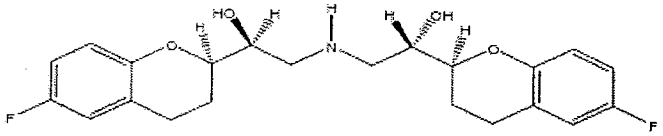
5. The chemical structure of nebivolol hydrochloride provided in the "Description" section is not an accurate representation of the nebivolol hydrochloride drug substance. Since the drug substance is a racemic mixture of d- and l-nebivolol hydrochloride, its structure should be shown as follows:



• HCl

SRRR – or d-nebivolol hydrochloride

+



• HCl

RSSS – or l-nebivolol hydrochloride

Please submit a request for a USAN for (±) nebivolol hydrochloride and provide a copy of the USAN request to this NDA as a part of your response. Please note that the current USP Dictionary lists only nebivolol free base with inadequate structure representation since no stereochemistry is shown.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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6 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

2/24/05

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

Bertek Pharmaceuticals Inc.
Attention: Andrea B. Miller, R.Ph., Esq
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your April 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for nebivolol — 2.5, 5, 10, —— mg Tablets.

On February 9, 2005, we received your February 8, 2005 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 31, 2005.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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Edward Fromm
2/24/05 06:20:26 AM

2/15/05

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

DISCIPLINE REVIEW LETTER

Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea B. Miller, R.Ph., Esq
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your April 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (nebivolol) Tablets.

We also refer to your submission dated December 15, 2004.

A review by the Division of Medication Errors and Technical Support (DMETS) of your submission is complete, and we have the following comments:

1. In reviewing the proprietary name ——— , the primary concerns related to look-alike confusion with Betaxolol and Betimol.

   Betaxolol was identified to have look-alike potential with ——— . Betaxolol is an established name and currently marketed under the brand names Kerlone, Betoptic, and Betoptic S. Kerlone is a beta-adrenergic blocking agent used in the management of hypertension. Kerlone is available in 10 mg and 20 mg oral tablets and is dosed as 10 mg once daily. Betoptic and Betoptic S are beta-adrenergic blocking agents used in the treatment of ocular hypertension. Betoptic is an ophthalmic solution (0.5%) and Betoptic S is an ophthalmic suspension (0.25%) dosed as one to two drops into the affected eye(s) twice daily. Betaxolol and ——— have look-alike similarities in that they share the same ——— letters ———. While the ending letters of each name are different (———————), when scripted they can look similar (———————). Each of the Betaxolol products have overlapping characteristics with ——— . Betaxolol (Kerlone) and ——— share overlapping dosage form (tablet), route of administration (oral), strength (10 mg), and dosing regimen (once daily). Betaxolol (Betoptic) and ——— also have similar numerical strengths (0.25% and 0.5% vs. 2.5 mg and 5 mg). Betoptic and ——— have different dosage forms (ophthalmic solution vs. tablet), route of administration (topical to eye vs. oral), and dosing regimens (twice daily vs. once daily). Although the products share some differences, DMETS believes the look-alike similarities, as well as the overlapping product characteristics increase the risk for confusion and error between Betaxolol and ——— .

Betaxolol ———

Betimol was identified to have look-alike similarities with ———. Betimol is a beta-adrenergic blocking agent used in the treatment of elevated intraocular pressure in open-angle glaucoma and ocular hypertension. Betimol is available as a 0.25% and 0.5% ophthalmic solution. The initial recommended therapy is one drop of the solution in the affected eye(s) twice daily. If the intraocular pressure is maintained at satisfactory levels, the dosage may be changed to one drop in the affected eye once daily. When scripted, the letters "Betimo" ——— look similar and the last letter of each name ——— can look alike if one does not pick up the pen from the paper when writing the letter — thus creating a loop which looks like the letter "l". Besides look-alike similarities, the two drugs have possible overlapping daily dosing regimens and share similar numerical values for strength (0.25% and 0.5% vs. 2.5 mg and 5 mg). Confusion may occur if an inpatient order calls for ——— 5 mg, 1 QD" and is misinterpreted as "Betimol .5%, 1 QD" as the decimal point (.5) may be overlooked and '%' can look similar to 'mg' when scripted. Furthermore, confusion may occur in an outpatient setting if an order for "Betimol .5%, 1 QD, #15" is misinterpreted as ' ——— 5 mg, 1QD, #15". Betimol is available in several bottle sizes (2.5 mL, 5 mL, 10 mL, and 15 mL), several of which can be interpreted as number of tablets to be dispensed (i.e., #15) instead of a volume. In contrast, the two drugs have different dosage forms (ophthalmic solution vs. tablet), route of administration (topical to the eye vs. oral), and indications for use (open-angle glaucoma vs. hypertension). DMETS believes that based on the overwhelming look-alike characteristics, as well as the above-mentioned overlapping product similarities, there is increased risk of confusion and error between Betimol and ———.

Betimol ———

2. Draft copies of the labels and labeling were reviewed, in black and white, and may not represent the true color of the labels and labeling. It is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used in the marketplace (i.e. color, placement of name, design, etc.). Please forward copies of the final printed labels and labeling when they are available.

———

.e.

iii. Ensure the product strengths are prominent and clearly differentiated from one another by using contrasting color, boxing, or some other means.

iv. For each individual blister, decrease the prominence of the sponsors name and relocate the name away from the proprietary name, established name, and strength.

———

d. CONTAINER LABELS (Physician Sample, 30 tabs, 100 tabs, [redacted]

i. See comments a(i), a(iii) and b(iii).

ii. Include the lot number and expiration date on the container.

iii. Ensure the 30 tablet unit of use container has a child resistant closure in compliance with the Poison Prevention Act.

e. CARTON LABELING

i. See comments a(i), a(iii) and b(iii).

ii. Revise the commercial package net quantity statement "4 x 7 tablets" to read "4 cards x 7 tablets". Revise the physician sample net quantity "1 x 7 tablets" to read "1 card x 7 tablets".

iii. [redacted]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Edward Fromm
2/15/05 07:45:47 AM

2/15/05

MEMORANDUM

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

DATE: February 11, 2005

FROM: Karen M. Storms, Consumer Safety Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

THROUGH: Leslie K. Ball, M.D., Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Clinical Inspections Summary - **NDA 21-742**

TO: Melissa Robb, Regulatory Project Manager
Karen Hicks, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

APPLICANT: Bertek Pharmaceuticals

DRUG: Nebivolol

CHEMICAL CLASSIFICATION: 1

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of hypertension

ACTION GOAL DATE: February 28, 2005

I. BACKGROUND:

Hypertension is a very common disorder that is associated with atherosclerosis, coronary artery disease, and stroke. Hypertension is treated with a wide variety of pharmacologic agents that include beta blockers, calcium channel blockers, alpha blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, direct vasodilators (nitrates), and centrally acting agents.

Nebivolol is an antihypertensive drug with two physiologic properties. One isomer acts as a classical beta-blocker that slows the heart and decreases the strength of contractility. The other isomer has nitric oxide (NO) dependent vasodilation. Both of these mechanisms act to lower

blood pressure. Product development work has shown that patients segregate into two groups based on their metabolism of the drug, poor and extensive metabolizers.

This was a double blind, randomized, placebo controlled hypertension trial comparing nebivolol in strengths of 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg versus placebo. There was a minimum 28-day placebo run in period, followed by 84 days of double-blind treatment. The primary efficacy endpoint is the change in average diastolic blood pressure at end of treatment compared to baseline. The study population consisted of approximately 300 African American subjects at approximately 12 sites with mild to moderate hypertension

The following sites were selected to validate data submitted in support of the pending application.

II. RESULTS (by site):

Name	City	State	IN	Assigned	Action Date	Reviewer	Class
Herron	Chicago	IL	DA	06-Jun-04	28-Feb-05	KMS	VAI*
Lasseter	Miami	FL	DA	06-Jun-04	28-Feb-05	KMS	VAI
Graff	Ft. Lauderdale	FL	DA	06-Jun-04	28-Feb-05	KMS	VAI*

* Classifications are based on review of the 483 and written portion of the establishment inspection report.

James R. Herron, M.D.

This site enrolled 42 subjects with 30 subjects completing the study. According to the screening log, 4 subjects withdrew voluntarily; 7 subjects were lost to follow-up; and 3 subjects did not meet inclusion criteria. Two subjects were enrolled that did not meet the protocol required blood pressure readings at screening. For 8 out 10 subjects records reviewed, the blood pressure readings were not taken at the protocol required two hours post-dose of study medication. For 3 of the 10 subjects records reviewed, the 12 lead electrocardiograms were not taken at the protocol required two hours-dose of study medication.

Kenneth Lasseter, M.D.

This site enrolled 62 subjects; all subjects met inclusion criteria. The records reviewed included drug accountability, case report forms; source documents; laboratory reports; and all screening logs. Review of data listing against source documents revealed no discrepancies.

Although there was no Form FDA 483 issued, the inspection is classified VAI for a minor protocol violation; one subject did not have the final visit evaluation performed.

Alan Graff, M.D.

This site screened 71 and enrolled 67 subjects. According to the screening log, 4 subjects withdrew voluntarily, 7 subjects were lost to follow-up and 3 subjects that were randomized were

not enrolled due to exclusion criteria. All subjects from this site were recruited from Dr. Graff's private practice. The records reviewed during the inspection included screening records, medical charts, laboratory testing reports, drug accountability records, and subject diaries. One subject was enrolled that did not meet inclusion criteria. There were no serious adverse events reported at this site.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

No major deficiencies were noted in the three sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable. No subsequent actions or follow up inspections should be undertaken.

There were no limitations to these inspections.

Key to Classification:

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
VAI-r = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

Karen M. Storms

Leslie K. Ball, M.D. 2/11/05

Concurrence:

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47

cc:
HFD-45
HFD-47 Storms
HFD-47/rf/cf
O:kms:2005:21742InspectSummary

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/s/

Karen Storms
2/15/05 12:27:29 PM
TECHNICAL

Ni Aye Khin
2/15/05 12:29:37 PM
MEDICAL OFFICER

2/10/05

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

DISCIPLINE REVIEW LETTER

Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea B. Miller, R.Ph., Esq
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your April 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (nebivolol) Tablets.

We also refer to your submissions dated June 24, July 9, 14, and 15, October 27, November 12, 16, 19, 23, and 30, and December 15 and 21, 2004.

A review by the Office of Clinical Pharmacology and Biopharmaceutics of your submission is complete, and we have the following comments:

1. The requested biowaiver for the 2.5-mg dosage strength of the nebivolol tablet is granted.

2. The following dissolution method and specifications are recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed USP Apparatus II	50 rpm
Volume	900 mL
Specifications	> [redacted] in 15 minutes

3. The pharmacokinetics of the active metabolites of nebivolol was not assessed. This led to the inability to explain why the striking difference in pharmacokinetics of the parent drug in extensive and poor metabolizers of CYP2D6 did not show any differences in the drug effect.

4. The relationship between pharmacokinetics and pharmacodynamics of nebivolol was not established. The reasons include poor study design and inability to measure all pharmacologically active moieties.

5. Please evaluate the PK/PD relationship in African-American hypertensive patients.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
2/10/05 03:30:33 PM

1/25/05

Minutes of Telecon

Date of telecom: January 5, 2005

Mylan Bertek Attendees

Andrea Miller, R.Ph. Esq. Vice President, Regulatory Affairs
John O'Donnell, Ph.D., Chief Scientific Officer
Jeff Smith, Ph.D. Assistant Director, Pharmacology and Toxicology
James H. Sherry, M.D., Ph.D., Medical Director
Bruce Bottini, Pharm D. , Executive Director, Drug Safety
Betty Riggs, M.D., Vice President, Clinical Research
Will Sullivan, Vice President Clinical Operations
Kelly Tate, M.S., Director, Regulatory Affairs

Bertek Consultants

FDA Attendees:

Elizabeth Hausner, D.V.M., Pharmacologist
Al DeFelice, Ph.D., Supervisory Pharmacologist

The purpose of the telecom was to clarify certain points to be covered in the proposed endocrine studies. The Division asked the sponsor to explain the choice of positive controls for the 3 month rodent study. Finasteride was picked for use in mice as it has been demonstrated to cause Leydig Cell tumors quickly and possibly by an increase in lutenizing hormone (LH). Therefore, if the mechanism by which nebivolol causes LCT is similar to that of finasteride, the endocrine profiles are expected to be similar. Flutamide was chosen for the rats as a dependable, rapid tumorigen.

The Division requested sperm analysis (to include at least number, motility, morphology) also to address questions that have been raised in the past(2002) and the inconsistent textual reports of low sperm counts and various testicular effects. The sponsor stated that incorporating this into the study design will require some consideration so that the overall study is not compromised. Dr Creasy also noted that testicular histopathology will be included in the study and that STP guidelines for evaluation of the male reproductive tract will be followed.

The histopathology incidence table should also include the dog studies. A presentation of the findings for the endocrine organs/reproductive tracts should be presented without filtering. That is, findings should not be omitted because they did not achieve statistical significance in one or more studies or because the sponsor does not consider the findings to be endocrine related.

The protocols should be submitted to the NDA as soon as possible. It was agreed that it was not necessary for the sponsor to wait for further notification of concurrence from the Division before beginning the study.

Meeting minutes prepared by E. Hausner

Elizabeth Hausner, D.V.M.
Pharmacologist

Al DeFelice, Ph.D.
Supervisory Pharmacologist

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/s/

Elizabeth Hausner
1/25/05 10:18:42 AM
PHARMACOLOGIST
Elizabeth Hausner

Albert Defelice
1/26/05 03:51:17 PM
PHARMACOLOGIST

11/05

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

DISCIPLINE REVIEW LETTER

Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea B. Miller, R.Ph., Esq
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your April 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (nebivolol) Tablets.

We also refer to your submission dated December 15, 2004.

A review by the Division of Drug Marketing, Advertising and Communications (DDMAC) of your submission is complete, and we have the following comments:

> DDMAC objects to the trade name ' ——— ' because it is overly fanciful. The ——— suggests that the drug works on the beta receptors and has "NO" beta effect or complete beta-adrenergic receptor blockade. The name is misleading in the absence of supporting substantial evidence or substantial clinical experience. Please note that the statute provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
1/10/05 03:31:19 PM

8/31/04

Teleconference Minutes

Date:	**September 2, 2004**
Application:	**NDA 21-742**
Drug:	**Nebivolol**
Sponsor:	**Bertek Pharmaceuticals**
Purpose:	**Discuss NDA Review Issues**

FDA Participants:

Karen Hicks, M.D.	Medical Officer
Salma Lemtouni, M.D., M.P.H.	Medical Officer
Elizabeth Hausner, D.V.M., DABVT	Pharmacologist
Al DeFelice, Ph.D.	Pharmacology Team Leader
Russell Fortney	Regulatory Health Project Manager

Bertek Participants:

James Sherry, M.D., Ph.D.	Medical Director
Peter Bruce Bottini, Pharm.D.	Executive Director, Product Safety
Betty Riggs, M.D.	Vice President, Clinical Research
Kelly Tate	Director, Regulatory Affairs
Andrea Miller, R.Ph., Esq.	Vice President, Regulatory Affairs

Background:

NDA 21-742 (nebivolol tablets) was received on April 30, 2004. This teleconference was requested by the Division to discuss multiple review-related issues.

Teleconference:

Dr. Hicks asked the sponsor if the nebivolol formulation used in the pivotal trials was different than the formulation used when development began. The sponsor said that the formulation is essentially the same, with only minor changes. The changes are detailed in the CMC section of the NDA, and also in a recent e-mail to the Division.

Dr. Hicks asked what doses will be marketed. The sponsor said they are planning to market 2.5, 5, and 10 mg doses.

Dr. Hicks asked when the data from the Menarini angina studies would be available. The sponsor said that they are currently working on getting the data sets, and that the final study report is not yet complete.

Dr. Hicks asked if any other nebivolol studies that have been conducted. The sponsor said that there have been some minor studies with small numbers of patients.

Dr. Hicks said she is having difficulty accessing data from the electronic submission for studies NEB-321 and NEB-306. The sponsor agreed to look into this, and reformat and resubmit the data.

Dr. Hicks referred to page 625, table 50.1 (12-lead ECG data). She said that she did not see any tables for the ITT-LOCF population. She asked the sponsor to submit this data. The sponsor agreed to do this.

Dr. Hausner informed the sponsor that the Executive CAC met recently and concluded that the two studies are adequate. However, they also found that the Leydig cell tumors in mice were drug-related. She said the sponsor should make an argument as to why these results are not clinically relevant. The sponsor asked if the Dr. Hausner has seen their white paper related to this issue. Dr. Hausner said she had seen it. She recommended that the sponsor submit any additional supporting information that they have. Dr. Hausner said that it might be useful to look into the clinical database for any general prostate issues and also effects in women.

The sponsor asked if another teleconference could be arranged with their toxicology group. The Division agreed. Dr. DeFelice recommended that the sponsor have their pharmacologist look into the literature related to this issue, including any pharmacology common to nebivolol and that of drugs associated with Leydig tumors, prior to further discussions with the Division.

Dr. Lemtouni asked the sponsor to differentiate between the meaning of legacy vs. non-legacy trials. The sponsor said that the term legacy describes older trials that were not conducted by Bertek.

Dr. Lemtouni said that she was not able to locate some of the case report forms (CRFs) for some adverse events from the Janssen trials. The sponsor said that they submitted all of the information they were able to obtain from the Janssen trials. They said that CRFs for all deaths in the Janssen trials were submitted and agreed to assist Dr. Lemtouni in locating them.

Dr. Lemtouni asked the sponsor to describe the role of Johnson and Johnson in the nebivolol development program. The sponsor said that nebivolol is owned by Janssen Pharmaceuticals. During nebivolol development, Johnson and Johnson purchased Janssen. Nebivolol development in Europe continued under Janssen-Belgium, which has now licensed nebivolol to Menarini. However, Johnson and Johnson decided, for business reasons, not to continue the North American development program. Bertek now licenses the North American rights to nebivolol.

Dr. Lemtouni asked if any nebivolol trials were conducted between 1989 and 1994. The sponsor agreed to investigate this issue.

Dr. Lemtouni asked if any African or Asian studies are included in the NDA package. The sponsor said they will look into this.

Minutes preparation: _____
Russell Fortney

Concurrence, Chair: _____
Karen Hicks, M.D.

Drafted-9/20/04; Final-9/21/04

Reviewed: E.Hausner-9/20/04
A.DeFelice-9/20/04
S.Lemtouni-9/21/04

K.Hicks-9/21/04

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/s/

Russell Fortney
9/21/04 02:00:17 PM

Karen Hicks
9/22/04 04:39:35 PM

Executive CAC
Date of Meeting: August 24, 2004

Committtee: Abby Jacobs, Ph.D. HFD-540, Acting Chair
Joe Contrera, Ph.D. HFD-901, Alternate Member
Jeri El-Hage, Ph.D. HFD-510, Alternate Member
Charles Resnick, Ph.D. HFD-110, Alternate Member
Al DeFelice, Ph.D., HFD-110, Team Leader
Elizabeth Hausner, D.V.M., HFD-110, Presenting Reviewer

Author of minutes: Elizabeth Hausner

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in Dr Hausner's review.

NDA#21,742
Nebivolol
Bertek Pharmaceuticals

Nebivolol is a beta adrenergic receptor blocker under development for [redacted] hypertension. It is a racemic mixture with 10 stereoisomers. The SRRR enantiomer (d-nebivolol) is reported to be the more pharmacologically active form with 175 times the β1 binding affinity of l-nebivolol. A number of the metabolites, both hydroxylated and glucuronidated, appear to be active. Qualitatively, the major human metabolites are represented in both rats and mice. The drug does not appear to be genotoxic in the material presented to date.

Mouse Study
The mouse carcinogenicity study used dietary administration to provide doses of 2.5, 10 and 40 mg/kg/day. The duration of the study was extended from 18 months to 20 to achieve a 50% mortality rate. Leydig cell tumors were present in the males 2/50(veh), 0/50 (LD), 1/50(MD), 21(HD). This was significant by the Exact Method and the Asymptotic Method with the p value close to 0 for both tests.

Rat Study
The rat study used dietary administration to provide doses of 0(untreated control), vehicle control, 2.5, 10 and 40 mg/kg/day. The study duration was extended from 22 to a total of 25 months to achieve a 50% mortality rate. By the end of the study, the HD males weighed on average 22%($p<0.001$) less than the control groups. The HD females weighed on average 28% ($p<0.001$) less than the control groups. Significant differences in weight gain were apparent in the males from the Week 1 determination through the end of the study. In females, significant differences in weight gain were apparent from the Week 16 determination through the end of the study. A maximally tolerated dose was thus achieved, but the reduction in body weight gain may also have provided a protective effect for the HD animals. The CDER statistician found no evidence of a carcinogenic effect of nebivolol.

Executive CAC Recommendations and Conclusions

1. It was concluded that the mouse study was adequate.
2. The Leydig cell tumors seen in male mice were considered drug-related.
3. It was agreed that the rat study was adequate.
4. Because of the possibility of body weight effects in the rat study altering the tumor incidence in the HD groups, it was requested that the mammary tumors be re-analyzed omitting the HD group. The re-analysis consists of a trend test comparing the vehicle control, LD and MD groups but omitting the HD group. Benign (adenomatous) neoplasia will be analyzed separately from carcinoma/sarcoma neoplasms. A combination of all mammary tumors will then be analyzed also.
5. The rat study was negative for carcinogenicity when associated tumor types were analyzed separately. When mammary neoplasma were reanalyzed in accordance with the recommendations of the committee, neither trend tests (vehicle control, LD and MD) nor pairwise comparisons (vehicle control vs MD) resulted in statistically significant findings.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

Cc:\
Division File, HFD-110
Al DeFelice, Ph.D., HFD-110
Elizabeth Hausner, D.V.M., HFD-110
CSO Russell Fortney, HFD-110
ASeifried, HFD-024

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/s/

Jeri El Hage
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6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

7/12/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-742

Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea B. Miller
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your April 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nebivolol —, 2.5, 5, 10 — mg Tablets.

We also refer to your submissions dated June 4, 22, 23, 24, 25, and 28, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 29, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. An endocrine disruption is indicated by the standard toxicology studies, the reproductive toxicology, and the mouse carcinogenicity study. The original sponsor identified this effect in the standard toxicology studies. Studies to elaborate on this are uninformative as presented.
2. The reproductive toxicology studies have been submitted to the Reproductive Toxicology Committee for comment as to a possible teratogenic effect with the drug.
3. Inadequate characterization of the active metabolites has been submitted.
4. The file PKCONC.xpt does not have any data for Nebivolol PK.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Previously requested information regarding a PK/ADME study that compares BID vs. QD dosing of Nebivolol and dose-response curve.
2. The data in NONMEM format (xpt file) that was used for modeling:
   - studies 0126 and 0127 (rich data files)
   - study 0302 both for popPK and PK/PD
3. All POSTHOC files with the estimated parameter values, including all demographics, ETAs and covariates.

4. The raw ECG data file for the study 0122 (QT study) with plasma concentrations of Nebivolol and all PD measurements (RR, QTcB, QTcF, HR). Demographics and other possible covariates should be included.
5. Please clarify the ratio of beta-1/alpha-2 selectivity for Nebivolol. In one part of the submission it is noted to be greater than or equal to 60, and in another part it is stated to be greater than 400.
6. Please clarify which of the following studies NEB 122, 302, 305, 202, 203, 321, and/or 306 used the final formulation which you plan to market.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
7/12/04 09:26:15 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-742

Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea B. Miller
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your submission dated April 30, 2004, requesting a deferral of pediatric studies for Nebivolol Hydrochloride —— 2.5, 5, 10 —— mg Tablets.

We have reviewed the submission and agree that a deferral of pediatric studies in patients aged 0-16 years is justified for Nebivolol for hypertension because adult studies are ready for approval.

Accordingly, pediatric studies are deferred for your application under 21 CFR 314.55 until 3 years from the date of this letter. However, agreement with the Division on a plan to study Nebivolol in pediatric patients must be reached within 6 months from the date of this letter.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301)594-5313

Sincerely

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

Bertek Pharmaceuticals Inc.
Attention: Andrea B. Miller, R.Ph, Esq.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Nebivolol Hydrochloride Tablets	2.5, 5, 10,	mg
Review Priority Classification:	Standard (S)		
Date of Application:	April 30, 2004		
Date of Receipt:	April 30, 2004		
Our Reference Number:	NDA 21-742		

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 29, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 28, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Edward Fromm
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
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12/5/03

Minutes of a Meeting

Meeting Date:	November 25, 2003
Requested in writing:	October 2, 2003
Meeting Classification:	B
IND:	33,060 nebivolol hydrochloride
External Participant:	Mylan Pharmaceuticals
Type of Meeting:	Pre-NDA
Meeting Chair:	Douglas C. Throckmorton, M.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Andrea Miller, R.Ph., Esq.

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Akinwole Williams, M.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
James Hung, Ph.D.	Team Leader Statistics, HFD-710
John Lawrence, Ph.D.	Statistician, HFD-710
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Robert Shibuya, M.D.	Medical Officer, Div. of Scientific Investigations, HFD-47
Zelda McDonald	Chief, Project Management Staff, HFD-110

Mylan Participants:

John O'Donnell, Ph.D.	Chief, Scientific Officer, Mylan Pharmaceuticals
Frank Sisto	Corp. Vice President, Regulatory Affairs, Mylan Pharmaceuticals
Betty Riggs, M.D.	Vice President, Clinical Research, Bertek Pharmaceuticals
Will Sullivan	Vice President, Clinical Operations, Bertek Pharmaceuticals
James Sherry, M.D., Ph.D.	Vice President, Medical Affairs, Mylan Pharmaceuticals
Russ Rackley, Ph.D.	Executive Director, Pharmacokinetics/Drug Metabolism, Mylan Pharmaceuticals
Mei-Ying Huang, Ph.D.	Executive Director, Pharmacokinetics, Mylan Pharmaceuticals
Jeffrey Smith, Ph.D.	Senior Pharmacologist/Toxicologist, Bertek Pharmaceuticals
Andrea Miller, R. Ph.	Executive Director, Regulatory Affairs, Bertek Pharmaceuticals
Kelly Tate	Director, Regulatory Affairs, Bertek Pharmaceuticals
Diane Burke	Project Manager, Mylan Pharmaceuticals

Background:

Mylan has met with representatives from the Division of Cardio-Renal Drug Products as follows:

November 6, 1998:	Pre-NDA Meeting
July 7, 2000:	End of Phase 2 Meeting
September 29, 2000:	Revised Development Plan
April 11, 2001:	Development Plan Telephone Conference
October 9, 2002:	Protocol Review

The IND was originally submitted by Mylan Pharmaceuticals and they are finalizing the development of nebivolol tablets. Mylan Pharmaceuticals and Bertek Pharmaceuticals are both wholly owned subsidiaries of Mylan Laboratories and are referred to interchangeably in their submissions and these minutes. Bertek is Mylan's marketing division for branded products and will be marketing the reference product if it is approved. Accordingly, the NDA will be submitted by Bertek Pharmaceuticals, and they expect this to occur sometime in March 2004. They are seeking approval of nebivolol for the management of essential hypertension used alone or in combination with other hypertensive agents. Mylan requested this meeting to provide an overview of the data that will be presented in the NDA to support the safety and efficacy of Nebivolol Tablets in the treatment of essential hypertension, to reach agreement with the Division regarding the content and format of the technical sections of the NDA, and to present the proposed format of the electronic submission and obtain the Division's review preferences for electronic submissions.

Meeting:
Mylan gave a brief overview that included summaries of their non-clinical, biopharmaceutics and clinical program, the clinical history of nebivolol, and what they expect to include in their integrated summaries of safety and efficacy. Dr. Throckmorton stated that the Division had reviewed the background package and did not find any major deficiencies in Mylan's proposal noting that they had a substantial program. He asked if Mylan was developing a nebivolol/hydrochlorothiazide combination product since that had been discussed in previous meetings with the Agency. Mylan said they planned to submit an NDA for the single product and submit a protocol after the first of the year (2004) for the combination product. They expect to initiate a large, multifactorial trial sometime in 2004 to study the combination product.

Questions/Discussion Points:

1. **Chemistry, Manufacturing and Controls (CMC)**

   - It was noted that Mylan met with the Division on November 19, 2003 to discuss any CMC issues related to the NDA submission, and no issues were identified.

2. **Pre-clinical Pharmacology/Toxicology**

   a) Because the toxicology work was conducted a decade or more ago, Bertek has reassessed the results in light of more current approaches. The net result is a somewhat more conservative interpretation, although the overall conclusions remain the same. The original Janssen reports have not been altered nor reissued to incorporate the contemporary interpretation. Does the Division concur with this approach?

- The Division agreed, but asked if histology readings would be included in the long-term toxicology data in particular for the targeted testicular and adrenal findings. Bertek stated that data would be included.

b) FDA has previously reviewed some toxicology work on nebivolol, and asked question for which Mylan has recently submitted answers. Does the reviewer have any additional questions that should be addressed regarding these studies?

- Dr. Throckmorton mentioned that the carcinogenicity SAS data sets had been sent back for Mylan to redo. Mylan stated that those data sets had already been redone and resubmitted.

- Dr. Hausner said that although Mylan commented in their background package that there was no evidence of reproductive toxicity, she believed that there were signs of toxicity in pregnant animals e.g., decreased pup birth weight and decreased pup survival. PK data may help in understanding this. She also said the Mylan mentioned active metabolites, but there were no details. Mylan said ^{14}C studies had been conducted that showed pathways similar to those in man. Large amounts of nebivolol glucuronide were seen including several isomers, and both nebivolol and the glucuronide have activity. In addition, there was back conversion to nebivolol, with the glucuronide acting as a reservoir, which would explain nebivolol's long acting property. Bridging studies have been done between animal and man and have been provided. It was agreed that discussion of the bridging studies would take place outside this meeting.

- Dr. Throckmorton noted that QT_c effects were seen in the early dog studies and emphasized that any QT_c effect would have to adequately addressed in the NDA at the time of filing. Mylan stated that the full complement of information would be included in the NDA.

3. Clinical Biopharmaceutics and Pharmacokinetics

a) Mylan/Bertek performed many clinical pharmacokinetic studies to support the safety and efficacy of nebivolol that were summarized in the background document. Bertek believes that these studies comprise a complete nebivolol pharmacokinetic package to support the safety and efficacy of nebivolol in the treatment of essential hypertension, does the Division agree?

- Dr. Throckmorton said the Division agreed in general. He pointed out that typically a sponsor will provide summary tables with the biopharmaceutical information (dissolution data, bridging BE studies with the to-be-marketed formulation) and assay methodology. Mylan said they have all that data, and it will be included in the NDA.

- Dr. Throckmorton stated that Mylan talked about the racemate in general terms, and asked if there were any data on stereospecific metabolites. Mylan said that only the (d) and (l) form of Nebivolol was seen in all populations as well as the glucuronide metabolite. They said they will be submitting PK and PD data on the (d), (l), and glucuronide of nebivolol noting that they had phenotyped all the patients.

4. **Clinical**

a) Trough to Peak: Trough to peak ratios will be calculated from standard cuff trough to peak blood pressure measurements performed in the investigators' offices during the primary nebivolol alone studies (NEB202/NEB302/NEB305). Although ambulatory blood pressure data was obtained in study NEB321, it will not be used in the calculations because it will be confounded by existing antihypertensive therapy in the study. Does the Division concur with this approach?

- The Division concurred.

b) ISS Organization: The organization of the Integrated Summary of Safety (ISS) follows a standard approach. The ISS will not combine the Janssen, Menarini and Bertek experience. Serious adverse experiences, withdrawals due to AEs, and deaths reported in the Janssen clinical study reports will be discussed independently. Likewise the Janssen/Menarini post marketing experience will be described separately. The ISS will review the safety experience from the clinical pharmacology studies separately from that in the clinical studies. Regarding safety subgroups, adverse events and the extent of nebivolol treatment have been analyzed by age, race, gender, metabolic status, body mass index, evidence of diabetes mellitus, and for selected concomitant medications emphasizing those compounds judged to produce vasodilation.

- Dr. Throckmorton stated that the ISS is, in general, acceptable. He asked what safety information Mylan was planning to make available with respect to the Janssen studies. Mylan said they would provide all reports and case report forms on deaths and serious AEs that are available to them. They have about 90% of the information, but emphasized there will be information for some of the studies they will not be able to provide.

- Dr. Throckmorton asked if Mylan had data on African Americans. Mylan said they have study 202 that was a dose ranging study in African Americans. They also have data on African Americans in studies 302 and 305. They will combine the data from those three studies and do a race analysis.

- Dr. Stockbridge asked if Mylan planned to summarize safety data from any other indications that were studied. Dr. Throckmorton added that the Division's major interest would be mortality, i.e., adverse events most easily captured. Mylan said they would summarize the Janssen studies for which they can collect case report forms for those events. Mylan said they also have U.S. data on 400 patients that were studied for about a month and foreign post marketing data.

c) Labeling: Dr. Throckmorton asked Mylan if they planned to propose removing the standard language that says beta blockers work less well in blacks or would they propose some kind of affirmative language. He stated that affirmative language may require a different level of

data than that needed to remove the standard language. He recommended that Mylan make a case for their proposed language when they submit the NDA.

- Mylan said they had looked at the effect of nebivolol on blacks versus whites and found no difference, which would make nebivolol different from other beta blockers. Dr. Throckmorton said he had seen those models, but the Division would still have to look at the data. Mylan asked if a description of the study would be included in the labeling if the standard labeling was removed and there was no affirmative wording. Dr. Throckmorton said that those studies have not typically been described in the labeling if no difference was seen by race, gender, and/or age. However, lately, with large studies for other drugs, the Division has recently been using a box and whisker plot in the labeling to provide information on the effects of the drug in relevant demographics. He was not sure whether Mylan's studies would be appropriate for that. Again, Mylan would need to make the case that the studies were sufficiently robust to warrant inclusion other than an affect was not seen.

- Mylan asked what impact their add-on study would have on the labeling, pointing out that when nebivolol was added, they still saw efficacy. They believe nebivolol is different from other beta blockers in that instance as well, since even after add on, it is effective. Dr. Throckmorton said that Mylan may not have tested the limits pointing out that adding submaximal pharmacology is not the same as being able to conclude that the drug was effective in a truly resistant population. Mylan would need to make the argument and provide any real data that demonstrates long-term efficacy (blood pressure reduction). He noted that a withdrawal study was suggested in previous meetings. If such a study came out positively, then there definitely could be a change in the labeling.

- Mylan asked how the mechanism for vasodilation would be described in the labeling. Dr. Throckmorton said the Division would be open to describing the data and how the drug works, but an implied indication would be avoided.

- Mylan asked if they proposed labeling that is not typical for a beta blocker, would that prompt the Division to take nebivolol before an Advisory Committee. Dr. Throckmorton said he did not know at this time. If there are issues identified at the time of filing, then that would be the time to consider consulting the Advisory Committee.

d) Other Clinical issues:

- Dr. Throckmorton stated that Mylan would need a thorough evaluation of any QT prolongation. Mylan stated that they planned to provide a thorough evaluation in the NDA, noting that they had done a pre-clinical work-up and an active control study with moxifloxacin.

- Dr. Stockbridge asked if Mylan has any data that clarifies that the dosing need not be b.i.d. Mylan said they did not have any, but the trough/peak ratio is 85-90% so b.i.d. dosing was not considered.

- Dr. Stockbridge asked if Mylan had done an interactive study with nebivolol and a PDE5 inhibitor. Mylan said they had not. Dr. Stockbridge postulated that without such data, nebivolol may be treated like any other nitric oxide donor and be contra-indicated for use with PDE5 inhibitors.

e) Electronic Submission:

- Mylan stated that they plan to submit the NDA electronically and asked if the reviewers would want to see any portion in paper. Dr. Throckmorton said if they do, they will contact Mylan directly after the NDA is submitted.

Signature minutes preparer: _____

Concurrence, Chair: _____

Drafted: 12/1/03 Finaled 12/05/03
RD:
Throckmorton 12/4/03
Stockbridge 12/4/03
Karkowsky
Williams 12/4/03
DeFelice 12/4/03
Hausner 12/4/03
Hung 12/3/03
Lawrence 12/1/03
Mishina 12/1/03
Shibuya

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/s/

Doug Throckmorton
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12/12/03

November 19, 2003

IND#	33,060
Drug:	Nebivolol (R67,555) Tablets
Sponsor:	Mylan Pharmaceuticals Inc.
Type of Meeting:	Pre-NDA, CMC
Classification:	B
Date Requested:	October 2, 2003
Date Confirmation Faxed:	October 15, 2003
Briefing Package Received:	October 21, 2003

FDA Participants:

Hasmukh Patel, Ph.D.	Deputy Director, Division of New Drug Chemistry I, HFD-810
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-810
Javher Advani, Ph.D.	Chemist, HFD-810
Angelica Dorantes, Ph.D.	Pharmacokineticist, HFD-860
Melissa Robb	Regulatory Health Project Manager, HFD-110

Mylan Participants

John P. O'Donnell, Ph.D.	Chief Scientific Officer, Mylan Laboratories
Frank Sisto	Corporate Vice President, Regulatory Affairs, Mylan Laboratories
Wayne Talton, M.S.	Executive Director, Regulatory Affairs, Mylan Pharmaceuticals
William Addicks, Ph.D.	Vice President, Product Development, Mylan Pharmaceuticals
Walt Owens, Ph.D.	Vice President, Laboratories, Mylan Pharmaceuticals
Dan Snider, Ph.D.	Executive Director, Analytical Chemistry
Wendy Mavroudakis	Director, Global Regulatory Affairs, Johnson and Johnson
Ruud Leemans, Ph.D.	Director, Global Chemical and Pharmaceutical Development, Janssen

Background:

The sponsor is planning on submitting a New Drug Application (NDA) for Nebivolol tablets on or about February 28, 2004. The sponsor is seeking approval of nebivolol for the management of essential hypertension used alone or in combination with other hypertensive agents. The sponsor requested this meeting to reach agreement with the Division on the format and content of the Chemistry, Manufacturing and Controls (CMC) section of the NDA.

Meeting:

Dr. Dorantes began by noting that in her review of the briefing document, it appeared that the two lower strengths of the drug product have changed from the clinical formulations to those that the sponsor plans to market. Dr. Dorantes requested that the sponsor include a summary table outlining the formulations and batches that were used in both the pharmacokinetic and clinical trials. She added that the sponsor should submit a request for a biowaiver for the———— mg strengths with the appropriate supportive dissolution data. Dr. Dorantes stated that all this information (i.e., validation of the dissolution methodology, complete dissolution data for the bio-batches, and biowaiver's supportive data) should be included in Section 6 of the NDA. The sponsor stated that they are using the dissolution process used by Janssen.

The sponsor presented a brief presentation that including an introduction, summary of the drug substance and a

summary of the drug product.

Dr. Srinivasachar inquired if the sponsor is conducting in-process testing on the drug substance. The sponsor confirmed they are performing these tests. Dr. Srinivasachar added that specifications of the intermediates will have to be included in the NDA. The sponsor stated they plan to include that information in the Drug Master File (DMF).

Dr. Srinivasachar advised the sponsor that they will need to apply for a USAN for the HCl salt. He stated that currently the USAN is for the free base.

The Agency then focused the discussion on the drug substance. The Agency inquired if the starting materials are commercially available. The sponsor stated they are not and are currently made in house. Dr. Srinivasachar stated that the sponsor would need to justify the starting materials, as there are concerns of carryover of potential impurities. The Agency would require assurances that the starting materials or their impurities would not carryover to the final drug substance. The sponsor stated they have evidence of the purity and stability of the starting material. The Agency clarified that they are not looking at the purity. The Agency referred the sponsor to the 1987 Guidance entitled "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances". The Agency noted that this guidance is currently being updated to be more specific and include criteria that should be met for starting materials. The sponsor stated that they were aware of the Agency's thinking by attending public lectures on this topic and believes they will be able to justify the starting materials in a science based manner that will meet the Agency's criteria.

[redacted]

The sponsor stated this was done because of the large number of lots it was based on. The sponsor added that the specifications listed are only interim specifications and are based on what they anticipate to submit. The Agency stated they don't discuss acceptance criteria at this time, but noted that the sponsor will need to justify all specifications.

Dr. Srinivasachar also inquired about the Class III solvents which were not specified. The sponsor stated that these solvents, [redacted] were not specified because they were detected at levels which were in accordance with ICH. Additionally, they would be detected in the residual solvent parameter. The Agency stated that all solvents should be individually specified. The sponsor agreed to include this information in the DMF.

The Agency inquired about the limits assigned for methanol and methylbenzene. The Agency stated that the ICH limits are the upper limits of safety and the assignment of a limit based on [redacted] of ICH guidelines is arbitrary. The sponsor believed that an alternative would be to perform a more specific test and determine that the residual solvents were not present and stop looking for them in testing.

The Agency also noted that the Identification test does not address the racemic nature of the drug substance.

The Agency added that the sponsor would need to justify the limits of the particle size since they have noted that it was critical to the dissolution.

The Drug Product was then discussed. The Agency inquired about the Magnesium Stearate/Sodium Lauryl Sulfate which was listed as one of the inactive ingredients of the drug product. The sponsor stated that they purchase this product which is marketed [redacted]. The sponsor will reference a DMF in their NDA

submission. The sponsor added that the two components of the compound are compendial products.

The Agency noted that, in the drug product also, the sponsor does not identify the product's racemic nature. The sponsor stated they wouldn't expect conversion and have not seen any in vitro conversion. The Agency added that conversion is at least theoretically possible in the presence of optically active excipients. The sponsor proposed checking the batches used for the stability programs. The Agency stated that if the sponsor were able to show that there was no conversion, further testing would not be needed. The Agency agreed that an optical rotation test would be acceptable to address the racemate issue.

The Agency inquired if the sponsor had seen any degradation product. The sponsor stated the formulation has been very stable, even under harsh conditions.

The Agency commented that the limit for water content was high at —. The sponsor agreed that it was high, but stated that many of the excipients were high in water content. The Agency stated that data would be needed to justify the proposed level.

Questions

1. Does the Agency have any comments on the proposed format and content of the CMC section of our new NDA as described in the enclosed draft Table of Contents?

   Dr. Srinivasachar requested that a list of all facilities that will require inspection (manufacturing, packaging, contract testing labs, etc.) be included in the beginning of the NDA. The sponsor stated they would include this as an attachment to the FDA Form 356h. This will include CFN numbers of the sites.

   Dr. Srinivasachar also requested the sponsor include a table in the NDA with a listing of impurities, qualification levels and reference to appropriate safety/clinical batches. The sponsor agreed to compile such a table to aid in ease of review.

   The Agency commented on the sponsor's plan to revise and replace the current DMF with an electronic DMF in CTD format. Dr. Advani stated there is currently a pilot program in place for this. Dr. Advani referred the sponsor to follow the criteria outlined on the web. Additionally, Dr. Advani referred the sponsor to Art Shaw for any further inquiries. The Division stated they have no preference for how the information is submitted as long as it is in accordance with Agency policies.

2. To satisfy the Field Copy requirements, Mylan proposes to submit executed batch records and associated documentation for one batch of each tablet strength used in pivotal clinical trials and one batch of each tablet strength from the primary stability batches (i.e. 10 batch records total). Does the Agency concur with this proposal?

   The Agency agreed with this proposal, but requested all COAs be submitted for review as these are used to justify specifications.

3. Given the extent of supportive stability data available from batches used in clinical studies, does the Agency have any comment on the amount of stability data to be included in the NDA at time of filing as described in the enclosed Stability Data Overview section?

   The Agency agrees that 12 months of stability data is sufficient and is in accordance with ICH recommendations. However, there is concern regarding strengths for which only 3 months of data are going to be available. The sponsor stated that they plan to augment the stability data during the review cycle. The sponsor stated that this drug is marketed in Europe at only the 5 mg dose. The sponsor stated that since Americans typically have a higher BMI than Europeans and beta blockade is related to BMI,

higher doses were needed for marketing in the United States. After meeting with the Agency, the sponsor conducted clinical trials using doses ranging from 1.25-40 mg. The sponsor stated that all doses revealed statistically significant results. The sponsor is unsure of what dosing regimen will be approved, but is prepared to accept shorter expiration dates on the [redacted] 2.5 mg strengths, if approved. Dr. Srinivasachar cautioned the sponsor stating that it is more common to find stability problems in the lower strengths. Dr. Srinivasachar inquired about what differences there were between the supportive data and that which is to be marketed. The sponsor stated the dyes are the only difference. The Agency inquired about the [redacted] packaging, noting that there was no supportive data available. The sponsor stated the [redacted] packaging is to be used for physician samples only and would probably only contain the 5 mg tablets. The sponsor added that if the [redacted] 2.5 mg tablets were to be used as physician samples, they would be packaged in the bottles. [redacted]. The sponsor stated that they are trying to be conservative in their approach. The sponsor also added that they are testing blister packs of 10, but plan to distribute only packs of 7.

The Agency noted no information was included on the container and closure system. The sponsor stated they will provide specifications for packaging components.

Signature, minutes preparer:_____

Concurrence Chair:_____

Drafted: 11/19/03 Finaled: 12/12/03

RD:

Patel	12/12/03
Srinivasachar	12/8/03
Advani	11/21/03
Dorantes	11/21/03

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/s/

Melissa Robb
12/12/03 03:07:56 PM
Signed by Dr. Srinivasachar 12/12/03; Faxed to sponsor 12/12/03

10/24/02

Minutes of Telecon

IND 33,060
Drug: Nebivolol
Sponsor: Mylan Pharmaceuticals, Inc, Morgantown, WV

Date of telecon: October 22, 2002
Time 11:30 am
Minutes prepared by E. Hausner, DVM.

FDA participants:

Al DeFelice, Ph.D., D.A.B.T., Supervisory Pharmacologist, HFD-110
Akinwole Williams, M.D., Medical Officer, HFD-110
Elizabeth Hausner, D.V.M., D.A.B.T., Pharmacologist, HFD-110

Mylan Participants:

Andrea Miller, Pharm. D., J.D., Director, Regulatory Affairs
Jeffrey Smith, Ph.D., Senior Scientist, Toxicology

James Sherry M.D., Ph.D., Vice President, Clinical Research

Issue: The agency presented a summary of the data in the pre-clinical toxicology reports that led to a concern about endocrine effects. Did the sponsor have any information in hand that might help to elucidate these observations? The sponsor said no, they did not think that they had material available to address these questions.

The Division asked for the following information:

1. What is the level of β-blocking effect found in the toxicology studies and was there any kind of veterinary concern for the effects?
2. What were the blood levels of drug for mice, rats and dogs, the species where potentially endocrine related effects have been seen.
3. What are the comparative metabolic profiles in animals compared to humans? Are the major human metabolites represented in the animal studies?
4. What is the receptor binding profile for nebivolol, in particular, with respect to the glucocorticoid receptor, estrogen, testosterone, DHT, progesterone and mineralocorticoid receptors and the dopamine receptors?
5. Has a male fertility study been done and did it include a reversibility component? If this has not been done, such a study should be conducted.
6. Is the testicular amyloid primary or secondary based on its morphologic distribution? Is this local or systemic amyloidosis? A detailed histopathological description would be helpful.

The sponsor replied that they did not know the relative β-blocking effect in animals but that the information could be generated. Blood levels had been determined for the carcinogenicity

studies and the data would be provided. A study on glucocorticoid effects had been done, probably in rats and would be provided.

Ms Miller noted that the company is planning a 2003 NDA submission and offered to supply a pre-submission of the toxicology data pertinent to this issue. The sponsor promised to supply the requested data as it became available from the European partner.

Elizabeth Hausner, D.V.M.
October 24, 2002

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10/30/02

Minutes of a Meeting

Meeting Date:	October 9, 2002
Date Requested:	August 29, 2002
Date Confirmation Faxed:	September 5, 2002
Date Briefing Pkg Received:	August 29, 2002
Type:	Critical Path
Classification:	A
IND:	33,060 nebivolol hydrochloride
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Andrea Miller, R.Ph.

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Douglas C. Throckmorton, M.D.	Division Director, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
John Lawrence, Ph.D.	Statistician, HFD-710
Patrick Marroum, Ph.D.	Team Leader, Biopharmaceutics, HFD-860
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Zelda McDonald	Regulatory Health Project Manager, HFD-110

Mylan

John P. O'Donnell, Ph.D.	Executive Vice President of Research
James Sherry, M.D., Ph.D.	Vice President, Bertek Pharmaceuticals, Clinical Research
Peter Bruce Bottini, Pharm.D.	Director, Bertek Pharmaceuticals, Clinical Research
Thomas S. Clark, M.D.	Medical Director
Andrea B. Miller, R. Ph.D., Esq.	Director, Bertek Pharmaceuticals, Regulatory Affairs

Background:

Mylan requested this meeting to discuss the Agency's comments regarding clinical protocol NEB-307 (exercise tolerance study) that were provided in a July 24, 2002 correspondence from the Agency that was a response to a Special Protocol Assessment. Mylan was seeking to clarify their intended use of the study results and the contribution of the study to the overall development program. In addition, they sought further understanding of the issues raised by the Agency and the implications of these issues. Mylan also requested this meeting to discuss protocol NEB-321, an additional pivotal safety and efficacy study to assess the effect of nebivolol on blood pressure when added to patient's existing medications.

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Meeting:
After introductions, Mylan presented a brief overview of the Nebivolol Clinical Development Program in Hypertension. This program consists of the following seven studies:

1. NEB-302 – Phase 3, General Population Pivotal Study #1 including PK study
2. NEB-305 – Phase 3, General Population Pivotal Study #2
3. NEB-202 – Phase 2, Dosing Study in the Black Population
4. NEB-306 – A Safety & Tolerance Extension Study of Studies NEB-302, 305 and 202
5. NEB-203 – Phase 2 Vasodilator Exercise Study, Nebivolol vs Atenolol
6. NEB-307 – Phase 3 Pivotal Exercise Study, Nebivolol vs Atenolol
7. NEB-321 – Phase 3 General Population Add-on Therapy Pivotal Study

- Dr. Temple asked if study NEB-306 had a randomized withdrawal phase, i.e., patients are randomized at the end of the trial to either Nebivolol or placebo and observed for a short period, 2-4 weeks. Mylan responded that a randomized withdrawal was currently not planned. Dr. Temple encouraged Mylan to include such a plan to establish the long-term efficacy of nebivolol. He also pointed out that currently marketed beta blockers have a warning about acute withdrawal in the labeling, something that could be eliminated if adequate data showed no withdrawal, a possibility with a long half-life drug like nebivolol.

NEB-307
Mylan proposed the following statistical analysis plan for Study NEB-307; an active control comparison with atenolol:

The primary response variable will be the change in sub-maximal exercise endurance time. An Analysis of Covariance (ANCOVA) with change in trough diastolic blood pressure, site, treatment by site and other important covariates (age, race diabetes, etc.) will be used to analyze the data. The ANCOVA can be regarded as a comparison between treatments of change in exercise endurance time adjusted by change in trough sitting diastolic blood pressure (and other possible co-variates). For this model to be interpretable, the relationships between exercise endurance time and blood pressure should be similar in the two treatments. This will be tested by examining the interaction between the slopes of the regression lines and treatments. The use of the change in trough sitting diastolic blood pressure (which will be affected by treatment) as a covariate leads to the following interpretation: if a significant difference between treatments is observed for exercise endurance time, it will be interpreted as a difference between treatments at comparable effects on blood pressure.

- The Agency still has questions about the details of the analysis plan. One recommendation made at the meeting is that the analysis could be confined to doses where there is a dose response effect seen, i.e., exclude use of the 200 mg dose of atenolol if there is no evidence that 200 mg is better than 100 mg of atenolol; likewise with nebivolol. If the decision to include or exclude doses is made based on observed data, then attention should be paid to possible type 1 error inflation. If Mylan wants to claim that there exists a dose of nebivolol that achieves comparable blood pressure reduction with less fatigue, then a head-to-head comparison with a pre-specified non-inferiority margin (for the blood pressure comparison) maybe the easiest to interpret. Comparisons of average effects over doses that depend on model-based assumptions and adjust for post-baseline covariates may be difficult to interpret. Adjustment for post-baseline covariates requires strong model-based assumption to have valid type 1 error rate for interpretation. A formal analysis plan and precise wording regarding what Mylan wants to claim based on the study results should be submitted to the Agency for review.

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- Mylan asked if they would need more than one study. Dr. Temple stated that more than one study is usually needed, but the current study had some features that would make it more robust than a single study. He suggested that further analyses of the study data should include a pair-wise comparison of the effect of the different dose groups on exercise. He cautioned that it is somewhat risky not having an independent study. Dr. Throckmorton noted that with a comparative study intended to serve as the only pivotal study, the Agency may have to consult the Cardiovascular and Renal Drugs Advisory Committee. He also noted that there were other controlled studies (321, the possible randomized withdrawal in 307, and perhaps others).

- Dr. Temple said a limited database, e.g. only one study, raises the issue of whether there is some hidden adverse effect that undermines the benefit and asked if nebivolol causes QT prolongation. Mylan stated that they are in the process of looking into that and asked for the Agency's current thoughts on QT analysis.

- Dr. Temple said that there is a meeting in the planning stages on the clinical assessment of QT interval effects that the sponsor might find useful. He also suggested that Mylan refer to the S7B ICH Guidance discussing animal data on drugs with potential effects on the QT interval. Mylan noted that it was reassuring to them that in 10 years of pharmacovigilance in Europe, there has not been a single case of torsade reported.

- Mylan said they would revise the NEB-307 protocol and submit it to the Agency for agreement before they start the study. The Agency concurred, noting that the statistical plan is acceptable, it only needs to be refined.

NEB-321

Mylan plans to add a third pivotal clinical trial to asses the safety and efficacy of nebivolol (placebo, 5, 10 and 20 mg) in the treatment of hypertension when added to a patient's existing antihypertensive therapy. Mylan asked for the Agency's guidance on the utility of this study in combination with the two ongoing pivotal, monotherapy studies (NEB-302 and NEB-305) to support the following proposed indication:

> Nebivolol is indicated for the treatment of ——— hypertension. It can be used alone or in combination with other antihypertensive agents.

- Dr. Temple said that the Agency would not require the study, but it might be a good idea to know what other drugs can be taken with nebivolol. Dr. Temple asked Mylan why calcium channel blockers (CCBs) were excluded from this study. Mylan said that the use of CCBs with beta blockers is low in clinical practice. Clinicians have concerns about using drugs with negative inotropic effects on top of another drug with negative inotropic effects. Mylan asked if they did not do the study, would the labeling say the same thing as above. Dr. Temple said it would only if the studies were poorly done. The studies would be described in the labeling if the data are good, as it is certainly the interest of the Agency to describe the concomitant use of medications when possible.

- Mylan asked if the Agency still wanted a factorial design for studies with a diuretic. Dr. Temple said yes and encouraged Mylan to use low, even sub-therapeutic doses of diuretic and nebivolol since the data showing that two sub-therapeutic doses had had efficacy could support a claim as initial therapy.

- Mylan asked if the adverse events reported in the "add-on" therapy study could be reported in a table separately from the adverse events reported in the monotherapy studies or must all adverse reactions from all studies be integrated and reported in one table in the ADVERSE EVENTS section of the labeling? Dr. Temple said the labeling will include the events from the placebo controlled trials and anything else will be added as needed.

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The Agency had the following general comments/questions:

1. It is not clear whether Mylan will be looking at drug/drug interactions except for 2D6 and whether they are looking for liver and/or renal impairment. Mylan stated that they were looking at drug/drug interactions and liver and/or renal impairment in all trials.

2. Is there a difference between EM's and PM's. Mylan said they do not expect so, since the metabolites are active. The net activity would be therefore the same.

3. Will there be ambulatory blood pressure monitoring data? Mylan said yes.

4. Had Mylan talked with the Agency's chemists about drug with respect to drug used in the trials versus the to-be-marketed product? Mylan said they had not since the drug used in the trials was the commercial product that has been available in Europe for some period of time.

Signature minutes preparer: _____

Concurrence, Chair: _____

Drafted 10/10/02 Finaled 10/29/02

RD:	
Temple	10/29/02
Throckmorton	10/21/02
Stockbridge	10/18/02
Karkowsky	10/18/02
Hung	10/18/02
Lawrence	10/16/02
Marroum	
Mishina	10/23/02

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

/s/

Zelda McDonald
10/30/02 10:43:26 AM
These minutes were signed by Dr. Temple on 10/29/02
and faxed to the sponsor on 10/30/02.

5/1/01

Minutes of a teleconference

Date of teleconference:	April 11, 2001
Application:	IND 33,060
Product:	Nebivolol Tablets
Sponsor:	Mylan Pharmaceuticals Inc.
Purpose:	to discuss the revised clinical development plan for nebivolol, as described in the sponsor's March 12, 2001 submission
Participants:	
FDA	
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Mylan Pharmaceuticals Inc.	
John P. O'Donnell, Ph.D.	Executive Vice President, Research and Quality Control
Thomas S. Clark, M.D.	Medical Director
Frank R. Sisto	Vice President, Regulatory Affairs
Andrea B. Miller, R.Ph., Esq.	Associate Director, Regulatory Affairs
Bertek Pharmaceuticals Inc.	
Bhaskar Chaudhuri, Ph.D.	Executive Vice President, Scientific Affairs
James H. Sherry, M.D., Ph.D.	Vice President, Clinical Research
Peter Bruce Bottini, Pharm.D.	Executive Director, Clinical Research
Patrick McGrath, Ph.D.	Director, Clinical Operations
Charity Metz, Pharm.D.	Regulatory Affairs Associate, Regulatory Affairs

Background

The sponsor requested this teleconference to discuss their revised clinical development program, as described in their March 12, 2001 submission to the IND.

The teleconference

Discussion Point #1: Characterization of the dose-response effect

Dr. Lipicky did not believe the sponsor's proposed clinical development program would adequately characterize the dose-response effect of nebivolol, as the dose range is too narrow. A wider range of doses would be needed to adequately characterize this effect. A six-arm, dose-ranging study consisting

of a placebo arm and five active dose arms (0.2 mg, 1 mg., 5 mg., 20 mg., and 60 mg.) would be more appropriate.

Mylan noted that their interpretation of the nebivolol data from European studies is that the data demonstrate a maximum antihypertensive effect at 5 and 10 mg. The European data demonstrate that 0.5 and 1 mg doses of nebivolol do not have an antihypertensive effect. Antihypertensive activity appears to begin at 2.5 mg, with a maximal antihypertensive effect at 5 and 10 mg. No (statistically significant) additional antihypertensive effect is observed at 30 mg doses. However, the European data demonstrate a higher incidence of adverse effects at the 30 mg dose (e.g., a 9.6% incidence of diarrhea at 30 mg versus a 1.3% incidence at 10 mg).

In light of nebivolol's hepatic metabolism and genetic polymorphisms, Dr. Lipicky would anticipate a wide range of plasma concentrations. If the ED_{50} is not adequately characterized and plasma concentrations vary depending on metabolism, it would not be possible to say with certainty that 5 and 10 mg are the appropriate doses for everyone. If Mylan proceeds with the study as proposed, the Agency would probably accept it, although it is not optimal. Studying the dose range Dr. Lipicky proposed would not be unreasonable and would explore the full dose range, putting into perspective the effects of differences in metabolism.

Discussion Point #2: Labeling of nitric oxide release hypothesis

The sponsor has proposed a comparator study of nebivolol versus atenolol to demonstrate nebivolol's unique nitric oxide-releasing and vasodilating effects. Mylan anticipates that nebivolol will maintain exercise capacity while atenolol will reduce it. Provided the results of this study are as they expect, Mylan proposes to include the following language in the Clinical Pharmacology section of the nebivolol labeling:

To include a comparator claim against atenolol in labeling, two positive comparator studies would be needed. Provided both studies are positive, it might be acceptable to include the first sentence of the proposed text in the labeling (probably the Clinical Pharmacology section). However, it is not likely that the language on nitric oxide release would be permitted in labeling, even with two positive studies. Dr. Lipicky could not say exactly what would be necessary to include language on nitric oxide release in the labeling. Although the nitric oxide release hypothesis is reasonable, it has not been proven and we do not know that it has clinical significance. The sponsor would need to demonstrate beyond a doubt that nitric oxide release is the mechanism responsible for the effect on exercise capacity and that this effect is clinically significant. This would be extremely difficult to do, as it is difficult to link a specific mechanism of action to a specific effect.

Discussion Point #3: African American Study

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Although the sponsor has planned two doses for the African American study, Dr. Lipicky did not believe the two selected doses optimal, as they differ by a factor of two only. Dr. Lipicky was skeptical that the difference between the doses would be sufficient to detect a difference in effect, but indicated that the plan, as proposed, would probably be acceptable, but would require two studies.

Dr. Lipicky indicated initially that a substantial number of African American subjects in the pivotal studies might be sufficient to keep out of the labeling the traditional β-blocker language describing a smaller effect in black patients as compared to non-black patients. However, Dr. Lipicky reconsidered this later and retracted his statement.

A single, reasonably sized study of African Americans versus non-African Americans covering a reasonable range of doses and demonstrating an equivalent or greater point estimate for efficacy in African Americans as compared to non-African Americans that is supported by a similar finding in a substantial number of African American subjects pooled from the other pivotal studies might be adequate to eliminate the traditional language from the nebivolol labeling. Dr. Lipicky was skeptical, however, noting that these biases are typically difficult to reverse.

Two African American studies that demonstrate no difference in the point estimate or a greater point estimate for efficacy in African Americans versus non-African Americans would provide the best support for keeping the traditional language out of the nebivolol labeling. The outcome of this labeling issue is result dependent.

The sponsor asked about a recent Press Release reportedly by the FDA concerning an application for an indication in heart failure in black patients. Dr. Lipicky was unaware of the press release, noting that he was not the source of the statements in the release and did not support them.

Discussion Point #4: Safety database

The Division would accept a 1500 subject safety database. Dr. Lipicky noted, however, that a single serious adverse event at an incidence of one in 500 could go undetected easily in a database of this size. This issue is really a liability issue for the sponsor. Dr. Lipicky encouraged the sponsor to consider further the size of the safety database needed to adequately address the post-marketing safety concerns that might arise.

Signature, Teleconference Recorder:_____Colleen LoCicero

Concurrence, Teleconference Chair:_____Raymond Lipicky, M.D.

drafted: 4/19/01 finaled: 4/27/01

rd:
Lipicky/4/23/01

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/s/

Colleen LoCicero
5/1/01 09:35:11 AM
These final teleconference minutes were signed by Dr. Lipicky on 4/30/01 and faxed to the sponsor on 5/1/01.

Entered in DFS on 10/25/00

OCT 25 2000

Minutes of a Meeting

Meeting Date:	September 29, 2000
Date Requested:	September 11, 2000
Date Confirmation Faxed:	September 15, 2000
Date Briefing Pkg Received:	September 19, 2000
Type:	CMC & BIOEQ
Classification:	C
IND:	33,060 nebivolol hydrochloride
External Participant:	Mylan
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Andrea Miller, R.Ph.

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas Throckmorton, M.D.	Deputy Director, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Shari Targum, M.D.	Medical Officer, HFD-110
Gabriel Robbie, Ph.D.	Pharmacokineticist, HFD-860
John Lawrence, Ph.D.	Statistician, HFD-710
Zelda McDonald	Regulatory Health Project Manager, HFD-110

Mylan

Thomas Clark, M.D.	Medical Director
John O'Donnell, Ph.D.	Executive Vice President of Research
Walter Owens, Ph.D.	Executive Director, Laboratories
Mei-Ying Huang, Ph.D.	Director, Pharmacokinetics
Peter Bruce Bottini, Pharm.D.	Executive Director, Clinical Research
Mie-Yin Huang, Ph.D.	Executive Director, Pharmacokinetics
Tracey Lawrence, Ph.D.	Pre-Clinical/Clinical Research Associate, Clinical Research
Andrea Miller, R. Ph.	Associate Director, Regulatory Affairs

JANSSEN (Johnson & Johnson)

Tracy Acker, Pharm.D.	Director, Regulatory Affairs, FDA Liaison

Via Telephone

Mylan:

James Sherry, M.D., Ph.D.	Vice president, Clinical Research
Frank Sisto	Vice President, Regulatory Affairs

Via Telephone Janssen Belgium

Luc Van Neuten, M.D.	Director, Internal Medicine
Ache Van Peer, M.D.	Vice President Clinical Research
Willem Meuldermans, Ph.D.	Senior Director, Pharmacokinetics
Hilde Walgraeve	Associate Director, Global Regulatory Affairs
Rik Carlier	Director, Licensing

Background:
An End-of-Phase 2 meeting was held on July 7, 2000 where in the Agency raised several Issues/questions regarding nebivolol. Mylan requested this meeting to discuss and resolve those issues as well as discuss the acceptability of their revised development plans.

Meeting:

1. Single vs Combination Product

During the July 7, 2000 meeting, the Agency noted that there is a policy regarding diastereoisomers that can be found on the FDA WEB site. This policy states, " diastereoisomers and geometric isomers are both chemically distinct and pharmacologically different (unless they are interconverted in vivo) and are generally readily separated without chiral techniques. Geometric isomers and diastereoisomers therefore should, with the rare exception of cases where in vivo interconversion occurs, be treated as separate drugs and developed accordingly." The Agency believed that Nebivolol consists of diastereoisomers that should be worked up as separate drugs unless a case can be made as to why it is just the right combination product.

In their briefing document for this meeting, Mylan made the case that the nebivolol drug substance is isolated as a racemic mixture of mirror image enantiomers (SRRR and RSSS) without the inclusion of significant levels of diasterioisomers or other sterioisomers. In addition, both Janssen and Mylan have placed strict controls on the stereochemical composition of the drug substance to ensure that the manufacturing process yields only the desired racemate.

The Agency agreed that nebivolol would not have to be worked up separately or as a combination product.

2. Pharmacokinetic (PK) and Hypertension Studies

The Agency raised concerns about the differences in nebivolol plasma levels between slow and fast metabolizers and the possibility that a difference may exist in nebivolol's beta blocking activity. Nebivolol hydrochloride undergoes hepatic metabolism by CYP2D6 and is subject to [redacted]like genetic polymorphisms. Therefore, nebivolol is metabolized differently by extensive metabolizer (EM) versus poor metabolizers (PM), an effect also seen in some other beta blockers.

Janssen conducted a comparison of the anti-hypertensive efficacy and safety of nebivolol in mild to moderate hypertensive subjects characterized as poor metabolizers for [redacted] (NEB-CAN-10). The data from this study were not available for the July 7, 2000 meeting. It was found that there was no statistically significant difference in hypotensive response to nebivolol in extensive and poor metabolizers. Although the number of subjects in this study was too small to formally assess the comparative safety of nebivolol in extensive and poor metabolizers, the data from this study suggest that differences in metabolic phenotypes and concentrations of unchanged drug did not appear to significantly affect the incidence or severity of adverse events or clinical laboratory parameters, probably because effect id mediated by both parent drug and active metabolites.

Mylan plans to compare the safety and efficacy of nebivolol in poor and extensive metabolizers during the clinical development of nebivolol for the treatment of mild to moderate systemic hypertension. In order to obtain long term data on nebivolol in slow metabolizers, Mylan is proposing an additional double-blind, randomized, parallel group study to compare the safety and efficacy of nebivolol in subjects with mild to moderate systemic hypertension who are characterized as poor metabolizers (N=60) versus extensive metabolizers (N=60). Subjects will be stratified by metabolic pathway, race, and age and randomized equally to either nebivolol 5 mg once daily or nebivolol 10 mg once daily for up to 364 days.

The Agency agreed that the proposed plan will address the concerns, but recommended that Mylan look at the dose response of nebivolol to make sure that maximum effect has been reached with the 10 mg dose.

The Agency stated that: 1) Both extensive metabolizers (EM) and poor metabolizers (PM) would have to be enrolled in the mass balance study, and 2) Sparse sampling should be performed in Phase 3 clinical trials for measurement of nebivolol and metabolite concentrations in an effort to correlate concentrations in extensive and poor metabolizers with both blood pressure and heart rate.

3. Severe Congestive Heart Failure Study

At the time of the July 7, 2000 meeting with the Agency, Mylan was considering a non-inferiority trial design to show effectiveness of nebivolol in advanced heart failure. Since that time, the data from the BEST and COPERNICUS trials addressing the use of beta blocker therapy in advanced heart failure have been presented at international congresses. Mylan believes that these data re-open the opportunity for a superiority trial testing nebivolol versus placebo in subjects with advanced heart failure. Mylan believes the question of what constitutes the standard-of-care for subjects with advanced heart failure remains unresolved at this time because of:

1) the absence of spironolactone as background therapy in COPERNICUS,
2) the highly selective inclusion criteria used in COPERNICUS, AND
3) the failure of the BEST data to support the results of COPERNICUS.

The Agency was concerned about the ethics of the proposed trial. The Agency's position has always been that patients can not be denied a therapy that is known to be life saving. Mylan will have to support the view that there is a well-defined population in which responsible investigators find it medically appropriate to omit beta-blocker therlpy. To support this view, they need a detailed analysis of available data, showing lack of evidence of benefit in the proposed population. They should also consult with ethicists, IRBs etc. The Agency also pointed out that if data from the COPERNICUS study became available to the Agency and we do not agree that the population is distinct from the one proposed for the nebivolol study, we believe the study could not be conducted. We have not, however, seen the COPERNICUS study.

4. **Clinical Questions**

Hypertension:

- Does the Division agree with Mylan's proposed Phase 3 clinical program to support the approval of nebivolol [redacted] for the treatment of [redacted] hypertension?

  The Agency agreed. The Agency noted that if Mylan believes nebivolol is effective in blacks and intends to make a comparative claim, there would have to be enough blacks to allow a pre-planned group analysis showing a clear effect..

- Does the Division agree that the combination of molecular pharmacology and BART studies will be adequate to support labeling describing an NO-dependent effect of nebivolol on endothelial function?

  The Agency stated that Mylan would have to show that the nitric oxide releasing effect of nebivolol on human endothelial cells is advantageous in some way in order for it to be mentioned in the labeling. The Agency recommended adding an active comparator to the studies such as carvedilol or metoprolol and showing a superior effect. Mylan would need two studies to claim superiority.

- Mylan plans to submit a single NDA for nebivolol monotherapy [redacted] . Is this acceptable to the Agency?

  Mylan will need to submit an NDA : [redacted]

- Does the Agency agree with Mylan's proposal to add an extension study (approximately nine months) to the [redacted] combination trial in order to meet ICH guidelines on population exposure?

  The Agency agreed.

- Does the Agency agree with Mylan's proposal to file the extension study safety data as a four month safety update to the nebivolol NDA?

  The Agency agreed.

Chronic Stable Angina pectoris

- Mylan believes that the proposed Phase 3 clinical trials in patients with chronic stable angina pectoris will provide sufficient information to characterize the efficacy of nebivolol in the treatment of chronic stable angina pectoris and support approval for this indication. Does the Agency agree?

  The Agency agreed.

- Mylan intends to use the extension safety data acquired in subjects with hypertension as evidence for the safety of nebivolol in subjects with chronic stable angina pectoris who do not have significant left ventricular dysfunction. Does the Agency agree?

  The Agency agreed.

Chronic Heart Failure

Does the Agency agree with Mylan's proposal for the nebivolol clinical development program in chronic heart failure, which consists of:

- a Phase 2 placebo-controlled dosing/physiology study of nebivolol in advanced heart failure
- a Phase 3 placebo-controlled superiority study of nebivolol in advanced heart failure, and
- a Phase 3 placebo-controlled superiority study of nebivolol in left ventricular dysfunction with absent or at most minimally symptomatic heart failure.

The Agency agreed but emphasized that there was still the issue of whether therapy that increases survival could be omitted in the Phase 3 superiority study of nebivolol in advanced heart failure. Mylan would need to provide more documentation and verification from people in the field.

Signature minutes preparer: Linda McDonald 10/24/00

Concurrence, Chair: Robert Temple 10/24/00

Orig. IND
HFD-110
HFD-111/McDonald
HFD-111/Matthews
HFD-101/RTemple
Drafted 10/5/00 Finaled 10/24/00
RD:

Temple	10/20/00
Throckmorton	10/12/00
Stockbridge	10/16/00
Targum	10/10/00
Lawrence	10/5/00
Robbie	10/10/00

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-742

Trade Name: None submitted
Generic Name: Nebivolol Hydrochloride
Strengths: — 2.5, 5, 10, ——mg Tablets

Applicant: Bertek Pharmaceuticals Inc.

Date of Application: April 30, 2004
Date of Receipt: April 30, 2004
Date clock started after UN: N/A
Date of Filing Meeting: June 16, 2004
Filing Date: June 29, 2004
Action Goal Date (optional): N/A User Fee Goal Date: February 28, 2005

Indication(s) requested: Hypertension

Type of Original NDA: (b)(1) ___X_____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ____X_____
Resubmission after withdrawal? No Resubmission after refuse to file? No
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid ____X_____

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # 4747
Clinical data? YES

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

If yes, explain: N/A NO

Does another drug have orphan drug exclusivity for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A

Is the application affected by the Application Integrity Policy (AIP)? NO

If yes, explain: N/A

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES

  If no, explain: N/A
- If an electronic NDA, does it follow the Guidance? NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Entire application

  Additional comments:

  Paper review copies not provided by sponsor. Sponsor stated review copies would be provided if they were requested by the Division.
- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  N/A

  Additional comments:

  N/A
- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? YES, 5 years

  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
  "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."
  Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? YES
  If not, have the Document Room make the corrections.

- List referenced IND numbers: 33,060

- End-of-Phase 2 Meeting(s)? Date(s) 7/7/00
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 11/25/03
  11/19/03 (CMC)
  11/6/98

  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES

  Consult sent to ODS, Tradename not submitted at this time.

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? N/A
  If EA submitted, consulted to Nancy Sager (HFD-357)? N/A

- Establishment Evaluation Request (EER) submitted to DMPQ? YES, per Dr. Mittal

- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

If 505(b)(2) application, complete the following section: **N/A**

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed

[21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    OR IND # _____ NO

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

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On Original

ATTACHMENT

MEMO OF FILING MEETING

NDA: 21-742, Nebivolol Tablets

DATE: June 16, 2004

BACKGROUND:

Bertek Pharmaceuticals submitted a New Drug Application (NDA) for Nebivolol Hydrochloride – 2.5, 5, 10 – —mg tablets on April 30, 2004. The data submitted is to support an indication for the use of nebivolol in the management of hypertension when used alone or in combination with other antihypertensive agents. The sponsor has requested a deferral for the submission of pediatric information.

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Karen Hicks, M.D.	Medical Officer, HFD-110
Jasmine Choi, Ph.D.	Statistician, HFD-710
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-110
Ramsharan Mittal, Ph.D.	Chemist, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Elizabeth Hausner, D.V.M.	Pharmacologist, HFD-110
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Robert Kumi, Ph.D.	Pharmacokineticist, HFD-860
Catherine Miller	DDMAC, HFD-42
Edward Fromm	Acting Chief, Project Management Staff, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

Discipline	**Reviewer**	**Review Due**
Medical:	Karen Hicks, M.D.	December 23, 2004
Statistical:	Jasmine Choi, Ph.D.	December 23, 2004
Pharmacology:	Elizabeth Hausner, D.V.M.	December 23, 2004
Chemistry:	Ramsharan Mittal, Ph.D.	December 23, 2004
Biopharmaceutical:	Elena Mishina, Ph.D.	December 23, 2004
	Robert Kumi, Ph.D.	December 23, 2004
Regulatory Project Management:	Melissa Robb	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: YES
- Advisory Committee Meeting needed? NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

CLINICAL MICROBIOLOGY	NA ___X___	FILE _____	REFUSE TO FILE _____
STATISTICS		FILE ___X___	REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE ___X___	REFUSE TO FILE _____

- Biopharm. inspection needed: NO

PHARMACOLOGY	NA _____	FILE ___X___	REFUSE TO FILE _____

- GLP inspection needed: YES

CHEMISTRY		FILE ___X___	REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES
- Microbiology N/A

ELECTRONIC SUBMISSION: YES
Any comments:

None

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

___X___ Filing issues to be communicated by Day 74.

ACTION ITEMS:

Document filing issues/ conveyed to applicant by Day 74.

_____
Melissa Robb
Regulatory Health Project Manager, HFD-110

RD:

Stockbridge	7/12/04
Fromm	7/02/04
Karkowsky	7/02/04

Hicks	6/30/04
Choi	6/29/04
Srinivasachar	6/29/04
Mittal	6/29/04
DeFelice	6/22/04
Hausner	6/21/04
Mishina	6/17/04
Kumi	6/16/04

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/s/

Melissa Robb
7/12/04 01:23:49 PM
CSO

cycle 3

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-742	Efficacy Supplement Type N/A	Supplement Number N/A	
Drug: Bystolic (nebivolol) 2.5, 5, and 10 mg Tablets		Applicant: Mylan Bertek Pharmaceuticals, Inc.	
RPM: Daniel Brum		HFD-110	Phone # 301-796-0578

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	February 5, 2008
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4747
• User Fee waiver	N/A ( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	N/A ( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	N/A 21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	N/A ( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee	( ) Yes ( ) No ( ) Yes ( ) No

filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	( ) Yes ( ) No
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	N/A ( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X PM 5/31/05; 11/30/07; 12/17/07

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 5/31/05; AE 11/30/07
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	11/30/07
• Original applicant-proposed labeling	4/30/04
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X DMETS 8/11/04; 2/3/05; 10/18/07; 11/16/07; 11/29/07 X DDMAC 2/9/05; 3/10/05; 10/29/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	11/30/07
• Reviews	X DMETS 8/11/04; Chemistry 11/2/07; 11/30/07
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	11/30/07
• Documentation of discussions and/or agreements relating to post-marketing commitments	11/30/07
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X 7/7/00
• Pre-NDA meeting (indicate date)	X 11/6/98; 11/19/03; 11/25/03
• Pre-Approval Safety Conference (indicate date; approvals only)	X 10/26/07
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical Team Leader DCRP 2/23/05; 11/17/07 Division Director DCRP 5/9/05 Office Director 6/21/05
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X Efficacy 10/19/07; 1/31/05 X Safety 10/19/07; 3/10/05; 2/9/05 X Supportive Studies 4/11/05; 4/22/05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Safety Review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	11/14/07
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	12/17/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	1/31/05; 5/11/05
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	2/15/05
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	2/15/05; 3/11/05; 4/29/05; 11/2/07; 11/30/07
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	2/15/05
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 12/10/07 **(X)** Acceptable 11/9/07 **(X)** Withhold recommendation 2/23/05: **(X)** Acceptable
❖ Methods validation	**( )** Completed **( )** Requested **(X)** Not yet requested (not needed)
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X 12/30/04; 1/4/05; 1/24/05; 2/24/05; 3/24/05; 4/11/05; 4/11/05; 11/1/07
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X 7/22/04; 10/22/07; 11/20/07
❖ CAC/ECAC report	X 8/31/04

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/s/

Dan Brum
12/17/2007 05:52:01 PM