

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-421

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Part 2



NDA 22-421

ACKNOWLEDGE CLASS 1 COMPLETE RESPONSE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Coleman:

We acknowledge receipt on December 14, 2009 of your December 14, 2009 resubmission to your new drug application for Mirapex® ER (pramipexole dihydrochloride) Extended-release Tablets, 0.375 mg, 0.75 mg, 1.5mg, 3 mg, and 4.5 mg.

We consider this a complete, class 1 response to our August 24, 2009 action letter. Therefore, the user fee goal date is February 14, 2010.

If you have any questions call me at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Stacy Metz, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22421

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRAMIPEXOLE
DIHYDROCHLORIDE

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/s/

STACY M METZ
01/13/2010

From: [Podskalny, Gerald](#)
To: daniel.coleman@boehringer-ingelheim.com;
cc: [Metz, Stacy](#);
Subject: Draft responses
Date: Thursday, October 08, 2009 6:06:51 PM
Attachments: [Draft Resp to Sponsor CR letter NDA 22421\(2\).doc](#)

Hi Dan,

Here are the responses. They are labeled draft but this is essentially the final version that will be entered into our document system. Sorry for the wait.

Dave

Gerald David Podskalny, D.O.
Team Leader
Division of Neurology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Bldg 22, Room 4338
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone 301-796-2778 (DNP 796-2250)
DNP Fax 301-796-9842
Email gerald.podskalny@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22421

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRAMIPEXOLE
DIHYDROCHLORIDE

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/s/

STACY M METZ
10/14/2009



NDA 22-421

INFORMATION REQUEST LETTER

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your October 23, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex (pramipexole dihydrochloride) ER Tablets.

We have reviewed your drug product specification and have the following comments regarding the dissolution acceptance criteria. We request a prompt written response in order to continue our evaluation of your NDA.

- We recommend adding [redacted] (b) (4) We propose the following acceptance criteria:

At 2 hours	[redacted] (b) (4)
At 9 hours	[redacted] (b) (4)
[redacted] (b) (4)	[redacted] (b) (4)
At 24 hours	[redacted] (b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
07/27/2009



NDA 22-421

INFORMATION REQUEST LETTER

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your October 23, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex (pramipexole dihydrochloride) ER Tablets.

We also refer to your submissions dated June 19, 2009, and June 24, 2009 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. To further clarify our initial request of a lower limit for drug product moisture content, the Agency seeks to establish an acceptable range for drug product moisture content, instead of a one-sided limit, based on the use of the monohydrate form of the drug substance. Revise the current single point drug product moisture content limit to an acceptable range with both a lower limit and an upper limit. Provide a revised drug product specification for each tablet strength that reflects all of the revised acceptance criteria.
2. Based on the decrease in resistance to crushing observed at high humidity, we recommend adding a test for tablet friability or hardness as part of the stability protocol for the post-approval stability commitment batches for each strength.
3. Your submission does not include adequate data to support (b) (4) at ambient warehouse conditions prior to final packaging. Provide stability data, including a comparison of the stability when stored (b) (4), to support this hold time or limit your hold time to (b) (4). Based on the propensity of the tablets to swell when exposed to high humidity, we also recommend that you evaluate the need to store the (b) (4) tablets in a controlled humidity environment prior to packaging or include an adequate desiccant in the (b) (4) container closure.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

7/1/2009 02:02:58 PM

From: daniel.coleman@boehringer-ingelheim.com
To: [Conner, Beverly;](#)
Subject: RE: Internal Site Audits NDA 22-421
Date: Friday, June 19, 2009 5:50:27 PM
Attachments: [248.524 Site Audit Summary 19 June Final.doc](#)

Dear Dr. Conner,

Thank you for your e-mail communication of June 19 (below) . As per our e-mail to you on June 12, we are providing you with a summary of the major findings from the eight audit reports from Study 248.524 and also a summary of our internal site audit process (Attached).

As noted in the attachment, there were no critical compliance issues that led to site closure, and corrective actions were implemented for each of findings. We hope this information is adequate to support your data integrity review. If you have any questions or concerns, please do not hesitate to contact me.

Best regards,

Dan

Daniel T. Coleman, Ph.D.
Associate. Director, Regulatory Affairs
Office Phone: (203) 798-5081
Office Fax: (203) 791-6262
E-mail: daniel.coleman@boehringer-ingelheim.com

-----Original Message-----

From: Conner, Beverly [mailto:Beverly.Conner@fda.hhs.gov]
Sent: Tuesday, June 16, 2009 4:13 PM
To: Coleman,Dr.,Daniel DRA BIP-US-R
Subject: Internal Site Audits NDA 22-421

Dear Dr. Coleman,

Thank you, for sharing the information we requested. A summary of BI's findings for the internal site audits would be fine, it is not necessary to send copies of the actual

forms and inspection site documents. The documentation problems we found are site specific and do not indicate a problem with the BI study database. The site problem will not significantly alter the efficacy finding of the study. The Information regarding data integrity in the sponsor's early PD submission is limited to the fact that audits were conducted. The reviewer could not find a summary of the audit findings in the sponsor's submission, this information is a critical component of the data integrity review. Currently the DSI inspector's findings are the only information we have concerning data integrity for this trial.

[Beverly Conner, Pharm.D.](#)
[Regulatory Health Project Manager](#)
[Division of Neurology](#)
[Office of Drug Evaluation I](#)
[Center for Drug Evaluation and Research](#)
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 01:15:37 PM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenelheim.com"](mailto:daniel.coleman@boehringer-ingenelheim.com);
Subject: Request for Information
Date: Thursday, June 18, 2009 8:28:01 AM

Dear Dr. Coleman,

The Mirapex ER review team met today, a concern was raised by Dr. Katz along with reviewers from other disciplines regarding the potential for confusion between Mirapex and Mirapex ER tablets. The photograph BI forwarded to Bev Connor was helpful but it lacked sufficient detail to make an accurate assessment of their appearance. Dr. Katz is requesting we make a direct comparison of the actual tablets to assess the potential for confusion between the two products. To make the best possible comparison, the Agency is requesting 5 sets of sample tablets of all marketed strengths of Mirapex (IR) and 5 sets of Mirapex ER tablets, all of tablet strengths BI plans to market in the U.S. Please label all of the tablets as Mirapex or Mirapex ER and indicate the strength of each tablet. Send the sample tablets to Beverly Connor, Pharm.D., Regulatory Health Project Manager. Please contact me if you have any questions. Thank you.

Sincerely,

Gerald David Podskalny, D.O.
Acting Team Leader
Division of Neurology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Bldg 22, Room 4321
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone 301-796-2778 (DNP 796-2250)
DNP Fax 301-796-9842
Email gerald.podskalny@fda.hhs.gov

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/s/

Beverly A. Conner
6/18/2009 04:21:53 PM
CSO

Beverly A. Conner
6/23/2009 09:04:43 AM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenheim.com"](mailto:daniel.coleman@boehringer-ingenheim.com);
Subject: Clinical Pharmacology request for information
Date: Thursday, June 18, 2009 12:00:55 PM

Dear Dr. Coleman,

The Clinical Pharmacology Reviewer has the following request for information:

Only a summary of the in vitro alcohol interaction study could be found in the EDR without the supporting data. Please submit tabulated data to support the in vitro dissolution experiments with varying amounts of ethanol in the dissolution medium. This data should be on the highest strength (4.5 mg) using 12 units per run.

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/25/2009 02:26:15 PM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenelheim.com"](mailto:daniel.coleman@boehringer-ingenelheim.com);
Subject: Internal Site Audits NDA 22-421
Date: Tuesday, June 16, 2009 4:12:46 PM

Dear Dr. Coleman,

Thank you, for sharing the information we requested. A summary of BI's findings for the internal site audits would be fine, it is not necessary to send copies of the actual forms and inspection site documents. The documentation problems we found are site specific and do not indicate a problem with the BI study database. The site problem will not significantly alter the efficacy finding of the study. The Information regarding data integrity in the sponsor's early PD submission is limited to the fact that audits were conducted. The reviewer could not find a summary of the audit findings in the sponsor's submission, this information is a critical component of the data integrity review. Currently the DSI inspector's findings are the only information we have concerning data integrity for this trial.

[Beverly Conner, Pharm.D.](#)
[Regulatory Health Project Manager](#)
[Division of Neurology](#)
[Office of Drug Evaluation I](#)
[Center for Drug Evaluation and Research](#)
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/24/2009 09:19:10 AM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenelheim.com"](mailto:daniel.coleman@boehringer-ingenelheim.com);
Subject: NDA 22-421; Mirapex
Date: Thursday, June 11, 2009 10:40:44 AM

Dear Mr. Coleman,

FDA found substantial documentation problems at one of the DSI inspection sites for study 248.524 . At this late stage of the review process we would like to see if the internal audits turned up other problems and we want to review the quality of the internal audits. The audit certificates won't give us this information. Given this set of circumstances, FDA feels this is the most efficient way to proceed. The request is not typical but the alternatives would be less efficient at this point in the cycle.

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Beverly A. Conner
6/24/2009 09:10:50 AM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenheim.com"](mailto:daniel.coleman@boehringer-ingenheim.com);
Subject: AUDIT REPORTS
Date: Wednesday, June 10, 2009 2:25:46 PM

Dear Dr. Coleman, FDA is aware of the audit certificates. What FDA is asking for are the actual audit reports. We would like the results, as soon as possible.

[Beverly Conner, Pharm.D.](#)
[Regulatory Health Project Manager](#)
[Division of Neurology](#)
[Office of Drug Evaluation I](#)
[Center for Drug Evaluation and Research](#)

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/s/

Beverly A. Conner
6/24/2009 11:11:39 AM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingelheim.com"](mailto:daniel.coleman@boehringer-ingelheim.com);
Subject: Site Audits for Study 248.524
Date: Wednesday, June 03, 2009 2:04:18 PM

Dear Dr. Coleman,
Please let us know where the reports for the site audits for Study 248.524 Early PD may be found in your NDA 22421 submission. If they were not submitted, we would like them as soon as possible.

Beverly Conner, Pharm.D.
White Oak Building 22
10903 New Hampshire Avenue
Silver Spring, Maryland 20903
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/24/2009 11:24:11 AM
CSO



NDA 22-421

INFORMATION REQUEST LETTER

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your October 23, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex (pramipexole dihydrochloride) ER Tablets.

We also refer to your submissions dated January 14, 2009, March 5, 2009, April 1, 2009, and May 14, 2009.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Provide any available data to confirm that the particle size distribution of the (b) (4) drug substance has no impact on the particle size distribution of the (b) (4) drug substance.
2. Provide information on criteria used to (b) (4) drug substance batches as well as criteria used to (b) (4) drug substance batches that meet the particle size specification. Identify the number of times a failed batch can be (b) (4). Provide information on process controls used during (b) (4) acceptable batches. Indicate if the (b) (4) is validated. Provide any available process development information for the (b) (4).
3. Provide justification for (b) (4)
(b) (4) Confirm if the system suitability testing conducted prior to routine sample analysis uses a certified reference standard of known particle size distribution, such as (b) (4).
4. Provide data on the residual (b) (4) content in the (b) (4) drug substance batches reported in Section 3.P.5.4.4 Batch Analyses of your submission, if available.
5. We recommend including a (b) (4) time point in the post-approval stability protocol to confirm the proposed re-test period. We also recommend adding the first three commercial batches of (b) (4) drug substance to the stability program as the (b) (4) operation supporting your NDA was not commercial scale.

Drug Product

6. You stated that equivalent carbomer types with a viscosity range of (b) (4) are suitable for use in the commercial drug product but did not provide data to support this statement. Provide data demonstrating that the use of other carbomer-type polymers with a viscosity range of (b) (4) provide equivalent tablet physical properties as well as dissolution performance. This data should also demonstrate that the alternate carbomer polymers do not introduce residual solvents into the drug product.

21. Explain how the annual stability commitment will account for drug product batches originally bracketed in the primary stability protocol if one of the bracketed strengths is not manufactured in a given year. Provide stability data for the third physician sample batch or justification for testing only two drug product batches packaged in the physician sample configuration as part of the stability protocol.
22. Provide the actual content levels for CD 10503, any unspecified degradation products, and the total degradation products reported in Table 3.P.8.3.2.6 - Table 6 to support your claim that the analytical method adjustments improved method robustness.
23. Explain why your statistical evaluation of assay projected increases in assay for the 1.5 mg strength drug product stored in the physician sample configuration and the 4.5 mg strength drug product stored in the proposed commercial configuration.

Regional Information

24. Explain why the master batch records and executed batch records omit the packaging procedure.
25. Identify the container used to hold the (b) (4). Identify the hold time and conditions for the (b) (4).
26. Explain why the German version of the executed batch records refer to (b) (4) (see page 42 of 89 of the original batch record submission for the 4.5 mg strength batch).
27. Revise the drug product carton and container labels to include “extended release tablets” as part of the drug product name. Update Section 16 of the Prescribing Information to include the “beveled” description for the 0.375 mg and 0.75 mg strength drug products.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
5/22/2009 11:36:06 AM

due date for completing this on this NDA 11/5/09.

\CDSESUB1\EVSPROD\NDA022421\

SIGNATURE OF REQUESTER
Beverly Conner 5/18/09

METHOD OF DELIVERY (Check one)
 MAIL HAND
e-mail

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Beverly A. Conner
5/18/2009 01:30:14 PM

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingelheim.com";](mailto:daniel.coleman@boehringer-ingelheim.com)
Subject: Datasets for Study 248.524 early parkinsonism disease
Date: Thursday, May 14, 2009 11:39:33 AM

Dear Dr. Coleman:

FDA has found discrepancies in the datasets for Study 248.524 Early Parkinson's Disease NDA 22-421 Mirapex ER and the errors call into question the data validation methods BI used in creating the datasets.

[Beverly Conner, Pharm.D.](#)
[Regulatory Health Project Manager](#)
[Division of Neurology](#)
[Office of Drug Evaluation I](#)
[Center for Drug Evaluation and Research](#)
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 02:30:31 PM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenelheim.com"](mailto:daniel.coleman@boehringer-ingenelheim.com);
Subject: Mirapex NDA 22-421
Date: Wednesday, April 29, 2009 1:09:22 PM

Data request on April 29, 2009

The FDA statistician requests the following information for Mirapex:

In our March 6 data request, we asked you to provide a variable with the last non-missing value before the start of any rescue/concomitant medicine carrying forward (LOCF), for primary and each of the secondary endpoints, respectively. However, in your March 27 submission, it seems that vast majority of these data (variable name: RUPD0, RUPD1, RCGI0, RCGI3, RPGI0, RPGI3) are missing in data set inder-1.xpt. Please provide a new inder-1.xpt data set including the following information:

*For primary and each of the secondary endpoints, respectively, please provide a variable with the last non-missing value before the start of any **rescue medicine** carrying forward (LOCF). For example, for RUPD1, if any of the selected PD medication was given as a rescue medicine then this is set to the last non-missing UPD1 value before medicine intake; otherwise it should be equal to UPD1. Please provide complete data for variables RUPD0, RUPD1, RCGI0, RCGI3, RPGI0, RPGI3 in data set inder-1.xpt.*

Please provide the requested data at your earliest convenience.

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 04:48:31 PM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): **OSE DRISK; Dan Brounstein**

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Neurology Products , Dr. Russell Katz**

DATE
4/15/09

IND NO.

NDA NO.
22-421

TYPE OF DOCUMENT
NDA

DATE OF DOCUMENT
October 23, 2008

NAME OF DRUG
Mirapex ER

PRIORITY CONSIDERATION
HIGH

CLASSIFICATION OF DRUG
Parkinson's Disease

DESIRED COMPLETION DATE
June 30, 2009

NAME OF FIRM: **Boehringer-Ingelheim**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: At the midcycle meeting there was a discussion of whether the Mirapex ER tablets were too physically similar to the Mirapex IR product and if this could potentially cause confusion and medication errors. It was suggested that the FDA request photos of the ER doses to see if there might be an issue that FDA should pursue. We would like DMEPA to determine the potential of medication errors occurring due to similarity of dosage forms to other other approved products (such as Mirapex IR). FDA requested that BI send photos of the tablets on May 15, 2009.

SIGNATURE OF REQUESTOR
Beverly A. Conner, RPM 301-796-1171

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Beverly A. Conner
5/18/2009 12:18:28 PM



NDA 22-421

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
ATTENTION: Daniel T. Coleman, Ph. D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, Connecticut 06877

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) dated October 23, 2008, received October 24, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pramipexole Dihydrochloride Extended-release Tablets 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, and 4.5 mg.

We also refer to your January 15, 2009, correspondence, received January 15, 2009, requesting review of your proposed proprietary name, Mirapex ER. We have completed our review of the proposed proprietary name, Mirapex ER and have concluded that it is acceptable.

The proposed proprietary name, Mirapex ER, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 15, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Daniel Brounstein, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0674. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Alice T. Hughes
4/15/2009 11:01:49 AM

From: [Conner, Beverly](#)
To: [Bergmann, Kenneth](#); [Podskalny, Gerald](#);
Subject: FW: Follow-up to Telecon Held May 19, 2009 for NDA 22-421 for pramipexole extended-release tablets
Date: Friday, May 29, 2009 4:17:39 PM

[For your information](#)

From: daniel.coleman@boehringer-ingenelheim.com [mailto:daniel.coleman@boehringer-ingenelheim.com]
Sent: Friday, May 29, 2009 4:01 PM
To: Conner, Beverly
Subject: Follow-up to Telecon Held May 19, 2009 for NDA 22-421 for pramipexole extended-release tablets

Dear Dr. Conner,

In the telecon with Drs. Podskalny and Bergmann held May 19, 2009, BI was asked to audit the analysis datasets provided in NDA 22-421. The analysis datasets were provided in the NDA and formatted according to BI standards as agreed with the Division at the preNDA meeting.

We note that the NDA also included data tabulation datasets in FDA-specified CDISC Study Data Tabulation Module (SDTM) format. These datasets were validated by the vendor (b) (4). The analysis datasets formatted according to BI standards were provided in the NDA as supplementary review information.

Although there were some findings related to decodes, the results of the audit confirm the integrity of the data in the analysis datasets. Given the findings related to the decodes, BI has identified options to ensure that the data can be correctly analyzed. More detailed description of the audit and its results are presented below.

Description:

BI audited all analysis datasets for studies 248.524, 248.525 and 248.636, namely:

- POPU (patient set assignments),
- BASCO (baseline and covariate data),
- INDER-E (individual and derived endpoint data-efficacy)
- INDER-S (individual and derived endpoint data-safety)
- IPV (important protocol violations)
- GENTRT (generic treatment file)

The following audits were carried out:

- A review to look for any missing decodes
- A review of un-coded items for valid interpretation
- Inspection of the content of coded variables for consistency across trials
- Inspection of plausibility between code and decode for all coded variables

The following findings were noted in the audit of the analysis datasets.

Findings previously discussed with FDA:

1) For trial 248.524 (cut-offs i1 and i2), the BASCO dataset contains the coded variable BHOYA but is missing the corresponding decoded variable BHOYADC that would provide the translation of the codes (1 to 7) assigned to Hoehn & Yahr stages 1, 1.5, 2, 2.5, 3, 4 and 5. For example 5 in BHOYA represents "Stage 3". Note that no patient had a code greater than 5.

2) For trial 248.524 (cut-offs i1 and i2), in the BASCO dataset the variable PRETRT, labeled as "Pre-treatment status: pre-treated" captures only discontinued PD therapy prior to baseline and not concomitant treatment for PD at baseline. The submission of the revised dataset INDER_1 (sequence 0007, submitted March 27, 2009), clarified the disposition of patients regarding pretreatment and treatment with rescue medication.

Additional findings:

1) For trials 248.524 (cut-offs i1 and i2), and 248.525 (cut-offs TS1 and TS2/3), in the INDER_S dataset, the decodes for the variable WT (weight) in the decoded variable EPTNMDC are not correct (they do not decode to "Weight (kg)").

For your information, the weight data are included in rows labeled "WT" under the column heading "EPTNM." Weight is listed three ways, in separate rows, as:

- No transformation,
- Difference from baseline, and
- Percentage change from baseline.

Analyses of any variables in INDER_E and INDER_S should be carried out using the coded variable under the column heading EPTNM to select data, and not the decoded variable under the column heading EPTNMDC. See screen-shot of the SAS-view showing relevant columns below (several columns are hidden for ease of viewing).

STUDY	PTNO	VISOT	STUDYDAY	VISNO	EPTNM	EPTNMDC	EPTTRS	EPTTRSDC	EPT	EPTDC
205	0248_0524	3601	04JAN08	93	70	DIA2	Standing Diastolic Blood Pr	0	No transformation	80
206	0248_0524	3601	04JAN08	93	70	DIA2	Standing Diastolic Blood Pr	1	Difference from base	-10
207	0248_0524	3601	04JAN08	93	70	DIA2	Standing Diastolic Blood Pr	2	Percentage change fr	-14.2857
208	0248_0524	3601	04JAN08	93	70	HYPO	Orthostatic hypotension	0	No transformation	0
209	0248_0524	3601	04JAN08	93	70	HYPOSYM	Symptomatic orthostatic hyp	0	No transformation	0
210	0248_0524	3601	04JAN08	93	70	PR1	Supine Pulse Rate	0	No transformation	84
211	0248_0524	3601	04JAN08	93	70	PR1	Supine Pulse Rate	1	Difference from base	12
212	0248_0524	3601	04JAN08	93	70	PR1	Supine Pulse Rate	2	Percentage change fr	16.6667
213	0248_0524	3601	04JAN08	93	70	PR2	Standing Pulse Rate	0	No transformation	84
214	0248_0524	3601	04JAN08	93	70	PR2	Standing Pulse Rate	1	Difference from base	12
215	0248_0524	3601	04JAN08	93	70	PR2	Standing Pulse Rate	2	Percentage change fr	16.6667
216	0248_0524	3601	04JAN08	93	70	SLSIG	Significant daytime sleepin	0	No transformation	0
217	0248_0524	3601	04JAN08	93	70	SYS1	Supine Systolic Blood Press	0	No transformation	112
218	0248_0524	3601	04JAN08	93	70	SYS1	Supine Systolic Blood Press	1	Difference from base	-10
219	0248_0524	3601	04JAN08	93	70	SYS1	Supine Systolic Blood Press	2	Percentage change fr	-8.19672
220	0248_0524	3601	04JAN08	93	70	SYS2	Standing Systolic Blood Pre	0	No transformation	110
221	0248_0524	3601	04JAN08	93	70	SYS2	Standing Systolic Blood Pre	1	Difference from base	-10
222	0248_0524	3601	04JAN08	93	70	SYS2	Standing Systolic Blood Pre	2	Percentage change fr	-8.33333
223	0248_0524	3601	04JAN08	93	70	WT	Standing Systolic Blood Pre	0	No transformation	55
224	0248_0524	3601	04JAN08	93	70	WT	Standing Systolic Blood Pre	1	Difference from base	1
225	0248_0524	3601	04JAN08	93	70	WT	Standing Systolic Blood Pre	2	Percentage change fr	1.851852
226	0248_0524	3601	05FEB08	125	80	ABNOTH	Other abnormal behavior or	0	No transformation	0
227	0248_0524	3601	05FEB08	125	80	BMI	Body Mass Index	0	No transformation	24.12175
228	0248_0524	3601	05FEB08	125	80	BMI	Body Mass Index	1	Difference from base	0.43858
229	0248_0524	3601	05FEB08	125	80	BMI	Body Mass Index	2	Percentage change fr	1.851864
230	0248_0524	3601	05FEB08	125	80	DIA1	Supine Diastolic Blood Pres	0	No transformation	80
231	0248_0524	3601	05FEB08	125	80	DIA1	Supine Diastolic Blood Pres	1	Difference from base	10
232	0248_0524	3601	05FEB08	125	80	DIA1	Supine Diastolic Blood Pres	2	Percentage change fr	14.28571

2) For trial 248.636, country name decodes were not provided for the country codes DE, F and NL. The codes DE, F, and NL represent Germany, France and The Netherlands.

Conclusion

A thorough audit of the analysis datasets revealed the decode issues outlined above. These decoding issues do not impact the analyses carried out by BI and included in the reports. Further, they do not affect the integrity of the data and should not cause an inability to analyze or interpret the data. If requested, amended datasets with corrected decode for WT, and addition of decodes for BHOYA and COUNTRY, can be provided.

If you have any questions or comments related to the audit, do not hesitate to contact me.

In addition, we recently became aware of a finding related to reporting of an adverse event in Study 248.524 during a

GCP inspection of a clinical site. We are looking into this matter and will provide you with additional information.

Best regards,

Daniel T. Coleman, Ph.D.
Associate. Director, Regulatory Affairs
Office Phone: (203) 798-5081
Office Fax: (203) 791-6262
Personal Cell: (203) 644-8689
E-mail: daniel.coleman@boehringer-ingelheim.com

Best regards,

Dan

Daniel T. Coleman, Ph.D.
Associate. Director, Regulatory Affairs
Office Phone: (203) 798-5081
Office Fax: (203) 791-6262
Personal Cell: (203) 644-8689
E-mail: daniel.coleman@boehringer-ingelheim.com

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/s/

Beverly A. Conner
6/23/2009 03:58:00 PM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenelheim.com"](mailto:daniel.coleman@boehringer-ingenelheim.com);
Subject: BI Data Requests for Mirapex NDA 22-421
Date: Wednesday, March 25, 2009 3:20:38 PM

Dear Dr. Coleman,
Please send the data requests as previously requested. The midcycle point is coming up very soon and in order to evaluate the this NDA we need this information in a timely matter

[Beverly Conner, Pharm.D.](#)
[Regulatory Health Project Manager](#)
[Division of Neurology](#)
[Office of Drug Evaluation I](#)
[Center for Drug Evaluation and Research](#)
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 02:18:21 PM
CSO

From: [Conner, Beverly](#)
To: [Bergmann, Kenneth](#)
Subject: FW: NDA 22-421 Mirapex ER Information Request
Date: Monday, March 23, 2009 12:27:40 PM

Here is the response from BI, regarding the adverse event data files (AE.xpt) for 4 month safety update report.

From: daniel.coleman@boehringer-ingenelheim.com [mailto:daniel.coleman@boehringer-ingenelheim.com]
Sent: Monday, March 23, 2009 9:11 AM
To: Conner, Beverly
Subject: RE: NDA 22-421 Mirapex ER Information Request

Dear Beverly,

We acknowledge receipt of the Division's request for adverse event data files (AE.xpt) reflecting the 4 month safety update report of adverse events in Studies 248.524, 248.525, and 248.610. (including updated variable names as previously requested for the datasets associated with the original NDA submission). We are preparing these datasets in CDISC format and will submit them as soon as they are available.

However, we would like to propose an alternative approach for the Division's consideration, provided it would not result in an extension of FDA's review period for NDA 22-421.

(b) (4)

Clearly, analyses of the adverse event data files (b) (4) will not match the numbers in the safety summary provided in the 4 month safety update, but the differences in overall exposure are limited. Outlined below is a high level comparison for each of the double-blind trials.

	248.524		248.525		248.610 (12W double blind period)	
	4M SU	(b) (4)	4M SU	(b) (4)	4M SU	(b) (4)
Data cut-off (or LPO)	1Sep08	25Nov08*	1Sep08	19Nov08*	1Sep08	~1Dec08*
Data cut-off SAEs	25Nov08*	25Nov08*	19Nov08*	19Nov08*	~1Dec08*	~1Dec08*
Total # patients treated (up to 33 weeks)	539	539	510	517	112**	112
Total # patient years on treatment	284.5 yrs	303.6 yrs	263.2 yrs	280.1 yrs	22.2 yrs	24.82 yrs

*clinically completed

**blinded

If it is agreed to incorporate the updated adverse event data as prepared (b) (4) for studies 248.524, 248.525, and 248.610 into the initial NDA for pramipexole ER tablets, we would propose to update the draft prescribing information with these data, as appropriate. With this approach, the safety profile based on results of controlled clinical studies (PPX ER vs placebo) described in the initial approved labeling for pramipexole ER tablets would not be expected to change (b) (4)

I ask you to please discuss this proposal with Dr. Katz and the medical reviewers to assess the most appropriate approach to respond to the Division's request for updated adverse event data files. We look forward to your response.

Best regards,

Dan

Daniel T. Coleman, Ph.D.
Associate, Director, Regulatory Affairs
Office Phone: (203) 798-5081
Office Fax: (203) 791-6262

Personal Cell: (203) 644-8689

E-mail: daniel.coleman@boehringer-ingelheim.com

-----Original Message-----

From: Conner, Beverly [mailto:Beverly.Conner@fda.hhs.gov]

Sent: Wednesday, March 18, 2009 4:02 PM

To: Coleman, Dr., Daniel DRA BIP-US-R

Subject: NDA 22-421 Mirapex ER Information Request

Dear Dr. Coleman,

Please provide the following requests for information regarding NDA 22-421 Mirapex ER as soon as possible.

Subject:

Request for additional data re: NDA 22-421 Mirapex ER

We request updated adverse event data files (AE.xpt) reflecting the 4 month safety update report of adverse events in Studies 248.524, 248.525, and 248.610.

As we requested recently for other AE files, these should also have the following variables:

- A variable for each visit number indicating whether the reported AE occurred at that visit (Yes vs. No);
- A variable indicating the dose at which this AE first occurred (numerical value, mg PPX/day);
- A variable indicating treatment arm: TPATTSLB.

Our thanks in advance for your prompt attention to this matter.

Beverly Conner, Pharm.D.

Regulatory Health Project Manager

Division of Neurology

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Phone: 301-796-1171

Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 01:32:37 PM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): **OND Div Cardio Renal IRT Review,
Attention Devi Kozeli**

FROM (Name, Office/Division, and Phone Number of Requestor): **HFD-120
(Division of Neurology Products); Russell Katz, MD**

DATE
March 11, 2009

IND NO.

NDA NO.
NDA 22-421

TYPE OF DOCUMENT
New Drug Application

DATE OF DOCUMENT
October 23, 2009

NAME OF DRUG
**Mirapex, (pramipexole
dihydrochloride)**

PRIORITY CONSIDERATION
High

CLASSIFICATION OF DRUG
**Tx of Idiopathic
Parkinson's disease**

DESIRED COMPLETION DATE
May 14, 2009

NAME OF FIRM: **Boehringer Ingelheim Pharmaceuticals, Inc**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review this NDA Qtc Study "A double-blind, randomized, placebo-controlled study with two sequential two-way cross-over parts to demonstrate that the influence of pramipexole up to 4.5 mg daily on the QT interval of the ECG in healthy male and female volunteers is comparable with placebo, with a positive control (two-way crossover moxifloxacin versus placebo)."

\\Cdsub1\evsprod\NDA022421\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\248-545

\\CDSESUB1\EVSPROD\NDA022421\0000

Please provide comments. Thanks for your help.
301-796-1171.

SIGNATURE OF REQUESTOR Beverly Conner, Pharm.D. Regulatory Project Manager Division of Neurology	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Beverly A. Conner
3/16/2009 02:16:28 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (<i>Division/Office</i>): Russell Katz, M.D. Director Division of Neurology Products (DNP)		FROM (<i>Division/Office</i>): Zarna Patel, PharmD Regulatory Review Officer Division of Drug Marketing, Advertising, and Communications (DDMAC)		
DATE: March 11, 2010	IND NO.	NDA NO. 22-421	TYPE OF DOCUMENT:	DATE OF DOCUMENTS: March 1, 2010
NAME OF DRUG Mirapex ER (pramipexole dihydrochloride) extended release tablets	PRIORITY CONSIDERATION High-Launch	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: March 25, 2010	
NAME OF FIRM: Boehringer Ingelheim Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE <input checked="" type="checkbox"/> DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY	PRE--NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>):		
COMMENTS/SPECIAL INSTRUCTIONS: Please see questions below. This consult will be entered into DARRTS, and I will be hand-carrying the promotional materials, references, and PI to the review division's office. Please let me know if there is any additional information you need to assist you during your review. If you have any questions, please call me at 301-796-3822. Thank you, Zarna				
SIGNATURE OF REQUESTER Zarna Patel, PharmD		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS and hand-carry <input type="checkbox"/> FACSIMILE		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Date: March 11, 2010

From: Zarna Patel, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

To: Russell Katz, M.D.
Director
Division of Neurology Products (DNP)

Re: Consult request from DDMAC on Mirapex ER (pramipexole dihydrochloride) Tablets
NDA #22-421

DDMAC is reviewing a proposed patient brochure for Mirapex ER in the treatment of the signs and symptoms of early Parkinson's disease and we have the following questions. Please feel free to comment on any other concerns you may have with the proposed patient brochure. Thank you in advance for your time.

1. [Redacted] (b) (4)
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted] (b) (4)
[Redacted]
[Redacted]
[Redacted]
[Redacted]

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22421

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRAMIPEXOLE
DIHYDROCHLORIDE

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/s/

ZARNA PATEL
03/11/2010

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenelheim.com"](mailto:daniel.coleman@boehringer-ingenelheim.com);
Subject: Information request for NDA 22-421
Date: Monday, March 09, 2009 3:41:23 PM

Dear Dr. Coleman,

Please provide a response as soon as possible:

Request for additional data re: NDA 22-421 Mirapex ER Study 248.524

For data set inder_1 submitted in January, 2009, some variables are not consistent with the same variables in other data sets in original submission. For example, subject ID number is named SUBJID in dm.xpt while named PTNO in inder_1; SEX is set as a character variable in dm.xpt while as a numeric variable in inder_1. Please make the variables in inder_1 consistent with the variables in other data sets in terms of variable name and type. This request also applies to the new variables to be added to inder_1 as requested by the Agency on March 6, 2009.

In addition, for variable COUNTRY in inder_1, the country names are not consistent. For example, Germany is coded as 'DEU' or 'Germany' and Taiwan is coded as 'CHN' or 'Taiwan'. Please make corrections.

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 10:47:25 AM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenheim.com"](mailto:daniel.coleman@boehringer-ingenheim.com);
Subject: NDA 22-421 Mirapex ER Information Request
Date: Wednesday, March 18, 2009 4:01:41 PM

Dear Dr. Coleman,

Please provide the following requests for information regarding NDA 22-421 Mirapex ER as soon as possible.

Subject:

Request for additional data re: NDA 22-421 Mirapex ER

We request updated adverse event data files (AE.xpt) reflecting the 4 month safety update report of adverse events in Studies 248.524, 248.525, and 248.610.

As we requested recently for other AE files, these should also have the following variables:

- A variable for each visit number indicating whether the reported AE occurred at that visit (Yes vs. No);
- A variable indicating the dose at which this AE first occurred (numerical value, mg PPX/day);
- A variable indicating treatment arm: TPATTSLB.

Our thanks in advance for your prompt attention to this matter.

Beverly Conner, Pharm.D.

Regulatory Health Project Manager

Division of Neurology

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Phone: 301-796-1171

Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 11:28:17 AM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenelheim.com"](mailto:daniel.coleman@boehringer-ingenelheim.com);
Subject: NDA 22-421 Mirapex ER: Request for additional Information
Date: Friday, March 06, 2009 10:07:40 AM

Dear. Dr. Coleman,

We have the following requests for additional information and FDA and would like this information within a couple of weeks. If you have any questions, please feel free to call me.

In Study 248.524 it is evident from Tables 11.2.1:4 and 11.2.1:5 in Doc. No. U08-1826-01 that additional anti PD medication was used during the trial for a number of subjects. However, based on data set inder_1.xpt submitted in January, 2009, it is not clear that if there was any addition or change in rescue or concomitant medication before a patient completed Visit 8 (week 18). Therefore, please ADD the following variables to data set inder_1 and submit to the Agency:

- Ø A variable indicating USUBJID corresponding to the PTNO for each subject;**
- Ø A variable indicating whether or not a patient completed Visit 8 (completer vs. non-completer);**
- Ø For each of the following rescue/concomitant medications, levodopa, amantadine, anticholinergics and / or MAOB-I, a variable indicating whether or not it was taken for each patient and each visit (Yes vs. No).**
- Ø For primary endpoint (UPDRS II+III) and each of the key secondary endpoints (PGI and CGI), respectively, a variable with the last non-missing value before the start of any rescue/concomitant medicine carrying forward (LOCF); that is, values recorded after the start of any rescue/concomitant medicine were replaced by carrying forward the last non-missing value recorded before the start of any rescue/concomitant medicine.**

In Study 248.524, to the adverse event data file, AE.xpt, please add the following:

Ø A variable for each visit number indicating whether the reported AE occurred at that visit (Yes vs. No);

Ø A variable indicating the dose at which this AE first occurred (numerical value, mg PPX/day).

Ø A variable indicating treatment arm: TPATTSLB

In addition, please update the data definition tables for these datasets accordingly.

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Phone: 301-796-1171
Email: Beverly.Conner@fda.hhs.gov

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/s/

Beverly A. Conner
6/23/2009 11:17:10 AM
CSO

From: [Conner, Beverly](#)
To: ["daniel.coleman@boehringer-ingenheim.com"](mailto:daniel.coleman@boehringer-ingenheim.com);
Subject: NDA 22-421 Mirapex ER
Date: Friday, March 06, 2009 10:44:41 AM

Dear Dr. Coleman,

I accidently missed one of the pages regarding the requests for additional information. As stated in the earlier e-mail today FDA and would like this information within a couple of weeks. If you have any questions, please feel free to call me.

In Study 248.524 it is evident from Tables 11.2.1:4 and 11.2.1:5 in Doc. No. U08-1826-01 that additional anti PD medication was used during the trial for a number of subjects. However, based on data set inder_1.xpt submitted in January, 2009, it is not clear that if there was any addition or change in rescue or concomitant medication before a patient completed Visit 8 (week 18). Therefore, please ADD the following variables to data set inder_1 and submit to the Agency:

- Ø A variable indicating USUBJID corresponding to the PTNO for each subject;**
- Ø A variable indicating whether or not a patient completed Visit 8 (completer vs. non-completer);**
- Ø For each of the following rescue/concomitant medications, levodopa, amantadine, anticholinergics and / or MAOB-I, a variable indicating whether or not it was taken for each patient and each visit (Yes vs. No).**
- Ø For primary endpoint (UPDRS II+III) and each of the key secondary endpoints (PGI and CGI), respectively, a variable with the last non-missing value before the start of any rescue/concomitant medicine carrying forward (LOCF); that is, values recorded after the start of any rescue/concomitant medicine were replaced by carrying forward the last non-missing value recorded before the start of any**

rescue/concomitant medicine.

In Study 248.524, to the adverse event data file, AE.xpt, please add the following:

Ø A variable for each visit number indicating whether the reported AE occurred at that visit (Yes vs. No);

Ø A variable indicating the dose at which this AE first occurred (numerical value, mg PPX/day).

Ø A variable indicating treatment arm: TPATTSLB

In addition, please update the data definition tables for these datasets accordingly.

Subject:

Request for clarification re: NDA 22-421 Mirapex ER

We understand from the protocol for study 248.524 that patients who required anti-PD rescue medication (only l-Dopa+) were to be seen and evaluated before beginning medication and that this would be the last observation carried forward for the efficacy analysis.

However, two tables in Study Doc. No. U08-1826-01 are not clear to us. Looking at Table 11.2.1:4, previous anti-parkinson therapy, it appears that 24 subjects were on medication, including 6 who were excluded from FAS1 because of l-dopa. Then in Table 11.2.1:5, 157 subjects have concomitant medications, with only 13 using levodopa. It appears that some subjects were taking more than one drug (216 occurrences in 157 patients). This has raised the following questions for us:

- 1. Were rescue drugs other than l-dopa+ used?**
- 2. When (i.e. visit number) were these additional medications begun for each subject?**
- 3. What adjustments of any anti-parkinson medications occurred**

- during the titration and maintenance periods in the trial?
4. Were there any adjustments in dose of pre-trial anti-parkinson medication at any time during the titration and maintenance period?

For items 2, 3, and 4, we would like to know for which subjects and for which drugs and at what visit(s) this occurred. This may be presented in a data file using standard format.

A narrative explaining this would also be helpful in evaluating whether these represent possible protocol deviations. It is understood that this may require considerable effort on short notice, but it is critical to our timely evaluation of your submission.

Beverly Conner, Pharm.D.
Regulatory Health Project Manager
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research
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/s/

Beverly A. Conner
6/23/2009 10:00:42 AM
CSO



NDA 22-421

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Associate Director Drug Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Dr. Colman:

We have received your new drug application (NDA) submitted under Section 505(b) pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: MIRPAX® ER™ (pramipexole dihydrochloride) extended-release tablets, 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg

Date of Application: October 23, 2008

Date of Receipt: October 24, 2008

Our Reference Number: NDA 22-421

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 December 23, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products

5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1171.

Sincerely,

{See appended electronic signature page}

Beverly Conner, Pharm. D.
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center of Drug Evaluation and Research

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/s/

Beverly A. Conner
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