

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-421**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER  
22-421

NAME OF APPLICANT/NDA HOLDER  
Boehringer Ingelheim Pharmaceuticals, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)  
MIRAPEX ER

ACTIVE INGREDIENT(S)  
Prampexole dihydrochloride

STRENGTH(S)  
0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg and 4.5 mg

DOSAGE FORM  
Extended Release Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number 4886812	b. Issue Date of Patent December 12, 1989	c. Expiration Date of Patent October 8, 2010
d. Name of Patent Owner Boehringer Ingelheim International GmbH	Address (of Patent Owner) Binger Strasse 173	
	City/State Ingelheim am Rhein, Germany	
	ZIP Code 55216	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  <b>Boehringer Ingelheim Pharmaceuticals, Inc.</b> Attn.: General Counsel	Address (of agent or representative named in 1.e.) 900 Ridgebury Road, PO Box 368	
	City/State Ridgefield, CT	
	ZIP Code 06877	FAX Number (if available) (203) 791-6180
	Telephone Number (203) 798-9988	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

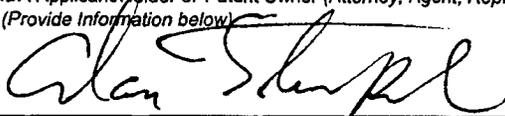
**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



7/29/08

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
Alan Stempel

Address  
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The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 022421

SUPPL #

HFD # 120

Trade Name Mirapex ER

Generic Name pramipexole dihydrochloride extended-release

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known February 19, 2010

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020667

Mirapex IR (pramipexole) Approved June 1, 2007

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

IND 75,961 Trial No. 248.524

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

IND 75,961 Trial No. 248.524

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 75,961      YES       ! NO   
! Explain:

Investigation #2  
IND #              YES       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====  
Name of person completing form: Stacy Metz, PharmD  
Title: RPM  
Date: March 3, 2010

Name of Office/Division Director signing form: Russell Katz, MD  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**DEBARMENT CERTIFICATION**

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Certification Requirement Section 306(k)(1) of the Act 21 U.S.C. 355a(k)

Boehringer Ingelheim Pharmaceuticals, Inc. 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

Signature:



Name of Applicant:

Christopher Corsico, M.D.  
Vice President, Drug Regulatory Affairs  
Boehringer Ingelheim Pharmaceuticals, Inc.

Date:



Mailing Address:

Boehringer Ingelheim Pharmaceuticals Inc.  
900 Ridgebury Road  
P.O. Box 368  
Ridgefield, CT 06877-0368

**CONFIDENTIAL**

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-421 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Division of Neurology Products PDUFA Goal Date: 8/24/09 Stamp Date: 10/24/2008

Proprietary Name: Mirapex ER

Established/Generic Name: pramipexole

Dosage Form: tablets

Applicant/Sponsor: Boehringer Ingelheim Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) none
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** treatment of patients with early Parkinson's Disease

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
  - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

- # Not feasible:**
  - Necessary studies would be impossible or highly impracticable because:
    - Disease/condition does not exist in children
    - Too few children with disease/condition to study
    - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- \* Not meaningful therapeutic benefit:**
  - Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

\_\_\_\_\_  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

## Metz, Stacy

---

**From:** Metz, Stacy  
**Sent:** Friday, February 19, 2010 8:41 AM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** NDA 22-421 Approval

**Attachments:** 22-421 Approval (COR-NDAACTION-03) (2) (3) (4) (2) (2).pdf

Dan,

Everything was finalized this morning. Here is your letter. I will be available briefly this morning if you should need anything else and then I will be on leave the rest of the day.



22-421 Approval  
(COR-NDAACTION...

Best Regards,  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

**Metz, Stacy**

---

**From:** Metz, Stacy  
**Sent:** Wednesday, February 17, 2010 1:52 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** RE: NDA 22-421 FDA Proposed Labeling  
**Attachments:** 22-421 FDA and sponsor agreed labeling 2 17 10 (3) (3).doc

Hi Dan,

As you discussed with Dave, here is the labeling with only 1 change in the Pregnancy section in the highlights. Please send me an email at your earliest convenience stating your agreement to this change.

I am going to continue to finalize documents and hope to take everything to Dr. Katz this afternoon.

Best Regards,  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

---

**From:** daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]  
**Sent:** Tuesday, February 16, 2010 7:04 PM  
**To:** Metz, Stacy  
**Subject:** FW: NDA 22-421 FDA Proposed Labeling

Dear Stacy,

This is to inform you that BI agrees to the FDA proposed changes to the labeling.

(b) (4)

**Dan**

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

3/4/2010

E-mail: [daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com)

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]  
**Sent:** Tuesday, February 16, 2010 3:55 PM  
**To:** Coleman, Dr., Daniel DRA BIP-US-R  
**Subject:** RE: NDA 22-421 FDA Proposed Labeling

Hi Dan,

Attached please find FDA's 2/16/10 proposed labeling for NDA 022421/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this proposed labeling was your labeling sent to us in the email below on 2/8/10. The attached is a marked up version where you are able to easily identify our revisions.

Please share this document with the appropriate folks at BI and confirm your agreement. If you have revisions, we ask that you use this document as the base and, if possible, show any revisions using the track changes function in WORD. Please respond our proposal as early as possible on Tuesday as we hope to meet and discuss/finalize at a meeting at 1pm EST Tuesday.

Best Regards,

Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

---

**From:** [daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com) [mailto:[daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com)]  
**Sent:** Monday, February 08, 2010 10:52 AM  
**To:** Metz, Stacy  
**Subject:** RE: NDA 22-421 FDA Proposed Labeling

Dear Stacy,

Please find attached our revised proposed labeling for MIRAPEX ER. As per your request, **we** used the text you sent on Feb. 4 as the basis text and we have shown our proposed changes in track changes mode. **In addition, we have provided a brief rationale for each of the proposed changes as a comment in the right-hand margin.**

We note that your team has used the final 33 week data from the 248.524 early PD trial for the adverse event numbers and frequencies.

We accept this approach but have had to make some slight corrections to the numbers; **for your convenience, we have provided references from the final trial report for all these changes.**

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](mailto:daniel.coleman@boehringer-ingelheim.com)

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]  
**Sent:** Thursday, February 04, 2010 4:04 PM  
**To:** Coleman, Dr., Daniel DRA BIP-US-R  
**Subject:** FW: NDA 22-421 FDA Proposed Labeling

Dan,

Apologies, but please note the addition of one further sentence.

Thank you.  
Stacy

---

**From:** Metz, Stacy  
**Sent:** Thursday, February 04, 2010 4:02 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** NDA 22-421 FDA Proposed Labeling

Hi Dan,  
Attached please find FDA's 2/4/10 revised labeling for NDA 022421/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this revised labeling was your labeling sent to us in the submission dated 12/14/09. The attached is not a marked up version where you are able to easily identify our revisions. It is possible that we will have a few more minor changes to this labeling, but in the interest of time we wanted to send this to you this week.

Please share this document with the appropriate folks at BI and confirm your agreement. If you have revisions, we ask that you use this document as the base and, if possible, show any revisions using the track changes function in WORD. Please respond our proposal as early as possible Monday morning, February 8, 2010.

<<22-421 FDA proposed labeling to sponsor 2 4 10.doc>>

If you have any questions, please let me know.

Thanks,  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

**Metz, Stacy**

---

**From:** Wilson, Wendy  
**Sent:** Wednesday, February 17, 2010 11:03 AM  
**To:** Metz, Stacy  
**Cc:** Heimann, Martha R; Podskalny, Gerald  
**Subject:** RE: NDA 22-421 FDA Proposed Labeling

it is fine. it is the NF name for the excipient they are using.

---

**From:** Metz, Stacy  
**Sent:** Wednesday, February 17, 2010 11:00 AM  
**To:** Wilson, Wendy  
**Cc:** Heimann, Martha R; Podskalny, Gerald  
**Subject:** FW: NDA 22-421 FDA Proposed Labeling  
**Importance:** High

Wendy,

Rusty wanted Dave/me to check with you regarding the use of the word homopolymer on the last page of the labeling. I know you already looked at this labeling, but since I didn't ask you specifically about this I wanted to check with you. We are meeting at 1pm today with Rusty so if you could get back to me by then it would be appreciated. Please disregard if Dave has already emailed you.

**Inactive Ingredients:** hypromellose, corn starch, carbomer homopolymer, colloidal silicon dioxide, and magnesium stearate.

Thank you.  
Stacy

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**From:** daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]  
**Sent:** Tuesday, February 16, 2010 7:04 PM  
**To:** Metz, Stacy  
**Subject:** FW: NDA 22-421 FDA Proposed Labeling

Dear Stacy,

This is to inform you that BI agrees to the FDA proposed changes to the labeling.

(b) (4)



**Dan**

Daniel T. Coleman, Ph.D.  
Associate Director, Regulatory Affairs

3/4/2010

Office Phone: (203) 798-5081  
Office Fax: (203) 791-6262  
E-mail: [daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com)

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Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
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Food and Drug Administration  
Phone: 301-796-2139

---

**From:** [daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com) [mailto:[daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com)]  
**Sent:** Monday, February 08, 2010 10:52 AM  
**To:** Metz, Stacy  
**Subject:** RE: NDA 22-421 FDA Proposed Labeling

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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](mailto:daniel.coleman@boehringer-ingelheim.com)

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]  
**Sent:** Thursday, February 04, 2010 4:04 PM  
**To:** Coleman, Dr., Daniel DRA BIP-US-R  
**Subject:** FW: NDA 22-421 FDA Proposed Labeling

Dan,

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Thank you.  
Stacy

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**From:** Metz, Stacy  
**Sent:** Thursday, February 04, 2010 4:02 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** NDA 22-421 FDA Proposed Labeling

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Attached please find FDA's 2/4/10 revised labeling for NDA 022421/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this revised labeling was your labeling sent to us in the submission dated 12/14/09. The attached is not a marked up version where you are able to easily identify our revisions. It is possible that we will have a few more minor changes to this labeling, but in the interest of time we wanted to send this to you this week.

Please share this document with the appropriate folks at BI and confirm your agreement. If you have revisions, we ask that you use this document as the base and, if possible, show any revisions using the track changes function in WORD. Please respond our proposal as early as possible Monday morning, February 8, 2010.

<<22-421 FDA proposed labeling to sponsor 2 4 10.doc>>

If you have any questions, please let me know.

Thanks,  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration

Phone: 301-796-2139

**Metz, Stacy**

---

**From:** Metz, Stacy  
**Sent:** Tuesday, February 16, 2010 3:55 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** RE: NDA 22-421 FDA Proposed Labeling  
**Attachments:** 22-421 FDA propopsed labeling 2 16 10 (3).doc

Hi Dan,

Attached please find FDA's 2/16/10 proposed labeling for NDA 022421/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this proposed labeling was your labeling sent to us in the email below on 2/8/10. The attached is a marked up version where you are able to easily identify our revisions.

Please share this document with the appropriate folks at BI and confirm your agreement. If you have revisions, we ask that you use this document as the base and, if possible, show any revisions using the track changes function in WORD. Please respond our proposal as early as possible on Tuesday as we hope to meet and discuss/finalize at a meeting at 1pm EST Tuesday.

Best Regards,

Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

---

**From:** daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]  
**Sent:** Monday, February 08, 2010 10:52 AM  
**To:** Metz, Stacy  
**Subject:** RE: NDA 22-421 FDA Proposed Labeling

Dear Stacy,  
Please find attached our revised proposed labeling for MIRAPEX ER. As per your request, we used the text you sent on Feb. 4 as the basis text and we have shown our proposed changes in track changes mode. **In addition, we have provided a brief rationale for each of the proposed changes as a comment in the right-hand margin.**

We note that your team has used the final 33 week data from the 248.524 early PD trial for the adverse event numbers and frequencies.

We accept this approach but have had to make some slight corrections to the numbers; **for your convenience, we have provided references from the final trial report for all these changes.**

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](mailto:daniel.coleman@boehringer-ingelheim.com)

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]  
**Sent:** Thursday, February 04, 2010 4:04 PM  
**To:** Coleman, Dr., Daniel DRA BIP-US-R  
**Subject:** FW: NDA 22-421 FDA Proposed Labeling

Dan,

Apologies, but please note the addition of one further sentence.

Thank you.  
Stacy

---

**From:** Metz, Stacy  
**Sent:** Thursday, February 04, 2010 4:02 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** NDA 22-421 FDA Proposed Labeling

Hi Dan,

Attached please find FDA's 2/4/10 revised labeling for NDA 022421/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this revised labeling was your labeling sent to us in the submission dated 12/14/09. The attached is not a marked up version where you are able to easily identify our revisions. It is possible that we will have a few more minor changes to this labeling, but in the interest of time we wanted to send this to you this week.

Please share this document with the appropriate folks at BI and confirm your agreement. If you have revisions, we ask that you use this document as the base and, if possible, show any revisions using the track changes function in WORD. Please respond our proposal as early as possible Monday morning, February 8, 2010.

<<22-421 FDA proposed labeling to sponsor 2 4 10.doc>>

If you have any questions, please let me know.

Thanks,  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

3/4/2010

**Metz, Stacy**

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**From:** Mena-Grillasca, Carlos  
**Sent:** Friday, February 05, 2010 8:50 AM  
**To:** Podskalny, Gerald; Metz, Stacy  
**Cc:** Toombs, LaToya (Shenee')  
**Subject:** RE: NDA 22-421

I agree, 1 month seems reasonable.

Carlos

Carlos M Mena-Grillasca | Team Leader | DMEPA/OSE/CDER/FDA |  301.796.4073 |  [carlos.mena-grillasca@fda.hhs.gov](mailto:carlos.mena-grillasca@fda.hhs.gov)

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**From:** Podskalny, Gerald  
**Sent:** Thursday, February 04, 2010 1:01 PM  
**To:** Metz, Stacy; Mena-Grillasca, Carlos  
**Cc:** Toombs, LaToya (Shenee')  
**Subject:** RE: NDA 22-421

We need to ask Rusty but I am OK with 1 month.

Dave Podskalny  
Clinical Team Leader  
Division of Neurology Products  
WO-22 Rm. 4338  
Phone 301 796-2778

---

**From:** Metz, Stacy  
**Sent:** Thursday, February 04, 2010 12:00 PM  
**To:** Metz, Stacy; Mena-Grillasca, Carlos  
**Cc:** Toombs, LaToya (Shenee'); Podskalny, Gerald  
**Subject:** RE: NDA 22-421

The sponsor just called and said they have just over a month supply so they would be out of them by the end of March. They are checking on exact numbers if needed.

Stacy

---

**From:** Metz, Stacy  
**Sent:** Thu 2/4/2010 10:45 AM  
**To:** Mena-Grillasca, Carlos  
**Cc:** Toombs, LaToya (Shenee'); Podskalny, Gerald

3/4/2010

**Subject:** RE: NDA 22-421

I will check and get back to you later today.

Stacy

---

**From:** Mena-Grillasca, Carlos  
**Sent:** Wednesday, February 03, 2010 4:58 PM  
**To:** Metz, Stacy  
**Cc:** Toombs, LaToya (Shenee'); Podskalny, Gerald  
**Subject:** RE: NDA 22-421

Hi Stacy,

Can the sponsor estimate how much product will be packaged/marketed with the old labels? Assuming they are only distributing a limited amount of product with the old labels we defer to the review division's decision.

Carlos

Carlos M Mena-Grillasca | Team Leader | DMEPA/OSE/CDER/FDA | ☎ 301.796.4073 | ✉ [carlos.mena-grillasca@fda.hhs.gov](mailto:carlos.mena-grillasca@fda.hhs.gov)

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**From:** Metz, Stacy  
**Sent:** Tuesday, February 02, 2010 10:49 AM  
**To:** Podskalny, Gerald; Toombs, LaToya (Shenee'); Mena-Grillasca, Carlos  
**Subject:** FW: NDA 22-421

See email below regarding sponsor recommendations that I was asked to send yesterday.

---

**From:** [daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com) [mailto:[daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com)]  
**Sent:** Tuesday, February 02, 2010 8:36 AM  
**To:** Metz, Stacy  
**Subject:** RE: NDA 22-421

Dear Stacy,

As per your email dated February 1, 2010 below, BI agrees to add the following statement to all container and carton labels for MIRAPEX ER:

“Tablets must be swallowed whole and must not be chewed, crushed, or divided.”

However, we respectfully request that the initial launch supplies for MIRAPEX ER utilize the carton and container labels proposed in our resubmission dated December 14, 2009, as we have begun packaging of launch supplies “at risk”. BI agrees to incorporate the new text in the next batch of container and carton labels to be printed.

Please let us know as soon as possible if this is acceptable.

Best regards,

***Dan***

Daniel T. Coleman, Ph.D.  
Associate Director, Regulatory Affairs

3/4/2010

Office Phone: (203) 798-5081  
Office Fax: (203) 791-6262  
E-mail: [daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com)

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]  
**Sent:** Monday, February 01, 2010 3:55 PM  
**To:** Coleman,Dr.,Daniel DRA BIP-US-R  
**Subject:** NDA 22-421

Hi Dan,

I have been asked to pass along this comment to you from the review team for your agreement and response.

Add the statement, "Tablets must be swallowed whole and must not be chewed, crushed, or divided." to all container labels and carton labeling to maintain consistency with the Dosage and Administration recommendations in the insert labeling.

Thank you.  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

**Metz, Stacy**

---

**From:** daniel.coleman@boehringer-ingelheim.com  
**Sent:** Thursday, February 04, 2010 12:25 PM  
**To:** Metz, Stacy  
**Subject:** RE: NDA 22-421

Dear Stacy,

We plan to launch with:

(b) (4) bottles of each of the 5 strengths of MIRAPEX ER (30 tablets in each bottle).  
(b) (4) bottles of each of the 3 strengths of samples (7 tablets each bottle).

This is expected to supply the market for approximately one month.

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

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]  
**Sent:** Thursday, February 04, 2010 10:47 AM  
**To:** Coleman, Dr., Daniel DRA BIP-US-R  
**Subject:** RE: NDA 22-421

Hi Dan,

The team would like to know an estimate of how much product will be packaged/marketed with the old labels?

Thank you.  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

---

**From:** daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]  
**Sent:** Tuesday, February 02, 2010 8:36 AM  
**To:** Metz, Stacy  
**Subject:** RE: NDA 22-421

Dear Stacy,

As per your email dated February 1, 2010 below, BI agrees to add the following statement to all container and carton labels for MIRAPEX ER:

3/4/2010

“Tablets must be swallowed whole and must not be chewed, crushed, or divided.”

However, we respectfully request that the initial launch supplies for MIRAPEX ER utilize the carton and container labels proposed in our resubmission dated December 14, 2009, as we have begun packaging of launch supplies “at risk”. BI agrees to incorporate the new text in the next batch of container and carton labels to be printed.

Please let us know as soon as possible if this is acceptable.

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-ingenelheim.com](mailto:daniel.coleman@boehringer-ingenelheim.com)

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]

**Sent:** Monday, February 01, 2010 3:55 PM

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

**Subject:** NDA 22-421

Hi Dan,

I have been asked to pass along this comment to you from the review team for your agreement and response.

Add the statement, “Tablets must be swallowed whole and must not be chewed, crushed, or divided.” to all container labels and carton labeling to maintain consistency with the Dosage and Administration recommendations in the insert labeling.

Thank you.

Stacy

Stacy M. Metz, PharmD

Regulatory Project Manager

Division of Neurology Products

Food and Drug Administration

Phone: 301-796-2139

## Metz, Stacy

---

**From:** Metz, Stacy  
**Sent:** Thursday, February 04, 2010 4:02 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** NDA 22-421 FDA Proposed Labeling

**Attachments:** 22-421 FDA proposed labeling to sponsor 2 4 10.doc

Hi Dan,

Attached please find FDA's 2/4/10 revised labeling for NDA 022421/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this revised labeling was your labeling sent to us in the submission dated 12/14/09. The attached is not a marked up version where you are able to easily identify our revisions.

Please share this document with the appropriate folks at BI and confirm your agreement. If you have revisions, we ask that you use this document as the base and, if possible, show any revisions using the track changes function in WORD. Please respond our proposal as early as possible Monday morning, February 8, 2010.



22-421 FDA  
proposed labeling t..

If you have any questions, please let me know.

Thanks,

Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

**Metz, Stacy**

---

**From:** Ware, Jacqueline H  
**Sent:** Thursday, February 04, 2010 2:30 PM  
**To:** Metz, Stacy  
**Subject:** FW: PeRC Schedule- NDA 22-421 Mirapex

---

**From:** Stowe, Ginneh D.  
**Sent:** Friday, August 14, 2009 5:36 PM  
**To:** Ware, Jacqueline H  
**Cc:** Greeley, George  
**Subject:** PeRC Schedule- NDA 22-421 Mirapex

Hi Jackie,

Mirapex is on the PeRC schedule for September 9, 2009. PeRC is usually held from 9 am to 11 am on Wednesdays, you will be notified of a specific time closer to the meeting date. Please send the completed documents covering ages birth to 16 years to be reviewed no later than **September 1, 2009**. **Failure to do so will result in your product being rescheduled to a later date.**

The information entered into the PREA Pediatric Record in DARRTS should reflect the opinions of the Division for each product and not merely those of the sponsor.

**Please note that the templates in CDER Standard Letters (CSL) are not current so please be sure to use the forms on the PMHS website.**

The Pediatric Plan submitted for deferrals **MUST** include a brief description of studies in addition to:  
Protocol Submission Date  
Study Start Date  
Final Report Submission Date

Here is the link to the webpage where the most current PREA language for the approval letters can be found.  
<http://wcms.fda.gov/InsideFDA/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/UCM027839>.

Thanks,  
Ginneh

---

Ginneh D. Stowe, MS  
Public Health Analyst, Regulatory Affairs Team  
Pediatric and Maternal Health Staff  
Office of New Drugs  
FDA-Center for Drug Evaluation and Research  
White Oak Complex  
Building #22, Room 6481  
Office: 301-796-4049  
Fax: 301-796-9855  
Email: [Ginneh.Stowe@fda.hhs.gov](mailto:Ginneh.Stowe@fda.hhs.gov)

**Metz, Stacy**

---

**From:** Metz, Stacy  
**Sent:** Thursday, February 04, 2010 12:00 PM  
**To:** Metz, Stacy; Mena-Grillasca, Carlos  
**Cc:** Toombs, LaToya (Shenee'); Podskalny, Gerald  
**Subject:** RE: NDA 22-421

The sponsor just called and said they have just over a month supply so they would be out of them by the end of March. They are checking on exact numbers if needed.

Stacy

---

**From:** Metz, Stacy  
**Sent:** Thu 2/4/2010 10:45 AM  
**To:** Mena-Grillasca, Carlos  
**Cc:** Toombs, LaToya (Shenee'); Podskalny, Gerald  
**Subject:** RE: NDA 22-421

I will check and get back to you later today.

Stacy

---

**From:** Mena-Grillasca, Carlos  
**Sent:** Wednesday, February 03, 2010 4:58 PM  
**To:** Metz, Stacy  
**Cc:** Toombs, LaToya (Shenee'); Podskalny, Gerald  
**Subject:** RE: NDA 22-421

Hi Stacy,

Can the sponsor estimate how much product will be packaged/marketed with the old labels? Assuming they are only distributing a limited amount of product with the old labels we defer to the review division's decision.

Carlos

Carlos M Mena-Grillasca | Team Leader | DMEPA/OSE/CDER/FDA |  301.796.4073 |  [carlos.mena-grillasca@fda.hhs.gov](mailto:carlos.mena-grillasca@fda.hhs.gov)

---

**From:** Metz, Stacy  
**Sent:** Tuesday, February 02, 2010 10:49 AM  
**To:** Podskalny, Gerald; Toombs, LaToya (Shenee'); Mena-Grillasca, Carlos  
**Subject:** FW: NDA 22-421

See email below regarding sponsor recommendations that I was asked to send yesterday.

---

**From:** [daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com) [mailto:[daniel.coleman@boehringer-ingelheim.com](mailto:daniel.coleman@boehringer-ingelheim.com)]  
**Sent:** Tuesday, February 02, 2010 8:36 AM

3/4/2010

**To:** Metz, Stacy  
**Subject:** RE: NDA 22-421

Dear Stacy,

As per your email dated February 1, 2010 below, BI agrees to add the following statement to all container and carton labels for MIRAPEX ER:

“Tablets must be swallowed whole and must not be chewed, crushed, or divided.”

However, we respectfully request that the initial launch supplies for MIRAPEX ER utilize the carton and container labels proposed in our resubmission dated December 14, 2009, as we have begun packaging of launch supplies “at risk”. BI agrees to incorporate the new text in the next batch of container and carton labels to be printed.

Please let us know as soon as possible if this is acceptable.

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](mailto:daniel.coleman@boehringer-ingelheim.com)

---

**From:** Metz, Stacy [mailto:Stacy.Metz@fda.hhs.gov]

**Sent:** Monday, February 01, 2010 3:55 PM

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

**Subject:** NDA 22-421

Hi Dan,

I have been asked to pass along this comment to you from the review team for your agreement and response.

Add the statement, “Tablets must be swallowed whole and must not be chewed, crushed, or divided.” to

all container labels and carton labeling to maintain consistency with the Dosage and Administration recommendations in the insert labeling.

Thank you.  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

**Metz, Stacy**

---

**From:** Metz, Stacy  
**Sent:** Monday, February 01, 2010 3:55 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** NDA 22-421

Hi Dan,

I have been asked to pass along this comment to you from the review team for your agreement and response.

Add the statement, "Tablets must be swallowed whole and must not be chewed, crushed, or divided." to all container labels and carton labeling to maintain consistency with the Dosage and Administration recommendations in the insert labeling.

Thank you.  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

## Metz, Stacy

---

**From:** Metz, Stacy  
**Sent:** Wednesday, January 27, 2010 4:54 PM  
**To:** Wilson, Wendy  
**Cc:** Heimann, Martha R  
**Subject:** RE: NDA 22-421/Mirapex ER Labeling

**Attachments:** 22-421 FDA revised label 1 27 10l.doc

Hi Wendy,

I know you emailed and didn't have anything to add to the labeling, but Rusty wanted me to double check and just make sure your sections were okay, particularly section 3 and the "What does MIRAPEX ER look like?" under the patient information.

Thank you.  
Stacy



22-421 FDA revised  
label 1 27 ...

---

**From:** Metz, Stacy  
**Sent:** Thursday, December 17, 2009 3:33 PM  
**To:** Metz, Stacy; Podskalny, Gerald; Katz, Russell G; Bergmann, Kenneth; Mena-Grillasca, Carlos; Toombs, LaToya (Shenee)  
**Cc:** Heimann, Martha R; Wilson, Wendy; CDER 120 Calendar; Men, Angela; Holquist, Carol A; Sood, Ramesh; Kelley, Laurie  
**Subject:** NDA 22-421/Mirapex ER Labeling  
**When:** Wednesday, January 27, 2010 3:00 PM-4:30 PM (GMT-05:00) Eastern Time (US & Canada).  
**Where:** CDER WO 4201 conf rm Bldg22

**UPDATED 1/26/10: We will start with this labeling that was sent to the sponsor in the CR letter in August. I will bring a copy of the sponsor proposed starting label (below) for reference. You may want to bring a copy of the labeling below as well. Thank you.**

**<< File: N22421 Mirapex ER CR lbl ver 24Aug09.doc >>**

**Updated 1/13/10: Due to the now pending PDUFA of 2/12/10 (2/14/10 Sunday) we will be using this previously scheduled meeting for NDA 22-421 for Mirapex ER in early PD.**

**We will start with the following labeling (in EDR):**  
**Please send me any changes prior to this meeting**

**<< File: 22-421 sponsor proposed starting label.doc >>**

<< File: 22-421 cr letter.pdf >> << File: Draft Resp to Sponsor CR letter NDA 22421(2).doc >>

EDR Location: \\CDSESUB1\EVSPROD\NDA022421\022421.enx

For Document Room Staff Use:

Application Type/Number: nda022421

Incoming Document Category/Sub Category: Electronic Gateway

Incoming Document Category/Sub Category Number: 0022

Letter Date: 12/14/2009

Stamp Date: 12/14/2009

## Metz, Stacy

---

**From:** Metz, Stacy  
**Sent:** Wednesday, January 27, 2010 4:58 PM  
**To:** Men, Angela  
**Subject:** RE: NDA 22-421/Mirapex ER Labeling

**Attachments:** 22-421 FDA revised label 1 27 10l.doc

Hi Angela,

Rusty wanted me to follow up with you regarding one section of this labeling and make sure that I have you take a look at this and see if you have any input. It is the highlighted paragraph just before section 13. We don't have another labeling meeting for the ER until Feb 9th so no hurry.



22-421 FDA revised  
label 1 27 ...

Thank you.  
Stacy

---

**From:** Metz, Stacy  
**Sent:** Thursday, December 17, 2009 3:33 PM  
**To:** Metz, Stacy; Podskalny, Gerald; Katz, Russell G; Bergmann, Kenneth; Mena-Grillasca, Carlos; Toombs, LaToya (Shene'e)  
**Cc:** Heimann, Martha R; Wilson, Wendy; CDER 120 Calendar; Men, Angela; Holquist, Carol A; Sood, Ramesh; Kelley, Laurie  
**Subject:** NDA 22-421/Mirapex ER Labeling  
**When:** Wednesday, January 27, 2010 3:00 PM-4:30 PM (GMT-05:00) Eastern Time (US & Canada).  
**Where:** CDER WO 4201 conf rm Bldg22

**UPDATED 1/26/10: We will start with this labeling that was sent to the sponsor in the CR letter in August. I will bring a copy of the sponsor proposed starting label (below) for reference. You may want to bring a copy of the labeling below as well. Thank you.**

**<< File: N22421 Mirapex ER CR lbl ver 24Aug09.doc >>**

**Updated 1/13/10: Due to the now pending PDUFA of 2/12/10 (2/14/10 Sunday) we will be using this previously scheduled meeting for NDA 22-421 for Mirapex ER in early PD.**

**We will start with the following labeling (in EDR):**  
**Please send me any changes prior to this meeting**

**<< File: 22-421 sponsor proposed starting label.doc >>**

<< File: 22-421 cr letter.pdf >> << File: Draft Resp to Sponsor CR letter NDA 22421(2).doc >>

EDR Location: \\CDSESUB1\EVSPROD\NDA022421\022421.enx

For Document Room Staff Use:  
Application Type/Number: nda022421

Incoming Document Category/Sub Category: Electronic Gateway

Incoming Document Category/Sub Category Number: 0022

Letter Date: 12/14/2009

Stamp Date: 12/14/2009

## Metz, Stacy

---

**From:** Metz, Stacy  
**Sent:** Wednesday, January 13, 2010 4:21 PM  
**To:** 'daniel.coleman@boehringer-ingelheim.com'  
**Subject:** NDA 22-421 Acknowledgement letter

**Attachments:** NDA 22-421 Acknowledge Class 1 Resubmission (COR-NDAACK-07).pdf

Hi Dan,

Here is the acknowledgement letter. I don't have any other information for you as I just found out about the decision that was made yesterday.



NDA 22-421  
cknowledge Class 1.

Best Regards,  
Stacy

Stacy M. Metz, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Food and Drug Administration  
Phone: 301-796-2139

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

*Memorandum*

**Date:** August 6, 2009  
**To:** Kenneth Bergmann, MD, Medical Officer, DNP  
Beverly Connor, Senior Regulatory Health Project Manager, DNP  
**From:** Sharon Watson, Regulatory Review Officer, DDMAC  
**Subject:** Mirapex ER (pramipexole dihydrochloride) extended-release tablets  
NDA: 22-421

---

DDMAC has reviewed the 7/31/09 marked up version of the proposed FDA-approved Patient Package Insert (PPI) for Mirapex ER and we offer the following comments. Our comments are provided directly on the marked up version of this document as obtained from the review division's e-room, attached below. Comments on the proposed FDA-approved product labeling (PI) will be provided under separate cover.

Thank you for the opportunity to comment on this proposed PPI.

If you have any questions or concerns regarding these comments, please contact me.

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

-----  
SHARON M WATSON  
08/27/2009

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** April 15, 2008  
**TIME:** 9 AM – 10 AM  
**LOCATION:** White Oak Bldg. 22, Conference Room 1313  
**APPLICATION:** 75961  
**DRUG NAME:** Pramipexole ER Extended Release  
**TYPE OF MEETING:** Pre-NDA – Parkinson's disease  
**MEETING CHAIR:** Russell Katz, MD  
**MEETING RECORDER:** CDR Teresa Wheelous

### **FDA ATTENDEES: (Title and Office/Division)**

Dr. Russell Katz - Division Director  
Dr. Norman Hershkowitz – Group Leader  
Dr. Martin Rusinowitz – Clinical Reviewer  
Dr. John Marler – Visiting Neurologist  
Dr. Martha Heimann – CMC Supervisor  
Dr. Wendy Wilson – CMC Reviewer  
Dr. Lois Freed – Nonclinical Supervisor  
Terry Peters, D.V.M. – Nonclinical Reviewer  
Kristina Armwine – DMETS Reviewer  
Dr. Jagan Parepally – Clinical Pharmacology Reviewer  
CDR Teresa Wheelous -Sr. Regulatory Management Officer

### **BOEHRINGER-INGELHEIM PHARM. INC. ATTENDEES:**

Dan Coleman, Ph.D. Associate Director, US, Drug Regulatory Affairs  
Christopher Corsico, M.D. Vice President, US, Drug Regulatory Affairs  
Bettina Doepner, Ph.D. International Project Team, Drug Regulatory Affairs  
George Destefano, M.S. Associate Director, US, Technical Drug Regulatory Affairs  
Mark Gordon, M.D. Senior Associate Director, US, Medical Affairs  
Sebastian Haertter, Ph.D. International Project Team, Pharmacokineticist  
Kathryn Jason, Ph.D. Director, US, Drug Regulatory Affairs  
Juergen Koester, Ph.D. International Project Team, Statistician  
Jennifer LaFleur Electronic Publications Manager, US, Drug Regulatory Affairs  
Annerose Mauz, Ph.D. International Project Team, Toxicologist  
Stephan Harnisch,, Ph.D. International Project Team, R&D  
Juergen Reess, M.D. Vice President, Therapeutic Area Head, CNS  
Ronald Rosenberg, M.D. International Project Team Leader  
Laurence Salin, M.D. International Project Team, Medicine  
Susanne Stolz International Project Team, Data Manager

### **BACKGROUND:**

The February 1, 2008 meeting request was granted on February 12, 2008, and the meeting package was received on March 14, 2008. The purpose of the meeting is to further clarify the safety and efficacy data required in the NDA for pramipexole extended release tablet for the idiopathic Parkinson's disease indication as discussed at the End of Phase 2 meeting held on August 22, 2007.

**DISCUSSION QUESTIONS:**

**Module 1**

1. Based on the draft table of contents for Module 1 (Attachment 2), does the Division have any comments about the general organization or content of the information in Module 1?

**Preliminary Meeting Comments**

No further comments. This module appears acceptable.

**Meeting Comments: Not Discussed**

2. Draft bottle and container labels will be submitted for only one strength and configuration in the initial NDA. Final labeling for all proposed strengths and configurations supported by the application will be submitted shortly before approval. Is this proposal acceptable to the Division?

**Preliminary Meeting Comments:**

**DMEDP Comments:**

No. Draft labels and labeling should be provided for each strength and packaging configuration in the initial NDA. The label and labeling review for a NDA includes an assessment of the content (e.g., graphics, use of color, etc.), presentation of information and design of the proposed labels and labeling. The primary focus of the assessment is to identify and remedy potential sources of medication errors prior to approval of the application. Submission of labels and labeling shortly before approval, as proposed by the sponsor, would not allow sufficient time for such an assessment, especially if extensive label and labeling revisions are necessary.

**Meeting Comments: Not Discussed**

**Module 2**

3. The Summary sections of the NDA will refer to a number of study reports previously submitted to NDA 20-667 for the immediate release (IR) form of pramipexole. Is it acceptable that these study reports will not be resubmitted to the new NDA?

**Preliminary Meeting Comments**

Yes, this is acceptable.

**Meeting Comments: Not Discussed**

4. Modules 2.4 and 2.6 will summarize and tabulate the pre-clinical data related specifically to the ER formulation submitted in this NDA and will otherwise refer to the complete pre-clinical program which was previously submitted to NDA 20-667. Is this plan acceptable to the Division?

**Preliminary Meeting Comments**

Yes

**Meeting Comments: Not Discussed**

5. Does the Division have any comments on the organization and/or information proposed to be included in 2.7.1, Summary of Biopharmaceutics Studies and Associated Analytical Methods? (See Item 9.2 below and Attachment 3, draft Module 2.7.1.)

**Preliminary Meeting Comments**

Yes the organization and/or information proposed to be included is acceptable.

**Meeting Comments: Not Discussed**

6. Does the Division have any comments on the organization and/or information proposed to be included in 2.7.2, Summary of Clinical Pharmacology Studies? (See Item 9.3 below and Attachment 4, draft Module 2.7.2)

**Preliminary Meeting Comments**

Refer to question 5 response

**Meeting Comments: Not Discussed**

7. The following questions pertain to Module 2.7.3, Summary of Clinical Efficacy (See Items 9.5 and 9.6 below and Attachment 5, draft Module 2.7.3):

- a) Based on the outline provided, does the Division concur that the Summary of Clinical Efficacy incorporates all requirements as per 21 CFR 314.50(d)(5)(v), Integrated Summary of Effectiveness Data?

**Preliminary Meeting Comments**

Yes.

**Meeting Comments: Not Discussed**

- b) Does the Division concur that the proposed primary and secondary efficacy analyses are adequate?

**Preliminary Meeting Comments**

The sponsor should refer to discussions at the end of phase 2 trials. We generally agree with endpoints for the early Parkinson's double-blind placebo-control trial, but all else remains a review issue. It is understood that the Sponsor does not wish to use the advanced Parkinson's double-blind placebo-control trial as a pivotal efficacy trial. If this is used as a pivotal trial (see below), it should be noted that the primary endpoint (i.e. UPDRS) is not one typically used in advanced Parkinson's study (OFF time). While we believe the endpoint may be adequate it will have to remain a review issue.

**Meeting Comments: Not Discussed**

- c) Does the Division concur with the defined subpopulations for analysis of efficacy in special groups and situations?

**Preliminary Meeting Comments**

Yes.

**Meeting Comments: Not Discussed**

- d) Does the Division have any other comments on the proposed content and/or format of this document?

**Preliminary Meeting Comments**

No

**Meeting Comments: Not Discussed**

8. The following questions pertain to Module 2.7.4, Summary of Clinical Safety (See Items 9.5 and 9.7 below and Attachment 6, draft Module 2.7.4):

- a) Based on the outline provided, does the Division concur that the Summary of Clinical Safety incorporates all requirements as per 21 CFR 314.50(d)(5)(vi), Integrated Summary of Safety Information?

**Preliminary Meeting Comments**

It generally appears adequate.

**Meeting Comments: Not Discussed**

- b) Does the Division have any comments concerning the grouping of studies for the proposed combined safety analysis, or to the proposals for assessment of ongoing studies?

**Preliminary Meeting Comments**

It generally appears adequate, however, we could not identify a pooled analysis of all Parkinson's patients in control and open label studies. This should be included.

**Meeting Comments:**

- The sponsor views the open label safety data of around 200 subjects as being too small to be contributory, and planned to submit the data with the 4-month safety data submission.
- The Division requests that exposure data from the approximately 200 patients be provided with the initial submission.

- c) Does the Division concur with the defined subpopulations for analysis of safety in special groups and situations?

**Preliminary Meeting Comments**

Yes.

**Meeting Comments: Not Discussed**

- d) BI proposes to limit the information presented in this summary to safety data from the ER-Parkinson's disease (PD) clinical program, and not to include safety information from other clinical trials with pramipexole ER or IR tablets in other patient populations. If appropriate, "overview" comparisons to safety information described in the approved US labeling for MIRAPEX immediate release tablets will be included. Does the Division concur with this approach?

### **Preliminary Meeting Comments**

We would like to have any and all Pramipexole ER data available in this application for review.

### **Meeting Comments: Not Discussed**

- e) Does the Division have any other comments on the proposed content and/or format of this document or the overall clinical safety data package?

### **Preliminary Meeting Comments**

It is unclear if you intend to include an ISS. Please note that the Summary of Clinical safety in this Module is not a replacement for the ISS which must be included in Module 5. Appendix A contains element that should be included in the ISS.

### **Meeting Comments:**

- **The sponsor inadvertently did not include the ISS, however, the ISS will be included in Module 5.3. as referenced in the guidance.**
- **The Division requested that the ISS be a stand alone document with hyperlinks.**

### **Module 3**

9. BI intends to submit a new Type II Drug Master File for pramipexole drug substance to consolidate all information in a single regulatory file that can be incorporated by reference into this NDA and, where appropriate, other applications. The Type II DMF will be in CTD format but it will be a paper submission. BI plans to include a drug substance "S" section in Module 3 of the NDA that contains only documents specific to (b) (4) drug substance and incorporate all other relevant drug substance CMC information via reference to the Type II DMF. Given that the NDA will be an eCTD submission, does FDA agree that there is no requirement for the drug substance information to be submitted in the eCTD, but may be incorporated by reference to BI's paper Type II DMF? If so, does the FDA agree with the proposed content of the "S" section of Module 3?

### **Agency Preliminary Response**

We acknowledge your proposal to submit a Type II DMF for (b) (4) pramipexole drug substance. We would like to note that as owners of approved NDA 20-667 for (b) (4) pramipexole drug substance, you may cross-reference NDA 20-667 for most of the drug substance CMC information. If you choose to submit a DMF, we will review the complete CMC section in accordance with current standards. However, if you cross-reference NDA 20-667 for (b) (4) pramipexole and include pertinent CMC information relevant to the (b) (4) drug substance in your submission, our review will focus on the new CMC information only. Additionally, if you intend to use the DMF to support the existing approved NDA, a separate supplement should be submitted to the approved NDA. Irrespective of your choice to file a DMF or cross-reference the approved NDA, provide the (b) (4) drug substance specification, (b) (4) drug substance facilities information, (b) (4) drug substance analytical procedures. Include all CMC information regarding the (b) (4) drug substance as well, including the

manufacturing process, characterization, drug substance specification, batch analysis results, and stability data.

**Meeting Comments:**

**The sponsor requested guidance on how to manage updates to the DMF post-approval. We indicated that the sponsor may cross-reference the DMF as part of their life cycle management.**

10. Based on the summary of information to be included for Module 3, does the Division have any comments about the general organization and proposed structure of the information in Module 3 (See Item 11 below and Attachment 2, Module 3 in draft TOC)?

**Agency Preliminary Response**

The proposed Module 3 organization is acceptable. However, the TOCs listed in Attachment 2 and Attachment 8 differs slightly. Be sure to include both the relevant appendices and regional information in Module 3.

**Meeting Comments: Not Discussed**

11. Does the Division agree with the proposed strategy for formatting the methods validation section? (See Item 11 below)

**Agency Preliminary Response**

We agree.

**Meeting Comments: Not Discussed**

12. Does the Division agree with the number and the selection of the executed batch records for submission?

**Agency Preliminary Response**

We agree.

**Meeting Comments: Not Discussed**

**Module 4**

13. Based on the draft table of contents for Module 4 and information provided in Item 10 below, does the Division have any comments about the general organization and proposed content of the information in Module 4? (See Item 10 below and Attachment 2, Module 4 in draft TOC).

**Agency Preliminary Response:**

- We remind you of the post-approval commitments stated in the Agency's approval letter of 7/30/07 for your supplemental NDA dated April 10, 2006. If Products Z and V are present in the extended release formulation, you will need to submit the genotoxicity studies for these impurities. If these studies have previously been submitted, please provide the IND/NDA number and date(s) of submission.

- Please provide hyperlinks within study reports and summary documents to referenced published literature submitted in the NDA

**Meeting Comments:**

**The sponsor stated that Products Z and V are not expected to be present in the ER formulation. Drug batches are currently being tested and preliminary data should be available soon. However, if Products Z and V are present, the plan is to submit draft study reports of the genotoxicity studies with the supplement (proposed for October 2008); final study reports are to be submitted at the end of 2008. The Division noted that if the studies are needed only final study reports are acceptable and that this will be a potential filing issue.**

**Module 5**

**Study 248.524 in Early PD**

14. As proposed by the Division during the End of Phase II meeting, it is planned that the formal statistical primary efficacy analysis will be based on 250 patients from trial 248.524 who have completed 18 weeks of treatment (or have discontinued treatment prior to week 18). The full alpha (0.05) will be used for this analysis, testing for superiority of pramipexole ER versus placebo. In addition, the efficacy analyses in the initial NDA will include an analysis of 100 patients from study 248.524 who have completed 33 weeks of treatment (or have discontinued treatment prior to week 33). This descriptive efficacy analysis will compare efficacy at three and six months in these 100 completer patients, and demonstrate that efficacy is maintained for 6-months of treatment. Note that separate data cut-offs are planned for the confirmatory analysis of 250 patients treated for 18 weeks and for the descriptive analysis of 100 patients treated for 33 weeks .
- a) Does the Division agree that these clinical datasets are adequate to demonstrate proof of efficacy of pramipexole ER in early PD patients?

**Preliminary Meeting Comments**

This appears consistent with the end of phase 2 meeting agreements and is therefore appears adequate. All else is a review issue.

**Meeting Comments: Not Discussed**

- b) Does the Division have any comments to the proposed statistical approach?

**Preliminary Meeting Comments**

No new comments.

**Meeting Comments: Not Discussed**

**Study 248.525 in Advanced PD**

15. BI plans to stop and unblind the advanced PD trial 248.525 if efficacy is demonstrated in 250 patients treated for 18 weeks in the early PD trial 248.524 (see question 14). All patients in 248.525 will be offered the opportunity to enter an OL-extension trial, where all of them will be treated with pramipexole ER for more than 1 year to collect long-term safety data. It is expected



We recommend that BI uses the reviewer's template, which can be provided by the division, as a navigational tool in this submission. This document is used by the division for review purposes. Thus, BI might hypertext link sections in this document to the pertinent areas in the application. It is our understanding that BI has done this before.

**Meeting Comments:**

- **The Division reviewers request a stand alone ISS in the appropriate section of the electronic submission to be helpful.**
- **The sponsor inquired about submitting the stand alone ISS separately later in the review cycle, and was informed that submitting the separate ISS may not be helpful depending upon how late in the review cycle it is submitted.**
- **Hypertext links should be very granular.**

17. Does the Division have any comment about the proposed safety dataset to be included in the 4-month safety update (See Item 9.7 below)?

**Preliminary Meeting Comments**

We would like to see all Pramipexole ER data, not just that related to Parkinson's disease.

**Meeting Comments:**

See comments above

18. Given the extensive clinical experience with pramipexole IR tablets in patients with idiopathic Parkinson's disease, does the Division concur that the proposed clinical registration package is adequate to:

- a. support efficacy of pramipexole ER tablets for the treatment of the signs and symptoms of idiopathic Parkinson's disease?

**Preliminary Meeting Comments**

This remains a review issue.

**Meeting Comments: Not Discussed**

- b. support safety of pramipexole ER tablets for the treatment of the signs and symptoms of idiopathic Parkinson's disease?

**Preliminary Meeting Comments**

This remains a review issue.

**Meeting Comments: Not Discussed**

19. [REDACTED] (b) (4)

[REDACTED]

**Preliminary Meeting Comments**

We ask you to submit all CRFs which are associated with deaths, serious adverse events and discontinuations for reasons of AEs to be submitted in a pdf or other readable graphic/ alpha-numeric format.

**Meeting Comments:**

**Audit trails and discrepancy details will not be included.**

20. For all Phase III studies included in the NDA (248.524, 248.525, 248.636), BI proposes to submit narratives for all serious adverse events (including deaths), for drop-outs due to non-serious adverse events and for cases related to treatment emergent impulse control disorders (ICD). Is this acceptable to the Division?

**Preliminary Meeting Comments**

Narratives must be complete. Time line must be easily gleaned. Pertinent labs should be included as well as pertinent negative signs, symptoms and labs: e.g. reports of elevated liver functions should include not only the values of the transaminases but that for bilirubin and alkaline phosphatase, even if these labs are normal- if the labs were not available, that should be noted. The narrations should be hypertext linked to the CRFs. All narrations should be contained at one location in a single pdf file.

**Meeting Comments: Not Discussed**

**Pharmacokinetics**

21. Please see Section 9.2-9.4 of the Clinical Data Summary for an overview of the pharmacokinetic data and the planned analyses to be provided to support registration of an extended release formulation of pramipexole.
- a. Does the Division have any comments to the proposed pharmacokinetic data package and planned analysis?

**Preliminary Meeting Comments**

**Meeting Comments: Not Discussed**

- b. Given the known pharmacokinetic profile of pramipexole IR tablets and the results of Study 248.530 which demonstrates bioequivalence between pramipexole IR tablets given three times a day and pramipexole ER tablets given once daily, does the FDA agree that a population PK analysis as described in section 9.3 below based on the subset of approximately 100 patients treated with the ER formulation that were used for the 18 week efficacy analysis of study 248.524 in the initial NDA submission is adequate?

**Preliminary Meeting Comments**

*Acceptable pending review of the data submitted.*

**Meeting Comments: Not Discussed**

- c. Does the Division agree with the proposed endpoints for the descriptive PK/PD analyses?

**Preliminary Meeting Comments**

*Efficacy endpoints CGI-I, PGI-I, or UPDRS II (change from baseline) related to AUCs are acceptable.*

**Meeting Comments: Not Discussed**

- d. Does the Division agree that the completed Phase I PK studies with the ER tablet and the Population PK analysis from the early PD trial 248.524 will be adequate to develop appropriate labeling for pramipexole ER, notably to propose dose recommendations in patients with renal impairment?

**Preliminary Meeting Comments**

**Meeting Comments: Not Discussed**

*Appears to be adequate as agreed at the end of Phase 2 meeting and pending review of the data from 100 subjects treated with ER in combination with those subjects taking IR along with the data from Phase I PK studies to quantitate renal function.*

- e. To develop the structure of the PK model, data previously submitted to NDA 20-667 for pramipexole immediate release tablets may be used. It is not planned to resubmit reports only used for basic model development. Is this acceptable to the Division?

**Preliminary Meeting Comments**

*Yes. Please refer to the study reports and data from NDA 20-667 used for basic model development. Also provide the renal impairment study report.*

Please submit the following datasets to support the population analysis:

All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.:myfile\_ctl.txt, myfile\_out.txt). A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

We request that you provide the summary section as a review aid for CPB reviewer. Outline of the summary section of the HPBIO section is provided. At the time of NDA submission the sponsor can use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to the agency as a review aid. This summary

section should be submitted electronically with appropriate hyperlinks to the relevant supporting data (Appendix B attached).

**Meeting Comments: Not Discussed**

### **Electronic Submission Proposal**

The following questions pertain to the overview of the electronic submission plans for the pramipexole ER NDA for Parkinson's disease included as Attachment 8.

22. Does the FDA have any comments related to the electronic submission proposal or the proposed structure and/or format of the tabulation and analysis datasets?

#### **Preliminary Meeting Comments:**

**No comment**

**Meeting Comments: Not Discussed**

23. For the thorough QT study 248.545, drug concentration data used for pharmacodynamic analyses will be provided in the initial NDA submission. No further pharmacokinetic (PK) datasets are planned to be provided in the initial NDA submission. Does the FDA concur with this proposal?

#### **Preliminary Meeting Comments (from QT team)**

This seems OK if we plan to review the QT study during the NDA review. If it is to be submitted prior to the NDA, then we will need the dataset when the TQT study is submitted. **Meeting Comments: Not Discussed**

24. What is the maximum file size for SDTM and for analysis datasets in proprietary database format?

#### **Preliminary Meeting Comments**

**Analysis Datasets:**

If any datasets will be greater than 400 MB, the sponsor should contact with the review division and discuss whether they would like to split the datasets in a special way.

**SDTM datasets:**

Do not split any datasets. However please consult with the review division if the datasets will be greater than 400 MB.

Please follow the Study Data Specification for creating SAS V5 transport file format and the folder structure to store the datasets.

**Meeting Comments: Not Discussed**

## Appendix A:

### General elements that should be included in the ISS.

- *The ISS should clearly state what safety assessments were carried out in each study included in the ISS. A tabular presentation of schedule of events might be helpful.*
- *All deaths that occurred in the clinical development program or found during a literature search and from various commercial and non-commercial databases (ex AERS) should be described in a single section and individual deaths should be listed in a table.*
- *All non-fatal serious adverse events, regardless of assigned causality, that occurred during the clinical development program or were reported from secondary sources (i.e. literature and/or post marketing reports) should be described in a single section. Serious adverse events may, in addition to signs, symptoms, and diagnosable events, include changes in laboratory parameters, vital signs, ECG, or other parameters of sufficient magnitude to meet the regulatory definition of a serious adverse event [21 CFR 312.32(a); 314.80(a)].*
- *Dropouts due to adverse events should be clearly described in a single section of the ISS. CRF/narratives should be provided for all dropouts. An overall profile of these patients by reason for dropping out (e.g. adverse events, treatment failures, lost to follow up) should be provided. For the more common adverse events associated with dropouts, the ISS should present the incidence of these adverse events, preferably in a table. Investigator causality assessment can be described but should be justified. The ISS should also describe any dose-response, time dependency of the dropout, drug-demographic, drug-disease, and drug-drug interactions. With respect to rarer events that could represent an important adverse event, the ISS should critically assess whether any of these may represent treatment-induced injury. Finally the ISS should consider these events individually with narratives and reference to other data as appropriate.*
- *The ISS should contain a section entitled "Other Significant Adverse Events." This section should describe significant safety findings such as marked hematological or other lab abnormalities not meeting the definition of serious, any events that led to an adverse dropout or any other intervention such as dose reduction or significant additional concomitant therapy (an expansion of the adverse dropout concept) and potentially important abnormalities not meeting the above definition of serious and not leading to death or modification of therapy (e.g., a single seizure, syncopal episode, orthostatic symptoms). Those adverse events that did not lead to discontinuation but otherwise meet the definition described above should be described in this section.*
- *If preclinical pharmacology/toxicology, post-marketing and/or literature reports provide insight into possible safety signals with the investigational drug product the ISS should describe any findings relative to these signals. This is especially important for new chemical entities. Similarly, if there are particular safety concerns evident from other drug products that are members of the same pharmacological class as the investigational drug product, the ISS should describe a thorough safety analysis of these concerns.*
- *The ISS should contain a section entitled "Common Adverse Events". You should include a table (or tables) that presents the best overall display of commonly occurring adverse events, generally those occurring at a rate of 1% or more (but lower rates can be presented for very large data bases). This table or tables will be the basis for the ADR table in labeling, which may, however, use a higher cut off if this does not lose important information, and will eliminate ADRs that are equally common on drug and placebo. This table or tables should compare the incidence of common adverse events between cohorts regardless of the investigator's assignment of causality from the pooled studies. You should justify any decision for not including a particular study in the pooled adverse event incidence tables. For development programs with a significant amount of severe adverse events it would be helpful to include a table that compares the incidence of severe adverse events between cohorts from the pooled studies.*
- *For adverse events that seem clearly drug related (i.e., consistent difference from control across studies, evidence of dose response etc.) you should provide the following additional analysis as appropriate:*
  1. *exploration for dose dependency, exploration of time to onset (for those that show a delay in onset)*
  2. *exploration of adaptation (for common, troublesome events such as somnolence, nausea)*
  3. *explorations of demographic interactions, explorations of drug-disease and drug-drug interactions (if there is a strong signal for an interaction, or a good rationale for expecting an interaction)*
  4. *selective exploration of individual cases in an attempt to better characterize the events.*
- *For each trial described in the ISS you should include a brief discussion on how adverse events were captured (i.e. checklist, open-ended questions on follow up visits etc.). The frequency of assessments should also be described.*

- *For each trial described in the ISS you should clearly state which translation dictionary (MedDRA, COSTART) was used to categorize verbatim adverse event terms.*
- *The ISS should include a discussion of the less common adverse events of significant concern seen across all studies in the clinical development program. Since the overall database is typically very heterogeneous, it is unlikely to lend itself to meaningful estimations of rates or assessments of causality. Thus it may be sufficient to group these events by incidence and by body system. For example, it may be useful to categorize less common adverse events in order of decreasing frequency within certain ranges: e.g.  $\leq 1\%$ , between 0.1% and 1%;  $\leq 0.1\%$ .*
- *The ISS should clearly provide an overview of what laboratory testing (chemistry, hematology, and urinalysis) was carried out in each study. It is best to summarize the overall approach, rather than provide detailed comments about laboratory testing for each study. The ISS should also describe any discrepancies between planned analyses and those actually conducted, as well as the procedures used to evaluate abnormal values. Provide a summary table identifying the numbers of patients exposed to test drug who had baseline laboratory values and follow-up assessments.*
- *The ISS should include an integrated discussion of significant laboratory findings from the clinical development program. Controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. However placebo-controlled trials are generally short term, and unsuitable for assessing late-developing abnormalities, so that longer term data need to be therefore examined also. If there is no concomitant control in the long term studies the comparison may need to be with similar populations outside the NDA. The ISS should explain which studies were pooled relative to the evaluation of laboratory findings and why they were selected.*
- *The ISS should generally include three standard approaches to the analysis of laboratory data. The first two analyses are based on comparative trial data. The third analysis should focus on all patients in the phase 2-3 experience. Analyses are intended to be descriptive and should not be thought of as hypothesis testing. P-values or confidence intervals can provide some evidence of the strength of the finding, but unless the trials are designed for hypothesis testing (rarely the case), these should be thought of as descriptive. The analysis of all laboratory findings should include a comparative description of mean or median changes from baseline across treatment groups. The ISS should include a discussion on individual patients whose laboratory values deviate substantially from the reference range and describe what criteria were used to identify outliers. Additional analyses may be appropriate for certain laboratory findings, including analyses for dose dependency, time dependency, and also drug-demographic, drug-disease, and drug-drug interactions. The ISS should discuss the rationale for additional explorations, the methods used, and the results and interpretations.*
- *The ISS should include an evaluation of vital sign assessment using a similar approach as described for laboratory data (i.e., description of vital sign assessment in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc).*
- *The ISS should include an evaluation of ECG findings using a similar approach as described for laboratory data (i.e., description of ECG assessments in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc). Particular attention should be given to ECG findings where the timing of the assessment was done at or near the time of maximum concentration for the drug product (generally during phase I or phase II studies) in order to assess QT prolongation effects. A brief discussion on any preclinical cardiac findings would be helpful in orienting the reviewer to any potential concerns.*
- *The ISS should include a discussion of the impact of immunogenicity (if applicable) on safety, efficacy and/or clinical pharmacology and pharmacokinetics.*
- *The ISS should include a brief discussion of human carcinogenicity data if available. A systematic discussion of all human tumors reported during drug development can provide useful safety information, particularly in the case of drugs or biologics that have positive genotoxicity or animal carcinogenicity findings, or those that are known immune modulators.*
- *The ISS should include a summary of any studies designed to evaluate a specific safety concern(s). These studies may include:*
  1. *studies to assess whether a drug has safety concerns common to its pharmacological class*
  2. *studies in topical products to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity*
  3. *studies to characterize the effect on the QT interval (part of most modern development efforts)*
  4. *studies intended to demonstrate a safety advantage over therapeutic alternatives*
- *The ISS should contain a discussion of abuse potential and any apparent withdrawal symptoms seen during the clinical development program. This discussion should contain a summary of findings from any non-clinical and*

- clinical abuse liability studies (if done), problems in medication accounting encountered while monitoring the investigational supply of medication, chemistry and pharmacology issues that relate to abuse potential, and relevant adverse events and epidemiologic data. The ISS should describe any adverse events that emerge after discontinuation of the drug in order to determine whether they may indicate a withdrawal phenomenon. If studies evaluated the potential for withdrawal phenomena, the ISS should indicate whether there was a prospective or post-hoc assessment of withdrawal emergent signs and symptoms (during drug taper or following discontinuation) and discuss the implications of the approach used on the reliability of the findings.*
- *The ISS should include a discussion of all pregnancies that occur during the clinical development program. A brief description of each pregnancy should include outcome, duration on therapy, use of drug relative to trimester.*
  - *The ISS should summarize all overdose experience with the investigational drug/biologic in humans. The summary should include a description of the constellation of signs and symptoms that might be associated with overdose. A description of phase I or phase II safety findings in subjects exposed to doses higher than planned for marketing should be included. Patients with certain physiological differences that would compromise their ability to clear the drug (e.g. renal impairment, limited CYP450 2D6 activity for a drug cleared by this isozyme) may provide relevant data to the clinical implications of overdose.*
  - *The ISS should include relevant findings from U.S. and foreign post-marketing experience if available.*
  - *The ISS should include a clear description of all patient exposures from the entire clinical development program. The exposure summary should describe various demographic subsets such as race, gender and age. Additionally the summary should include a clear description of dose and duration of exposure. Tables and graphs may be helpful in describing the data sources for the ISS. If applicable the ISS should describe any secondary sources of safety data (ex. studies not conducted under the IND and not meeting the standards for inclusion as primary, post marketing data, and/or literature reports). Secondary sources should be briefly described. Original articles and study reports should be provided.*
  - *The ISS should briefly describe the findings from any preclinical studies that were conducted in order to explore certain potential adverse events, using preclinical models based either on a drug's pharmacology or on clinical findings that emerged early in clinical development. For example, for a drug anticipated to cause QT prolongation because of its drug class or because QT prolongation was seen in phase I studies, were there any preclinical (in-vitro) studies done to evaluate this potential.*
  - *The ISS should include a discussion of any in vitro and in vivo studies done to evaluate how a drug is metabolized and excreted. Issues to be included should include the following:*
    1. *The enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins.*
    2. *The effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds.*
    3. *The major potential safety consequences of drug-drug interactions.*
  - *The ISS should describe the general methodology used to construct the integrated safety review. This discussion should include a rationale for pooling safety data (if done) and the method employed. For example a justification for pooling safety data may include an argument that a larger data base will permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population or pooling data from different studies can improve the precision of an incidence estimate (i.e., narrow the confidence intervals by enlarging the sample size). In pooling safety data, usually the numerator events and denominators for the selected studies are simply combined. If other more formal weighting methods are used (e.g., weighting studies on the basis of study size or inversely to their variance) the ISS should justify why and how it was done. Information on baseline risk factors of concern should be retrievable from the case report tabulations.*
  - *Since adverse reaction rates may differ considerably from one patient population to another and may change over time the ISS should explore factors that may affect the safety profile of a drug. For example the ISS could explore common drug related predictive factors, such as dose, plasma level, duration of treatment and concomitant medications, and patient related predictive factors such as age, sex, race, concomitant illnesses. In general, these explorations are meaningful only for adverse reactions that appear to be drug-related. The ISS may present these explorations using the following subheadings: exploration of dose-dependency for adverse findings, explorations for time dependency for adverse findings, exploration for drug-demographic interactions, exploration for drug-disease interactions and exploration for drug drug interactions. It may be helpful to link individual safety observations with other on-therapy data such as dose, duration of treatment, concomitant therapy, other adverse effects, lab data or effectiveness results.*

## **APPENDIX B**

### **CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW AID**

**This is only an example of the requested review aid. This can also replace the summary section of Clinical Pharmacology and Biopharmaceutics:**

- **Please fill the headings as it applies to your drug**
- **Additional specific headings can be included to suit the development of your drug/ dosage form (for e.g. For extended release products, headings like comparability of the ER to IR product, for transdermal products section on effect of application site on the PK and adhesiveness of the product etc should be included)**
- **All statements in this summary section should be annotated with links similar to your “annotated label” that would allow the reader to locate all relevant data supporting the statement. Additional links should be provided, whenever possible, for the study report and any raw data located in a SAS transport file or other format that supports the QBR statement.**
- **Within the summary section text, relevant Tables and Figures to understand the data should be included and should not be referred to some Appendix.**
- **Results from various studies, pop pk analyses should be pooled to provide information under each heading, so that consistencies across studies can be determined. If results from two similar studies are different, plausible explanations of these differences should be included.**
- **If different formulations were used during the development, the section should mention what formulation was used (to-be marketed vs. clinical service formulation)**

#### **1.0 GENERAL ATTRIBUTES OF THE DRUG**

This section contains background information about the drug and drug product to provide a context for assessing the results of the clinical pharmacology and biopharmaceutics studies.

**1.1 Drug/Drug Product Information:**

Dosage Form/Strengths:

Pharmacologic Class:

**Chemical Name:**

**Physical Characteristics:**

Formulation: Quantitative formula for all the dose strengths

Ingredients	Wt (mg/capsule)							
	<i>Formulation #/Capsule Strength</i>							
Total Size								

1.2 Proposed mechanism(s) of action and indication(s)

1.3 Proposed dosage(s) and route(s) of administration?

**2.0 GENERAL CLINICAL PHARMACOLOGY**

2.1 Design features of the clinical pharmacology and clinical studies used to support dosing or claims:

Here describe the type of pivotal clinical studies in brief for each indication.

For treatment of A: For e.g.

The efficacy of Drug X in patients was established in X Phase 3 randomized, double-blind, parallel, placebo-controlled multi-center trials of Y weeks duration conducted as Z treatment of patients. Of these Z studies only Y studies used the proposed dosing regimen. The X mg/day dose was not replicated in any study. Should use key studies and supportive studies that are used for labeling the product.

Short tabular descriptions may be useful here, for example:

Protocol	N	Duration	Population	X Dose
----------	---	----------	------------	--------

101

PER DAY AND OR BID OR TID

102

e.g. X MG/DAY

103

---

Should repeat this information for each indication if multiple indications are proposed.

**2.2. Clinical endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies**

For treatment of A: For e.g.

The primary criterion to establish the efficacy of Drug X was the .....

The primary efficacy parameter was:

The secondary efficacy parameters were:

**2.3 Exposure-response relationships**

**2.3.1 Characteristics of exposure/effectiveness relationship**

For Efficacy in patients with Y:

An exposure (dose)-response analysis was conducted in Y patients pooled from X studies (Study numbers). Provide exposure or dose/response analyses data. This section should include information on all proposed doses and should also include relevant Tables and Figures of dose-response or exposure-response either from the PK-PD study conducted or from pivotal clinical trials that were used to label the drug product.

This section should also include information on any differences of exposure/dose –response for covariates such as dose, regimen, gender, age, race etc.

**2.3.2 Characteristics of the exposure-response relationships for safety (dose- response, concentration-response)**

If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

This section should include relevant safety information on all proposed doses and should also include relevant Tables and Figures.

This section should also include information on any differences of exposure/dose –response relationship for safety in covariates such as dose, regimen, gender, age, race etc.

e.g. Dizziness and somnolence were the most prevalent adverse events associated with treatment.

The probability for a subject to experience dizziness (AE1) increased with the dose. At the X mg/day, the incidence of AE1 averaged to be approximately 30% (range: from >20% to <50%). Female patients apparently reported

higher incidence of dizziness. It is clear that the variability was high among various trials as shown in the following figure (). The ED<sub>50</sub> for incidence of dizziness was estimated to be  $X \pm Z$  mg/day. ED<sub>50</sub> for severity of somnolence was estimated to be  $Y \pm Z$  mg/day.

The incidence and severity of AEI can also be depicted by the following figures that differentiate the incidence of adverse events for the BID and TID regimens.

### 2.3.3 Effect on QT or QTc interval

Should include relevant Tables and figure showing Concentration-QTc relationship.

### 2.3.4 Justification of dose and dosing regimen based on known relationship between dose-concentration-response (In some cases, it may be possible to combine this with 2.3.2 and 2.3.3.)

The following are the sponsor proposed dosage regimen for .....patients:

Patient Population	Age Group	Starting Dose	Maximum Dose	Increments
A				
B				

#### Age Group:

This section should include what information is available for justifying the dose in a particular age group.

#### Regimen:

#### **From a pharmacokinetic perspective:**

Based on a half-life of x hours, .....appears to be suitable for the Y regimen. However, the sponsor has conducted pharmacokinetic studies to show that X mg q8h vs. Y mg q12h showed similar pharmacokinetic profiles.

Include figure where possible

Figure: Pharmacokinetics over one dosing interval

Differences in steady state plasma concentration versus time profiles for q8h and q12h dosing regimens can also be evaluated by comparing the differences in C<sub>maxss</sub> and C<sub>minss</sub> for these two dosing regimens. As the dosing interval is increased from q8h to q12h, the fluctuation between C<sub>maxss</sub> and C<sub>minss</sub> would be expected to increase, while C<sub>ave</sub> would be expected to remain constant. The following figure illustrates that the differences between regimens are small when individual and mean steady-state C<sub>maxss</sub>, C<sub>minss</sub>, and C<sub>ave</sub> values are compared following a dose of Y mg/day administered q8h and q12h in healthy subjects.

Include figures and Tables as necessary

#### **From a pharmacodynamic perspective:**

Include figures and Tables justifying the dose and regimen from an efficacy standpoint. Should include information on other regimens studied, but not selected for dosing recommendations and reasons why. This information can be obtained from efficacy studies, PK-PD analysis if conducted or simulation performed.

Conclusions from such analyses must be included. For e.g. These figures show that doses Y mg and above may perform better than the lowest recommended dose in patients based on the EC50 values. However, titrating with a lower dose is desirable for tolerability reasons.

These also show that both X/day and Y/day doses may be acceptable, however, for practical administration reasons X/day may be the preferred choice.

Summary efficacy Tables such as the following should be included.

Study - Summary of RRatio analysis (ITT)				
Treatment group	N	Treatment differences**		P value***
		Mean (SE)	95% CI	

\* Statistically significant based on Hochberg's procedure (p 0.049).

\*\* Based on treatment means for the raw RRatio

\*\*\* Hochberg procedure applied to the ranked RRatio

Summary of secondary endpoints (ITT)							
Study	Placebo	X dose and regimen					
		BID	BID	TID	BID	BID	TID

\*statistical significance for difference between X dose and placebo (and/or 95% CI exclude zero for Median change figures)

\*\*subject numbers for ITT population are constant across secondary parameters in this table

**From a safety perspective:**

The two main adverse events of dizziness and somnolence were evaluated in terms of various doses given X/day and Y/day conditioned on severity of the adverse event. The following plots show that Y/day regimen had higher percent of observation for both dizziness and somnolence. This could be due to sustained concentration of Drug X with Y dosing.

**Titration Scheme:**

If a titration scheme is recommended information relevant to its selection should be included.

**2.4 PK characteristics of the drug and its major metabolite?**

**2.4.1 Single dose and multiple dose PK pharmacokinetics?**

Here provide tables and figures on mean pharmacokinetic parameters and refer to them in the subsequent sections.

Also include in this section whether the pharmacokinetics of the drug change with chronic dose. And information on whether the multiple dose PK is predicted from single dose PK, accumulation ratio, time to reach steady state etc

**2.4.2 General ADME characteristics of the drug**

Absorption: may include information on transporter as well

Distribution: include information on protein binding etc

Metabolism:

Elimination:

**2.4.3 Fate of drug as seen in mass balance studies**

Include tables and figures from the mass balance study, also state whether these studies suggest renal or hepatic as the major route of elimination.

**2.4.4 Comparison on PK between healthy subjects and patients**

This section should also include information obtained from population analysis if conducted along with any definitive PK study conducted. Table and figures showing the differences in the two populations should be included.

**2.4.5 Degree of linearity or nonlinearity in the dose-concentration relationship**

The non-linearity can be due to multiple dosing or due to increase of doses. Both should be described in this section.

This section must include Tables showing dose proportionality with statistical evaluation of the data using power model analysis.

This section should also include figures of dose normalized PK parameters versus dose for all relevant PK parameters.

An example Table given below:

**Multiple dosing Day 1 vs Day 10 --X-Y mg/day.**

Table	Study - Summary Results of the Assessment of Dose Proportionality Using the Power Model Analysis			
PK Parameter	Day	AUC	$\beta$ Estimate (95% CI)*	R- Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)**

\* ANOVA (SAS GLM Procedure)

The results of the analysis demonstrate dose proportionality in AUC.

#### 2.4.5 Inter-subject variability in PK parameter

Include Tables to show variability, information from different studies should be included This section should also mention the possible causes of this variability.

### 3.0 INTRINSIC FACTORS

In the introductory paragraph of this section highlight the key intrinsic factors that influence exposure and/response and what is the impact of such differences in efficacy and safety.

The following intrinsic factors should be discussed:

#### 3.1 Effect of Renal Impairment:

This section should include information on the type of data available, can be presented in Tables such as....

Group Creatinine Clearance*	Renal function	N
1 > 80 mL/min	Normal	8
2 50-80 mL/min	Mildly	8
3 30-49 mL/min	Moderately impaired	8

\* according to Cockcroft and Gault

Include relevant figures and Tables showing the renal clearance with change of creatinine clearance. Include 90% CI in the Tables.

Dosage Adjustment: State if needed or not, If yes then what

Dosing recommendations should be provided in tabulate format

**Sponsor's Proposal for Dosage Adjustment Based on Renal Function**

Creatinine Clearance (CLcr) (mL/min)	Total X Daily Dose <sup>a</sup>		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	

BID = Two divided doses; QD = Single daily dose.

<sup>a</sup> Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

<sup>b</sup> Supplementary dose is a single additional dose.

**3.2 Effect of Hepatic Impairment:**

information same as above should be included

**3.3 Effect of age:**

Elderly:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

Pediatrics:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

**3.4 Effect of Gender:**

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

**3.5 Effect of Race:**

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

### 3.6. Effect of pregnancy or lactation:

Similar information as above, if no information available state so.

## 4.0 EXTRINSIC FACTORS

In the introductory paragraph of this section highlight the key extrinsic factors (such as herbal, diet, smoking, alcohol) that influence exposure and/response and what is the impact of such differences in efficacy and safety.

Also indicate in brief whether there are any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered.

### 4.1 In vitro basis of drug interactions

Include information on the following, this section should not be descriptive only but should include relevant Tables to show the results and indicate which of these can lead to possible in vivo drug interactions under each of these sub headings:

- Drug as substrate of CYP 450
- Drug as inhibitor of CYP 450
- Drug as inducer of CYP 450
- Drug interaction based on protein binding
- Drug as substrate of p-glycoprotein
- Drug as inhibitor of p-glycoprotein
- Any other transporter involved

This section can also include information from mass balance studies that suggest possible interaction, for e.g. if totally renally eliminated then there is a possibility of an interaction with drugs that are also renally eliminated.

Also indicate whether the in vitro studies are conducted at relevant therapeutic concentrations (in the same units as for the plasma data (e.g. ng/ml as opposed to  $\mu\text{M}$  or  $\mu\text{mole/liter}$ )).

### 4.2 In vivo drug interactions

Give a tabular listing of all drugs and indicate whether a dosage adjustment is necessary. This section can be subdivided into pharmacokinetic and pharmacodynamic interactions.

#### Pharmacokinetic Interactions:

For e.g. Influence of Drug X on the pharmacokinetics of concomitant drugs and the influence of these drugs on the pharmacokinetics of Drug X is summarized in the following Table:

Concomitant Medication	doses evaluated	Drug X on Co-Med PK	Co-Med on Drug X PK	Evaluation Method	Dosage Adjustment
------------------------	-----------------	---------------------	---------------------	-------------------	-------------------


**Pharmacodynamic interactions:**

List any pharmacodynamic interactions observed, if any.

## 5.0 GENERAL BIOPHARMACEUTICS

### 5.1 BCS Classification of the drug

This section should include information on solubility, permeability and dissolution of the drug product, which are the basis of classifying the drug and formulation. All relevant Tables and figures should be included.

### 5.2 Relative Bioavailability of the to-be marketed formulation to those used in the clinical studies

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

If the formulations are not bioequivalent this section should also indicate what safety and efficacy issues may arise, if any. In case of failed BE studies, this section should provide other supporting data regarding the to-be-marketed formulation that would aid in the decision making for the approval of the product.

### 5.3 Absolute Bioavailability and Relative Bioavailability to other dosage forms/route of administrations

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

### 5.4 Food effect

Provide Tables as well showing the ratios and 90% CI. Also indicate if type of meal (light, medium, high) has an effect, if necessary.

Also provide the dosing recommendations based on the results of the Food Effect study. Indication if clinical trials were done with or without regard to food. If different across studies tabular listing of clinical studies and their dosing administration in relation to meals. Include any population analysis data if available.

If a fed BE study was conducted, provide justification for doing so, that will help reviewers in decision making.

**5.5 Dissolution and IVIVC if appropriate**

This section should include dissolution method and specifications and justification for selecting the method (for example stirring speed, media etc).

**5.6 Alcohol Effect (for ER products):**

This is to rule out dose dumping. Should provide the data in tabular format based on in vitro dissolution in different concentrations of alcohol. If in vivo data are available, include in this section as well.

**6.0 ANALYTICAL**

This section should highlight the method used in analytical assays and provide its validation parameters. This can be done in a tabular format.

Parameter	parent	-metabolite
Method	LC/MS/MS	LC/MS/MS
LLOQ		
Linear range		
QC samples		
Inter-day accuracy and precision		
Intra-day accuracy and precision		
Freeze-thaw stability		
Benchtop Stability at RT		
Long term at – 70° C		
Recovery Low Med High		

If several different analytical methods were used, the difference in method and the LLOQs should be given, for example in a Table

Analyte	Method	Assay Sensitivity ng/ml
340	LC/MS	X
344	LC/MS	Y

Assay cross validation results should also be provided.

In this section in Tabular format also provide the assay performance from each study (QC data).

Linked Applications

Sponsor Name

Drug Name

IND 75961

BOEHRINGER  
INGELHEIM

PRAMIPEXOLE EXTENDED RELEASE  
TABLE

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

/s/

RUSSELL G KATZ  
05/15/2008

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** August 22, 2007  
**TIME:** 3 PM – 4:30 PM  
**LOCATION:** White Oak Bldg. 22, Conference Room 1313  
**APPLICATION:** 75961  
**DRUG NAME:** Pramipexole ER Extended Release  
**TYPE OF MEETING:** End of Phase 2 – Parkinson's disease  
**MEETING CHAIR:** Russell Katz, MD  
**MEETING RECORDER:** CDR Teresa Wheelous

**FDA ATTENDEES: (Title and Office/Division)**

Dr. Russell Katz Division Director  
Dr. John Feeney Group Leader  
Dr. Devanand Jilapalli Medical Reviewer  
Dr. Kun Jin Biometrics Team Leader  
Dr. Sally Yasuda Clinical Pharmacology Reviewer  
Mr. Marshall Loeb Patient Advocate  
CAPT David Banks Office of Special Affairs  
Dr. Yaning Wang Pharmacometrics Team Leader  
Troy Driesel Pharmacy Student  
CDR Teresa Wheelous Sr. Regulatory Management Officer

**BOEHRINGER-INGELHEIM PHARM. INC. ATTENDEES:**

Dan Coleman, Ph.D. Associate Director, Drug Regulatory Affairs (BI-US)  
Sebastian Haertter, Ph.D. Project Pharmacokineticist (BI-Germany)  
Kathryn Jason, Ph.D. Director, Drug Regulatory Affairs (BI-US)  
Juergen Koester, Ph.D. Project Statistician (BI-Germany)  
Ronald Rosenberg, Ph.D. International Project Leader (BI-Corporate)  
Laurence Salin, M.D. Team Member Medicine, Pramipexole ER (BI-France)

**BACKGROUND:**

The May 7, 2007 meeting request, was received May 8, 2007, and granted May 16, 2007. The meeting package was received July 23, 2007. The purpose of the meeting is to further clarify the safety and efficacy data needed to support an NDA for the ER formulation of pramipexole for treatment in the same population, Parkinson's disease, as the current approved immediate release formulation.

**MEETING OBJECTIVES:**

To agree with the Division on the timing of and the number and type of studies to be included in the original filing and safety updates for the NDA application for pramipexole ER tablets for idiopathic Parkinson's disease.

**DISCUSSION QUESTIONS:****Clinical****Question 1:**

Study 248.524 (see Protocol in Ref. 9) is a 33-week flexible-dose study intended to demonstrate the efficacy and safety of pramipexole ER tablets for the treatment of early Parkinson's disease. The total planned sample size is 500 patients (pramipexole ER: 200; pramipexole IR: 200; placebo: 100).

An interim efficacy analysis (see Statistical Analysis Plan in Ref. 16) is planned once approximately 250 randomized patients (pramipexole ER: 100; pramipexole IR: 100; placebo: 50) have completed at least 18 weeks of therapy or have discontinued treatment prior to week 18. At the time of data cut-off for the interim analysis of Study 248.524, it is expected that approximately 10 patients will have completed the total study duration (i.e. patients treated 33 weeks, or having discontinued prior to week 33).

The interim efficacy analysis will test the primary efficacy endpoint (UPDRS II+III score) in a confirmatory way for the comparison of pramipexole ER versus placebo for patients who have completed at least 18 weeks or have discontinued treatment prior to week 18. Descriptive methods will be used for all secondary efficacy endpoints and for safety endpoints. Further detail on the analysis plan is provided in Section 9.6 of the Clinical Data Summary (below), in the protocol for Study 248.524 (Ref. 9) and in the "Interim Trial Statistical Analysis Plan for trial 248.524" (Ref. 16) included in this submission.

As described in the "Operating Procedure for the Interim Efficacy Analysis of the Early Parkinson's Disease Trial 248.524" (Ref. 17), an independent contract research organization (CRO) will perform the interim analysis, in order to ensure that BI staff directly involved in the trial has no access to the randomization list.

As outlined in Question 3 below, BI is proposing that the results of this interim efficacy analysis will be a key component of demonstration of efficacy of pramipexole ER tablets for the treatment of Parkinson's disease.

***Does the Division have any comments regarding:***

- (a) The Trial Statistical Analysis Plan for the interim efficacy analysis described in Reference 16?***
- (b) The number of patients included in the interim efficacy analysis to demonstrate efficacy after 18 weeks of treatment?***
- (c) The number of patients who will have completed the study at the time of the data cut-off, considering that the full report will be submitted with the 4-month safety update?***
- (d) The operating procedure for the interim efficacy analysis of Trial 248.524 described in Reference 17?***

**Pre-Meeting Comments:**

The interim statistical analysis plan describes that an alpha = 0.042 will be spent for the interim analysis (after 18 weeks of treatment) leaving only an alpha of 0.008 for the final 33 week data analysis of the superiority of pramipexole ER versus placebo in the study 248.524 (early PD). However, the potential situation where this study achieves significance during interim analysis but fails at the final analysis needs to be addressed in the context of the overall development program for this formulation.

During the pre-IND meeting on 1/11/07, you indicated in response to the question of whether the efficacy seen at the 3 month interim analysis will be maintained out to 6 months, that an estimated 40-50% of the total enrolled subjects will have had their 6 month data available during the interim analysis. However, now it appears that only approximately 10 patients (see above) will have completed the total study duration (i.e. patients treated 33 weeks, or having discontinued prior to week 33). This number seems inadequate.

Additionally, in the interim statistical analysis plan, modified MIDI scores are evaluated using descriptive statistics. There does not appear to be a confirmatory mechanism to check that subjects identified via modified MIDI (as having compulsive behaviors) do indeed have those behaviors.

### **Statistics**

You need to state the exact rule of pooling the small centers in Protocol 248.524 & 248.525. You include the interaction term (b) (4) in the primary ANCOVA model. The interaction term should be excluded from the primary ANCOVA model. As secondary analysis, significance of the interaction term should be explored, and if it is significant, further exploratory analysis needs to be done to find the specific centers for which treatment has differential effects. All of the findings of exploratory analyses need to be reported.

You plan to use LOCF ANCOVA analysis as the primary method. Longitudinal analysis (MMRM) needs to be done as a sensitivity analysis (i.e., as secondary analysis) on the primary outcome measure.

### **Meeting Comments:**

*Clinical: The sponsor expressed confidence that study 248.524 will be able to demonstrate superiority of pramipexole ER over placebo at the final 33 week data analysis at an alpha of only 0.008. Nevertheless, there remains the possibility that statistical significance may be achieved at the interim but not at the final analysis, leading to difficulties in interpreting the overall results of this key study which supports the NDA application. After discussion, it was agreed that once this study achieves statistical significance at the interim analysis at an alpha of 0.05, all further efficacy assessments and efficacy analysis would stop, and that collection of blinded safety data would continue for the full 6 month duration. Further, it was agreed that the interim data analysis will include 6 month data from at least 100 subjects who have completed the study in order to assess maintenance of efficacy out to 6 months.*

*The sponsor agreed to require that all subjects identified via modified MIDI undergo formal psychiatric evaluation using standardized interview such as the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) to confirm impulse control disorders. In the interest of time, this requirement will initially be communicated to individual investigators via a letter and later will be formally incorporated into the study protocol through an amendment.*

### **Question 2:**

Study 248.636 (see Protocol in Ref. 11) is a 9-week study intended to demonstrate the safety and efficacy of switching (overnight switch) from pramipexole IR to pramipexole ER in early PD patients.

***Does the Division have any comments regarding:***

- (a) The design / duration of the trial?*
- (b) The efficacy endpoint proposed to define maintenance of efficacy (no worsening of the UPDRS II+III score by more than 15% from baseline)?*
- (c) The planned statistical analysis?*

### **Pre-Meeting Comments:**

In this study, subjects on stable doses of pramipexole IR are randomly switched to either Pramipexole IR or Pramipexole ER. The difference in proportions of patients who successfully switched from IR to IR or ER at the end of 9 weeks of maintenance (primary endpoint) is to be tested with a one-sided non-inferiority statistical test at the 5% level of significance. However, you must first define an appropriate non-inferiority margin, which does not appear to be reflected in the analysis plan. In the context of the difficulty in setting up such a margin, the utility of this study will be a matter of discussion at the meeting.

In addition, for the primary efficacy analyses, you propose to use the Per Protocol Set. However, inclusion of drop outs (particularly due to lack of efficacy) would be important. Since there are two visits during the maintenance phase, using Full Analyses Set with Last Observation Carried Forward would be preferable.

We note that you have now included active solicitation of significant daytime sleepiness or episodes of falling asleep at every visit/telephone encounter, and included an open-ended question to capture other treatment-emergent compulsive behaviours (in addition to gambling, sexual and buying) in study 248.524. Please include these assessments in Study 248.636 and Study 248.525.

**Meeting Comments:**

**Clinical:** *The division acknowledged that a study intended to compare safety and efficacy of pramipexole IR versus ER after switching from pramipexole IR using descriptive statistics may provide useful information which potentially can be included in the Dosage and Administration section of the label. However, the division expressed reservations about using non-inferiority statistical tests to compare the efficacy of the two formulations following switching because we do not know the appropriate non-inferiority margin.*

**Question 3:**

As further detailed below in **Section 9.6** of the **Clinical Data Summary**, to support registration of pramipexole ER tablets for treatment of the signs and symptoms of (b) early (b) (4) Parkinson's disease, BI is proposing that the original NDA submission consist of the following clinical efficacy and safety packages:

**Efficacy:**

- Study 248.524, results of the interim efficacy analysis in patients with early Parkinson's disease
- Study 248.530, data establishing bioequivalence between the ER and IR pramipexole formulations

**Safety:**

- Study 248.524 unblinded data for approximately 100 patients with early Parkinson's disease treated with PPX ER for at least 18 weeks (or having discontinued prior to week 18) and approximately 10 patients (treated with PPX ER, PPX IR, or placebo) who will have completed the study (or having discontinued prior to week 33)
- Study 248.524 blinded data for all patients as of the cut-off date; this dataset is expected to include approximately 500 patients with early Parkinson's disease treated with PPX ER, PPX IR, or placebo (PL) for up to 33 weeks
- Study 248.525 blinded data for all patients as of the cut-off date; this dataset is expected to include approximately 500 patients with advanced Parkinson's disease treated with either PPX ER, PPX IR or PL for up to 33 weeks
- Study 248.636 blinded data for all patients as of the cut-off date; this dataset is expected to include approximately 75 patients with early Parkinson's disease treated with either PPX ER, or PPX IR for up to 9 weeks
- Unblinded information for all patients who experienced a serious, unlisted, and related adverse event
- Study 248.545 unblinded data for approximately 60 healthy volunteers (Thorough QT trial)

In addition, BI proposes to provide with the 4-month safety update:

- Study 248.524 (Early PD), final report
- Study 248.636 (Switch study in Early PD), final report

- Study 248.525, (Advanced PD) updated blinded safety dataset and unblinded information for patients who experienced a serious, unexpected, and related adverse event

**Regarding the proposed submission plan:**

- (a) Given the extensive clinical experience with pramipexole IR tablets in patients with idiopathic Parkinson's disease, does the Division concur that the proposed clinical registration package is adequate to support approval of pramipexole ER tablets for the treatment of the signs and symptoms of (b) early (b) (4) Parkinson's disease?*
- (b) Does the Division concur with the proposal to provide efficacy and unblinded safety data, in the form of individual study reports from trials 248.524 and 248.636, as outlined above, at the time of the 4-month safety update?*
- (c) Does the Division have any other comments related to the proposed clinical package and/or registration strategy?*

**Pre-Meeting Comments:**

As discussed during the pre-IND meeting, efficacy data from the early PD study may lead to approval of pramipexole ER for use only in an early PD population. (b) (4)  
(b) (4).

The bulk of the unblinded safety data across studies will be submitted at the 4 month-safety update. Logistically, this leaves little time in the review clock for a comprehensive safety review of the unblinded data.

**Meeting Comments:**

**Clinical:** (b) (4)  
[Redacted]

**Question 4:**

The final report of the switch trial 248.636 (*see Ref. 11*) will be submitted at the time of the 4-month safety update. Based on the results of this study, BI proposes to provide instructions to physicians for safely switching patients treated with pramipexole IR tablets to pramipexole ER tablets in the Prescribing Information for pramipexole ER tablets.

*If it is shown that it is possible to switch safely from pramipexole IR to ER, while maintaining efficacy, is it acceptable by the Division to include this information in the labeling, without delaying the review?*

**Pre-Meeting Comments:**

It is unlikely that we will be in a position to review this study and include its results in labeling if it is submitted with the 4 month safety update rather than with the original submission. In addition, see comments under question 2.

**Meeting Comments:**

**Clinical:** *The sponsor indicated that they understand the division's concern as stated above and plan on submitting the final switch study report with the original NDA submission.*

## **Pharmacokinetics**

### **Question 5:**

The pharmacokinetic properties of pramipexole from the IR formulation are well established and basic pharmacokinetic properties (clearance, volume of distribution) are expected to be maintained in the ER formulation. Additional pharmacokinetic properties for the ER formulation have been evaluated in male healthy volunteers in Phase 1 studies and will be further characterized in PD patients in the planned Phase 3 study 248.524 (Ref. 9). Please see **Section 9.2-9.4** of the **Clinical Data Summary** for an overview, and enclosed individual study synopses in Refs. 2-8 for more details.

A Population PK analysis will be performed for Study 248.524 in 200 patients treated with pramipexole ER and 200 patients treated with pramipexole IR, resulting in a total of 1200 plasma concentration measurements for each formulation. The Population PK analysis and its objectives are described in **Section 9.4** of the **Clinical Data Summary**. As this full analysis will not be available at time of the initial submission, it is proposed to submit the interim PopPK analysis on 100 patients treated with pramipexole ER at the time of initial submission:

- (a) *Does the FDA have any comments to the proposed pharmacokinetic analysis?*
- (b) *Given the known pharmacokinetic profile of pramipexole IR tablets and the results of Study 248.530 which demonstrates bioequivalence between pramipexole IR tablets and pramipexole ER tablets, does the FDA agree that it is adequate to provide the interim Population PK analysis on 100 patients treated with pramipexole ER at the time of initial submission to describe PK of pramipexole ER in Parkinson's disease patients?*
- (c) *Does the Division agree that the proposed PK studies and interim Population PK analysis will be adequate to develop appropriate labeling for pramipexole ER, notably to propose dose recommendations in patients with renal impairment?*

### **Pre-Meeting Comments:**

We have the following comments with respect to the PK plan:

- In order to capture the maximum information about the PK profile of ER formulation, we recommend that PK sampling points at visit 7 should be: before, and 1, 2, and 6 hours after drug administration
- To quantitate the effect of renal function, data from 100 subjects treated with ER will be sufficient in combination with those subjects taking IR, along with the rich PK data from Phase 1 and your prior knowledge of IR. Please provide all of these data so that they can be taken into consideration.
- Please include the rich PK data from phase 1 in the population PK analysis.
- Given the collected PK information in the efficacy trial, please explore exposure-response relationship for both efficacy and safety endpoints.

### **Meeting Comments:**

*At the meeting, the Sponsor and Agency agreed to PK sampling at 1, 2, and 4 hours. The Sponsor agreed to the rest of the PK comments.*

### **Procedural:**

#### **Question 6:**

*We are considering submitting the NDA in eCTD format. We are expecting to refer to but not resubmit Clinical and non-Clinical reports previously submitted to NDA 20-667. Is it acceptable to not resubmit in eCTD format "legacy documents" that have previously been submitted to NDA 20-667?*

**Pre-Meeting Comments:**

**Non-Clinical and Clinical**

In general, the nonclinical and clinical data previously submitted to NDA 20-667 do not need to be resubmitted. However, if you refer to nonclinical and clinical data to support an action (e.g., labeling changes), the relevant nonclinical and clinical study reports should be resubmitted.

**OCP**

If the renal impairment study U96-0093 is a legacy document that was submitted to NDA 20-667, it would be very helpful to have it submitted in the proposed NDA since it will form the basis of modeling the data for the recommendations for renal impairment.

***Meeting Comments:***

*Not discussed*

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Russell Katz  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-667/S-016

Boehringer Ingelheim Pharmaceuticals Inc.  
Mr. George DeStefano  
900 Ridgebury Rd., P.O. Box 368  
Ridgefield, CT 06877-0368

**RECEIVED**  
**AUG 02 2007**

Dear Mr. DeStefano:

Please refer to your supplemental new drug application dated April 10, 2006, received April 12, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex (pramipexole dihydrochloride) 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 1.5 mg Tablets.

We acknowledge receipt of your submission dated January 25, 2007. This submission constituted a complete response to our August 11, 2006 action letter.

This supplemental new drug application provides for a 0.75 mg tablet as a new strength.

We completed our review of this supplemental new drug application and it is approved.

However, the drug lot (Lot No. 010426) tested in the in vitro chromosomal aberration assay (Study 2001BT211) was reproducibly positive for clastogenicity, both in the absence and presence of metabolic activation. Lot No. 010326 contained 21.3% pramipexole, (b) (4) Product Z, and (b) (4) Product V. Since pramipexole itself was negative in a battery of genotoxicity studies, it must be assumed that the photodegradation products, Product Z and/or Product V, are genotoxic.

To address this issue, as stated in your submissions dated June 6, 2007, and July 22, 2007 you have agreed to the following post-approval commitments:

1. Description of Commitment:

An in vitro chromosomal aberration assay in mammalian cells to assess the potential genotoxicity of Products Z and V.

Protocol Submission:	July 20, 2007
Study Start:	Beginning of November 2007
Final Report Submission:	End of January 2008

**2. Description of Commitment**

An in vitro mouse lymphoma tk assay (with colony sizing) to assess the potential genotoxicity of Products Z and V.

Protocol Submission: July 20, 2007  
Study Start: Beginning of November 2007  
Final Report Submission: End of January 2008

**3. Description of Commitment**

An in vivo micronucleus assay to assess the potential genotoxicity of Products Z and V.

Protocol Submission: July 20, 2007  
Study Start: Beginning of November 2007  
Final Report Submission: End of January 2008

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 796-1161.

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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Russell Katz  
7/30/2007 10:54:38 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 67,465

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

Dear Dr. Coleman:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex (pramipexole) Tablets.

We also refer to your amendment dated March 5, 2007 (serial # 043), containing a new protocol titled, "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 Cross-Over Moxifloxacin versus Placebo)."

We have completed the review of your submission and have the following recommendations and requests for information:

1. You propose a dose of 4.5 mg pramipexole ER (extended-release) q.d. for the up-titration phase because it is the maximum tolerated dose in healthy volunteers and will result in systemic exposure equivalent to pramipexole 1.5 mg IR (immediate release) t.i.d. We agree that your proposed dosing scheme will result in evaluation of higher doses and plasma levels than if the IR formulation alone was used. The dose of 4.5 mg/day is expected to cover the highest expected clinical exposure levels because higher exposures (due to e.g. renal impairment or drug interactions) are unlikely to remain undetected due to side effects. Therefore, administering the IR formulation tablet at the time of ECG recording to get a more discrete  $t_{\max}$  compared to the ER tablet is reasonable.
2. The ECG/PK sampling is adequate and is expected to cover  $t_{\max}$  (1-3 hours).
3. We do not agree with the proposed two-stage design. We recommend all treatment arms be conducted concurrently so that assay sensitivity is established at the same time that the effect of pramipexole on the QTc is being evaluated. You could modify your protocol to perform a three-arm parallel study with one arm being administration of moxifloxacin at day 21. However, that design would require an increase in the number of subjects. A crossover design may be possible.

4. We also recommend calculating the time-matched raw mean difference (baseline adjusted) between pramipexole and placebo as well as the one-sided 95% upper confidence interval at each time point.
5. You should make an effort to retain subjects for the primary analysis. Your estimated dropout rate of 40% may jeopardize the analysis results. The plan to recruit more subjects to achieve 44 evaluable patients will likely violate the randomization principle. In addition, having to recruit more subjects during the trial may pose logistical problems that may affect the quality of the trial.
6. In terms of assay sensitivity, we want to see that at least at one time point, the mean difference of moxifloxacin and placebo is greater than 5 msec. The statistical hypotheses can be set up as follows:

$$H_0: \cap \{ \mu_{\text{moxi}(i)} - \mu_{\text{placebo}(i)} \} \leq 5, i = 1, 2, \dots, K \text{ and}$$
$$H_1: \cup \{ \mu_{\text{moxi}(i)} - \mu_{\text{placebo}(i)} \} > 5, i = 1, 2, \dots, K,$$

where  $\mu_{\text{moxi}(i)}$  and  $\mu_{\text{placebo}(i)}$  are the mean change from baseline of QTcI for moxifloxacin and placebo at time point  $i$ , respectively.  $K$  is the number of time points picked to evaluate moxifloxacin effect. Because multiple time points are examined, you should employ an appropriate procedure (e.g., Bonferroni) to protect the type I error. You can pre-specify the number of time points for the assay sensitivity analysis. We encourage collecting ECG data for moxifloxacin at the same time points as the drug and placebo because we will examine the profile of moxifloxacin.

7. In addition to the primary statistical analysis of the data as outlined in the ICH E14 guidance, we recommend using a linear/nonlinear mixed effects modeling approach to quantify the relationship between the plasma concentration and ddQTc (time-matched placebo and baseline-adjusted QTc) interval and to estimate the expected ddQTc and its 90% confidence interval at relevant concentration levels, e.g. the mean maximum plasma concentrations under therapeutic and suprathreshold doses or other concentrations of interest. This should be done for each analyte (e.g. parent, any metabolite(s)).

In addition to fitting a direct pharmacodynamic model (without a delay between concentration and effect) to the data, the need for a delayed-effect model should also be evaluated (via graphical displays and/or model estimation). Please provide justification for your choice of pharmacodynamic model. If necessary, individual predicted concentrations can be used to drive the pharmacodynamic model. All model codes and data sets to support this analysis should be submitted as SAS transport files (\*.xpt) for review.

8. In order to minimize the effect of phlebotomy on QT measurement, we recommend that you perform all time-matched venipunctures after acquisition of the ECGs.

9. We believe you have incorporated the following elements into your assessment of the ECGs recorded during this study but reiterate them to emphasize their importance:
  - a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation,
  - b. Blinding of ECG readers to subject identifiers, treatment, time, and day (i.e., Day -1; Day 1),
  - c. Review of all ECGs from a particular subject by a single reader on one day, and
  - d. Assessment of inter-reader variability by having a subset of tracings interpreted by a second reader.
  
10. When you submit your ‘thorough QT study’ report, please include the following items:
  - a. Copies of the study reports for any other clinical QT study of this product that has been performed
  - b. Electronic or hard copy of the study report
  - c. Electronic or hard copy of the clinical protocol
  - d. Electronic or hard copy of the Investigator’s Brochure
  - e. Annotated CRF
  - f. A Define file which describes the contents of the electronic data sets
  - g. Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
  - h. Narrative summaries and case report forms for any
    - i. Deaths
    - ii. Serious adverse events
    - iii. Episodes of ventricular tachycardia or fibrillation
    - iv. Episodes of syncope
    - v. Episodes of seizure
    - vi. Adverse events resulting in the subject discontinuing from the study
  - i. ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
  - j. A completed Highlights of Clinical Pharmacology Table as follows:

**Highlights of Clinical Pharmacology**

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> </ul>

		<ul style="list-style-type: none"> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C <sub>max</sub> and AUC
	Sex	Specify mean changes in C <sub>max</sub> and AUC
	Race	Specify mean changes in C <sub>max</sub> and AUC
	Hepatic & Renal Impairment	Specify mean changes in C <sub>max</sub> and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C <sub>max</sub> and AUC
	Food Effects	Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C <sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

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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Russell Katz  
6/27/2007 10:27:59 AM

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** January 11, 2007  
**TIME:** 10 AM – 11 AM  
**LOCATION:** White Oak, Building #22, Conference Room 1311  
**APPLICATION:** PIND 75961 Pramipexole Extended Release for Parkinson's  
**TYPE OF MEETING:** Pre-IND  
**MEETING CHAIR:** Dr. Russell Katz  
**MEETING RECORDER:** CDR Teresa Wheelous

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

Dr. Russell Katz – Division Director  
Dr. John Feeney – Group Leader  
Dr. Devanand Jillapalli – Medical Reviewer  
Dr. Kun Jin – Biometrics Team Leader  
CPT David Banks  
Dr. Wendy Galpern  
Dr. Sally Yasuda – Clinical Pharmacology Reviewer  
Dr. Martha Heimann – CMC Team Leader

**BOEHRINGER INGLEHEIM Pharmaceuticals, Inc. Attendees**

Dan Coleman, Ph.D. - Associate Director, DRA (US)  
George Destefano, M.S. - Associate Director, Technical DRA (US)  
Sebastian Haertter, Ph.D. - Project Pharmacokineticist (Germany)  
Marty Kaplan, M.D., J.D. - VP, Drug Regulatory Affairs (US)  
Michael Koenen-Bergmann, M.D.- Project Clin Pharmacologist (Germany)  
Juergen Koester, Ph.D - Project Statistician (Germany)  
Juergen Reess, M.D. - Therapeutic Area Head, CNS (Corporate)  
Ronald Rosenberg, Ph.D. - International Project Leader (Corporate)  
Heidi Reidies, M.S. - Executive Director, DRA (US)  
Laurence Salin, M.D. - Team Member Medicine (France)

**BACKGROUND:**

The meeting request dated, November 2, 2006 was granted on November 14, 2006. The meeting package was received on December 13, 2006. The purpose of this meeting is to discuss the acceptability of the IND filing plans for pramipexole ER tablets and to secure agency feedback on the proposed Phase 3 studies using pramipexole ER tablets for treatment of Parkinson's disease. BI is also seeking feedback from the FDA as to the suitability of BI's proposed dissolution test procedure that will be used with the formal stability studies.

**MEETING OBJECTIVES:**

The purpose of this meeting is to discuss the acceptability of the IND filing plans for pramipexole ER.

**DISCUSSION QUESTIONS:****Question 1**

(b) (4) the pramipexole drug substance used to manufacture the new ER tablets is the same as that used for the approved immediate release (IR) pramipexole tablets. As a result, BI plans to provide information pertaining exclusively to the (b) (4) drug substance in the new IND for the ER tablets and, otherwise, refer to drug substance documentation previously submitted to the existing IND 34,850 and NDA 20-667 (for immediate release (IR) pramipexole tablets in Parkinson's disease). **Does FDA agree to this proposal?**

**Pre-Meeting Comments:**

Yes, this is acceptable for the IND filing. We remind you that when the NDA is filed you will need to submit facility information for all drug substance manufacturing sites.

**Meeting Discussion Comments:**

None

**Question 2**

To support the conduct of a 6-month Phase 3 study in patients with early Parkinson's disease, BI plans to refer in the IND for the new pramipexole ER tablets to the existing IND 34,850 and NDA 20-667 (for immediate release (IR) pramipexole tablets in Parkinson's disease) for available information regarding drug pharmacology and toxicology. **Does FDA agree to this proposal?**

**Pre-Meeting Comments:**

Yes.

**Meeting Discussion Comments:**

None

**Question 3**

In addition, BI plans to refer to the previous human experience with pramipexole IR tablets already submitted to the Division under IND 34,850 and NDA 20-667, and to submit the final study reports from three Phase 1 clinical pharmacology studies with pramipexole ER tablets (see Appendices 1-3) to support the conduct of a 6-month Phase 3 study in early Parkinson's disease patients. **Given the extensive clinical safety database for IR pramipexole tablets, does the Division agree that this is acceptable?**

**Pre-Meeting Comments:**

Yes.

**Meeting Discussion Comments:**

None

**Chemistry, Manufacturing and Control Question****Question 4**

BI has developed a dissolution test procedure in accordance with the current FDA guidance. Details of the development of the method are included in this briefing package (Appendix 9). **Does the FDA concur that this method is suitable for use in formal stability testing?**

**Pre-Meeting Comments:**

From the OCP perspective, the method seems generally acceptable. The Sponsor should note that the final dissolution specifications should be based on data from 12 tablets from clinical/bioavailability lots. According to the IVIVC Guidance, the last time point in the profile should be the time point where at least 80% of the drug has dissolved, and if the amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached. Based on the results presented, (b) (4) considered. The proposed dissolution method appears generally suitable for use in formal stability studies; however, the comments below will need to be addressed before the method would be considered suitable for regulatory purposes. We recommend that any changes to the method be finalized prior to initiation of the registration stability studies.

From the OCP perspective, the method seems generally acceptable. The Sponsor should note that the final dissolution specifications should be based on data from 12 tablets from clinical/bioavailability lots. According to the IVIVC Guidance, the last time point in the profile should be the time point where at least 80% of the drug has dissolved, and if the amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached. Based on the results presented, (b) (4) considered.

**Meeting Discussion Comments:**

The Division agreed to have future discussion if additional clarification is needed.

**Clinical and Clinical Pharmacology Questions****Question 5**

The single dose, five-way, cross-over study to establish an *in vivo* - *in vitro* correlation with the pramipexole ER formulation (see Appendix 2 for synopsis of Study 248.560) shows that pramipexole is evenly absorbed throughout the intestinal tract and food does not affect total exposure after a single dose of 0.375 mg pramipexole ER tablets. These *in vivo* results are corroborated by *in vitro* data showing that the release of the pramipexole ER tablets is pH independent (Appendix 2).

**Does the Division concur that no further studies are required as part of the overall development program to elucidate the *in vivo* bioavailability of the pramipexole ER tablets under modified gastrointestinal conditions (such as co-medication lowering/accelerating GI transit or increasing gastric pH)?**

**Pre-Meeting Comments:**

Only a synopsis has been provided and data are not presented to clearly show that in Study 248.560 pramipexole is evenly absorbed throughout the intestinal tract, since the  $t_{max}$  values for the individual formulations as well as  $C_{max}$  and AUC have not been provided. Generally, the Sponsor's proposal is reasonable. However, dose dumping with alcohol should be evaluated. First in vitro dissolution studies in various concentrations of alcohol (e. g. 5, 10, 20 and 40%) should be conducted. Once results are available, the sponsor should discuss this with the Office of Clinical Pharmacology for assessing the need for in vivo study.

**Meeting Discussion Comments:**

As discussed at the Sponsor meeting, the alcohol study can be performed by adding the alcohol to the selected dissolution media using the selected dissolution method (after the revisions as outlined in the Agency's response to Question 4). As a post-meeting note, the *in vitro* alcohol studies can be done with the highest strength ER tablet since the % of hypromellose (relative to the total weight of the tablet) (b) (4) proposed method appears to be similar across all strengths in an exploratory stability study.

**Question 6**

All pharmacokinetic (PK) studies with pramipexole ER tablets have been conducted in males only. BI intends to evaluate PK in females within the Phase 3 Study 248.524 in early PD patients by means of population PK analyses (see Appendix 5). **Does the Division concur that the BI proposal should provide sufficient gender-specific pharmacokinetic information to support the NDA for the ER tablets?**

**Pre-Meeting Comments:**

This seems reasonable based on what is known about the pharmacokinetics in females based on the approved Mirapex labeling. However, the Sponsor should justify this when the NDA is submitted.

**Meeting Discussion Comments:**

None

**Question 7**

BI has conducted three Phase 1 studies using the pramipexole ER tablets (Appendices 1-3). The multiple

dose Study 248.530 (Appendix 3) assesses the PK performance of the ER tablets at all dose levels (0.375 - 4.5 mg) and compares the ER tablets to IR tablets at the highest ER dose strength of 4.5 mg daily and compares the bioavailability of this highest dose strength in the fasted and fed state. Food effect was additionally assessed in trial 248.560 (Appendix 2) after a single dose of the lowest dose strength of 0.375 mg. In addition to the population PK planned for the Phase 3 trial planned in early PD, Study 248.524 (Appendix 5), no further PK studies are planned for the characterization of the PK of the ER tablets.

**Does FDA concur that this clinical program adequately characterizes the PK of the ER tablets for an NDA?**

**Pre-Meeting Comments:**

The Phase 1 studies, if adequately performed, would adequately characterize the PK of the ER tablets for an NDA, although the final evaluation is dependent on review of the NDA.

**Meeting Discussion Comments:**

None

**Question 8**

Study 248.524 is intended to demonstrate the efficacy and safety of pramipexole ER tablets for treatment of early Parkinson's disease (Appendix 5) and will be the only study with the ER tablets currently planned to be conducted, in part, in the US. **Does the Division have any comments regarding:**

**(a) the design/duration of the trial?**

**(b) the primary endpoint (change from baseline in the sum of UPDRS Parts II and III)?**

**(c) the statistical analysis plan (primary analysis = superiority of pramipexole ER tablets to placebo)?**

**Pre-Meeting Comments:**

The duration (6 months) of the study is acceptable, as this duration will provide important information on maintenance of efficacy out to 6 months. The primary endpoint and the demonstration of superiority of ER to placebo are acceptable. The planned statistical analysis is a hierarchical plan testing for superiority of ER to placebo, then non-inferiority of ER to IR. While demonstration of non-inferiority is not a regulatory requirement, we believe this comparison will provide important information and should be performed. However, the non-inferiority analysis uses a margin of 3 point difference in the change from baseline UPDRS II + III scores. We note that page 54 of the synopsis for study states "The relevance of 3 points was confirmed by an external expert ..." The sponsor should expand on this statement and justify the choice of a 3 point margin.

In study 248.530 (MRD), the  $C_{max}$  for the sustained-release formulation in the fed state was 5.94 ng/ml as compared to 4.89 ng/ml in the fasted state, and the upper limit of 90% CI was 127% slightly outside the bioequivalence boundary of 125%. This slight food effect on  $C_{max}$  was also seen in study 248.560 using the 0.375 mg single dose. While the sponsor considers the food effect for ER formulation on  $C_{max}$  'slight' as the values lay just outside the bioequivalency upper bound, this occurred consistently in two phase I studies using small samples and raises some concern. Any concerns about higher levels might be

addressed if vital signs, ECGs, and adverse event assessments are collected at  $T_{max}$  post ER dose in a pre-defined subgroup on some visits during phase III studies (controlling for fed/fasted state), as was suggested by the division during the pre-IND meeting on 8/30/02.

#### Meeting Discussion Comments:

DNP raised reservations about using a non-inferiority margin of 3 point difference in change from baseline UPDRS II+III scores which is about 50% of the effect size. The sponsor indicated that the choice was based on published literature which was in agreement with their IR formulation data in Parkinson's disease trials. DNP reminded that sponsor to provide full justification regarding their choice in the submission.

#### Question 9

[REDACTED] (b) (4)

[REDACTED] :

[REDACTED]

(b) the primary endpoint (change from baseline in the sum of UP [REDACTED])

[REDACTED]

[REDACTED]

#### Pre-Meeting Comments:

The duration (6 months) of the study, the primary endpoint and the demonstration of [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

#### Meeting Discussion Comments:

[REDACTED] (b) (4)

[REDACTED] is

[REDACTED]

#### Question 10

Does the Division concur that Phase 3 studies 248.524 and 248.525 are adequate to characterize the efficacy of pramipexole ER tablets for the treatment of the signs and symptoms of idiopathic early and advanced Parkinson's disease, respectively?

#### Pre-Meeting Comments:

Yes.

**Meeting Discussion Comments:**

None

**Question 11**

**Does the Division concur, considering the broad overall clinical experience with pramipexole IR tablets, that patient numbers and duration of exposure in studies 248.524 and 248.525 will be sufficient to evaluate the safety of pramipexole ER tablets in early and advanced Parkinson's disease, respectively?**

**Pre-Meeting Comments:**

Yes.

**Meeting Discussion Comments:**

None

**Question 12**

The FDA guidance, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (May 1998), states that in some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate release form. In Study 248.530, it has been shown that pramipexole ER tablets given q.d. resulted in about the same 24h exposure ( $AUC$ ,  $C_{max}$ ,  $C_{min}$ ) as the IR tablet given t.i.d., with about the same inter-individual variability. Different dose strengths provided a dose proportional exposure and concomitant food intake did not result in any irregular release and absorption of pramipexole from the ER tablet formulation (see Appendix 3).

Individual dose titration of pramipexole IR tablets is done on the basis of efficacy and tolerability. The data from Study 248.530 demonstrate that the same exposure can be expected at each dose level after multiple dosing with ER or IR tablets. Given that the ER tablets will cover the same dose range and use the same up-titration scheme as the IR tablets, there is no reason to expect a different effect when pramipexole ER tablets are administered to patients with Parkinson's disease.

In addition, we note that WELLBUTRIN SR (NDA 20-358 approved October 4, 1996) and WELLBUTRIN XL (NDA 21-515 approved August 29, 2003) both relied on bioequivalence data to establish effectiveness.

**In light of these data and precedents, would the Division be willing to further consider an NDA proposal (to be submitted separately) that would rely on:**

**-- for demonstration of efficacy, a pharmacokinetic package (with 248.530 as the basis) linking the pramipexole ER tablets to the pramipexole IR tablets for treatment of Parkinson's disease, and  
-- for demonstration of safety, interim (~3-month) safety results from Phase 3 studies 248.524 and 248.525 [with updated (6-month) safety data submitted in the 4-month safety update], as well as safety data with the ER formation from the Phase 1 healthy volunteer studies?**

**Pre-Meeting Comments:**

If bioequivalence, based on both  $C_{max}$  and AUC, is demonstrated between the IR and the ER formulations, it may be possible to support approval of the ER formulation without submitting controlled trial data. However, before taking that approach, the sponsor would need to provide PK/PD evidence supporting the fact that the same effect is achieved with pramipexole, whether the levels are continuous or fluctuate over the course of the day. The effect of differences in  $t_{max}$  and shape of the PK profile for the ER vs IR should be evaluated. Such evidence may come from either clinical or nonclinical studies.

In the absence of this information on the PK-PD relationship for pramipexole, phase III trials may be required to provide efficacy information to support approval. We should note that even if approval can be supported based on the PK/PD approach for efficacy, DNP does have some reservations that the occurrence of some neuropsychiatric adverse events (such as compulsive behaviors) will not be the same with long term treatment with an ER formulation versus an IR formulation. In addition, since an ER formulation presumably provides continuous dopaminergic exposure to post-synaptic dopamine receptors as opposed to fluctuating levels provided by IR, this may have a bearing on the natural history of the disease (such as time to development of motor complications in early PD patients). Controlled studies of 6 month duration (or even longer) may be necessary to assess some of these issues.

**Meeting Discussion Comments:**

The sponsor stated that having established bioequivalence between the IR and ER formulations based on  $C_{max}$  and AUC, they now propose to submit an NDA based mainly on this bioequivalence and supplementing it with a 3 month interim comparable efficacy data between IR and ER in the 6 month study on patients with early Parkinson's disease. There was discussion regarding the use of this 3 month data showing comparability of effectiveness between the IR and ER formulations based on single (outcome) measurements per day versus the information obtained from multiple assessments done over a 24 hour period in a PK-PD study assessing the effect with continuous versus fluctuating plasma levels over the course of the day and the effect of differences in the  $T_{max}$  and shape of PK profile between the two formulations. The sponsor indicated that based on statistical consideration, logistics involving recruitment of subjects and other considerations, they prefer to submit the above 3 month interim efficacy data from the study in early Parkinson's disease rather than from the study in advanced Parkinson's disease. DNP acknowledged that it was willing to accept the sponsor's above proposal; however, the sponsor was reminded that using data from the early Parkinson's disease study may lead to approval for ER formulation use only in early Parkinson's disease population, and that the decision to review advanced Parkinson's disease data in relation to the proposed NDA cycle may be discretionary. Further, DNP asked sponsor to justify the basis for the assumption that the efficacy seen at 3 month interim analysis will be maintained out to 6 months. The sponsor replied that the assumption will be based, in part, on the

analysis of an estimated 40 - 50% of total enrolled subjects who will have had their 6 month data available during the interim analysis.

The sponsor also commits to submit available safety data along with the 3 month interim efficacy data, and submit the all updated safety with the 4 month safety update. Please see comment under question # 14 regarding plans for surveillance for neuropsychiatric adverse events.

### **Question 13**

Reference is made to general correspondence to IND 67,465 for RLS, dated May 11, 2005, Serial No. 20, describing the design of a thorough QT study with 1.5 mg qd pramipexole IR tablets (Appendix 7) and the enclosed QT protocol synopsis(Appendix 8). BI plans to conduct this study and include the results in the NDA for pramipexole ER tablets. **Does the Division concur with this proposal?**

### **Pre-Meeting Comments:**

The synopsis included in Appendix 8 is the synopsis of study 248.545 which, per synopsis page 1 of Appendix 8 was scheduled to be completed two years ago (Aug 2004 – January 2005). Please provide results of this study (not available in the pre-meeting brief). The dose used in this study, 1.5 mg q.d. (dose likely is RLS-specific), is smaller than the planned exposure of 4.5 mg q.d for ER formulation. Please provide justification for not studying higher doses. Assuming, that there are no safety problems with the above QT study, then ECG (linked to Tmax) data (see question #8) may provide adequate safety information of ER formulation effect on QT interval, but the sponsor should provide justification for not studying higher doses.

We note that, according to the current MIRAPEX labeling, clearance of pramipexole is 60-75% lower in patients with moderate and severe renal impairment compared with healthy volunteers. DNP raises the question whether the renal function study for MIRAPEX would have had some QT data with higher than usual exposures that the sponsor could use to support their QT proposal.

### **Meeting Discussion Comments:**

During the Sponsor meeting it was noted that the QT study described above has not yet been performed, and a plan for conducting a QT study with titration to 4.5 mg daily was discussed. As a post-meeting note: The QT study could use the maximum tolerated dose and could be performed in Parkinson's disease patients instead of healthy subjects if tolerability is an issue. Using the IR tablet (with a more discrete tmax than the ER tablet) is reasonable. The Sponsor should justify the dose that is selected with respect to ensuring that exposure after the IR dose will cover the exposures that would occur after accumulation of the ER tablet at steady state, any extrinsic or intrinsic factors that could result in increased Cmax, and justify that the proposed dose is the maximum tolerated dose and why a supra-

therapeutic dose can't be used. The proposal for the QT study protocol should be submitted for review by the IRT (the QT team).

**Question 14**

**Does the Division have any additional comments to our proposed development program?**

**Pre-Meeting Comments:**

Any controlled trials should include active surveillance for neuropsychiatric adverse events (such as compulsive behaviors). We also recommend the inclusion of a rating scale for evaluating predisposition to these abnormal behaviors.

**Meeting Discussion Comments:**

The sponsor stated that they plan to screen for compulsive behaviors potential using modified Minnesota Impulsive Disorders Interview (MIDI) scale at the baseline and at the end of the 6 month study. DNP requested sponsor to include another modified MDI evaluation in all patient around 2-3 months as it has been shown that these adverse events begin to emerge early during trials, and in individual cases when suggestion of compulsive behaviors is detected during questioning at each visit.

DNP also suggested that the protocol include mechanisms to actively solicit information regarding whether subjects are experiencing these adverse events during every visit.

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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.**  
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/s/

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Russell Katz  
1/30/2007 08:18:40 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 75,961

Boehringer Ingelheim  
Attention: George DeStefano, Associate Director  
Technical DRA  
900 Ridgebury Road  
PO Box 368  
Ridgefield, CT 06877-0368

**RECEIVED**  
**NOV 17 2006**

Dear Mr. DeStefano:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Pramipexole Dihydrochloride Extended-Release Tablets.

We also refer to your November 1, 2006, correspondence, received November 2, 2006, requesting a meeting to discuss Chemistry, Manufacturing and Controls issues. We have considered your request and concluded that the meeting is unnecessary. However, in order to assist you in your drug development program, we are providing the following information in response to questions included in your meeting request.

**Question 1:**

***BI is proposing to use a bracketed stability protocol design for the primary stability studies to support a future NDA submission for pramipexole extended release tablets. Justification for this protocol design has been provided in accordance with the International Conference of Harmonization (ICH) Q1D Guideline. Does the FDA agree that the bracketed stability protocol design is acceptable for the primary stability studies and adequately supports the commercial and physician sample configurations?***

**Response to Question 1**

The proposed bracketed stability protocol design is acceptable, as described in your submission, for the commercial presentation. With respect to the physician sample presentation, although we agree with the proposal to use the 0.375 mg and 1.5 mg strengths to bracket the 0.75 mg strength; (b) (4)  
(b) (4). We request that at least one additional batch of these strengths be placed on stability in the physician sample configuration to provide for a more robust stability package.

Your submission does not address storage of samples at the ICH intermediate storage condition (30°C/65% R.H.), or photostability testing of the drug product. We recommend that stability batches be placed into storage at 30°C/65% R.H. for use as a backup condition for the accelerated studies. Whether you will need to include photostability testing of the extended-release formulation in the stability protocol will depend on the available information on the photostability of the drug substance.

**Question 2:**

***Does the FDA concur with the proposed stability testing parameters?***

**Response to Question 2**

The proposed stability test parameters appear appropriate for an extended release tablet formulation; however the suitability of the proposed acceptance criteria will be evaluated during review of the NDA. As no specific information regarding analytical procedures is provided, we are not able to comment on suitability of analytical methods, especially the proposed dissolution method and sampling time points. As you indicate that a meeting with the clinical division will be requested in the near future, we suggest that you request feedback on the suitability of the proposed dissolution method as part of the clinical meeting. This will allow for ONDQA and the Office of Clinical Pharmacology (OCP) to review your dissolution development program and provide feedback.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager for Quality, at (301) 796-2055.

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

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Ramesh Sood  
11/14/2006 02:22:51 PM

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-421 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Mirapax® ER™ Established/Proper Name: pramipexole dihydrochloride Dosage Form: Extended-release tablets Strengths: 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg		
Applicant: Boehringer-Ingelheim Agent for Applicant (if applicable): N/A		
Date of Application: October 31, 2008 Date of Receipt: October 24, 2008 Date clock started after UN: N/A		
PDUFA Goal Date: August 24, 2009		Action Goal Date (if different): August 24, 2009
Filing Date: Date of Filing Meeting: December 11, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Treatment of idiopathic Parkinson's disease		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b>Refer to Appendix A for further information.</b>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> N/A Resubmission after refuse to file? <input type="checkbox"/> N/A		
Part 3 Combination Product? Mirapex is not a combination drug product	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): 75961, 34,850	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aip.html">http://www.fda.gov/ora/compliance_ref/aip.html</a>  <b>If yes, explain:</b>  <b>If yes, has OC/DMPQ been notified of the submission?</b>  <b>Comments:</b> NONE	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  <b>Comments:</b>	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b> None</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113).</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that 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 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b>  <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<b>Format and Content</b>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>		N/A	
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission</b>, does it follow the eCTD guidance? (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not</b>, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NOT Applicable
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b> Patent #4886812, issued December 12, 1989. Expiration October 8, 2010</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>sign the certification.</b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;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...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b><u>PREA</u></b></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b> SPL has been submitted	
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b> Waiver statement in 74 day ltr	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b> Not applicable</p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): August 22, 2007 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): April 25, 2008 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** December 11, 2008, 4:00 PM

**NDA #:** 22-421

**PROPRIETARY/ESTABLISHED NAMES:** Mirapex (pramipexole dihydrochloride)

**APPLICANT:** Boehringer Ingelheim

**BACKGROUND:** The following extended-release tablets are being proposed for commercial distribution for the treatment of idiopathic Parkinson's disease, 0.375 mg, 0.76 mg, 2.5 mg, and 4.5 mg. Boehringer formally requested use of the brandname Mirapex. BI submitted a formal tradename request on January 15, 2009. The tradename was accepted by DNP.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Beverly Conner	Yes
	CPMS/TL:	Robbin Nighswander & Jackie Nighswander	No
Cross-Discipline Team Leader (CDTL)	Dave Potskalny		Yes
Clinical	Reviewer:	Ken Bergmann	Yes
	TL:	Dave Potskalny	Yes
Social Scientist Review (for OTC products)	Reviewer:	NONE	N/A
	TL:	NONE	N/A
Labeling Review (for OTC products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OSE	Reviewer:	Dan Brounstein Regulatory, RPM Project Manager	Yes
	TL:	Todd Bridges	Yes
Clinical Microbiology (for antimicrobial products)	Reviewer:	None	N/A

	TL:	None	N/A
Clinical Pharmacology	Reviewer:	Sripal R. Mada	No
	TL:	Veneeta Tandon	No
Biostatistics	Reviewer:	Jingyu Luan	No
	TL:	Kun Jin	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Terry Peters	Yes
	TL:	Lois Freed	Yes
Statistics, carcinogenicity	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Wendy Wilson	Yes
	TL:	Martha Heimann	Yes
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Bioresearch Monitoring (DSI)	Reviewer:	Antoine EL Hage	no
	TL:	Constance Lewin	No
Other reviewers			

**OTHER ATTENDEES:** Jagan Parepally

505(b)(2) filing issues? <b>If yes, list issues:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> <li>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?</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s)</li> </ul>	<input type="checkbox"/> YES

needed?	<input checked="" type="checkbox"/> NO
<b>BIostatistics</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?  <b>If no</b>, was a complete EA submitted?  <b>If EA submitted</b>, consulted to EA officer (OPS)?  <b>Comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?  <b>Comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product?  <b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>FACILITY (BLAs only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE

<b>Comments:</b>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority: Dr. Russell Katz</b>	
<b>GRMP Timeline Milestones:</b> August 24, 2009	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74: In a letter we noted that we had not identified any potential review issues. We asked for bioavailability data files (as xpt file) for Studies 248.524 and 248.636.
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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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.**  
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/s/

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Beverly A. Conner  
5/8/2009 03:52:20 PM  
CSO

Beverly A. Conner  
6/17/2009 10:32:25 AM  
CSO