CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-514

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022514 SUPPL # HFD # 120

Trade Name Mirapex ER

Generic Name pramipexole dihydrochloride extended-release

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known March 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 July 1, 1997

NDA# 022421 Mirapex ER (pramipexole) Approved February 19, 2010

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:

1. Trial 248.525

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"):

Trial 248.525

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 # YES ☐ NO ☒

Explain:
525 Non US Study, Non IND Study

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 17, 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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22514	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	TBD (PRAMIPEXOLE DIHYDROCHLORIDE)ER TABS

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

/s/

STACY M METZ
03/19/2010

RUSSELL G KATZ
03/19/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-514 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:Division of Neurology Products PDUFA Goal Date: 3/22/10 Stamp Date: 5/21/09

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) signs and symptoms of early Parkinson's Disease (under NDA 22-421)
(2) _____
(3) _____
(4) _____

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 advance 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[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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}

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#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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.*)

∆ 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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: Ware, Jacqueline H
Sent: Thursday, March 18, 2010 10:30 AM
To: Metz, Stacy
Subject: FW: PeRC PREA Subcommittee Meeting on 3/24/2010-ROOM 1419 BLDG 22- AGENDA
Importance: High

From: Stowe, Ginneh D.
Sent: Thursday, March 18, 2010 10:29 AM
To: Kosko, Robert; Ford, Elizabeth; Gorski, Lori M; Parise, Cecelia M; Ware, Jacqueline H
Cc: Greeley, George
Subject: PeRC PREA Subcommittee Meeting on 3/24/2010-ROOM 1419 BLDG 22- AGENDA
Importance: High

All,

Below is the agenda for next weeks' PeRC meeting scheduled for Wednesday, March 24th. We ask that each Division arrive at least **ten minutes** prior to the start time listed for your product. The meeting invites have been sent as this meeting will occur in conference room 1419 in building 22.

PREA

(b) (4)

10:20 (b) (4)

Mirapex ER - Full Waiver

Review division staff are not being requested to attend PeRC for the (b) (4) **Mirapex ER** waiver applications. If staff are still inclined to do so the discussion for the waiver can occur anytime as filler between applications starting at or around 9:30 that morning. The call-in number for the meeting is 866-815-7591 and the pass code is 239100.

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

Metz, Stacy

From: Stowe, Ginneh D.
Sent: Wednesday, March 17, 2010 9:46 AM
To: Ware, Jacqueline H
Cc: Addy, Rosemary; Metz, Stacy; Podskalny, Gerald; Greeley, George
Subject: RE: PeRC documents for NDA 22-514/Mirapex ER (full waiver)

Hi Jackie,

The PeRC will review this waiver on March 24th and George Greeley will send you the PeRC's recommendations via email after the meeting.

Thanks,
Ginneh

From: Ware, Jacqueline H
Sent: Tuesday, March 16, 2010 6:04 PM
To: Stowe, Ginneh D.
Cc: Addy, Rosemary; Metz, Stacy; Podskalny, Gerald
Subject: PeRC documents for NDA 22-514/Mirapex ER (full waiver)

Hi Ginneh,

As we discussed, attached are the PeRC documents for NDA 22-514/Mirapex ER for the treatment of advanced Parkinson's Disease - to be discussed at the 3/24/10 PeRC meeting. Specifically, attached are:
1. Peds page
2. Waiver document
3. AP letter language
4. draft labeling

As a reminder, DNP plans to approve this NDA on Monday, 3/22/10. We realize that approval action will occur prior to review by PeRC, and apologize. However, the indication is advanced Parkinson's Disease, and we mistakenly thought that all Parkinson's Disease received automatic PREA waivers. We understand now that this is not the case and will bring future PD applications to PeRC prior to approval.

If you have any questions, please don't hesitate to contact me.

Many thanks,
Jackie
****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Supervisory Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842

email: jacqueline.ware@fda.hhs.gov

Metz, Stacy

From: Metz, Stacy
Sent: Wednesday, March 17, 2010 11:38 AM
To: 'daniel.coleman@boehringer-ingelheim.com'
Subject: RE: NDA 022514 FDA Proposed Final Labeling

Hi Dan,

I have included the rationale for the decision to delete the text about the switch study.

(b) (4)

Best Regards,
Stacy

From: daniel.coleman@boehringer-ingelheim.com [mailto:daniel.coleman@boehringer-ingelheim.com]
Sent: Wednesday, March 17, 2010 8:46 AM
To: Metz, Stacy
Subject: RE: NDA 022514 FDA Proposed Final Labeling

Dear Stacy,
Before we discuss, we would greatly appreciate any insight you can give about the FDA rationale for deleting the approved text about the switch study.
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: Tuesday, March 16, 2010 5:23 PM
To: Coleman,Dr.,Daniel DRA BIP-US-R
Subject: NDA 022514 FDA Proposed Final Labeling
Importance: High

Hi Dan,
Attached please find FDA's 3/16/10 proposed final labeling for NDA 022514/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this revised labeling was your labeling sent to us via email on 3/12/10. 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 feel the need to have a discussion with the FDA prior to coming to an agreement we are available Thursday, March 18th at 3:30pm EST to discuss with you.

<<22 514 MIRAPEX ER 3 16 10 FDA final proposed labeling.doc>>

Please contact me if you have any further questions.
Stacy

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

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Russell Katz, M.D., Director
Division of Neurology Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901- B Ammendale Road
Beltsville, MD 20705-1266

March 16, 2010

Kelly Billingham
Telephone (203) 791-6118
Telefax (203) 791-6262
e-mail
kellylbillingham@boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Re: NDA 22-421
Mirapex® ER™ (pramipexole dihydrochloride) extended-release tablets 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg

Sequence 0030
Updated Final Printed Carton and Container Labels

Dear Dr. Katz:

Please refer to the approval letter dated February 19, 2010 for NDA 22-421 for Mirapex® ER™ (pramipexole dihydrochloride) extended-release tablets.

As requested in the approval letter, please find enclosed updated final printed carton and container labels containing the statement "Tablets must be swallowed whole, and must not be chewed, crushed or divided". These labels are identical to the carton and immediate container labels that will be used for shipments after February 19, 2010. These labels are being provided electronically according to the guidance for industry entitled *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).*

This submission is compiled in electronic format to closely match the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format – General Considerations, Jan. 1999, and Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, June 2008. TREND™ MICRO OfficeScan™ version 8.0 was used to check for viruses; the submission is virus free. The top level folder is 022421.

For technical questions or comments regarding the electronic format of this submission, please contact:

Boehringer Ingelheim

Jennifer LaFleur
Manager, DRA Operations Technology
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals
203-778-7959
jennifer.lafleur@boehringer-ingelheim.com

If you have any questions regarding this submission, please contact me at the telephone number listed above.

Sincerely,

Kelly Billingham
Associate Director
Product Labeling, Drug Regulatory Affairs

16 page(s) of Draft Carton and Container Labels have been Withheld in Full immediately following this page as B4 (CCI/TS)

Metz, Stacy

From: Ware, Jacqueline H
Sent: Tuesday, March 16, 2010 6:04 PM
To: Stowe, Ginneh D.
Cc: Addy, Rosemary; Metz, Stacy; Podskalny, Gerald
Subject: PeRC documents for NDA 22-514/Mirapex ER (full waiver)
Attachments: PREA Language for NDA 022514 Approval Letter.doc; 22 514 MIRAPEX ER 3 16 10 FDA final proposed labeling.doc; N22514 Peds Page.doc; N22514 Waiver form.doc'.doc

Hi Ginneh,

As we discussed, attached are the PeRC documents for NDA 22-514/Mirapex ER for the treatment of advanced Parkinson's Disease - to be discussed at the 3/24/10 PeRC meeting. Specifically, attached are:
1. Peds page
2. Waiver document
3. AP letter language
4. draft labeling

As a reminder, DNP plans to approve this NDA on Monday, 3/22/10. We realize that approval action will occur prior to review by PeRC, and apologize. However, the indication is advanced Parkinson's Disease, and we mistakenly thought that all Parkinson's Disease received automatic PREA waivers. We understand now that this is not the case and will bring future PD applications to PeRC prior to approval.

If you have any questions, please don't hesitate to contact me.

Many thanks,
Jackie
****

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Supervisory Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

Metz, Stacy

From: Metz, Stacy
Sent: Tuesday, March 16, 2010 5:23 PM
To: 'daniel.coleman@boehringer-ingelheim.com'
Subject: NDA 022514 FDA Proposed Final Labeling

Importance: High

Attachments: 22 514 MIRAPEX ER 3 16 10 FDA final proposed labeling.doc

Hi Dan,

Attached please find FDA's 3/16/10 proposed final labeling for NDA 022514/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this revised labeling was your labeling sent to us via email on 3/12/10. 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 feel the need to have a discussion with the FDA prior to coming to an agreement we are available Thursday, March 18th at 3:30pm EST to discuss with you.

22 514 MIRAPEX ER
3 16 10 FDA ...

Please contact me if you have any further questions.
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, March 10, 2010 12:30 PM
To: 'daniel.coleman@boehringer-ingelheim.com'
Subject: NDA 022514 FDA Proposed Labeling

Importance: High

Attachments: 22 514 MIRAPEX ER revised labeling 3 10 2010 Proposed Advanced PI.doc

Hi Dan,

Attached please find FDA's 3/10/10 revised labeling for NDA 022514/Mirapex (pramipexole dihydrochloride) ER tablets. The base document used for this revised labeling was your labeling sent to us via email on 2/26/10 (also submitted to the EDR). 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. It would probably be best to send us your revisions in this document, but also send a "clean document" that ONLY shows your new revisions to this labeling sent to you today. Please respond our proposal as early as possible Monday morning, March 15, 2010.

Please let me know if you have any questions.

Thanks.

Stacy

22 514 MIRAPEX ER revised labe...

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

Metz, Stacy

Subject: NDA 22-514/Mirapex ER Tabs (pramipexole dihydrochloride)--Hold for Labeling
Location: CDER WO 4201 conf rm Bldg22

Start: Tue 3/9/2010 3:00 PM
End: Tue 3/9/2010 4:00 PM

Recurrence: (none)

Meeting Status: Meeting organizer

Required Attendees: Metz, Stacy; Katz, Russell G; Podskalny, Gerald; Bergmann, Kenneth; Jin, Kun; Luan, Jingyu
Optional Attendees: Freed, Lois M; Heimann, Martha R; CDER 120 Calendar; Men, Angela
Resources: CDER WO 4201 conf rm Bldg22

Updated 3/3/10: Labeling for meeting (base labeling from recently approved NDA 022421).

MIRAPEX ER
oposed Advanced P

Hold for Labeling--will be updated at a later time

Boehringer Ingelheim Pharmaceuticals, Inc. has submitted NDA 22-514 for Mirapex ER Tabs (pramipexole dihydrochloride) for the treatment of early and advanced Parkinson's disease. It is directly related to NDA 22-421 with a PDUFA date in August.
This submission is entirely electronic. Please use the included link to information.

Lois, Martha, and Vaneeta--per the following information I have included you as optional at this meeting.
"As previously discussed with DNP, NDA 22-514 refers to NDA 22-421 for all CMC, nonclinical, and clinical pharmacology information regarding Mirapex ER tablets."

Stamp Date 5/22/09
Standard Review PDUFA Date 3/22/2010

EDR Location: \\CDSESUB1\EVSPROD\NDA022514\022514.enx

Cover Letter: \\CDSESUB1\EVSPROD\NDA022514\0000\m1\us\cover-letter-nda-22514.pdf

{Scheduled by S. Metz on 1/13/10; 301-796-2139}

Metz, Stacy

Subject: NDA 22-514/Mirapex ER Tabs (pramipexole dihydrochloride)--Hold for Labeling
Location: CDER WO 4201 conf rm Bldg22

Start: Tue 3/16/2010 3:00 PM
End: Tue 3/16/2010 4:00 PM

Recurrence: (none)

Meeting Status: Meeting organizer

Required Attendees: Metz, Stacy; Katz, Russell G; Podskalny, Gerald; Bergmann, Kenneth
Optional Attendees: Freed, Lois M; CDER 120 Calendar
Resources: CDER WO 4201 conf rm Bldg22

UPDATED 3/15/10: Revised labeling from BI


22 514 MIRAPEX ER
all changes ...


22 514 MIRAPEX ER
latest chang...

Hold for Labeling--will be updated at a later time

Boehringer Ingelheim Pharmaceuticals, Inc. has submitted NDA 22-514 for Mirapex ER Tabs (pramipexole dihydrochloride) for the treatment of early and advanced Parkinson's disease. It is directly related to NDA 22-421 with a PDUFA date in August.
This submission is entirely electronic. Please use the included link to information.

Lois, Martha, and Vaneeta--per the following information I have included you as optional at this meeting.
"As previously discussed with DNP, NDA 22-514 refers to NDA 22-421 for all CMC, nonclinical, and clinical pharmacology information regarding Mirapex ER tablets."

Stamp Date 5/22/09
Standard Review PDUFA Date 3/22/2010

EDR Location: \\CDSESUB1\EVSPROD\NDA022514\022514.enx

Cover Letter: \\CDSESUB1\EVSPROD\NDA022514\0000\m1\us\cover-letter-nda-22514.pdf

{Scheduled by S. Metz on 1/13/10; 301-796-2139}

Metz, Stacy

Subject: NDA 22-514/Mirapex ER Tabs (pramipexole dihydrochloride)--Hold for Labeling
Location: CDER WO 4201 conf rm Bldg22

Start: Thu 3/18/2010 3:30 PM
End: Thu 3/18/2010 4:30 PM

Recurrence: (none)

Meeting Status: Meeting organizer

Required Attendees: Metz, Stacy; Katz, Russell G; Podskalny, Gerald; Bergmann, Kenneth
Optional Attendees: CDER 120 Calendar
Resources: CDER WO 4201 conf rm Bldg22

Hold for Labeling--will be updated at a later time

Boehringer Ingelheim Pharmaceuticals, Inc. has submitted NDA 22-514 for Mirapex ER Tabs (pramipexole dihydrochloride) for the treatment of early and advanced Parkinson's disease. It is directly related to NDA 22-421 with a PDUFA date in August.
This submission is entirely electronic. Please use the included link to information.

Lois, Martha, and Vaneeta--per the following information I have included you as optional at this meeting.
"As previously discussed with DNP, NDA 22-514 refers to NDA 22-421 for all CMC, nonclinical, and clinical pharmacology information regarding Mirapex ER tablets."

Stamp Date 5/22/09
Standard Review PDUFA Date 3/22/2010

EDR Location: \\CDSESUB1\EVSPROD\NDA022514\022514.enx

Cover Letter: \\CDSESUB1\EVSPROD\NDA022514\0000\m1\us\cover-letter-nda-22514.pdf

{Scheduled by S. Metz on 1/13/10; 301-796-2139}

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Russell Katz, M.D., Director
Division of Neurology Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901- B Ammendale Road
Beltsville, MD 20705-1266

March 3, 2010

Re: NDA 22-514
Mirapex® ER™ (pramipexole dihydrochloride) extended-release tablets

Sequence 0004
Amendment - Revised Draft Labeling

Daniel T. Coleman, Ph.D.
Telephone (203) 798-5081
Telefax (203) 791-6262
e-mail
daniel.coleman@boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Katz:

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) is hereby amending the above referenced NDA to provide revised draft labeling (proposed.doc). The text of the proposed label is identical to the proposed text sent to the FDA by email on Friday February 26, 2010.

Please note that the original submission of NDA 22-514 (Sequence 0000) contained draft carton and container labeling. These proposed carton and container labels have been superseded by the carton and container labels approved in NDA 22-421 for this product. By way of this letter, BI requests that FDA refer to NDA 22-421 for all MIRAPEX ER carton and container labels for NDA 22-514.

The content of this amendment is formatted as defined by the ICH Common Technical Document and presented as Sequence 0004 to this eCTD application.

TREND™ MICRO OfficeScan™ version 8.0 was used to check for viruses; the submission is virus free. The top level folder is 022514.

For technical questions or comments regarding the electronic format of this submission, please contact:
Jennifer LaFleur
Manager, DRA Operations Technology
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals
203-778-7959
jennifer.lafleur@boehringer-ingelheim.com

Boehringer Ingelheim

If you have any other questions or comments concerning this submission, I can be reached by telephone at (203) 798-5081, by fax at (203) 791-6262, or by e-mail at daniel.coleman@boehringer-ingelheim.com.

Sincerely,

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

Metz, Stacy

From: daniel.coleman@boehringer-ingelheim.com
Sent: Wednesday, July 29, 2009 8:29 AM
To: Metz, Stacy
Subject: NDA 22-514

Dear Dr. Metz,
Thank you for your filing communication regarding NDA 22-514 for MIRAPEX ER.
I received this letter yesterday. We are working to provide the requested information as soon as possible.
In the interest of time, we would greatly appreciate it if you could email any future requests for information directly to me.
I look forward to working with you on this NDA.
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

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022514 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type: Type 3 - new dosage form (Type 6 NDA)
Proprietary Name: Mirapex ER Established/Proper Name: pramipexole dihydrochloride extended release tabs Dosage Form:		Applicant: Boehringer Ingelheim Pharmaceuticals Inc. Agent for Applicant (if applicable): Daniel Coleman
RPM: Stacy Metz		Division: DNP

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

<u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.

❖ Actions	
• Proposed action • User Fee Goal Date is 3/22/10	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received N/A
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No N/A
• Press Office notified of action (by OEP)	☐ Yes ☐ No N/A
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE	
#1 Copy of this Action Package Checklist[3]	
Officer/Employee List	
#2a List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☑ Included
Documentation of consent/non-consent by officers/employees	☑ Included
Action Letters	
#3 Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)
Labeling	
#4 Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	See approval letter
✓ • Original applicant-proposed labeling	
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

(5) ❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert (Patient Info in PI) ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format. Also – (see approval letter)	
• Original applicant-proposed labeling (see Section 4)	
• Example of class labeling, if applicable	
(6) ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	
(7) ❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A Type 6 NDA
(8) ❖ Labeling reviews *(indicate dates of reviews and meetings)* – see meeting notices	☐ RPM ☐ DMEDP ☐ DRISK ☐ DDMAC ☐ CSS ☐ Other reviews N/A Type 6 NDA so no formal review
Administrative / Regulatory Documents	
(9) ❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Clinical Filing Checklist
(10) ❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
(11) ❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 3/24/10 If PeRC review not necessary, explain: _____ • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	Full waiver – Type 6 NDA Approval 3/22 + PeRC scheduled for 3/24/10 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
(12) ❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	
Internal memoranda, telecons, etc.	N/A

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) *(indicates dates)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
(13) ❖ Office Director Decisional Memo *(indicate date for each review)* [redacted]	☒ None
Division Director Summary Review *(indicate date for each review)* 3/19/10	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)* 3/19/10	[redacted] None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
(14) • Clinical Team Leader Review(s) *(indicate date for each review)* Sel CDTL review 3/19/10	
• Clinical review(s) *(indicate date for each review)* 3/19/10	
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	N/A Type 6 NDA
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
(15) ❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None > combined dated 1/28/10
Statistical Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology ☒ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
Product Quality ☒ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None

❖ Environmental Assessment (check one) (original and supplemental applications)	N/A Type 6 NDA
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☒ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection N/A	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)* N/A	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE's ADRA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-514

FILING COMMUNICATION

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

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated May 20, 2009, received May 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Mirapex Extended-Release Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is March 22, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

1. In calculating exposure data for Mirapex ER, we have not always been able to know which patients from a given treatment arm in double blind studies went on to enter the open label follow-up trials. Specifically, we do not know who began to take open label

ER after being in the blinded IR or placebo arms, and who entered open label ER from the ER blinded arm. We also do not know modal dose and duration of exposure to ER in the open label trials up to the data cut off date. Please complete this table for the following trials and create an analysis dataset that reflects the information for each unique USUBJID:

"Subjects not discontinued"	N	How many completers in each of these arms went on to ER open label?	Modal dose (mg/d) in open label group	Duration, to cut off date
Study 248.636 Switch		Open Label Study 248.633		
ER				
IR				

Study 248.524 Early PD		Open Label Study 248.633		
Placebo				
ER				
IR				

Study 248.525		Open Label Study 248.634		
Placebo				
ER				
IR				

2. For Studies 246.524 and 246.525, in all submitted analysis datasets that do not have one, create a variable USUBJID that corresponds to the PTNO for each subject.

3. For Studies 246.524 and 246.525, send the CRF and a brief narrative providing what information is available for each subject who ended participation in the trial due to withdrawal of consent, i.e. non AE related reasons.

4. Provide updated datasets for all additional safety information at the time of the 4 Month Safety Update. Data should be pooled and identifiable by trial.

5. For Study 246.525, Site 63204, Quezon, Philippines, Roland Dominic Jamora is listed as PI. However, in the analysis and individual datasets (DM.xpt), the PI is identified as [redacted] (b) (4). Please provide documentation of qualifications and certification of financial disclosure for this individual.

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

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

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

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

/s/

Russell Katz

7/22/2009 04:53:53 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Kun Jin, Ph.D., Division of Biometrics I			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Russell Katz, MD, Division of Neurology Products	
DATE 6/3/09	IND NO.	NDA NO. 22-514	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT Stamp Date 5/22/09 PDUFA Date 3/22/2010
NAME OF DRUG Mirapex ER (pramipexole dihydrochloride) Tablets	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 7/9/09 (Filing Meeting)

NAME OF FIRM: Boehringer Ingelheim

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ PAPER NDA	☒ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY	☐ CONTROL SUPPLEMENT	

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☒ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☒ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Boehringer Ingelheim Pharmaceuticals, Inc. has submitted NDA 22-514 for Mirapex ER Tabs (pramipexole dihydrochloride) for the treatment of early and advanced Parkinson's disease. This is an entirely electronic submission.

NDA 22-514 refers to NDA 22-421 for all CMC, nonclinical, and clinical pharmacology information regarding Mirapex ER tablets."

Stamp Date 5/22/09
74 Day Letter Date 8/4/09
Standard Review PDUFA Date 3/22/2010

EDR Location: \\CDSESUB1\EVSPROD\NDA022514\022514.enx

Cover Letter: \\CDSESUB1\EVSPROD\NDA022514\0000\m1\us\cover-letter-nda-22514.pdf

SIGNATURE OF REQUESTOR Stacy Metz, PharmD, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-2139 email:stacy.metz@fda.hhs.gov	METHOD OF DELIVERY (Check one) ☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Stacy Metz

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-514

NDA ACKNOWLEDGMENT

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

Dear Dr. Coleman:

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

Name of Drug Product: Mirapex ER (pramipexole dihydrochloride) Tablets

Date of Application: May 20, 2009

Date of Receipt: May 22, 2009

Our Reference Number: NDA 22-514

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 21, 2009 in accordance with 21 CFR 314.101(a).

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Stacy Metz

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