

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-514**

**OTHER REVIEW(S)**

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** February 12, 2010

**TO:** Stacy Metz, Regulatory Health Project Manager  
Kenneth Bergman, M. D., Medical Officer  
Division of Neurology Products

**THROUGH:** Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**FROM:** Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22-514

**APPLICANT:** Boehringer Ingelheim.

**DRUG:** Mirapex E (Pramipexole ER)

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of patients with advanced Parkinson's Disease

**CONSULTATION REQUEST DATE:** May 22, 2009

**DIVISION ACTION GOAL DATE:** March 22, 2010

**PDUFA DATE:** March 22, 2010

**I. BACKGROUND:**

The Sponsor, Boehringer Ingelheim submitted a New Drug Application for the marketing approval of Mirapex (Pramipexole ER) for the use in patients with advanced Parkinson’s Disease (PD). The results of one pivotal study was submitted in support of the application, Protocol BI 248-525: “A double-blind, double-dummy, placebo-controlled, randomized, three parallel group study comparing the efficacy, safety and tolerability of pramipexole ER versus placebo and versus pramipexole IR administered orally over 26-weeks maintenance phase in L-dopa treated patients with advanced Parkinson’s disease (PD).”

This was a randomized double-blind, placebo and active controlled trial. At the end of the double-blind maintenance phase, patients were eligible to enter an open label extension study. The duration of the study for a given subject was 26-weeks. The patients were assigned to treatment groups: 0.375 mg once daily, 075 mg once daily, 3.0 mg once daily, or 4.5 mg once daily, and a placebo once daily. The treatment included male and female subjects over 18 years of age.

The primary objective of study Protocol BI 248-525 was to determine the efficacy (as measured by the change from baseline to the end of the maintenance phase in the total score from UPDRS parts II and III combined), safety and tolerability of pramipexole ER compared with placebo in L-dopa treated patients with advanced PD. In addition, a numerical comparison of the efficacy of pramipexole IR was performed. Pramipexole ER was administered once daily at doses of 0.375mg, 0.75 mg, 1.5mg, 3.0mg, or 4.5mg and compared with placebo matching the ER tablets.

The review division requested inspection of Protocol BI 248-525, and three foreign clinical investigators were targeted for inspection due to enrollment of relatively large number of subjects.

**II. RESULTS (by protocol/site):**

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Roland D. Jamora, M.D 2789 E. Rodriguez Sr. Blv. 1102 Quezon City Philippines	Protocol BI 248- 525 20 subjects	12/1-4/09	NAI
Ernest Balaguer, M.D. Hospital General de Catalunya 08190 San Cuga del Valles, Barcelona, Spain	Protocol BI 248- 525 7 subjects	12/3-9/09	NAI
Miguel Aguilar, M.D. Hospital Mutua de Tarrasa Neurology Dept. Plaza Dr.	Protocol BI248- 525 5 subjects	Nov.30- Nov. 30- 12/2/09	NAI

Robert, 5 08221 Tarrasa, Spain			
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Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol BI 248-525

1. **Ronald Jamora, M.D.**  
**Philippines**

**a. What Was Inspected:** At this site, a total of 24 subjects were screened; and 4 subjects were reported as screen failures. Twenty (20) subjects were randomized and completed the study. One subject was not treated due to elevation of liver function tests. Informed consent, for records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 24 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, UPDRS and PDSS scores, IRB records, and source documents were compared to data listings, including primary efficacy endpoints and adverse events.

**b. General observations/commentary:** Our investigation found no evidence of under reporting of adverse events. No significant violations were noted and a Form FDA 483 was not issued.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

**c. Assessment of Data Integrity**

The data appear acceptable in support of the pending application.

2. **Ernest Balageur, M.D.**  
**Barcelona, Spain**

**a. What Was Inspected:** At this site, a total of 8 subjects were screened and 7 subjects were randomized into the study and six (6) subjects completed the study. Informed consent, for all subjects reviewed, verified that subjects signed prior to enrollment.

The medical records/source data for 7 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, patients' diaries for inclusion/exclusion criteria, and source documents were compared to data listings for primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** Our investigation found no evidence of under reporting of adverse events. No significant violations were noted and no Form FDA 483 was issued.

The medical records reviewed disclosed no adverse finding that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. There were no limitations to this inspection.

**c. Assessment of Data Integrity**

The data from Dr. Balageur's site are considered reliable and appear acceptable in support of the pending application.

**Note:** During the review of Subjects' diaries it was noted that some of the entries made in the diaries appeared to have been completed by someone other than the caregiver or the patients. When Dr. Balageur was asked if he had assisted in completing the diaries, he stated he did not complete the diaries, but agreed that the entries/marks were different. These changes have no impact on the acceptability of the data.

**3. Miguel Aguilar, M.D.  
Tarrasa, Spain**

**a. What Was Inspected:** At this site, a total of 6 subjects were screened, 5 subjects were randomized, and 4 subjects completed the study. Informed consent, for all subjects reviewed, verified that all subjects signed prior to enrollment.

The medical records/source documents for six (6) subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, concomitant medications, and source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. There were no known limitations to this inspection.

**c. Assessment of Data Integrity**

The data from Dr. Aguilar's site are considered reliable and appear acceptable in support of the pending application.

Note: During the review of subjects' diaries it was noted that some of the entries made in the diaries appeared to have been completed by someone other than the caregiver or the patients. When the clinical investigator was asked if he had assisted in completing the diaries, Dr. Aguilar admitted that for at least one subject he assisted the subject in completing the diary. The completion of the diary by the investigator does not affect the acceptability of the data. The FDA investigators reiterated to Dr. Aguilar on the importance of study subjects or their caregivers to complete their own diaries as this was required by the protocol. Dr. Aguilar acknowledged the observation.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three foreign clinical investigators were inspected in support of this application. The inspections of Drs. Jamora, Balaguer, and Aguilar revealed no significant problems that would adversely impact data acceptability. The completion of subjects' diaries by someone other than the subject was discussed with the review division and found no significant issues. The data submitted from these three sites are acceptable in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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

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/s/

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ANTOINE N EL HAGE  
02/17/2010

TEJASHRI S PUROHIT-SHETH  
02/17/2010

## DSI CONSULT: Request for Clinical Inspections

**Date:** July 22, 2009

**To:** Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Antoine El Hage, DSI Reviewer  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** *Kenneth Bergmann, MD, Medical Reviewer, Division of Neurology Products*  
*Gerald David Podskalny, DO, Medical Team Leader DNP*

**From:** *Stacy Metz, PharmD, Regulatory Health Project Manager, DNP*

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA-22-514

Applicant/ Boehringer-Ingelheim, Contact: Daniel Coleman, Ph.D., FAX 203-791-6262; Telephone (203)-798-5081;

e-mail [Daniel.coleman@boehringer-ingelheim.com](mailto:Daniel.coleman@boehringer-ingelheim.com)

Address: 900 Ridgebury Road, PO Box 368 Ridgefield, CT 06877

Drug Proprietary Name: Mirapex ER

NME or Original BLA (Yes/No): No

Review Priority: Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of Adults with early and advanced Parkinson's Disease

Received: May 22, 2009

Action Goal Date: March 22, 2010

Inspection Summary: February 22, 2010

**II. Protocol/Site Identification**

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site: 63204 Dr. Roland Dominic Jamora (PI) St Lukes Medical Center Neurology 2789 E. Rodriguez Sr. Boulevard 1102 Quezon City, PHILIPPINES	248.525	N=20	Parkinson's disease
Site: 34002 Dr. Ernest Balaguer (PI) Hospital General de Catalunya Neurology Department Peidro i Pons, 1 08190 San Cugat del Valles, (Barcelona), SPAIN	248.525	N=7	Parkinson's disease
Site: 34008 Dr. Miguel Aguilar (PI) Hospital Mutua de Terrassa Neurology Department Plaza Dr Robert, 5 08221 Tarrasa (Barcelona) SPAIN	248.525	N=5	Parkinson's disease

**III. Site Selection/Rationale**

*This trial in advanced Parkinson's disease was performed in Europe and the Far East. These three sites are requested on the basis of their high enrollment of 76 sites in this NDA's pivotal efficacy/safety trial The Philippines site represents 20 % of all patients entered in that country. The two clinical sites in Barcelona represent almost half of that country's contribution to the trial.*

*All three sites have well qualified investigators but we have not had previous experience with these sites' performance. There is nothing in our analysis to indicate that any site in the study had a disproportionate effect on study outcome, question of scientific misconduct, or disproportionate number of protocol violations or safety issues. However the Philippines site did have a different response profile for the major outcome variable in the placebo arm of the trial (when compared to the performance of patient groups from other sites in the trial).*

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: Enrollment of large numbers of study subjects.

**IV. Tables of Specific Data to be Verified (if applicable)**

Should you require any additional information, please contact *Stacy Metz, RPM at 301-796-2139 or Ken Bergmann, Medical Officer at 301-796-2151.*

Concurrence: (as needed)

\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer  
\_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

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Russell Katz

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## **PREA Language for NDA 022514 Approval Letter**

### **Background:**

Product:

Mirapex® ER (pramipexole dihydrochloride) Extended-release Tablets, 0.375 mg, 0.75 mg, 1.5mg, 3 mg, and 4.5 mg.

Indication:

This new drug application provides for an extended-release dosage of Mirapex® ER (pramipexole) for the treatment of the signs and symptoms of advanced Parkinson's disease.

### **For the letter:**

#### **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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Studies are impossible or highly impracticable because Parkinson's disease typically occurs in adults over the age of 40 and it does not occur in the pediatric population.

## Pediatric Research and Equity Act Waivers

NDA #: 22-514

Supplement Type:

Supplement Number:

***Note: This is a Type 6 NDA and is only expanding the approved claims for Mirapex ER to include advanced Parkinson's Disease. Mirapex ER was approved under NDA 22-421 for early Parkinson's Disease on February 19, 2010.***

Product name and active ingredient/dosage form:

Mirapex® ER (pramipexole dihydrochloride) Extended-release Tablets,

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Indication: Treatment of advanced Parkinson's Disease

1. Pediatric age group(s) to be waived – ages 0 to 16 years
2. Reason for waiving pediatric assessment requirements –

Studies are impossible or highly impractical because Parkinson's Disease is an adult-related condition (see Attachment 1) that does not occur in the pediatric population.

## Attachment I

### Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration

Alzheimer's disease

Amyotrophic lateral sclerosis

Atherosclerotic cardiovascular disease

Benign prostatic hypertrophy

Chronic Obstructive Pulmonary Disease

Erectile Dysfunction

Infertility

Menopausal and perimenopausal disorders

Organic amnesic syndrome

(not caused by alcohol or other psychoactive substances)

Osteoarthritis

Parkinson's disease

Postmenopausal Osteoporosis

Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:

Basal cell

Bladder

Breast

Cervical

Colorectal

Endometrial

Gastric

Hairy cell leukemia

Lung (small & non-small cell)

Multiple myeloma

Oropharynx (squamous cell)

Ovarian (non-germ cell)

Pancreatic

Prostate

Renal cell

Uterine