

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-421

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 28, 2010

To: Russell Katz, MD, Director
Division of Neurology Products

Through: Carlos M Mena-Grillasca, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: L. Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Mirapex ER (Pramipexole Dihydrochloride) Extended-release Tablets
0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg

Application Type/Number: NDA 022421

Applicant: Boehringer Ingelheim

OSE RCM #: 2010-17

1 INTRODUCTION

This review is written in response to a request from the Division of Neurology Products for a review of the revised Mirapex ER container labels, carton and insert labeling in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed container labels, carton and insert labeling under OSE RCM #2009-119, 2009-988 and 2006-377 dated August 14, 2009.

2 REGULATORY HISTORY

DMEPA originally reviewed container labels, carton labeling and insert labeling for Mirapex ER with the NDA submission in OSE Reviews #2009-119, 2009-988 and 2006-377 dated August 14, 2009. In addition, the review included an assessment to determine the potential for medication errors due to tablet similarity (i.e. size, color, shape, etc.) between the formulations of Mirapex (immediate release) and Mirapex ER (extended release) tablets.

Subsequently, this application received a Complete Response on August 24, 2009 due to similarities in container labels, carton labeling and between the Mirapex and Mirapex ER tablets, which may increase the potential for medication errors. Recommendations provided to the Sponsor included: 1) changes to the trade dress and color scheme to allow for clear visual differentiation between formulations, 2) modification of the imprint of the ER tablets to include the debossed "ER" designation on one side of the tablet and the product strength on the reverse side, 3) increasing the middle portion of the NDC number in a large font and prominence, 4) changing the NDC number for the Mirapex ER 0.75 mg tablets, and 5) providing color differentiation between each tablet strength of the ER product line. The complete response letter recommended that at a minimum the container labels and carton labeling needed to be changed, and that the imprint on the tablets (i.e. "ER" on one side and tablet strength on the reverse side) should be implemented.

3 MATERIAL REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the revised labels and labeling submitted by the Applicant on December 14, 2009 and product samples received on January 6, 2010. We also evaluated the recommendations pertaining to the previous reviews in OSE RCM #2009-119, 2009-988, 2006-377 and the Complete Response letter.

4 RECOMMENDATIONS

The Applicant addressed the minimum requirements communicated in the Complete Response letter (i.e. container labels and carton labeling differentiation and tablet imprint changes). We note the Applicant also added a "once daily" statement on the container labels and carton labeling principal display panel. DMEPA finds the Applicant's revisions to the physical appearance of the Mirapex ER tablets, the container labels and carton labeling acceptable.

However, we note that the container labels and carton labeling do not include the statement "Tablets must be swallowed whole and must not be chewed, crushed, or divided" in accordance with the Dosage and Administration section of the insert labeling.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Laurie Kelley, Project Manager, at 301-796-5068.

4.1 COMMENTS TO THE APPLICANT

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

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

Appendix A: Unit of Use Container Labels (30 Count)

Store at 25°C (77°F) (see insert). Protect from exposure to high humidity.
Dosage: Read accompanying prescribing information.
 Keep out of reach of children.
 Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA
 Manufactured by: Boehringer Ingelheim Pharma GmbH & Co. KG Ingelheim, Germany
 Product and trademark licensed from: Boehringer Ingelheim International GmbH
 ©2010 Boehringer Ingelheim International GmbH ALL RIGHTS RESERVED
 U.S. Patent No. 4,886,812

NDC 0597-0109-30 30 Tablets

Mirapex® ER™
 (pramipexole dihydrochloride)
Extended-release Tablets
0.375 mg Once Daily

Dispense in this ORIGINAL Unit of Use Container
Rx only

Boehringer Ingelheim

LOT EXP

0597-0109-30

74418-01

L5134A



Store at 25°C (77°F) (see insert). Protect from exposure to high humidity.
Dosage: Read accompanying prescribing information.
 Keep out of reach of children.
 Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA
 Manufactured by: Boehringer Ingelheim Pharma GmbH & Co. KG Ingelheim, Germany
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 U.S. Patent No. 4,886,812

NDC 0597-0285-30 30 Tablets

Mirapex® ER™
 (pramipexole dihydrochloride)
Extended-release Tablets
0.75 mg Once Daily

Dispense in this ORIGINAL Unit of Use Container
Rx only

Boehringer Ingelheim

LOT EXP

0597-0285-30

74435-01

L5126A



Store at 25°C (77°F) (see insert). Protect from exposure to high humidity.
Dosage: Read accompanying prescribing information.
 Keep out of reach of children.
 Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA
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 U.S. Patent No. 4,886,812

NDC 0597-0113-30 30 Tablets

Mirapex® ER™
 (pramipexole dihydrochloride)
Extended-release Tablets
1.5 mg Once Daily

Dispense in this ORIGINAL Unit of Use Container
Rx only

Boehringer Ingelheim

LOT EXP

0597-0113-30

74434-01

L5135A



Store at 25°C (77°F) (see insert). Protect from exposure to high humidity.
Dosage: Read accompanying prescribing information.
 Keep out of reach of children.
 Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA
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 U.S. Patent No. 4,886,812

NDC 0597-0115-30 30 Tablets

Mirapex® ER™
 (pramipexole dihydrochloride)
Extended-release Tablets
3 mg Once Daily

Dispense in this ORIGINAL Unit of Use Container
Rx only

Boehringer Ingelheim

LOT EXP

0597-0115-30

74433-01

L5133A



Store at 25°C (77°F) (see insert). Protect from exposure to high humidity.
Dosage: Read accompanying prescribing information.
 Keep out of reach of children.
 Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA
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 U.S. Patent No. 4,886,812

NDC 0597-0116-30 30 Tablets

Mirapex® ER™
 (pramipexole dihydrochloride)
Extended-release Tablets
4.5 mg Once Daily

Dispense in this ORIGINAL Unit of Use Container
Rx only

Boehringer Ingelheim

LOT EXP

0597-0116-30

74432-01

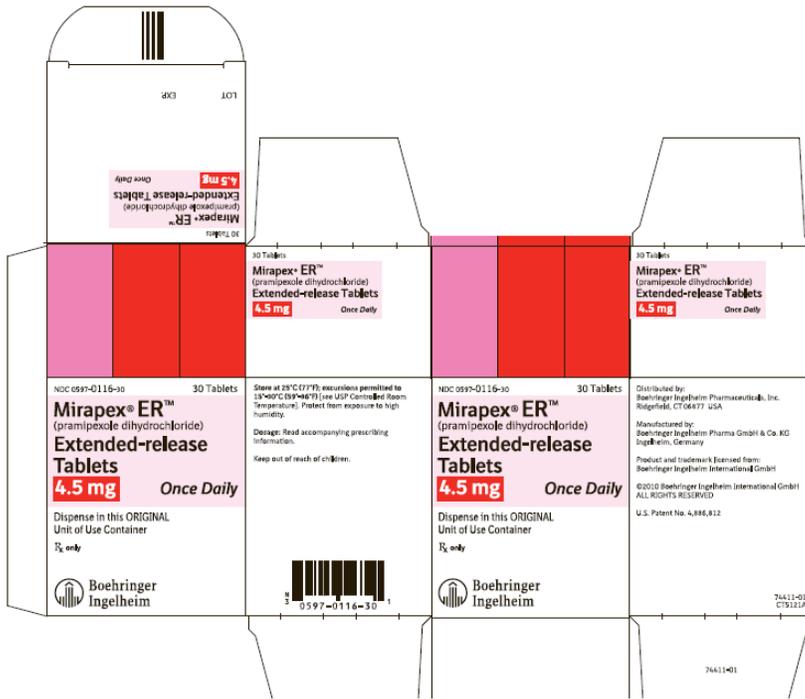
L5132A



Appendix B: Unit of Use Carton Labeling







Appendix C: Professional Sample Container Labels (7 count)

Store at 25°C (77°F) (see Insert). Protect from exposure to high humidity.

Dosage: Read accompanying prescribing information.

Keep out of reach of children.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim, Germany

Product and trademark licensed from:
Boehringer Ingelheim International GmbH

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U.S. Patent No. 4,886,812

7 Tablets

Mirapex® ER™
(pramipexole dihydrochloride)
Extended-release Tablets
0.375 mg Once Daily

Professional Sample

Rx only

Boehringer Ingelheim

0.375

LOT

EXP

L5128A

74420-01

Store at 25°C (77°F) (see insert). Protect from exposure to high humidity.

Dosage: Read accompanying prescribing information.

Keep out of reach of children.

Distributed by:
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Ridgefield, CT 06877 USA

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Ingelheim, Germany

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U.S. Patent No. 4,886,812

7 Tablets

Mirapex® ER™
(pramipexole dihydrochloride)
Extended-release Tablets
0.75 mg Once Daily

Professional Sample

Rx only

Boehringer Ingelheim

0.75

LOT

EXP

L5127A

74419-01

Store at 25°C (77°F) (see insert). Protect from exposure to high humidity.

Dosage: Read accompanying prescribing information.

Keep out of reach of children.

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Ridgefield, CT 06877 USA

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Ingelheim, Germany

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U.S. Patent No. 4,886,812



7 Tablets

Mirapex® ER™
(pramipexole dihydrochloride)
Extended-release Tablets
1.5 mg *Once Daily*

Professional Sample

Rx only



LOT

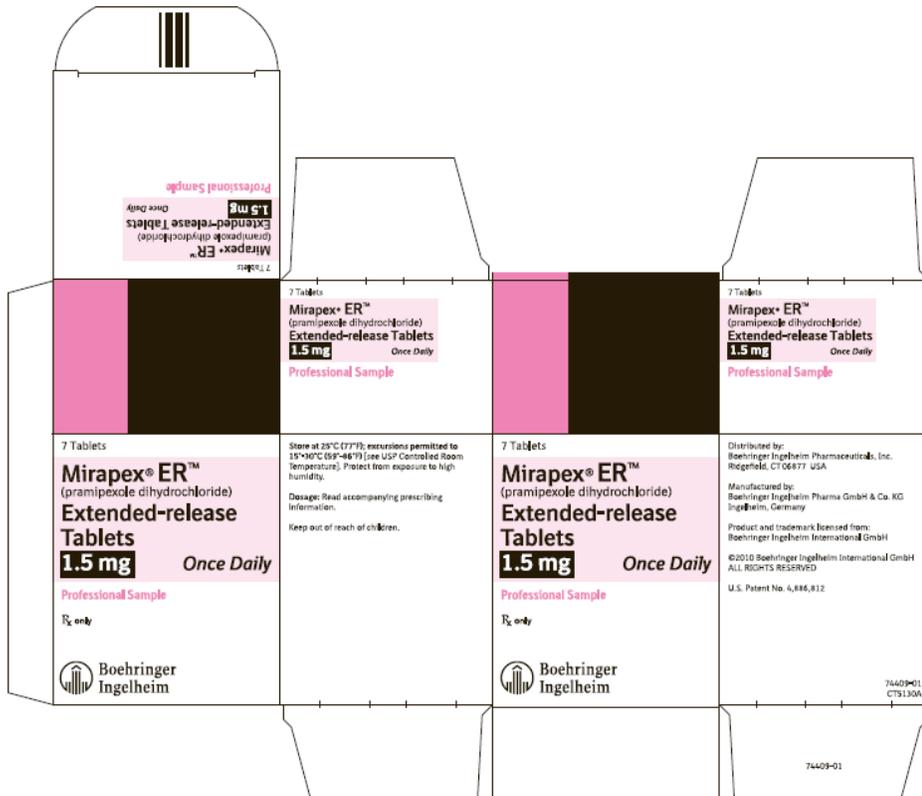
EXP

LS131A

74421-01

Appendix D: Professional Sample Carton Labeling





Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22421	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRAMIPEXOLE DIHYDROCHLORIDE

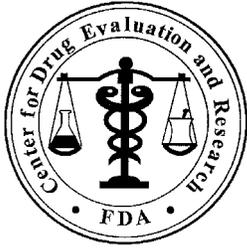
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Latoya S TOOMBS
01/28/2010

CARLOS M MENA-GRILLASCA
01/28/2010

DENISE P TOYER
01/29/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 14, 2009

To: Russell Katz, MD, Director
Division of Neurology Products

Through: Carlos M. Mena-Grillasca, RPh, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Mirapex ER (Pramipexole Dihydrochloride) Extended-release
Tablets
0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg

Application Type/Number: NDA 22-421

Applicant/sponsor: Boehringer Ingelheim

OSE RCM #: 2009-119
2009-988
2006-377

1 INTRODUCTION

This review was written in response to a request from the Division of Neurology Products to evaluate the container labels, carton and package insert labeling for the product Mirapex ER (NDA 22-421), for areas that could lead to medication errors. Additionally, DMEPA was consulted to determine whether medication errors may occur due to similarity (i.e. size, color, shape, etc.) of the dosage forms of Mirapex (immediate release) and Mirapex ER (extended release) tablets.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the Mirapex ER container labels, carton and insert labeling received on June 19, 2009 (see Appendix C thru F). In addition, samples of the immediate and extended release formulations were submitted for evaluation.

Since Mirapex has been marketed since 1997, DMEPA conducted a search of the Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with the currently marketed Mirapex product which may be indicative of potential confusion with Mirapex ER.

The MedDRA Higher Level Group Term (HLGT) Medication Error, the Preferred Term (PT) Product Quality Issues, verbatim substance names “Mira%”, “Mera%”, and “Myra%”, and the tradename “Mirapex”, were used as search criteria.

The cases were manually reviewed to determine if medication errors occurred involving the labels or labeling or tablet similarity. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify contributing factors.

3 RESULTS AND DISCUSSION

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE

A search of the AERS database was performed on August 5, 2009. We retrieved a total of 108 reports. Of the 108 reports, 102 reports were not evaluated further because they were deemed not related to labels and labeling or tablet similarity of the proposed product. The majority of these reports described overdoses and adverse events. Ten of the 102 reports described name confusion and these reports were evaluated separately in the Mirapex ER proprietary name review (OSE review # 2009-116).

A total of six cases were determined to be relevant to this review. All six cases described confusion between different strengths of Mirapex.

- A Mirapex order for 0.125 mg was dispensed as 1.25 mg. The error was discovered prior to administration of the wrong drug. No causality was provided.
- While a patient was in a long term care facility, the Mirapex dose was 0.25 mg QID but the patient was given 2.5 mg QID from (b) (4). On (b) (4), the patient developed hallucinations and at that time Mirapex was

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

discontinued. No causality was provided and the reporter did not indicate whether the hallucinations were a result of the wrong Mirapex dose.

- Patient received 0.25 mg QID instead of 0.125 mg qday for 10 days. Patient transferred to behavioral study with complaints of depression. Upon transfer the error was discovered. However, insufficient details were supplied in the case to detect if the depression was an adverse event resulting from the medication error and no causality was provided as to why the wrong dose was dispensed.
- Pharmacy technician scanned a bottle of Mirapex 1 mg, then proceeded to combine full bottles of 1 mg and 1.5 mg into the same prescription bottle. When the pharmacist checked the prescription and took the lid off, he only saw the 1 mg tablets on the top. The report did not indicate whether the patient received the medication nor did it provide causality as to why the 1 mg and 1.5 mg tablets were combined into the same bottle.
- Reporter stating, “Mirapex tablets-all strengths look exactly alike except the # of the dose. This can lead to serious misfills in strength!”
- A pharmacy technician re-packaged Mirapex 0.125 mg tablets as unit dose for hospital pharmacy use. However the label was mis-typed as “Mirapex 0.5 mg tablets” instead. The repackaged medication was mistakenly read as 0.5 mg tablets by other staff members because they had difficulty reading the strength on the bottle. The strength on the bottle was printed in lime-green. The combination of the lime-green font and the white background made it difficult to clearly read the strength. The error was caught by another pharmacist.

Although there have been post-marketing cases of strength confusion within the existing Mirapex immediate-release product line it is difficult to determine if the causality is based on product selection, transcription or prescribing errors because of the limited information provided in these cases. Therefore, DMEPA is not recommending any regulatory action at this time for Mirapex NDA 20-667.

3.2 MIRAPEX AND MIRAPEX ER TABLET COMPARISON

Mirapex ER will be added to an existing product line that already has an immediate-release oral dosage formulation. The Applicant proposes to use the root name Mirapex and the modifier ER to differentiate the extended-release formulation from the currently marketed product, Mirapex. This naming convention is commonly used when an extended-release dosage form is added to a product line with an existing immediate-release formulation.

DMEPA notes the Mirapex (immediate release) tablets are supplied in 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, and 1.5 mg strengths. All tablets are white, varying in size (small, medium, large) and shape (round, oval). All tablets are scored except the 0.125 mg and 0.75 mg strengths. Each tablet is debossed with “BI” on one side and an internal identification code on the reverse side.

The Mirapex ER (extended release) tablets are supplied in 0.375 mg, 0.75 mg, 1.5 mg, 3 mg and 4.5 mg strengths. All tablets are white, varying in size (medium, large) and shape (round, oval). None of the tablets are scored. Each tablet is debossed with an imprint of the Boehringer Ingelheim symbol on one side and an internal identification code on the reverse side. (see Appendix A for tablet comparison)

Comparison between the two formulations shows that all tablets are white, size differentiation is minimal, and although the overlapping strengths have different shapes, there is no clear pattern unique to one formulation that could be used to differentiate Mirapex from Mirapex ER. Similarly, comparison between tablets within the Mirapex ER product line, shows that all tablets are white, size differentiation is minimal, and although the varying strengths have two different shapes, there is no clear feature that pharmacists, patients and caregivers could use to differentiate one strength from the other. In addition, AERS reports for the immediate release formulation show that medication errors involving the wrong strength being dispensed and administered have occurred.

Additionally, we are concerned that the similar shapes and sizes used within the Mirapex ER product line may not provide adequate visual distinction between the various strengths. Specifically the 0.375 mg and 0.75 mg tablets; and the 1.5 mg, 3 mg, and 4.5 mg tablets look very similar to one another. If the wrong Mirapex ER strength is selected when filling a prescription the slight variation in size and imprint codes may not be adequate for a pharmacist to detect the error prior to dispensing or a patient to detect the error prior to administering. These concerns are supported by postmarketing errors with the immediate release Mirapex product which uses the same shape and color for the 0.25 mg, 0.5 mg, and 0.75 mg tablets; and the 1 mg and 1.5 mg tablets.

Optimally, the Applicant would have developed an extended-release formulation of pramipexole tablets with strengths that do not overlap with those of the currently marketed pramipexole immediate-release tablets. In not doing this, the Applicant has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. If the Applicant chose a product strength with a small deviation from the 0.75 mg and 1.5 mg immediate-release Mirapex strengths, the differences in strength would lessen the risk of error and increase the potential for an error to be detected before it reaches the patient, if the wrong pramipexole product were selected or if the modifier were omitted or overlooked.

In a nationwide survey, pharmacists perceived that non-tablet factors such as physician handwriting, similar product names and package labeling are the leading causes of dispensing errors; however, tablet similarity is cited more than half the time (56%) as a contributing factor.² DMEPA notes that confusion between Mirapex and Mirapex ER is likely to occur, and that collective measures to ensure product differentiation are necessary to help to minimize these potential errors.

4 RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling and tablet comparison noted areas of needed improvement in order to minimize the potential for medication errors.

The majority of our concerns relate to the potential for confusion between Mirapex and Mirapex ER tablets, particularly that both formulations share 0.75 mg and 1.5 mg strengths, in addition to confusion between the strengths within the Mirapex ER product line. Our recommendations to help minimize the risk of errors with the Mirapex and Mirapex ER products are included in section 4.1.

² <http://www.globenewswire.com/newsroom/news.html?id=101405> accessed 31JUL2009.

4.1 COMMENTS TO THE DIVISION

DMEPA believes that these measures could help minimize dispensing and/or administration errors by providing a visual means for pharmacists, patients and caregivers to readily identify the product formulation.

1. Modifying the imprint of the extended-release tablets to include the debossed “ER” designation on one side of the tablet and the product strength on the reverse side to ensure differentiation of the extended- and immediate-release formulations in the marketplace. Ensuring that the imprints are as prominent as physically possible.
2. Providing color differentiation between each tablet strength of the extended-release product line.

4.2 COMMENTS TO THE APPLICANT

A. General Comments (On all Carton Labeling and Container Labels)

1. The light-green color scheme and layout chosen for the Mirapex ER trade dress is similar to the currently marketed Mirapex immediate-release product. We are concerned this could lead to selection errors and the administration of the wrong product because these bottles will likely be stored side-by-side or in a similar environment. Change the trade dress and color scheme of Mirapex ER to provide more adequate visual differentiation between Mirapex and Mirapex ER.
2. Revise “Dosage” to read “Usual Dosage” and revise the statement to read, “See package insert for dosage information.”
3. Place the middle portion of the NDC number in a large font and prominence (e.g. xxxx-XXXX-xx) to help differentiate the Mirapex and Mirapex ER NDC numbers. Pharmacists use this portion of the NDC number to ensure the correct product is dispensed.
4. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the establish name shall be printed in letters that are at least half as large and with a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.
5. Since the tablets should not be chewed, crushed or divided, add the statement, “Swallow tablets whole. Do not chew, crush or divide.” on the label.

B. All Labels and Labeling (0.75 mg tablets)

Consider assigning a different NDC number to the Mirapex ER 0.75 mg tablets. The middle portion of the NDC number for this tablet (0111) is very similar to that of the immediate-release 0.75 mg Mirapex (0101). Assigning similar NDC numbers to products with overlapping strengths and with similar names, may lead to the incorrect drug being dispensed since pharmacists often use this portion of the NDC to identify the correct drug.

C. All Labels and Labeling (3 mg tablets)

Revise the presentation of the tablet strength to read “3 mg”. The use of trailing zeroes is included on ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations³ which states they should never be used when communicating medical information. Additionally, as part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed to not allow such designations to appear in the approved labeling of products.

³ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, accessed 15APR2009.

Appendix A: Mirapex and Mirapex ER Tablets Comparison

mg	Mirapex IR	Mirapex ER
0.125		
0.25		
0.375		(b) (4)
0.5		
0.75		(b) (4)
1.0		
1.5		(b) (4)
3.0		
4.5		

12 Page(s) of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

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

/s/

Latoya S TOOMBS
08/17/2009

CARLOS M MENA-GRILLASCA
08/17/2009

TODD D BRIDGES
08/17/2009

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 3, 2009

TO: Beverly Conner, Regulatory Health Project Manager
Kenneth Bergman, M.D., Medical Officer
Division of Neurology Drug 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: 22-421

APPLICANT: Boehringer Ingelheim

DRUG: Pramipexole ER oral tablets (Mirapex ER)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review (within 6 months)

INDICATION: Treatment of adults with early Parkinson's Disease

CONSULTATION REQUEST DATE: February 10, 2009

DIVISION ACTION GOAL DATE: August 24, 2009

PDUFA DATE: August 24, 2009

I. BACKGROUND:

The sponsor, Boehringer Ingelheim, has submitted a supplemental new drug application for marketing approval of Mirapex (pramipexole ER) when compared with Mirapex (pramipexole IR), and placebo when administered orally over a 26-week maintenance phase in patients with early Parkinson’s disease (PD). The duration of the study for a given subject is 26 weeks.

The review division requested inspection of Protocol 248.524 entitled “A double –blind, double-dummy, placebo-controlled, randomized, three parallel groups study comparing the efficacy, safety and tolerability of pramipexole ER versus placebo and versus pramipexole IR administered orally over a 26-week maintenance phase in patients with early Parkinson’s disease (PD)” The sponsor submitted results from above protocol in support of NDA 22-421.

The inspection targeted two clinical investigators one domestic and one foreign who enrolled a relatively large number of subjects. Both clinical investigators have expert knowledge in treating Parkinson’s in adults.

II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Andreas Kupsch, M.D. Charite Berlin, Neurologische Klinik and Poliklinik Augustenburger Platz 1 13353 Berlin, Germany Site # 49002	Protocol 248.524 22 subjects	5/18-20/09	Pending (preliminary classification) NAI
Stuart Isaacson, M.D Parkinson’s Disease and Movement Disorders of Boca Raton 951 NW 13 th Street Bldg 5-E Boca Raton, FL 33486 Site # 01010	Protocol 248.524 14 subjects	5/19-22/09	Pending (preliminary classification) VAI

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. An inspection addendum will be generated if the conclusions change significantly upon receipt and review of the EIR.

1. Andreas Kupsch, M.D.
Berlin, Germany

At this site, a total of 22 subjects were screened, 5 subjects were reported as screen failures, 17 subjects were randomized and 8 subjects completed the study and continued using the test article under another study. Nine subjects did not complete the study; five (5) of the 9 subjects who did not complete the study were discontinued for lack of efficacy. Informed consent for all subjects was verified to be signed by subjects prior to enrollment.

The medical records/source data for all subjects were reviewed in depth, including drug accountability, laboratory records, and the source data were compared to case report forms and data listings, including primary efficacy measures and adverse events. Adverse events experienced by subjects were reported to the IRB and the sponsor within the required time frames. One subject experienced sleep apnea. The inspection revealed the investigation was conducted according to the investigational plan. The records reviewed were accurate, and no regulatory violations were found. There were no limitations to this inspection.

Assessment of Data Integrity

The data appear acceptable in support of the pending application.

2. Stuart Isaacson M.D.
Boca Raton, FL 33486

At this site, a total of 11 subjects were screened and enrolled at this site. Three (3) subjects withdrew early consent, and one subject died from acute respiratory distress. Seven subjects completed the study and continued on the open label phase of the study. Informed consent for all subjects was verified to be signed by subjects prior to enrollment (except for 2 subjects).

The medical records/source data for all subjects were reviewed, including drug accountability records, protocol inclusion criteria, laboratory records, IRB records, and source documents were compared to data listings, including primary efficacy endpoints and adverse events. Adverse events experienced by subjects were reported to the IRB and the sponsor within the required time frames. Subject 2841 experienced headache, Subject 2842 was hospitalized for gallstones, atrial fibrillation and pneumonia, Subject 2824 discontinued due to severe tremor in his hands, and Subject 2845 experienced bloody stool, constipation/urinary retention and squamous cell carcinoma on the right cheek that was removed by surgery.

The medical records reviewed disclosed a lack of oversight by the clinical investigator, protocol deviations in that for six subjects who completed Visit 7 were administered the UPDRS testing outside the protocol specified time frame at 2 hours +/-20 minutes post-dosing, for 2 subjects the revised informed consent

was signed 2-6 months later, PK blood sampling was not done according to the amended protocol, dates for temperature logs for the product and PK(freezer log) samples were changed on holidays when the office was closed, three subjects were not randomized according to the plan as a result received the wrong medications. The protocol required evaluation of UPDRS and CGI were not done by the same rater, and transcription errors were found in few subjects records. In general, the records reviewed were found to be unreliable and therefore unacceptable. There were no known limitations to this inspection.

Assessment of Data Integrity

There were several deviations noted during the course of the inspection that led to some concerns with respect to data reliability. The findings were discussed with the review division and it is DSI's understanding that the division will not use the data from this site in support of the pending application.

Note that the clinical investigator provide adequate corrective plans to prevent the findings from recurring in the future.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Dr. Kupsch revealed no significant problems that would adversely impact data acceptability.

The data submitted from Dr. Isaacson revealed several deficiencies. The clinical investigator acknowledged the inspectional findings and provided during the inspection corrective action plan including SOPs to remedy the situation. The SOPs provided appear acceptable. Several deviations were noted and may have an impact on the reliability of the data.

{ 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

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/s/

ANTOINE N EL HAGE
08/04/2009

TEJASHRI S PUROHIT-SHETH
08/04/2009

MEMORANDUM

To: Beverly Conner
Division of Neurology Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: July 31, 2009

Re: Comments on draft labeling for Mirapex ER (pramipexole HCl)
extended-release tablets
NDA 22-421

We have reviewed the proposed label for Mirapex ER (FDA version received by SEALD 7/29/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

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/s/

IRIS P MASUCCI
09/08/2009

LAURIE B BURKE
09/10/2009

DSI CONSULT: Request for Clinical Inspections

Date: February 10, 2009, Revised 3/23/09

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Antoine EL Hage, DSI Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Division of Neurology Products

Through: Dr. Russell Katz, DNP Division Director
Dr. Gerald Podskalny, Medical Team Leader
Kenneth Bergmann, M.D., Medical Reviewer

From: *Beverly Conner, Regulatory Health Project Manager, DNP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22-421
Applicant/ Daniel Coleman, Ph.D., FAX 203-791-6262; Telephone (203)-798-5081;
e-mail Daniel.coleman@boehringer-ingelheim.com):
Drug Proprietary Name: Mirapex ER
NME or Original BLA (Yes/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 Parkinson's Disease

PDUFA:
Action Goal Date: August 24, 2009
Inspection Summary Goal Date: July 24, 2009

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site: 49002 Andreas Kupsch MD [PI] Charité Berlin Neurologische Klinik und Poliklinik Augustenburger Platz 1 13353 Berlin, GERMANY	248.524	Efficacy N=5 Safety N=17	Parkinson's disease
Site: 01010 Stuart Isaacson, MD [PI] Parkinson's Disease and Movement Disorders of Boca Raton 951 NW 13th Street, Bldg. 5-E Boca Raton, FL 33486, USA	248.524	Efficacy N=3 Safety N=11	Parkinson's disease

III. Site Selection/Rationale

These two sites are requested on the basis of being two of the highest enrolling of 94 sites in a pivotal efficacy/safety trial (the highest in their respective countries). The efficacy portion of the trial had N= 259, whereas the total safety enrollment had reached 539 as of the submission cutoff date: this study is ongoing.

Both sites have well qualified investigators. 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.

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 *Beverly Conner, RPM at 301-796-1171* or *Ken Bergmann, Medical Officer at 301-796-2151*.

Concurrence: (as needed)

Dave Podskalny Medical Team Leader
Kenneth Bergmann Medical Reviewer
Dr. Rusty Katz_Division Director
(for foreign inspection requests or requests for 5 or more sites only)

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/s/

Russell Katz
3/23/2009 05:17:39 PM