

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-421**

**CHEMISTRY REVIEW(S)**

**NDA 22-421**  
**Quality Review #2**

**Mirapex (Pramipexole Dihydrochloride) Extended-Release  
Tablets**

**Boehringer Ingelheim Pharmaceuticals, Inc.**

**Wendy I. Wilson-Lee, Ph. D.**  
**Office of New Drug Quality Assessment**  
**For**  
**Division of Neurology Drug Products**

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## Chemistry Review Data Sheet

1. NDA: 22-421
2. REVIEW: 02
3. REVIEW DATE: 04-JAN-2010
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Memo to File	16-JUL-2008
Quality Review #1	05-JUN-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	14-DEC-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Address:	900 Ridgebury Road PO Box 368 Ridgefield, CT 06877
Representative:	Daniel T. Coleman, Ph.D. Associate Director, Drug Regulatory Affairs
Telephone:	203-798-5081

8. DRUG PRODUCT NAME/CODE/TYPE:

- |   |                             |
|---|-----------------------------|
| a) Proprietary Name:                            | Mirapex® ER Tablets         |
| b) Non-Proprietary Name (USAN):                 | Pramipexole Dihydrochloride |
| c) Code Name/# (ONDQA only):                    | N/A                         |
| d) Chem. Type/Submission Priority (ONDQA only): |                             |
| ● Chem. Type:                                   | 3                           |
| ● Submission Priority:                          | S                           |

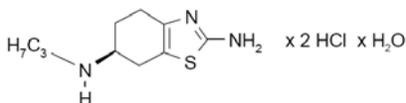
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Anti-Parkinson's disease
11. DOSAGE FORM: Tablet, Extended-Release
12. STRENGTH/POTENCY: 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, 4.5 mg

## Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:   X   Rx      OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
     SPOTS product – Form Completed  
  X   Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (S)-2-Amino-4,5,6,7-tetrahydro-6-propylaminobenzothiazole dihydrochloride monohydrate  
Mol. Formula: C<sub>10</sub>H<sub>17</sub>N<sub>3</sub>S x 2 HCl x H<sub>2</sub>O  
Mol. Weight: 302.26 (dihydrochloride monohydrate); 211.32 (free base)



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	3	Adequate	21-MAY-2008	
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
21413	II	Boehringer Ingelheim Pharma GmbH & Co. KG	Pramipexole Dihydrochloride Monohydrate	3	Adequate	28-JUL-2008	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-667	Immediate-Release Pramipexole Tablets for Parkinson's disease
IND	34,850	Immediate-Release Pramipexole Tablets for Parkinson's disease
IND	67,465	Immediate-Release Pramipexole Tablets for Restless Legs Syndrome

## Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76,936	Immediate-Release Pramipexole Tablets for Tourette Syndrome
IND	75,961	Extended-release Pramipexole Tablets for Parkinson's disease
(b)		

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable.	10-JUN-2009	E. Johnson
Pharm/Tox	Approval.	19-AUG-2009	T. Peters
Biopharm	Approval.	22-JUL-2009	C. Noory
LNC	N/A	N/A	N/A
Methods Validation	Validation by FDA not necessary.	04-JAN-2010	W. Wilson-Lee
DMEPA	Tradename Acceptable.	14-APR-2009	L. Toombs
EA	Categorical exclusion granted.	04-JAN-2010	W. Wilson-Lee
Microbiology	N/A	N/A	N/A

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## Chemistry Review for NDA 22-421

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From a CMC perspective, we recommend approval for 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, and 4.5 mg Mirapex ER Tablets. Based on our review of the stability data and in accordance with ICH Q1E, we grant a 24 month drug product expiry for all tablet strengths packaged in either 30-count or 7-count presentations in (b) (4) bottles with plastic screw caps containing desiccant and stored at USP controlled room temperature, protected from moisture. We also grant a (b) (4) retest period for (b) (4) pramipexole dihydrochloride monohydrate drug substance and a (b) (4) holding period for bulk drug product tablets prior to final packaging.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

We have no CMC Phase 4 recommendations.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

Pramipexole dihydrochloride monohydrate is a dopamine D2 receptor agonist, administered orally in previously approved commercial immediate-release tablets. The drug substance is a white or almost white highly crystalline powder without any known polymorphs. (b) (4)

(b) (4) Pramipexole dihydrochloride monohydrate is not hygroscopic under ICH long-term and accelerated conditions but uptakes significant amounts of water at  $\geq 80\%$  RH.

Pramipexole dihydrochloride monohydrate is freely soluble in water and methanol ( $> 20$  mg/mL) and slightly soluble in 96% ethanol ( $\sim 18$  mg/mL). Its solubility in buffer media is well above 10 mg/mL between pH 1 and pH 7.5. A saturated aqueous solution of the drug substance has a pH value of 3.3. The high permeability and the high solubility classify pramipexole dihydrochloride monohydrate as a BCS class 1 drug substance. Pramipexole dihydrochloride monohydrate drug substance is a very stable compound. In the solid state and in solutions stored at ambient temperature, pramipexole dihydrochloride monohydrate does not degrade. Long-term and accelerated stability testing of (b) (4) drug substance did not reveal any significant changes in its physical and chemical properties.

The proposed tradename for pramipexole dihydrochloride monohydrate extended release tablets is Mirapex ER. The recommended dose range of Mirapex ER tablets for treatment of Parkinson's disease is 1.5 mg/day to 4.5 mg/day. (b) (4)

The 0.375 mg and 0.75 mg strength Mirapex ER tablets are white to off-white, round, biconvex, beveled tablets. The 1.5 mg, 3 mg and 4.5 mg strength Mirapex ER tablets are white to off-white, oval, biconvex, tablets. Each tablet is debossed with the tablet strength on one side and the code ER on the other side to differentiate the tablets from the immediate release formulation as well as from each other. The ER tablet manufacturing process includes (b) (4) main steps – (b) (4)

## Executive Summary Section

(b) (4). All ER formulation excipients comply with their current USP/NF monographs. (b) (4)  
(b) (4)

Suitable specifications control the quality of the commercial drug product. The proposed tests and acceptance criteria ensure the overall quality, identity, and strength of the packaged tablets over the expected shelf-life period. For Mirapex ER tablets only one degradation product, CD 10503, was systematically detected above the reporting threshold during development. Primary stability results at long-term and accelerated conditions showed no significant changes for any of the test parameters under any of the storage condition. All primary stability results met the proposed regulatory specifications. The primary stability batches were packaged in the proposed commercial container closure system. The stability results support the recommended shelf-life period. The stress stability studies indicate that Mirapex ER tablets should be protected from high humidity (b) (4). The stress studies also show that no special packaging or labeling is needed to mitigate light exposure.

**B. Description of How the Drug Product is Intended to be Used**

The extended-release formulation of pramipexole dihydrochloride is for once daily administration in the treatment of Parkinson's disease. This is in contrast to the three times a day treatment required with the IR formulation. Mirapex ER tablets can be taken with or without food. Mirapex ER tablets should be swallowed whole. They should not be chewed, crushed, or divided. The starting dose is 0.375 mg given once per day. Based on efficacy and tolerability, dosages may be increased gradually every 5 to 7 days, first to 0.75 mg per day and then by 0.75 mg increments up to a maximum recommended dose of 4.5 mg per day. If a significant interruption in therapy with Mirapex ER tablets has occurred, re-titration of therapy may be warranted. The recommended storage condition is USP Controlled Room Temperature (25°C (77°F); excursions permitted to 15-30°C (59-86°F)), protected from exposure to high humidity for up to 24 months when stored in (b) (4) bottles with child-resistant caps and desiccant.

**C. Basis for Approvability or Not-Approval Recommendation**

We recommend approval of the 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg strengths of Mirapex (pramipexole dihydrochloride) ER Tablets. The drug substance and drug product information provided in the submission and subsequent amendments support the approval of this application. The drug substance and drug product regulatory specifications adequately control the identity, purity, strength, and quality of each. The drug substance and drug product stability data demonstrate that both remain stable through the proposed re-test and expiry periods. The drug substance and drug product container closures provide adequate protection to ensure the stability of both. The labeling adequately provides the storage conditions, expiry, ingredient, and how supplied information.

**III. Administrative****A. Reviewer's Signature**

*Wendy I. Wilson-Lee*

**B. Endorsement Block**

WWilson-Lee: 04-JAN-2010

MHeimann: 04-JAN-2010

RSood: 12-JAN-2010

**C. CC Block**

DHenry

SMetz

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/s/

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David Claffey  
11/24/2008 11:03:42 AM  
CHEMIST

Ramesh Sood  
11/24/2008 11:52:53 AM  
CHEMIST