

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-421**

**SUMMARY REVIEW**

## MEMORANDUM

DATE: February 19, 2010

FROM: Director  
Division of Neurology Products/HFD-120

TO: File, NDA 22-421

SUBJECT: Action Memo for NDA 22-421, for Mirapex ER (pramipexole dihydrochloride) Extended-release Tablets in patients with early Parkinson's Disease (PD)

NDA 22-421, for Mirapex ER (pramipexole dihydrochloride) Extended-release Tablets in patients with early Parkinson's Disease (PD), was submitted by Boehringer Ingelheim Pharmaceuticals, Inc., on 10/23/08. The division issued a Complete Response (CR) letter on 8/24/09. The reasons for the CR action were related to our concerns about potential medication errors, due to significant similarities in the appearance of the various ER tablet strengths to each other as well as to various of the strengths of the already marketed immediate release Mirapex tablets. In addition, we had concluded that the carton and container labels of these various products/strengths were also quite similar, increasing the risk for errors, and that the lack of a uniform shape within the specific formulations also was likely to result in medication errors.

We had noted, in the CR letter, various changes to the product(s) and labels that we believed would minimize this risk. We stated that, at a minimum, the carton and container labels should be changed, and that the, "...markings on the tablet should be revised to reflect the strength and the extended-release formulation by specifying the letters ER."

The sponsor responded to the CR letter with a Complete Response dated 12/14/09. In that submission, they proposed the minimum changes that we had mandated; namely, the carton and container labels were revised to further distinguish the various formulations and strengths, and the ER tablets were debossed with the strengths on one side and the letters "ER" on the other. They also submitted CMC information to support these changes.

The submission has been reviewed by Dr. L. Shenee' Toombs and Carlos M. Mena-Grillasca, Division of Medication Error Prevention and Analysis, Drs. Wendy Wilson-Lee and Ramesh Sood, Office of New Drug Quality Assessment, and Dr. David Podskalny, Neurology Team Leader. The review team recommends that the application be approved.

I agree. The sponsor has made changes that I believe will minimize the risk for medication errors of the sort that we had been concerned about. As Dr. Podskalny notes, we can never be certain that no errors will occur, or that additional changes might not

prevent additional errors. Nonetheless, I agree that the changes that the sponsor has made are appropriate and adequate at this time. Of course, we will continue to monitor for errors in the post-marketing setting, and if additional changes are warranted, these will be considered as appropriate.

We have agreed with the sponsor on product labeling.

For these reasons, I will issue the attached Approval letter with appended product labeling.

Russell Katz, M.D.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22421

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ORIG-1

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BOEHRINGER  
INGELHEIM  
PHARMACEUTICA  
LS INC

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PRAMIPEXOLE  
DIHYDROCHLORIDE

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUSSELL G KATZ  
02/19/2010

## Cross-Discipline Team Leader Review

|  |   |
|--|---|
| <b>Date</b>  | February 10, 2010   |
| <b>From</b>  | Gerald D. Podskalny   |
| <b>Subject</b>   | Cross-Discipline Team Leader Review                               |
| <b>NDA/BLA #<br/>Supplement#</b>                       | NDA 22-241 (0022)   |
| <b>Applicant</b>                                       | Boehringer Ingelheim  |
| <b>Date of Submission</b>                              | December 14, 2009   |
| <b>PDUFA Goal Date</b>                                 | February 14, 2010   |
| <b>Proprietary Name /<br/>Established (USAN) names</b> | Mirapex ER (pramipexole ER)                                       |
| <b>Dosage forms / Strength</b>                         | Extended Release Tablets 0.375mg, 0.75mg, 1.5mg, 3mg<br>and 4.5mg |
| <b>Proposed Indication(s)</b>                          | 1. Early Parkinson's Disease                                      |
| <b>Recommended:</b>                                    | APPROVAL  |

## Cross Discipline Team Leader Review

### 1. Introduction

Boehringer Ingelheim submitted their response to the Agency's "Complete Response" (CR) Action Letter regarding their product pramipexole extended release (Mirapex ER), for treatment of the signs and symptoms of idiopathic early Parkinson's disease. The original application was filed on October 24, 2008 as a 505b(1) application. Boehringer-Ingelheim is ultimately seeking FDA approval of Mirapex ER for the signs and of idiopathic Parkinson's disease by combining a separate sNDA for the treatment of advanced PD (currently under review). The CR action taken on August 24, 2009, resulted from the potential for medication errors associated with Mirapex ER tablets, which was not adequately addressed in the sponsor's original application. Although, the Complete Response action only affected the early PD indication, the same issue would also impact the advanced PD application (due March 22, 2010). The sponsor submitted their response on December 14, 2009 and the Division of Neurology Products (DNP), Quality/CMC and DMEPA decided it met criteria for a complete response.

### 2. Background

The DNP discussed the potential for medication errors with the other involved review divisions. DMEPA expressed very similar concerns for potential confusion between Mirapex and Mirapex ER as well as confusion between the appearances of the different tablets of Mirapex ER. The agency listed their concerns relating to the potential for medication errors in the CR letter (see below).

**Sources of Potential of Medication Errors Listed in the Agency’s Complete Response Action Letter.**

1. *similarities between the carton and container labels for the ER and IR formulations,*
2. *similarities in tablets*
  - a. *the lack of a uniform shape within specific formulations,*
  - b. *the size, shape, and color of ER and IR tablets,*
  - c. *similarities in the size and shape of several of the strengths within the ER formulation itself (for example, the ER 1.5 mg and 3 mg tablet are almost identical in appearance, and very similar to the 4.5 mg tablet),*
  - d. *overlapping strengths of the ER and IR formulations (0.75 mg and 1.5 mg),*
  - e. *the presence of symbols debossed on the ER tablet that are not readily meaningful to either pharmacists or patients.*

The “Complete Response” action letter also contained suggestions for product improvement and a potential pathway leading to approval of Mirapex ER.

*“Although there may be numerous approaches that might minimize the risk of these errors, several possible changes are given below:*

1. *Change the trade dress and color scheme to allow for clear contrast/differentiation between the Mirapex and Mirapex ER product formulations.*
2. *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. Additionally, 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)*
3. *Modify 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 to ensure differentiation of the ER and immediate release formulations in the marketplace. Ensure that the imprints are as prominent as physically possible.*
4. *Provide color differentiation between each tablet strength of the ER product line.*

*We believe, at a minimum, that the carton and container labels should be changed, and that the markings on the tablet should be revised to reflect the strength and the extended-release formulation by specifying the letters ER”.*

BI responded on September 2, 2009 stating their intention to respond to the agency’s complete response action. The sponsor also requested feedback regarding proposed changes to the tablet image and carton/container changes. (b) (4)

### 3. CMC/Device

In the Complete Response action letter, CMC/Product Quality provided specific requirement regarding the product appearance (debossing), dissolution, and post-approval monitoring of product stability. BI provided samples of the revised (debossed) Mirapex ER tablets and the marketed Mirapex (immediate release) tablets for comparison. The revisions proposed by BI were reviewed by Quality/CMC. The specific deficiencies included in the CR letter and the Quality reviewer's comments appear below.

#### **CHEMISTRY, MANUFACTURING, AND CONTROLS**

To support the recommended changes to the drug product image, the following chemistry, manufacturing, and controls information is needed:

- 1. A revised drug product specification reflecting the changes to the drug product image for each tablet strength.**

**Quality Reviewer's Evaluation: Adequate** – The division requested samples of both the immediate release tablets and the revised extended release tablets on 16-DEC-2009 and the sponsor complied with our request on 04-JAN-2010. From a CMC perspective, we want to ensure that the decimal point is distinguishable in the debossing, especially for the smaller, round tablets (0.375 mg and 0.75 mg). After viewing the tablets, we determined that the sponsor indeed complied with the debossing requests.

- 2. Batch release certificates of analysis for one drug product batch per tablet strength manufactured with the new drug product image.**

**Report individual dissolution results for each tablet tested using the regulatory dissolution method and provide a comparison of the dissolution profiles, including f2 similarity factors, to those observed for the original tablet images**

#### **Quality Reviewer Summary Table of Revised Mirapex ER Batch Release Results**

Table 3 - Summary of New Image Mirapex ER Batch Release Results

| Test Parameter   | Acceptance Criteria  | CoA Results  |   |  |  |  |
|--|--|--|---|--|--|--|
|  |  | 0.375 mg<br>Batch 909218   | 0.75 mg<br>Batch 909219   | 1.5 mg<br>Batch 909220   | 3 mg<br>Batch 909221   | 4.5 mg<br>Batch 909222   |
| Appearance   | 0.375 mg: White to off-white, round, biconvex, bevel-edged tablets, one side debossed with 0.375 and the other side debossed with ER | White to off-white, round, biconvex, bevel-edged tablets, one side debossed with 0.375 and the other side debossed with ER | White to off-white, round, biconvex, bevel-edged tablets, one side debossed with 0.75 and the other side debossed with ER | White to off-white, oval, biconvex tablets, one side debossed with 1.5 and the other side debossed with ER | White to off-white, oval, biconvex tablets, one side debossed with 3.0 and the other side debossed with ER | White to off-white, oval, biconvex tablets, one side debossed with 4.5 and the other side debossed with ER |
|  | 0.75 mg: White to off-white, round, biconvex, bevel-edged tablets, one side debossed with 0.75 and the other side debossed with ER   |  |   |  |  |  |
|  | 1.5 mg: White to off-white, oval, biconvex tablets, one side debossed with 1.5 and the other side debossed with ER                   |  |   |  |  |  |
|  | 3 mg: White to off-white, oval, biconvex tablets, one side debossed with 3.0 and the other side debossed with ER                     |  |   |  |  |  |
| 4.5 mg: White to off-white, oval, biconvex tablets, one side debossed with 4.5 and the other side debossed with ER |  |  |   |  |  |  |
| (b) (4)  |  |  |   |  |  |  |
| Identification   | Retention time and UV spectrum comply with SND 919 reference substance   | Conforms   | Conforms  | Conforms   | Conforms   | Conforms   |
| Dissolution  |  | (b) (4)  |   |  |  |  |
| 2 hours  | (b) (4)  |  |   |  |  |  |
| 9 hours  |  |  |   |  |  |  |
| 24 hours   |  |  |   |  |  |  |
| Test Parameter   | Acceptance Criteria  | CoA Results  |   |  |  |  |
|  |  | 0.375 mg<br>Batch 909218   | 0.75 mg<br>Batch 909219   | 1.5 mg<br>Batch 909220   | 3 mg<br>Batch 909221   | 4.5 mg<br>Batch 909222   |
| Degradation  |  |  |   |  |  |  |
| CD 10503   | (b) (4)  | (b) (4)  | (b) (4)   | (b) (4)  | (b) (4)  | (b) (4)  |
| Any unspecified  |  |  |   |  |  |  |
| Total  |  |  |   |  |  |  |
| Assay  |  | (b) (4)  |   |  |  |  |
| Uniformity of Dosage Units   | Meets USP <905>  | Conforms   | Conforms  | Conforms   | Conforms   | Conforms   |

**Certificates of Analysis**

**Quality Reviewer’s Evaluation: Adequate** –BI manufactured the demonstration batches at production scale for each tablet strength. The changes to the drug product specification reflect the changes in the drug product image. The Certificates of Analysis (CoA) results demonstrate that the changes in debossing did not negatively impact tablet properties, including dissolution. The sponsor provided a detailed comparative analysis of the dissolution results. The results confirm that the change in debossing did not impact dissolution.

**Comparative Dissolution**

**Quality Reviewer’s Evaluation: Adequate** – Comparative dissolution testing was performed for the five dosage strengths between tablets of equal strength, comparing the original tablet image to the new tablet image. Dissolution testing was conducted using the regulatory dissolution method. Dissolution

profile similarity according to the model independent approach using the similarity factor f2 was demonstrated for the tablets of all dosage strengths with the new tablet image versus the tablets with the original tablet image. Thus, the tablet image differences do not have an impact on the in vitro behavior of the drug product. As for the applied dissolution method, a correlation between in vitro dissolution data and the in vivo pharmacokinetics over time has been successfully established (Level A IVIVC) and accepted during the first cycle review. Therefore, similar in vivo performance is expected from the tablets bearing the new trade image.

- 3. A commitment to include the first three drug product batches per tablet strength manufactured at commercial scale with the new drug product images as part of the post-approval stability program based on the previously approved bracketing scheme.**

### Quality/CMC Reviewer's Comments

BI submitted a revised stability protocol with a commitment to test the first three batches of the new trade image tablets packaged in the commercial container closure and the first two batches of the new trade image tablets packaged in the physician sample container closure through (b) (4) based on the approved bracketing scheme. The bracketing scheme includes testing of the 0.375 mg, 1.5 mg, and 4.5 mg strength tablets. Additional primary stability samples were stored at 30°C/75%RH, as per ICH Q1A (R2), for conducting additional testing in case of observing significant changes after storage under accelerated conditions.

### Quality Reviewer's Comments

**BI commits to the following post-approval stability testing:**

#### **1. COMMITMENT TO CONTINUE TESTING THE PRIMARY STABILITY BATCHES**

Three primary stability batches of Mirapex ER tablets per tablet strength (0.375 mg, 1.5 mg, and 4.5 mg), packaged in the proposed commercial container closure (30-count bottles) and two primary stability batches per tablet strength (0.375 mg, 1.5 mg, 4.5 mg) packaged in the physician sample container closure system (7-count bottles), will be tested through (b) (4) according to the protocol shown in Table 5. The stability data thereof will be evaluated according to the regulatory release specification.

#### **2. COMMITMENT TO TEST THE FIRST FIVE PRODUCTION BATCHES WITH CHANGED DEBOSSING**

The first three production batches of pramipexole dihydrochloride monohydrate ER tablets per tablet strength (0.375 mg, 1.5 mg, and 4.5 mg) with changed debossing of the tablet strength on one side of the tablets and code "ER" on the other side, packaged in the proposed commercial container closure (30- count bottles) and the first two production batches per tablet strength (0.375 mg, 1.5 mg, and 4.5 mg) packaged in the proposed physician sample container closure (7-count bottles) will be tested through (b) (4) according to the protocol shown in Table 5. The stability data thereof will be evaluated according to the regulatory release specification.

**3. TEST NOT LESS THAN ONE BATCH OF DRUG PRODUCT PRODUCED DURING EACH YEAR OF COMMERCIAL MANUFACTURE**

Long-term stability testing at 25°C/60%RH will be carried out on at least one (1) commercial batch packaged in the commercial container closure, produced during each year of manufacture, if at least one (1) batch is produced. The batches will be tested according to the stability protocol in Table 6.

**4. PROVIDE RESULTS FROM THE STABILITY STUDIES TO THE U.S. FOOD AND DRUG ADMINISTRATION**

Boehringer Ingelheim Pharma GmbH & Co. KG commits that the stability data from the primary and annual follow-up stability batches of Mirapex ER tablets (0.375 mg, 1.5 mg, and 4.5 mg) will be reported to the FDA in the Annual Report. In accord with 21 CFR 314.70(d)(2)(vi), the shelf life for the drug product may be extended in the Annual Report based on acceptable stability data from the primary stability studies.

**5. WITHDRAW FROM THE MARKET ANY BATCH THAT FAILS APPROVED SPECIFICATIONS**

Any batch found to fall outside the approved specifications for the drug product will be withdrawn from the market. If there is evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, the deviation will be immediately discussed with the FDA Division and a justification will be provided for the continued distribution of that batch. The change or deterioration in the distributed drug product will be reported to the FDA.

**Quality Review Conclusion Regarding The Sponsor's Commitment For Post-Approval Stability Testing**

- **Evaluation: Adequate.**

**Quality Review Recommendation For Regulatory Action**

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.

***List Of Deficiencies To Be Communicated***

None.

## **4. Clinical/Statistical- Efficacy**

After review of the original NDA application, the agency concluded that BI submitted substantial evidence of effectiveness for Mirapex ER as a treatment for patients with early Parkinson's disease. The primary efficacy review for the original submission was performed by Dr. Ken Bergman, MD (August 5, 2009), the first level supervisory review was performed by Dr. Gerald Podskalny, DO (August 24, 2009) and the statistical review was performed by Jingyu (Julia) Luan, Ph.D. (July 30, 2009). All review personnel independently concluded the efficacy findings were adequate for Mirapex ER for the early PD indication.

## **5. Safety**

### **Clinical Safety Evaluation**

The primary safety review for the original submission was performed by Dr. Ken Bergman, MD (August 5, 2009), the first level supervisory review was performed by Dr. Gerald Podskalny, DO (August 24, 2009). Besides the potential for medication errors associated the appearance of the Mirapex ER tablets, there were no other safety issues that needed to be resolved before recommending approval.

**Photographs of Mirapex (IR), Initial Mirapex ER and New (Revised deposing) Mirapex ER**

| 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   |   |            |





The clinical review Division (DNP) reviewed the sponsor’s submission and the table samples provided by BI. The debossed Mirapex ER tablets with “ER” on one side of the tablet and the mg strength on the other, improves the possibility that patients will be able to distinguish the ER formulation from Mirapex (IR) and the different tablet strengths. Pharmacy staff will be able to visually recognize Mirapex ER tablets and distinguish them without having to look up the tablet code.

A failsafe method to eliminate all possible medication error does not exist, however the methods adopted by the sponsor can lower the risk for Mirapex ER tablet confusion. Although, additional changes to the shape or color of the tablet may increase the differences between Mirapex (IR) and Mirapex ER, it may create a new problem of a similar appearance between Mirapex ER to other marketed drug products with entirely different indications. Changes to the shape and color are also

unlikely to eliminate the potential for medication error and it may only trade the risk of one type of error for another.

The proposed carton and changes are acceptable. This clinical reviewer agrees with the recommendation of the CMC/Quality reviewer for approval based on the dissolution and post-approval stability commitments.

### **Clinical Reviewer Recommendation-Approval**

#### **Division of Medication Error Prevention and Analysis (DMEPA) Evaluation of The Sponsor's Complete Response**

DMEPA reviewed the revised tablet appearance and the revised packaging for Mirapex ER on January 28, 2010. Their original recommendations were communicated to the sponsor in the CR letter 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
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.

DMEPA performed a Failure Mode and Effects Analysis<sup>1</sup> (FMEA) to evaluate the revised Mirapex ER tablets, labels and labeling.

#### **DEMEPA Recommendation**

"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".

## **6. Pediatrics**

PeRC granted a PREA waiver for this application on August 19, 2009.

## 7. Recommendations/Risk Benefit Assessment

### Recommended Regulatory Action = Approval

#### Risk Benefit Assessment

The FDA review divisions involved in the evaluation of BI's response, agree that the response is indeed a complete response to the agency's comments. In addition, after review, all of the involved review divisions recommend approval of Mirapex ER for the early PD indication. Although, we recognize there are no methods that will eliminate the potential for medication error, we agree that the methods chosen by the sponsor represent a reasonable effort to reduce the risk for confusion between strength of Mirapex ER and for inadvertent substitution of Mirapex (IR) and Mirapex ER or vice versa.

### Recommended Comments to Applicant

#### Quality Approval Letter Comments

1. 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.
2. 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.

### Division of Medication Error Prevention and Analysis (DMEPA)

#### DMEPA Approval Letter Comments

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. BI must notify the agency when they start distribution of the new packaging that includes the revised wording.

An email was sent to Boehringer through Daniel T. Coleman, Ph.D, Boehringer's Associate Director Regulatory Affairs, regarding the addition of the revised carton and container language on February 1, 2010. His email reply was received on February 2, 2010 on behalf of Boehringer accepting the additional carton and container language "Tablets must be swallowed whole and must not be chewed, crushed, or divided." In this email, BI requested they be permitted to launch with the carton and containers that does not incorporate the new language. They estimate their supply of the present cartons and containers will last for approximately 1 month and there after the revised labeling will be used. The clinical division and DMEPA agreed to allow the distribution of the present carton and container omitting the phrase "Tablets must be swallowed whole and must not be chewed, crushed, or

divided” for approximately one month. BI should notify the agency when they start distribution of the new packaging.

## **8. Labeling**

The DNP is negotiating the final wording of the label with the sponsor at the time this review was completed. The final label will be attached to the approval letter.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22421

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ORIG-1

-----  
BOEHRINGER  
INGELHEIM  
PHARMACEUTICA  
LS INC

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PRAMIPEXOLE  
DIHYDROCHLORIDE

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GERALD D PODSKALNY  
02/12/2010