APPLICATION NUMBER:
22-421

OTHER ACTION LETTER(s)
Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated October 23, 2008, received on October 24, 2008 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex® ER (pramipexole dihydrochloride) Extended-release Tablets, 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg.

We acknowledge receipt of your amendments dated:

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<td>February 24, 2009</td>
<td>March 5, 2009</td>
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<td>June 30, 2009</td>
<td>July 17, 1009</td>
<td>August 5, 2009</td>
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We also acknowledge receipt of your amendment dated August 20, 2009, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

**CLINICAL SAFETY**

Although we have concluded that you have submitted substantial evidence of effectiveness for Mirapex ER as a treatment for patients with early Parkinson’s Disease (PD), we do not believe that you have established that it can be used safely because of the potential for medication errors.

Specifically, we believe that the following factors are likely to result in medication errors in various points of the medication’s use.

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.

We acknowledge that it is difficult to predict with certainty the types of errors that may occur. One can imagine, for example, the similarities in carton and container labels, combined with the lack of identifying marks on the ER tablet, the similarity in tablet color, along with the common and predictable practice of prescribers omitting the suffix when prescribing, may result in the wrong dosage form being dispensed and going unrecognized, both by pharmacist and patient (for example, the 0.75 mg ER tablet, in place of the 0.75 mg IR tablet, being dispensed for TID dosing, or the incorrect dispensing of the IR, instead of ER formulation, for once a day dosing). Another example might be a patient who is dispensed both the 1.5 and 3 mg ER tablets because their pharmacy might not stock the 4.5 mg tablet, and who cannot tell the two strengths apart because of their almost identical appearance and the lack of any helpful identifying marks on the tablets.

Although it may be difficult to predict the specific errors that may occur, we believe that the factors enumerated above on face raise the possibility of confusion between the IR and ER formulations and, as noted, among several of the strengths of the ER tablets. We also note surveys of pharmacists indicate that tablet similarity is frequently the cause of medication errors.

We believe these issues need to be addressed prior to marketing. 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 visual 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 revised to reflect the strength and the extended-release formulation by specifying the letters ER.

**CHEMISTRY, MANUFACTURING, AND CONTROLS**

To support the recommended debossing 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

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

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.

We are happy to discuss with you the implementation of these, or other possible changes, that would be expected to minimize the risk of medication errors.
LABELING

As part of your response to this letter, submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

Submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes (using the attached labeling as the base document), as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA’s *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Beverly Conner, Regulatory Project Manager, at (301) 796-1171.

Sincerely,

*See appended electronic signature page*

Russell Katz, M.D.
Director
Division of Neurology Products
Center of Drug Evaluation I
Center of Drug Evaluation and Research

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

/s/

RUSSELL G KATZ
08/24/2009