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RESEARCH**

*APPLICATION NUMBER:*

**203312Orig1s000**

**OTHER ACTION LETTERS**



NDA 203312

**COMPLETE RESPONSE**

Impax Laboratories, Inc.  
Attention: Jeff Mulchahey  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544

Dear Mr. Mulchahey:

Please refer to your New Drug Application (NDA) dated and received December 21, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Rytary (IPX066; carbidopa-levodopa extended-release capsules) 23.75-95 mg, 36.25-145 mg, 48.75-195 mg, 61.25-245 mg.

We acknowledge receipt of your amendments dated as follows:

January 17, 2012	February 6, 14, and 29, 2012
March 22 and 30, 2012	April 5, 9, 10, 23, and 30, 2012
May 1 and 7, 2012	July 24 and 27, 2012
August 10, 17, 23(2), 24, and 31, 2012	September 5, 25, and 28, 2012
October 2 and 5, 2012	November 1 and 12, 2012
December 7, 10, and 28, 2012	January 7, 9 and 17, 2013

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

During recent inspections of the Impax Laboratories (Hayward, CA) manufacturing facility for this application, our field investigators conveyed deficiencies to the representative of the facility. Although we note that, in an amendment to your NDA dated December 6, 2012, you stated that the Hayward facility was withdrawn from the application, this facility continues to perform operations in support of commercial manufacturing and distribution for NDA 203-312; this conclusion is based on current inspectional findings and corrective action commitments provided by the firm to FDA field investigators on January 16, 2013 and January 17, 2013. As you know, previous inspections of this facility have resulted in the identification of numerous significant deficiencies that have been communicated to you in the past; we refer you to the Warning Letter issued on May 31, 2011 and the June 12, 2012 regulatory meeting with the San Francisco District Office. Satisfactory resolution of the deficiencies identified in the recent inspections and

regulatory meeting on June 12, 2012 have not been verified and are required before this application may be approved.

Critical manufacturing data within the CMC section of the application (e.g., method validation, stability) were generated at the Hayward, CA facility. Therefore, these data may be unacceptable. Whether any of these critical studies may need to be repeated, and, if so, whether this will have implications for any of your clinical trials, will need to be assessed after the completion of our current, on-going inspection of the Hayward, CA facility.

### **LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

### **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/clinical trials 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. 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>.

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, call Tracy Peters, Regulatory Project Manager, at (301) 796-2953.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, MD  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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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  
01/18/2013

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