CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203312Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD
Subject	Summary Review
NDA/BLA # **Supplement #**	203,312
Applicant Name	Impax Laboratories
Date of Submission	April 9, 2014
PDUFA Goal Date	January 9, 2015
Proprietary Name / **Established (USAN) Name**	Rytary Capsules (carbidopa/levodopa extended release)
Dosage Forms / Strength	Oral Capsules of carbidopa/levodopa: 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, 61.25 mg/245 mg
Proposed Indication(s)	Treatment of Parkinson's disease
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Kenneth Bergmann, M.D.
CMC Review/OBP Review	Charles Jewell, Ph.D
Biopharmaceutics	Sandra Suarez Sharp, Ph. D.
CDTL Review	Gerald D. Podskalny DO, MPHS
Compliance	Christina Capacci-Daniel, Consumer Safety Officer
DMEPA	Justine Harris, RPh

1. Introduction and Background

The application under review is a second cycle submission for a new carbidopa-levodopa extended release oral capsule. The application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, referencing NDAs for Sinemet, Lodosyn, Sinemet CR, and Stalevo. The proposed product combines both immediate- and extended-release components, to produce immediate post-dosing and sustained levodopa levels.

In the first review cycle, the division issued a complete response letter because the application did not include an approved manufacturing facility. Inspection deficiencies were identified at the Hayward, CA, manufacturing facility for the application. Satisfactory resolution of the deficiencies identified in these inspections was necessary to support approval.

Efficacy and safety of the product were established in the first cycle. A nonclinical issue was however identified, related to one of the excipients of the new product, co-polymer (b) (4) (methacrylic acid copolymer, (b) (4)). In his first cycle summary memo, Dr. Katz, division director at the time, notes that patients receiving doses at the higher end of the

recommended dose range will be exposed to higher levels of [redacted] (b) (4), for longer durations, than is the case for patients taking other medications that contain this excipient. Dr. Katz further notes that animal studies did not provide any margin between the NOAEL for thyroid activation observed in the most sensitive species and levels of the [redacted] (b) (4) expected in humans. However, given the expectation of minimal bioavailability of the [redacted] (b) (4), and the age of the animal studies (conducted prior 1990), the team found it possible that the thyroid changes were due to an unidentified impurity. Therefore, additional non-clinical studies to assess whether [redacted] (b) (4) is causing the thyroid changes were considered necessary, but the team found it acceptable to conduct these studies during the post-marketing period, in part because of the expected minimal bioavailabity of [redacted] (b) (4), and in part because of evidence suggesting superiority of Rytary over immediate release carbidopa-levodopa.

This second cycle submission included a CMC stability update, information supporting for the proposed manufacturing facilities, and a safety update.

2. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Dr. Jewell notes that even though the applicant has withdrawn the Hayward manufacturing site from the application, the approval of the application depended on critical manufacturing data generated at the Hayward facility. The applicant's responses to the inspection deficiencies at the Hayward facility were found acceptable by the Office of Compliance. Inspection of a new manufacturing site (in Taiwan) was also acceptable. Stability testing supports an expiry of 30 months [redacted] (b) (4). The biopharmaceutics reviewer also recommends approval. There are no outstanding CMC or Biopharmaceutics issues.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this cycle. There are no outstanding nonclinical issues that preclude approval. As discussed above, postmarketing nonclinical studies to assess whether excipient [redacted] (b) (4) causes thyroid changes will be required.

4. Clinical Pharmacology

No new clinical pharmacology information was submitted in this cycle. There are no outstanding clinical pharmacology issues that preclude approval.

5. Clinical Microbiology

N/A.

6. Clinical/Statistical-Efficacy

Efficacy was established in the first cycle. I refer the reader to first cycle reviews. There is no new efficacy information in the second cycle submission.

7. Safety

The applicant submitted a safety update, which was reviewed by Dr. Bergmann. There is no new safety signal identified.

8. Advisory Committee Meeting

No advisory meeting was necessary for this 505(b)(2) application.

9. Pediatrics

Pediatric study requirements are waived for this application because necessary studies are impossible or highly impracticable as the disease does not occur in the pediatric population.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues. The proposed proprietary name, Rytary, was found acceptable.

11. Labeling

There is no unresolved labeling issue.

12. Decision/Action/Risk Benefit Assessment

As outstanding CMC issues and inspectional deficiencies have been resolved, I will issue an approval letter for this application. The letter will include the following two post-marketing requirements:

1996-1 Six-month oral toxicology study of methacrylic acid copolymer, (b) (4) in rat. The methacrylic acid copolymer, (b) (4), should be the same as the excipient in the to-be-marketed product.

1996-2 Oral absorption study of radiolabeled methacrylic acid copolymer, (b) (4) in rat. The methacrylic acid copolymer, (b) (4) should be the same as the excipient in the to-be-marketed product.

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/s/

ERIC P BASTINGS
01/07/2015