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APPLICATION NUMBER:

203312Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 22, 2014
From	Gerald D. Podskalny DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	203312
Supplement#	
Applicant	Impax Laboratories
Date of Submission	April 9, 2014
PDUFA Goal Date	January 9, 2015 with extension
Proprietary Name / Established (USAN) names	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)	1. Parkinson's disease
Recommended:	<i>Approval</i>

1. Introduction

Impax laboratories submitted their 505(b)(2) New Drug Application (NDA) on December 21, 2011, for a new carbidopa-levodopa (CD-LD) extended release oral capsule IPX066 (Rytary). The capsule contains coated beads of immediate, intermediate (b)(4) release) and an enteric-coated (b)(4) release CD-LD. The Agency acted with a Complete Response (CR) letter for the original NDA application on January 18, 2013, that included a three-month extension. The Agency issued a CR because the application did not include an approved manufacturing facility. The primary manufacturing facility in Hayward, California was withdrawn from the application after FDA inspectors found deficiencies that were not resolve before the end of the first review cycle. There was a second manufacturing facility included in the original NDA that was located in Taiwan. Deficiencies were found during the initial cGMP inspection of the facility in Taiwan but the facility needed to be re-inspected to resolve these deficiencies. The re-inspection was scheduled for some time after the PDUFA action date not anticipating the Sponsor withdrawing the Hayward facility from the application.

The sponsor resubmitted their NDA application, after the FDA completed a product specific inspection of the manufacturing site in Taiwan. The key remaining manufacturing issue was (b)(4)

2. Background

Review Discipline	Primary Reviewer	Recommended Action
Chemistry Manufacturing and Controls Chemistry/ONDQA	Charles Jewell, Ph.D	Approval

Office of New Drug Quality Assessment Biopharmaceutics Reviewer/Team Leader	Sandra Suarez Sharp, Ph. D.	Approval
Clinical Reviewer	Kenneth Bergmann, M.D.	Approval
Office of Compliance ,Office of Manufacturing and Product Quality/Division of Good Manufacturing Practice Assessment	Christina Capacci-Daniel Ph.D	

The information contained in the NDA provided substantial evidence of effectiveness. There were a greater number of cardiovascular ischemic adverse events were reported in patients treated IPX066 in the clinical trials program (IPX-066 N=7, Placebo = 0). The Duke Clinical Research Institute Clinical conducted a blinded review of the adverse event data from three controlled clinical efficacy studies. Patients in the control group in these studies received placebo or an active comparator (immediate release carbidopa and levodopa). In three the controlled trials (IR CD/LD or placebo) 15 ischemic events in 11 patients were identified (13 of the 15 events were cardiovascular and 2 were cerebrovascular events). All of these identified events occurred in patients receiving IPX066 and none occurred in the comparator arms. The events were examined without regard to possible causal relationship to treatment. Due to the small number of events, design limitations the small study population, short duration of follow-up with the understanding that these studies were not designed to compare the frequency of cardiovascular adverse reactions limits the ability to draw conclusions from this information however; this information is included in the product label.

A nonclinical safety concern raised during the review involved the qualification of an unprecedented daily amount of co-polymer (b) (4) ((b) (4)) that patients could ingest with high daily doses of IPX066. The Agency has required the Sponsor to complete two nonclinical studies as postmarketing studies (PMRs).

3. CMC/Device

Deficiencies noted by FDA inspectors at the Hayward, California manufacturing facility resulted in the Agency taking a CR action. Impax Laboratories was first made aware of serious deficiencies following a cGMP inspection completed during December 2010 – January 2011. The deficiencies cited included failure to monitor and validate manufacturing processes that resulting in a recommendation of Official Action Indicated (OAI) and the Agency issuing a Warning Letter. The company responded to the deficiencies listed in FDA form 483 and Warning Letter on May 31, 2011. The FDA re-inspected the Hayward facility from February 23 to March 28, 2012 finding additional cGMP violations. On December 6, 2012, the applicant decided to remove the Hayward manufacturing facility from the NDA, leaving the Impax Laboratories facility in Jhunan, Taiwan as the remaining drug product manufacturing facility. However, during the July 20-26, 2012 pre-approval and CGMP inspection at the Impax Taiwan facility that covered NDA 203312, the FDA investigator was unable to verify raw data

for critical studies to support manufacturing operations and data that was submitted in support of the NDA. The audit of this data could not be completed because the raw data was generated and stored at Impax Laboratories Hayward. During the Warning Letter and Regulatory Meeting, the Office of Manufacturing and Product Quality/Division of Good Manufacturing Practice Assessment (OMPQ/DGMPA) requested a follow-up inspection of Impax Laboratories to verify the raw data generated in support of the NDA.

In the January 8, 2013, a pre-approval inspection of the Hayward facility revealed new product specific issues addition to the cGMP related issues. Although the applicant removed Impax Laboratories Hayward, CA facility from the application, the OMPQ/DGMPA found that the Hayward facility continued to perform CGMP activities that supported the commercial manufacturing and distribution of IPX066. This inspection was ongoing at the time the Agency acted on this NDA.

Withdrawal of the Hayward, California facility from the NDA and outstanding deficiencies at the Jhunan, Taiwan facility meant there was no acceptable product manufacturing facility in the NDA, leading to the Agency's Complete Response action on January 18, 2013.

The Agency gave the sponsor a recommendation for resubmission of the application on April 7, 2014, after the sponsor had adequately addressed the deficiencies. During the teleconference, the sponsor was informed that additional inspections of the manufacturing site in Taiwan would be needed. The NDA was resubmitted to the FDA on April 9, 2014. The Taiwan facility was re-inspected from July 12-26, 2014. During re-inspection of the Taiwan facility, the [REDACTED] (b) (4) the different strengths of IPX-066 capsules was found to be deficient. [REDACTED] (b) (4)

All strengths of IPX-066 are dose proportional with the fixed ratio of CD/LD being 1:4. Each capsule also contains tartaric acid (TA) to enhance the bioavailability of the LD

There are (b) (4) components to the product:

[REDACTED] (b) (4)

The capsules are filled with the following components:

[REDACTED] (b) (4)

On August 29, 2014, the sponsor submitted a manufacturing amendment to change in the (b) (4) IPX-066 capsules at the Taiwan manufacturing site. (b) (4)

The sponsor's submission of the manufacturing amendment information was deemed a major amendment, and the submission led to an extension of the review cycle by three months.

The amendment included: (From Dr. Jewell's CMC review):

- An updated portion to section 3.2.P.3.3 Description of Manufacturing Process with Process controls. It also includes undated versions of the Master Batch Records for each capsule strength.
- Section 3.2.P.2.3 Manufacturing Process and Controls is updated to include a section for the (b) (4).
- Section 3.2.P.5.4 Batch Analysis for (b) (4) is provided covering Content Uniformity and Dissolution of levodopa, carbidopa and tartaric acid. This is provided for all four dosage strengths. These studies were conducted during October through December 2012, at the Taiwan site. This includes in-process weight verification data tables, showing (b) (4) determined data compared to capsule weights measured off-line on a balance instrument.

Dr. Jewell reviewed the data from the in-process weights verification for each of the (b) (4) that was performed on 12 replicate samples at intervals of (w) (4) minutes during operation. Filled capsule weight was monitored for 100% of sampled capsules. Filled capsule weight was also monitored by sampling and weighing 24 capsules at all stages of filling every (b) (4) minutes.

CMC Recommendations for the Manufacturing Equipment Change

Dr. Jewell noted in his review that the (b) (4) was shown to be as effective as the (b) (4) reviewed under the first cycle submission. It also has the added feature of (b) (4). The change to the (b) (4) does not require any changes to the release specification for this drug product. Dr. Jewell reviewed the batch analysis for content uniformity and dissolution data and it was found to be compliant with the release specification as indicated by the applicant. For the demonstration batches, the (b) (4) was found to be an adequate replacement for the (b) (4). Representative commercial size batches of all four capsule strengths produced at (w) (4) capsules /hour were sampled and were found to be within the specified limits for all (b) (4) filled components (b) (4). Testing for content uniformity was within the acceptance limits set for carbidopa, levodopa and tartaric acid.

Stability Data Update

The resubmission included updates to 36 months for Hayward lot 1, 30 months for Hayward lots 2, 3, 4 and 5 and 24 months for the Taiwan site qualification lots. Dr. Jewell concluded that in all cases, all limits comply with specifications except for growth in, (b) (4) a carbidopa degraded, and total impurities but they remained within specification for the specified test period. The data supports the applicant's

recommendation for 30 months expiration dating from the (b) (4). The 30-month expiration-dating period begins with the (b) (4).

This application is recommended for APPROVAL from the CMC perspective. Since our preliminary recommendation entered on 11/5/2014, the ONDQA Biopharmaceutics reviewer (Sandra Suarez) has submitted her approval recommendation (11/6/2014). The CDER Office of Compliance (Reviewer: Christina Capacci-Daniel via Ebern Dobbin) has entered the OVERALL ACCEPTABLE recommendation covering the cGMP status for all manufacturing sites on 12/23/2014.

CMC's Overall Recommendation for the application is to **Approve**.

4. Nonclinical Pharmacology/Toxicology

(b) (4) methacrylic acid copolymers (b) (4) and triethyl citrate are key excipients in IPX-066. The amount of triethyl citrate and (b) (4) in IPX-066 presents no major concerns. However, there were nonclinical concerns about an unprecedented amount of (b) (4) taken by patients taking 15 capsules per day of the highest capsule strength (61.25/245 mg) of IPX-066 (total (b) (4) of the levodopa component) raised during the review of the original submission. The nonclinical data suggest that a finding of thyroid activation in all species of animals tested represents systemic toxicity associated with (b) (4). The method for calculating the NOAEL based on thyroid activation in the mouse (most sensitive species) should be mg/m², instead of the mg/kg method proposed by the sponsor. The amount of (b) (4) is greatest in the 61.5/245 mg capsules and at 15 capsules per day, the highest proposed dose in the label there is no margin.

The clinical trials experience in patients with advance PD in Study IPX066-B09-02 finds that 23/183 patients took more than 10 capsules (61.5/245 mg strength) per day. Thirteen patients took greater than 2400 mg of the levodopa component of IPX-066 for 12 months or longer. Ten capsules of the 61.5/245 mg strength of IPX-066 would equal 2400 mg of the levodopa component daily. The supporting safety data indicates that few patients are likely to need more than 10 capsules per day. There is also limited long-term safety information in patients who have taken more than 10 capsules of IPX-066 (61.5/245 mg).

These findings are the basis of two nonclinical PMRs that the sponsor has agreed to conduct in the first review cycle. Impax Laboratories proposed PMR milestone dates however, because of the CR action, the FDA and the sponsor agreed to revised milestone dates.

CDTL Comment:

I recommend 10 capsules per day of the 61.5/245 mg strength of IPX-066 as the maximum recommended daily dose described in the label, at this time. The controlled and the long-term open label safety information indicate that few people require higher dosages.

5. Clinical Pharmacology/Biopharmaceutics

The dissolution information included in Amendment-0047 dated Aug 29, 2014, supports the approval of the proposed manufacturing equipment change. From the Biopharmaceutics perspective the Resubmission of NDA 203-312 for Carbidopa+Levodopa (23.75/95mg, 36.25/145mg, 48.75/195mg, and 61.25/245 mg) fixed dose combination (FDC) extended release (ER) capsules is recommended for APPROVAL.

6. Clinical Microbiology

The resubmission did not include new Microbiology information.

7. Clinical/Statistical- Efficacy

Efficacy was supported by the results of three controlled clinical studies.

- IPX-B-08-05 In Patients with Early Parkinson's disease
- IPX066-B09-02 A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson's disease
- Study IPX066-B09-06 (Part 1)

Study IPX-B-08-05 in patients with early Parkinson's disease was a double-blind, placebo-controlled, fixed-dose parallel groups study that compared 3 strengths of IPX-066 given 3 times/day to placebo. The study lasted 30 weeks total with 3 weeks of dose escalation,

Study IPX066-B09-02 was a Phase 3, randomized, double-blind, double-dummy, active-control, parallel-group study planned to compare the efficacy and safety of IPX066 to that of IR CD-LD in patients with advanced PD. Patients w a total daily LD dose of at least 400 mg at least four times daily and they must experience at least 2.5 hours of "off" time per day. Study IPX066-B09-06 was a randomized, double-blind, double-dummy, 2-treatment, two 2-week crossover study of IPX066 versus CLE (Part 1) followed by an open-label safety study (Part 2) of IPX066 in Advanced Parkinson's disease. The double-blind crossover portion included two 2-week treatment periods separated by a 1-week washout period of IPX066 treatment.

Dr. Massie’s Summary of results of the Pivotal Efficacy Studies (Statistical Review)

Table 1 Key Efficacy Studies

Study	# of Subjects per Arm	Follow-up Period	Completer N (%)	Primary Efficacy	Study Population
08-05: Parallel Group Study	\bar{N} Placebo: 92 145 mg: 87 245 mg: 104 390 mg: 98	30 weeks	71 (77%) 72 (83%) 83 (80%) 74 (76%)	Baseline UPDRS II+III: 36.7 Chg. UPDRS II+III: - 0.6 -11.7 vs -0.6 P < 0.0001 -12.9 vs -0.6 P < 0.0001 -14.9 vs -0.6 P < 0.0001	Early PD 36% US
09-02: Dose Conversion Study	\bar{N} IR LD-CD: 192 IPX066: 201	IR Titration: 3 weeks IPX Conversion: 6 weeks Maintenance: 13 weeks	182 (95%) 186 (93%)	Baseline % Off Time: 5.97 Ending % Off Time: 29.79±15.81 P < 0.0001 23.82±14.91	Adv. PD 52% US
09-06: Two period Two group, Crossover Study	N=91	Conversion period: 6 weeks Double Blind period: 2 weeks treatment/ 1 week washout/ 2 weeks treatment	84 (92%)	Baseline % Off Time: 36.1 Ending % Off Time: IPX: 24.0 P < 0.0001 CLE: 32.5 (first period only p=.0091)	Adv. PD 48% US

CLE= Carbidopa-Levodopa-Entacapone

There were no unresolved issues and both the clinical and statistical reviewers concluded that IPX-066 was effective for treating patients with early and advanced Parkinson’s disease.

8. Safety

Dr. Bergmann reviewed the Resubmission Safety Update. It contains new safety data on 89 subjects (46 human volunteers and 43 patients with advanced PD) collected after the 120-day Update cutoff date. These data are from one phase 3, open-label extension study in subjects with advanced PD, Study IPX066-B11-01. In addition, data from three Phase 1 studies (IPX066-B12-01, IPX066-B12-02, and IPX066-B12-03) in healthy subjects was presented. Subjects in the Phase 1 palatability study (Study IPX066-B12-02) did not receive IPX-066.

Deaths

A single death was reported in the resubmission update that occurred in an 85-year-old male patient with PD and dementia who experienced general physical decline. He died in hospice

one week after IPX066 was withdrawn. The patient's death was unrelated to study medication.

Nonfatal Serious Adverse Reactions

Nine additional nonfatal serious adverse reactions were reported in the resubmission update. Orthostatic hypotension was reported with the greatest frequency (n=2). Orthostatic hypotension is a known to occur in patients with Parkinson's disease who are treated with dopaminergic medications.

Premature Discontinuations

Fifteen patients discontinued from the study before completion. Fourteen patients never reached a stable conversion dose and 10 of these discontinued during the 6 week Part 1 phase of the study. Seven subjects reported an AE as reason for discontinuation but their complaints were related to underlying Parkinsonism. Other adverse events experienced by this group included, nausea (3), and single reports of orthostatic hypotension, hallucination, anxiety, vomiting, dyskinesia, confusional state, and agitation among others.

Nonserious Adverse Reactions

The Sponsor reported 34 additional patients with at least one nonserious adverse reaction. I concur with Dr. Bergmann's analysis that these events do not change the safety profile of IPX-066.

CDTL Comment:

The information in the Safety Update did not change the conclusion that IPX-066 is safe for the treatment of patients with Parkinson's disease.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for IPX-066 that contains two well-characterized drug substances.

10. Pediatrics

PeRC granted the Sponsor's request for a PREA waiver on August 8, 2012

11. Other Relevant Regulatory Issues

Postmarketing Requirements

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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.

The timetable you submitted on October 17, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2015
Study Completion: 10/2016
Final Report Submission: 12/2016

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.

The timetable you submitted on October 17, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 07/2015
Study Completion: 08/2016
Final Report Submission: 10/2016

12. Labeling

Proprietary Name:

Office of Medication Error Prevention and Risk Management granted the name Rytary. A letter was sent to the Sponsor on October 30, 2014.

Product Label

The Sponsor and the Division reached mutual agreement on the final version of the Product Label on December 22, 2014.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action APPROVAL.

The Office of Compliance, Office of Manufacturing and Product Quality/Division of Good Manufacturing Practice Assessment (OMPQ/DGMPA) provided their official recommendation for Approval after completion of their Manufacturing Facilities Inspection. This provides an approved manufacturing facility in the application and it adequately addresses the reason for the Agency's original Complete Response action.

Risk Benefit Assessment

Clinical studies of IPX-066 show that it is effective for treating patients with early PD (levodopa naïve) and advanced PD (already taking carbidopa and levodopa). The adverse effects are similar to those associated with other oral carbidopa and levodopa products.

Recommended Comments to Applicant

The Agency has assigned an expiration dating period of 30 months for each strength of the Rytary (IPX066; carbidopa-levodopa extended-release capsules) drug product in the

described packaging configurations. The 30-month expiration dating period begins ^{(b) (4)}

. No extension period is granted for hold time of components or bulk capsules.

Gerald David Podskalny, DO, MPHS
CDTL
FDA/CDER/OND/ODE-1
Division of Neurology Products

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/s/

GERALD D PODSKALNY
12/23/2014