

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203312Orig1s000**

**OTHER REVIEW(S)**

505(b)(2) ASSESSMENT

Application Information		
NDA # 203312	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: Rytary Established/Proper Name: IPX066 (carbidopa/levodopa extended release) Dosage Form: capsules Strengths: 23.75-95mg, 36.25-145mg, 48.75-195mg, 61.25-245mg		
Applicant: Impax		
Date of Receipt: 12/21/11		
PDUFA Goal Date: 10/21/12		Action Goal Date (if different): 10/19/12
Proposed Indication(s): treatment of (b) (4) Parkinson's Disease (b) (4) (b) (4), post-encephalitic parkinsonism and (b) (4) parkinsonism which may follow (b) (4) (b) (4) carbon monoxide intoxication (b) (4) or manganese intoxication		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Sinemet (carbidopa/levodopa) tab N17555	Labeling: sections 1,2,4,5,6,7,8,10,11,12,13,17
Sinemet CR (carbidopa/levodopa extended release) tab N19856	Labeling: sections 1,2,4,5,6,7,8,10,11,12,13,17
Stalevo (carbidopa/levodopa/entacapone) tab N21485	Labeling: sections 2,4,5,6,7,8,9,10,11,12,13,17

Literature	Nonclinical
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\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BE studies to Sinemet CR (IPX066-B05-07, B06-02, B07-02, B07-03)

BA studies to Sinemet CR (IPX066-B08-01, B08-03) + Sinemet (B08-04) + Stalevo (B08-10)

**ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

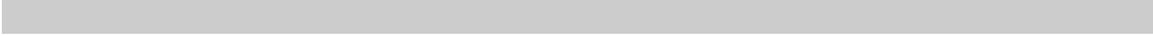
- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
YES  NO



APPEARS THIS WAY ON ORIGINAL

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Sinemet	N17555	Y
Sinemet CR	N19856	Y
Stalevo	N21485	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: Stalevo

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO   
If “**YES**”, please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO   
If “**YES**”, please list which drug(s) and answer question d) i. below.  
If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

- This application provides for a change in dosage form (extended release **capsules** with an IR and ER component) and different strengths

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.  
If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES  NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.  
If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

generic IR tablets, generic ER tablets, and generic disintegrating tablets

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

**Listed drug/Patent number(s): Listed drug/Patent number(s): Patent Data (Stalevo)**

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
<a href="#">N021485</a>	001	5446194	Oct 19, 2013	Y			
<a href="#">N021485</a>	001	6500867	Jun 29, 2020		Y	<a href="#">U - 219</a>	
<a href="#">N021485</a>	001	6797732	Jun 29, 2020		Y		

**Exclusivity Data**

**There is no unexpired exclusivity for this product.**

No patents listed  proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s): 5,135,950
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- Patent number(s): \_\_\_\_\_ Expiry date(s): \_\_\_\_\_
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):  
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): 5,446,194; 6,500,867; 6,797,732
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *US Agent, March 8, 2012; Orion, Finland, March 9, 2012*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

[\\cdsesub1\EVSPROD\NDA203312\0012](#) (May 1, 2012 – No Lawsuit submission)

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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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TRACY J PETERS  
01/07/2015

**PMR/PMC Development Template for RYTARY (levodopa-carbidopa ER)  
PMR # 1996-1**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 04/2015  
Study/Clinical trial Completion Date: 10/2016  
Final Report Submission Date: 12/2016  
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical data demonstrate efficacy and warrant approval at this time, and the nonclinical data on one of the drug product excipients (b) (4) suggest potential systemic toxicity that requires further characterization.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A six-month oral toxicology study of (b) (4) in rat is required to identify an unexpected serious risk of adverse effects of RYTARY, consistent with guidance set forth in *Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (CDER, May 2005)*. Previous studies of (b) (4) in multiple species (conducted prior to 1990) suggest the potential for systemic toxicity. This was unexpected because of the high molecular weight of the excipient (b) (4). These findings need to be confirmed, using a well-characterized drug product

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

**PMR/PMC Development Template for RYTARY (levodopa-carbidopa ER)  
PMR # 1996-2**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: 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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PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/2015  
Study/Clinical trial Completion Date: 08/2016  
Final Report Submission Date: 10/2016  
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical data demonstrate efficacy and warrant approval at this time, and the nonclinical data on one of the drug product excipients ( (b) (4) brand of methacrylic acid copolymer, (b) (4) ) suggest potential systemic toxicity that requires further characterization.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

An oral absorption study of radiolabeled (b) (4) in rat is required to identify an unexpected, serious risk of adverse effects of RYTARY, consistent with guidance set forth in *Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (CDER, May 2005)*. Previous studies of (b) (4) in multiple species (conducted prior to 1990) suggest the potential for systemic toxicity. This was unexpected because of the high molecular weight of the excipient (b) (4). No oral absorption study of (b) (4) has been conducted.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<p>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</p>
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Required

- Observational pharmacoepidemiologic study  
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)  
*In vivo* absorption study, in support of a toxicology safety study.
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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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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SALLY U YASUDA  
12/17/2014

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** 203312

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Rytary (carbidopa/levodopa extended release) capsules

**Applicant:** Impax Laboratories

**Receipt Date:** April 9, 2014

**Goal Date:** January 9, 2015 (including 3 month extension)

## 1. Regulatory History and Applicant's Main Proposals

The original 505(b)(2) new drug application with proposed labeling was received on December 21, 2011. On March 6, 2012, the following labeling deficiencies, which include components of the SRPI review and also the SEALD reviewer comments, were relayed to the applicant:

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. There is redundancy of information in the Highlights (HL). Information about the concomitant use with dopamine agonists, MAO inhibitors, anticholinergics is repeated in the Dosage and Administration section and the Drug Interactions section.
2. Several cross-references in the HL are incorrect (e.g., there is no information about hypersensitivity to carbidopa or levodopa in Section 11).
3. The product title line in the HL is under review. At this time we recommend the following product title line: TRADENAME (carbidopa and levadopa) extended-release capsules, for oral use.
4. Include the four digit year that the FDA initially approved the combination of active ingredients in the HL.
5. If a product belongs to an established pharmacologic class, the following statement is required in HL: [(Drug Product) is a (name of class) indicated for (indication(s))]. Identify the established pharmacologic class for the drug at: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
6. It is unclear whether there is a known serious hypersensitivity to the excipients of your proposed product. If this is theoretical, it should be not be a contraindication.

## RPM PLR Format Review of the Prescribing Information

7. For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. A general link to a company’s website cannot be used to meet the requirement to have adverse reactions reporting contact information in HL. Either remove the reference to the general website or include a specific website dedicated to reporting adverse reactions. Furthermore, we recommend that you use a toll free number.
8.  (b) (4)
9. A placeholder for the revision date, presented as “Revised: MM/YYYY or Month, Year”, must appear at the end of HL. The revision date is the month/year of application or supplement approval. The date should be revised when submitting new labeling and the month should be in sentence case; not all upper case.
10. The section headings and subheadings in the TOC must match the headings and subheadings in the FPI. For example in Section 7.2, the titles in the TOC and FPI are not consistent.
11. The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1). When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:  
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
12. If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”
13. A horizontal line must separate the TOC and FPI.
14. Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events”, should be avoided.
15. For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:  

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

During our preliminary review of your submitted labeling, we have identified the following major labeling content issues:

1. Your proposed Dosage and Administration section is not consistent with the 2010 *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* guidance. It is not an effective communication of important dosage and administration instructions to prescribers. See this guidance at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>

## RPM PLR Format Review of the Prescribing Information

2. The 2011 *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biologic Products — Content and Format* Guidance states that each subsection in the Warnings and Precautions “should accurately characterize the risk.” Subsections including “5.1 General”, “5.2 Laboratory Tests”, “5.4 CNS Effects”, “5.7 Special Population” are not consistent with this guidance. See this guidance at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>
3. According to 21 CFR 201.57c(8), the Drug Interactions section should only include “clinically significant interactions” and “details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.” Your proposed label is not consistent with this regulation.
4. Your proposed (b) (4) section may not be clear to prescribers. We recommend you revise this section, using command language, and include subsections for each individual concept.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

We request that you resubmit labeling that addresses these issues by March 27, 2012. The resubmitted labeling will be used for further labeling discussions.

The application was issued a Complete Response on January 18, 2013. On April 4, 2014, a Class 2 resubmission was received, and the basis for this review is the labeling included in that submission.

### 2. Review of the Prescribing Information

This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix).

### 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: "Dosage Forms and Strengths", "Contraindications" and "Drug Interactions" are not centered.

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

## Selected Requirements of Prescribing Information

• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: <sup>(b) (4)</sup> instead of “for”

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

## Selected Requirements of Prescribing Information

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

*Comment:*

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

*Comment:*

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

*Comment:*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:* *Revise just prior to approval*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:** *In 7.1 "Contraindications" needs italicized*

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

[REDACTED] (b) (4)

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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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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TRACY J PETERS  
12/05/2014

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** October 1, 2014

**Requesting Office or Division:** Division of Neurology Products (DNP)

**Application Type and Number:** NDA 203312

**Product Name and Strength:** Rytary (Carbidopa and Levodopa) Extended-Release Capsules  
Carbidopa 23.75 mg and Levodopa 95 mg;  
Carbidopa 36.25 mg and Levodopa 145 mg;  
Carbidopa 48.75 mg and Levodopa 195 mg;  
Carbidopa 61.25 mg and Levodopa 245 mg

**Product Type:** Multi-Ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Impax Laboratories, Inc.

**Submission Date:** April 9, 2014

**OSE RCM #:** 2014-1686

**DMEPA Primary Reviewer:** Jacqueline Sheppard, PharmD

**DMEPA Acting Team Leader:** Tingting Gao, PharmD

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## **1 REASON FOR REVIEW**

This review responds to a request from the Division of Neurology Products (DNP) for a review of the revised container labels and carton labeling for Rytary (Carbidopa and Levodopa) Extended-release capsules received on April 9, 2014. The container labels and carton labeling was found acceptable under OSE Review # 2012-152 dated January 8, 2013 but the sponsor made additional changes since that final review.

## **2 MATERIALS REVIEWED**

DMEPA reviewed the container labels and carton labeling received on April 9, 2014 (Appendix A) to determine if it is acceptable from a medication error perspective. Additionally, we compared the recommendations contained in OSE review # 2012-152 dated July 11, 2012, September 17, 2012, October 31, 2012, December 18, 2012, and January 8, 2013.

## **3 CONCLUSION & RECOMMENDATIONS**

The revised carton and container label and labeling is acceptable from a medication error perspective.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Rytary that Impax Pharmaceuticals submitted on August 9, 2014.

<b>Table 2. Relevant Product Information for Rytary</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Carbidopa and Levodopa
<b>Indication</b>	(b) (4) treatment of adult patients with (b) (4) Parkinson's disease (b) (4), post-encephalitic parkinsonism and (b) (4) parkinsonism which may follow (b) (4) carbon monoxide intoxication (b) (4) or manganese intoxication.
<b>Route of Administration</b>	oral
<b>Dosage Form</b>	Extended release oral capsules
<b>Strength</b>	Carbidopa 23.75 mg and Levodopa 95 mg Carbidopa 36.25 mg and Levodopa 145 mg Carbidopa 48.75 mg and Levodopa 195 mg Carbidopa 61.25 mg and Levodopa 245 mg
<b>Dose and Frequency</b>	(b) (4)
<b>How Supplied</b>	25 count physician samples, 100 count and 240 count bottles
<b>Storage</b>	Controlled Room Temperature

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

We searched the L: drive on September 29, 2014 using the terms, Rytary to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified five previous reviews<sup>1,2,3,4,5</sup> and we confirmed that our previous recommendations were implemented or considered.

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<sup>1</sup> Neshiewat J. Revised Label and Labeling Memo for RYTARY (NDA 203312). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 Jan 8. 14 p. OSE RCM No.: 2012-152.

<sup>2</sup> Neshiewat J. Label and Labeling Review for RYTARY (NDA 203312). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 Oct 31. 14 p. OSE RCM No.: 2012-152.

<sup>3</sup> Neshiewat J. Label and Labeling Review for RYTARY (NDA 203312). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 Dec 18. 14 p. OSE RCM No.: 2012-152.

<sup>4</sup> Neshiewat J. Label and Labeling Review for RYTARY (NDA 203312). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 Sept 17. 27 p. OSE RCM No.: 2012-152.

<sup>5</sup> Neshiewat J. Label and Labeling Review for RYTARY (NDA 203312). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 Jul 11. 24 p. OSE RCM No.: 2012-152.

## APPENDIX C. LABELS AND LABELING

### C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>6</sup> along with postmarket medication error data, we reviewed the following Rytary labels and labeling submitted by Impax Pharmaceuticals on April 9, 2014.

- Container label
- Carton labeling

### C.2 Label and Labeling Images

**Rytary 23.75 mg/ 95 mg**

Professional Sample 25 Count



12 Page(s) of Draft Labeling have been Withheld in Full as  
b4 (CCI/TS) immediately following this page

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<sup>6</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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JACQUELINE E SHEPPARD  
10/01/2014

TINGTING N GAO  
10/01/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
Revised Label and Labeling Memo**

Date: January 8, 2013

Reviewer: Julie Neshiewat, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Rytary (Carbidopa and Levodopa) Extended-release  
Capsules  
Carbidopa 23.75 mg and Levodopa 95 mg;  
Carbidopa 36.25 mg and Levodopa 145 mg;  
Carbidopa 48.75 mg and Levodopa 195 mg;  
Carbidopa 61.25 mg and Levodopa 245 mg

Application Type/Number: NDA 203312

Applicant/sponsor: Impax Laboratories, Inc.

OSE RCM #: 2012-152

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## **1 INTRODUCTION**

This review responds to a request from the Division of Neurology Products (DNP) for a review of the revised container labels and carton labeling for Rytary (Carbidopa and Levodopa) Extended-release Capsules received on December 28, 2012 (Appendix A). DMEPA has reviewed previous versions of the container labels and carton labeling under OSE Review # 2012-152 dated July 11, 2012, September 17, 2012, October 31, 2012, and December 18, 2012.

## **2 MATERIAL REVIEWED**

DMEPA reviewed the container labels and carton labeling received on December 28, 2012. We compared the revised container labels and carton labeling against the recommendations contained in OSE review # 2012-152 dated July 11, 2012, September 17, 2012, October 31, 2012, and December 18, 2012.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

Review of the revised container labels and carton labeling show that the Applicant implemented DMEPA's previous recommendations. We have no additional recommendations at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

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/s/  
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JULIE V NESHIEWAT  
01/08/2013

IRENE Z CHAN  
01/08/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
Label and Labeling Review**

Date: December 18, 2012

Reviewer: Julie Neshiewat, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Rytary (Carbidopa and Levodopa) Extended-release  
Capsules  
Carbidopa 23.75 mg and Levodopa 95 mg;  
Carbidopa 36.25 mg and Levodopa 145 mg;  
Carbidopa 48.75 mg and Levodopa 195 mg;  
Carbidopa 61.25 mg and Levodopa 245 mg

Application Type/Number: NDA 203312

Applicant/sponsor: Impax Laboratories, Inc.

OSE RCM #: 2012-152

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## **1 INTRODUCTION**

This review responds to a request from the Division of Neurology Products (DNP) for a review of the revised container labels and carton labeling for Rytary (Carbidopa and Levodopa) Extended-release Capsules received on November 13, 2012 (Appendix A). DMEPA has reviewed previous versions of the container labels and carton labeling under OSE Review # 2012-152 dated July 11, 2012, September 17, 2012, and October 31, 2012.

## **2 MATERIAL REVIEWED**

DMEPA reviewed the container labels and carton labeling received on November 13, 2012. We compared the revised container labels and carton labeling against the recommendations contained in OSE review # 2012-152 dated July 11, 2012, September 17, 2012, and October 31, 2012.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

Review of the revised container labels and carton labeling show that the Applicant has implemented DMEPA's previous recommendations. However, we have identified additional changes that should be made to ensure that the proprietary name, established name, and statement of strength are the most prominent information on the labels and labeling. DMEPA recommends the following recommendations be implemented prior to approval of this application:

- A. Container Labels and Carton Labeling (Retail and Professional Samples: all strengths)
  1. Increase the prominence of the established name, and ensure that the proprietary name, established name, and statement of strength are the most prominent information on the principal display panel. For example, on the 25-count professional sample 23.75 mg / 95 mg strength, the font size for the statement "Professional sample – Not for sale" appears larger than the font size for the established name.
  2. Debold the net quantity statement "XX Capsules" on the container labels and "X Bottles, Each Bottle contains XX Capsules" on the carton labeling since the net quantity is overly prominent.
- B. Carton Labeling (Professional Samples: all strengths)
  1. Debold the statements "Professional sample – Not for sale" and "Contact your Impax Pharmaceuticals sales rep for more materials and samples." since they are overly prominent.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

**Appendix A: Revised Container Labels and Carton Labeling**

**Rytary 23.75 mg / 95 mg**

Professional Sample 25-count: Manufactured in Taiwan



Carton containing six bottles of the Professional Sample 25-count: Manufactured in Taiwan



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JULIE V NESHIEWAT  
12/18/2012

IRENE Z CHAN  
12/18/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
Label and Labeling Review**

Date: October 31, 2012

Reviewer: Julie Neshiewat, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Rytary (Carbidopa and Levodopa) Extended-release  
Capsules  
Carbidopa 23.75 mg and Levodopa 95 mg;  
Carbidopa 36.25 mg and Levodopa 145 mg;  
Carbidopa 48.75 mg and Levodopa 195 mg;  
Carbidopa 61.25 mg and Levodopa 245 mg

Application Type/Number: NDA 203312

Applicant/sponsor: Impax Laboratories, Inc.

OSE RCM #: 2012-152

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## **1 INTRODUCTION**

This review responds to a request from the Division of Neurology Products (DNP) for a review of the revised container labels and carton labeling for Rytary (Carbidopa and Levodopa) Extended-release Capsules received on October 5, 2012 (Appendix A). DMEPA previously reviewed the proposed container labels and carton labeling under OSE Review # 2012-152 dated July 11, 2012 and the follow up review dated September 17, 2012.

## **2 MATERIAL REVIEWED**

DMEPA reviewed the container labels and carton labeling received on October 5, 2012. We compared the revised container labels and carton labeling against the recommendations contained in OSE review # 2012-152 dated July 11, 2012 and the follow up review dated September 17, 2012.

## **3 RESULTS**

Review of the revised container labels and carton labeling determined that not all of our previous recommendations were implemented by the Applicant. Furthermore, we have identified additional changes that should be made to improve readability.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

Review of the revised container labels and carton labeling determined that not all of our previous recommendations were implemented by the Applicant. Furthermore, we identified additional vulnerability that can lead to medication errors. DMEPA recommends the following recommendations be implemented prior to approval of this application:

### **A. Container Labels and Carton Labeling (Retail and Professional Samples)**

1. Revise statements that appear in all upper case to title case to improve readability. For example, revise the statement “PROFESSIONAL SAMPLE – NOT FOR SALE” to read “Professional sample – Not for sale.”

### **B. Carton Labeling (Retail, all strengths)**

1. On the panels containing the strength statement, increase the font size of the strength statement and the size of the color highlighting block for increased prominence.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

**Appendix A: Revised Container Labels and Carton Labeling**

**Rytary 23.75 mg / 95 mg**

Professional Sample 25-count: Manufactured in Taiwan



Carton containing six bottles of the Professional Sample 25-count: Manufactured in Taiwan



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JULIE V NESHIEWAT  
10/31/2012

IRENE Z CHAN  
10/31/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

## Memorandum

**Date:** September 29, 2012

**To:** Tracy Peters, PharmD  
Regulatory Project Manager  
Division of Neurology Products (DNP)

**From:** Quynh-Van Tran, PharmD, BCPP  
Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP)

**cc:** Meeta Patel, PharmD  
Regulatory Review Officer  
Division of Consumer Drug Promotion

Mathilda Fienkeng, PharmD  
Team Leader, Acting  
DPDP

**Subject:** DPDP's comment for NDA 203312  
Rytary™(carbidopa and levodopa) Extended Release Capsules.

---

Thank you for the opportunity to review the proposed Prescribing Information (PI) for Rytary™ (carbidopa and levodopa) extended release capsules (Rytary). (FDA dated version 9/21/2012). Please see attached PI with our comments incorporated therein. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185 or [Quynh-Van.Tran@fda.hhs.gov](mailto:Quynh-Van.Tran@fda.hhs.gov).

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QUYNH-VAN TRAN  
09/29/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Pharmacovigilance Review**

**Date** September 26, 2012

**Reviewers:** Charlene M. Flowers, R.Ph., Safety Evaluator,  
Jasmine Gatti, MD, Medical Officer,  
Division of Pharmacovigilance I (DPV I)

**Team Leaders:** Cindy Kortepeter, Pharm.D.  
Allen Brinker, MD, MPH  
Division of Pharmacovigilance I (DPV I)

**Division Director:** Linda Scarazzini, M.D., R.Ph.  
Division of Pharmacovigilance I (DPV I)

**Subject:** Misuse and Abuse

**Product Name(s) and applicant type/number:** Sinemet™ (levodopa and carbidopa)/NDA017555  
Sinemet CR (levodopa and carbidopa)/NDA019856  
Carbilev (levodopa and carbidopa)/ANDA076643  
Parcopa (levodopa and carbidopa)/ANDA 076699  
Stalevo (levodopa;carbidopa;entacapone)/NDA 021485  
Rytary/IPX066 (levodopa and carbidopa extended release capsule)/NDA203312

**Applicant/Sponsor:** Sinemet/ Merck Sharp Dohme  
Sinemet CR/Merck Sharp Dohme  
Carbilev/Ranbaxy  
Parcopa/UCB Inc  
Stalevo/Orion Pharma  
Rytary/IPX066/Impax Lab Inc.

**OSE RCM #:** 2012-1572

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## EXECUTIVE SUMMARY

Controlled Substance Staff (CSS) requested DPV to search FDA's Adverse Event Reporting System (AERS) database and published literature for case reports of levodopa-carbidopa associated drug abuse and misuse to assess if approved labeling is consistent across the class and accurately represents any known risks of abuse. Of note, proposed labeling for the new NDA submission, Rytary™, included abuse and misuse language adapted from the *Drug Abuse and Dependence* labeling section for Stalevo™.

A search of AERS and published literature revealed no cases that met our established case definition for drug abuse in association with the drug combination of levodopa-carbidopa. In general, the excluded cases described Parkinsonian patients who took excessive doses of their prescribed levodopa-carbidopa therapy to primarily avoid unwanted motor symptoms of Parkinson's disease such as the wearing-off state. Some patients required medical intervention to lower doses back to initially prescribed doses. In many of the reports, excessive drug dosing was often associated with behavior disorders that are characteristic of dopamine dysregulation syndrome (DDS) - also known as hedonistic homeostatic dysregulation - that is known to occur in association with Parkinson's disease.

It is unclear why Stalevo's labeling contains unique language referencing potential abuse and dependence to generally achieve a euphoric state. However, the labeling of numerous other drugs in the class does not suggest the potential for misuse or abuse. This potential discrepancy has prompted the Division of Neurology Products (DNP) to request that Orion Pharma, the sponsor of Stalevo, provide data to support their labeling claim of abuse and DNP will reassess the Rytary labeling.

## 1 INTRODUCTION

### 1.1 BACKGROUND

During NDA review of Rytary™, a new extended release formulation of levodopa-carbidopa, the Division of Neurology Products (DNP) asked the Controlled Substance Staff (CSS) to assist with labeling in order to align the label for Rytary™ with other dopaminergic products<sup>1</sup>. In turn, CSS requested DPV to search AERS and literature for case reports of abuse and misuse in association with levodopa-carbidopa combinations. Furthermore, DPV was asked to assess if approved labeling for abuse is consistent across the class and accurately represents any known risks of abuse.

### 1.2 PRODUCT LABELING

**Drug Abuse and Dependence section (excerpts):**

**Stalevo (Levodopa/carbidopa/entacapone):**

“Stalevo® has not been systematically studied, in animal or humans, for its potential for abuse, tolerance or physical dependence. In premarketing clinical experience, carbidopa-levodopa did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, there are rare postmarketing reports of abuse and dependence of medications containing levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve a euphoric state.”

**Sinemet and multiple generic equivalent products:** no text regarding abuse and misuse

**Mirapex and generic: pramipexole equivalent products:**

Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no effect.

**Requip and multiple generic ropinirole equivalent products:**

Animal studies and human clinical trials with REQUIP did not reveal any potential for drug-seeking behavior or physical dependence.

**Neupro (rotigotine):**

Animal studies and human clinical trials with rotigotine did not reveal potential for drug-seeking behavior or physical dependence.

**Apokyn (apomorphine):**

A rarely reported motivation for apomorphine abuse (escalation of dose beyond prescribed frequency) is the use of apomorphine to attempt to avoid all symptoms of all “off” events when “off” events occur frequently. A second, rarely reported, motivation for apomorphine abuse is a psychosexual reaction related to the stimulation of penile erection and increase in libido. Adverse events that have been reported in males with overuse include frequent penile erections, atypical sexual behavior, heightened libido, dyskinesias, agitation, confusion, and depression. No studies have been conducted to evaluate the potential for dependence when apomorphine is used as acute (rescue) treatment of “off” episodes in the patients with “on/off” or “wearing-off” effects associated with late stage Parkinson’s disease.

**Comtan and multiple generic entacapone equivalent products:**

Comtan (entacapone) is not a controlled substance. Animal studies to evaluate the drug abuse and potential dependence have not been conducted. Although clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence, systematic studies in humans designed to evaluate these effects have not been performed.

**Tasmar (tolcapone):**

Studies conducted in rats and monkeys did not reveal any potential for physical or psychological dependence. Although clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence, systematic studies in humans designed to evaluate these effects have not been performed.

**Eldepryl and multiple generic selegiline equivalent products:** no text regarding misuse and abuse

**Azilect (rasagiline):**

Studies conducted in mice and rats did not reveal any potential for drug abuse and dependence. Clinical trials have not revealed any evidence of the potential for abuse, tolerance or physical dependence; however, systematic studies in humans designed to evaluate these effects have not been performed.

## 2 METHODS AND MATERIALS

### 2.1 CASE DEFINITION

Cases included in this review met the following case definition below for drug abuse or misuse:

The narrative describes a non-Parkinsonian patient who displayed drug seeking behavior such as bribery, deception, or theft of the drug for achieving non-Parkinsonian benefits including euphoric states.

OR

A Parkinsonian patient not having the components of dopamine dysregulation syndrome or hedonistic homeostatic dysregulation (or other common names)

AND

seeking to use carbidopa/levodopa in a fashion characterized by drug seeking behaviors of covert and illicit use (stealing, lying) ignoring the self-detrimental effects of excess dosing, displaying drug withdrawal or dependence symptoms unlike the on-off symptoms seen with carbidopa/levodopa wearing-off in order to attain euphoria or other “high.”

### 2.2 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched with the strategy described as shown below in Table 1.

<b>Table 1. AERS Search Strategy*</b>	
Date of search	7/24/2012
Time period of search	01/01/1965 <sup>^</sup> - 07/24/2012
Product Terms	Levodopa and Carbidopa
MedDRA Search Terms	SMQ: “Drug Abuse, Dependence, and Withdrawal (broad)”
Additional criterion	Combination drug option (suspect only)

\* See Appendix A for description of the AERS database.

<sup>^</sup> Database initial (default) date

## 2.3 LITERATURE SEARCH

The medical literature was searched with the strategy described as shown below in Tables 2 and 3.

<b>Table 2. Literature Search Strategy #1</b>	
Date of search	≥ 1985 to 8/ 8/2012; 8/28/2012
Database	PubMed@FDA
Search Terms	“Carbidopa Levodopa AND Abuse.”
Years included in search	All
Inclusion criteria	English, human, clinical trials, case studies, cohort/observational studies

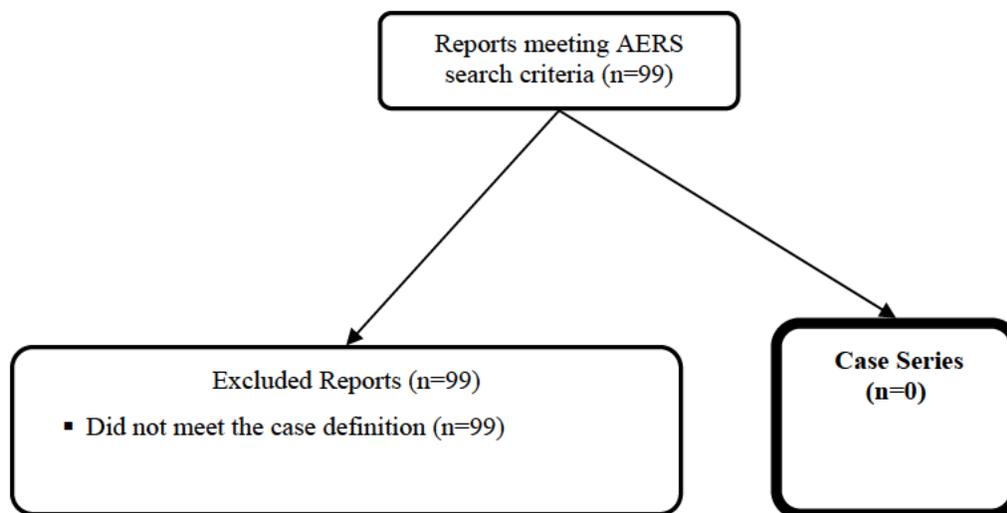
<b>Table 3. Literature Search Strategy #2</b>	
Date of search	8/ 8/2012; 8/28/2012
Database	PubMed@FDA
Search Terms	“Parkinson’s AND dopamine dysregulation syndrome AND addiction”
Years included in search	All
Inclusion criteria	English, human, clinical trials, case studies, cohort/observational studies

## 3 RESULTS

### 3.1 AERS CASE SELECTION

The AERS search retrieved 99 reports. After applying the case definition in Section 2.1, no cases were included in the case series of misuse or abuse reported with levodopa-carbidopa use (see Figure 1).

#### Figure 1. AERS Case Selection



### 3.2 LITERATURE SEARCH

Using the search term “carbidopa levodopa AND abuse” 60 articles were retrieved. Most were excluded due to factors such as intentional overdose/suicide, unrelated safety events, pre-clinical, pharmacology issues, efficacy/ therapy literature or general articles about the drugs. Non-human, non-English literature was also excluded. Only Nausieda’s 1985<sup>2</sup> and Teixeira’s 2005<sup>3</sup> articles cited 5 cases and 1 case respectively of “sinemet abuse,” which did not meet our case definition.

Appendix 8.2 includes the results for dopamine dysregulation syndrome and addiction.

## 4 DISCUSSION

Following a search of the AERS database and medical literature, no cases of abuse or misuse in association with levodopa-carbidopa were identified that met the DPV case definition for potential misuse or abuse. The AERS database included 99 non-duplicated reports that described Parkinsonian patients who took excessive doses of their prescribed levodopa-carbidopa therapy to primarily avoid unwanted motor symptoms of Parkinson’s disease such as the wearing-off state. Some patients required medical intervention to lower doses back to initially prescribed doses. In many of the reports, excessive drug dosing was associated with behavior disorders that are characteristic of dopamine dysregulation syndrome (DDS) - also known as hedonistic homeostatic dysregulation - that is known to occur in association with Parkinson’s disease.<sup>4,5,6</sup> In the literature search, the five older cases and one recent case were attributed to the dopamine dysregulation syndrome. Consistent with their DDS, the six cases often continued to escalate their daily Sinemet doses (up to 25/250, 10.5 tablets daily) even though their PD symptoms were controlled. Unfavorable adverse effects such as dystonia and chorea were tolerated to achieve “a sense of power, strength, animation, talkativeness” characteristic of DDS.

DDS is associated with many dopaminergic drugs or drugs affecting the reward system and other neurotransmitters that may be particularly addictive in patients with certain predisposing

personality, demographics or diagnoses.<sup>7,8</sup> Djamshidian<sup>9</sup> states DDS is included as an impulsive-compulsive behavior (ICB) in the ICB spectrum of DSM diagnosis. Farnikova<sup>10</sup> states that multiple authors “suggest underlying mechanistic similarities between PD patients and patients with substance abuse disorders.” Much is still unknown. Further evidence, research, and trials are necessary to elucidate more findings. Ambermoon,<sup>11</sup> in her 2011 review article states, “Research into these disorders has been limited. Prospective studies and case-control and cohort studies are needed to characterize DDS more accurately and estimate its prevalence, risk factors and prognosis more reliably.”

Stalevo<sup>TM</sup> is the only levodopa-carbidopa combination or dopaminergic product<sup>1</sup> labeled for Drug Abuse and Dependence (section 9.0 in the structured product labeling – SPL) that contains language related to abuse. Stalevo’s labeling is the prototype for Rytary's labeling. Clinical trial or animal data cited in the majority of the dopaminergic drug labels, including Stalevo's, state that they do not have the potential for abuse. However, postmarketing reports cited in Stalevo's labeling (b) (4). This potential discrepancy has prompted DNP to request that Orion Pharma, the sponsor of Stalevo, provide data to support their labeling claim of abuse and DNP will reassess the Rytary labeling. The Drug Abuse and Dependence section for Stalevo states the following (excerpt):

“Stalevo has not been systematically studied, in animal or humans, for its potential for abuse, tolerance or physical dependence. In premarketing clinical experience, carbidopa-levodopa did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, there are rare postmarketing reports of abuse and dependence of medications containing levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve a euphoric state.”

## 5 CONCLUSION

There is potential for abuse and misuse symptomatology to appear in Parkinsonian patients related to manifestations of the disease and treatment with levodopa-carbidopa. However, no cases were identified of drug in association with potential abuse or misuse involving individuals such as patients, caregivers, family members, or friends to achieve non-therapeutic benefits (e.g., euphoria).

It is unclear why Stalevo’s labeling contains unique language referencing potential abuse and dependence to generally achieve a euphoric state. However, the labeling of numerous other drugs in the class does not suggest the potential for misuse or abuse. This potential discrepancy has prompted the Division of Neurology Products (DNP) to request that Orion Pharma, the sponsor of Stalevo, provide data to support their labeling claim of abuse and DNP will reassess the Rytary labeling.

---

<sup>1</sup> Pramipexole, ropinirole, rotigotine, tolcapone, entacapone, selegiline, rasagiline, bromocriptine, and apomorphine.

## 6 RECOMMENDATION

No regulatory recommendations are offered.

## 7 REFERENCES

- 1 Sinemet, pramipexole, rotigotine, ropinirole, tolcapone, entacapone, selegiline, rasagiline, and apomorphine.
- 2 Nausieda, PA. "Sinemet Abusers". *Clinical Neuropharmacology*. 1985. 8(4):318-327.
- 3 Teixeira Al, Cardoso, f. Factitious disorder mimicking addiction to levodopa in a patient with advanced parkinson's disease. *Arq Neuropsiquiatr*.2005;63(2-A):324-326.
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- 5 R. Cantello, G giovannoni et al, Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies, *J Neurolo Neurosurg Psychiatry*, 2000; 69(4): 566-567.
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- 7 AntioniniA, et al, Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. *Drug Saf*. 2009; 32(6):475-88
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- 11 Ambermoon P, et al. compulsive use of dopamine replacement therapy: a model for stimulant drug addiction. *Addiction*. 2011; 107:241-247.
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- 15 Merim D, giladi N. dopamine dysregulation syndrome, addiction and behavioral changes in parkinson's disease. *Parkinsonism Relat Disord*. 2008;14(4):273-80.
- 16 Pezzella, et al. Prevalence and clinical features of hedonistic homeostatic dysregulation in parkinson's disease. *Movement Disorders*. 2005;20(1):77-81.

## **8 APPENDIX**

### **8.1 APPENDIX A. ADVERSE EVENT REPORTING SYSTEM (AERS)**

#### **Adverse Event Reporting System (AERS)**

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

### **8.2 ADDITIONAL SEARCH: RESULTS OF PARKINSON'S DISEASE AND DOPAMINE DYSREGULATION SYNDROME AND ADDICTION LITERATURE**

Results:

Citations were excluded based on non-English (4); treatment (3); neurobiology (2); general topic articles/other impulse compulsive disorders (3). Those reviewed included 4 review articles<sup>7,9,11,12</sup>, 6 articles related to impulse control, addiction or dependence<sup>7,8,10,13,14,15</sup>, and one article on prevalence of dopamine dysregulation or hedonistic homeostatic dysregulation<sup>16</sup>.

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/s/  
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CHARLENE M FLOWERS  
09/26/2012

JASMINE C GATTI  
09/26/2012

ALLEN D BRINKER  
09/26/2012

CINDY M KORTEPETER  
09/26/2012

MIN CHU CHEN  
09/26/2012

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: September 12, 2012

TO: Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 203-312 Carbidopa/Levodopa  
Extended Release Capsules from Impax Laboratories, USA

At the request of the Division of Neurology Products (DNP), the Division of Bioequivalence and GLP Compliance (DBGC) inspected the following BE study:

**IPX066-B10-01**: "A randomized, single-center, single-dose, open-label, two-sequence, two-treatment crossover study with a 6-day washout between treatment periods in healthy subjects under fasted conditions with an additional treatment after Period 2"

**Clinical:**

The inspection of clinical portion was conducted by Kathleen B. Swat (ORA) at [REDACTED] <sup>(b)(4)</sup> Following the inspection (July 23-26, 2012), no Form FDA-483 was issued.

**Analytical:**

The inspection of analytical portion was conducted by Sripal R. Mada, Ph.D (OSI) and Samantha J. Pinizzotto, D.V.M (ORA) at [REDACTED] (b) (4)

Following the inspection ([REDACTED] (b) (4)), Form FDA-483 was issued (**Attachment 1**). The firm's response was received on August 24, 2012 (**Attachment 2**).

The Form FDA-483 observation, [REDACTED] (b) (4) response to Form FDA-483 and our evaluation follow:

[REDACTED] (b) (4)

In their response to Form FDA-483, [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

In the opinion of the reviewer, [REDACTED] (b) (4) response is adequate.

**Conclusion:**

The DBGCC reviewer recommends that the clinical and analytical data from this study are acceptable for your review.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGCC, OSI

**Final Classifications:**

**NAI** - [REDACTED] (b) (4)  
**FEI:** [REDACTED] (b) (4)

**VAI** - [REDACTED] (b) (4)  
**FEI:** [REDACTED] (b) (4)

cc:

OSI/Moreno

OSI/DBGC/Taylor/Dejernet

OSI/DBGC/BB/Haidar/Skelly/Mada

OND/ODE1/DNP/Katz/Peters

OCP/DCP1/Men/Parepally

ORA/FLA-DO/Pinizzotto

ORA/KAN-DO/Swat

Draft: SRM 09/10/2012

Edit: MFS 09/12/2012

OSI: (b) (4); O:\Bioequiv\EIRCover\203312.imp.car

FACTS: (b) (4)

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SRIPAL R MADA  
09/12/2012

SAM H HAIDAR  
09/19/2012

WILLIAM H TAYLOR  
09/20/2012

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management

**Label and Labeling Review**

Date: September 17, 2012

Reviewer: Julie Neshiewat, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Rytary (Carbidopa and Levodopa) Extended-release  
Capsules  
Carbidopa 23.75 mg and Levodopa 95 mg;  
Carbidopa 36.25 mg and Levodopa 145 mg;  
Carbidopa 48.75 mg and Levodopa 195 mg;  
Carbidopa 61.25 mg and Levodopa 245 mg

Application Type/Number: NDA 203312

Applicant/sponsor: Impax Laboratories, Inc.

OSE RCM #: 2012-152

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1. INTRODUCTION

This review evaluates the revised container labels and carton labeling for Rytary (Carbidopa and Levodopa) Capsules submitted by the Applicant on August 23, 2012. The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the container labels, carton labeling, and insert labeling for Rytary and provided comments to the Applicant in OSE Review # 2012-152, dated July 11, 2012.

## 2. METHODS AND MATERIALS

We compared the revised container labels and carton labeling submitted on August 23, 2012 (see Appendix A) against our recommendations in OSE Review # 2012-152 dated July 11, 2012 to assess whether the revisions adequately address our concerns from a medication error perspective. In addition, the Division of Professional Drug Promotion (DPDP) was consulted to evaluate if the [REDACTED] (b) (4) [REDACTED] in the proprietary name are considered promotional.

## 3. RESULTS

Review of the revised container labels and carton labeling determined that not all of our previous recommendations were implemented by the Applicant. Furthermore, we have identified additional changes that should be made to the container labels and carton labeling to clarify information and improve readability. DPDP determined that the graphics above the [REDACTED] (b) (4) [REDACTED] of the product, which is promotional and may misleadingly overstate the efficacy of the drug.

## 4. CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels and carton labeling determined that not all our previous recommendations were implemented by the Applicant. Furthermore, we identified additional vulnerability that can lead to medication errors.

DMEPA recommends the following recommendations be implemented prior to approval of this application:

### Container Labels and Carton Labeling

1. The color blocking used to highlight the 23.75 mg / 95 mg strength is the [REDACTED] (b) (4) [REDACTED] with colors currently utilized for Sinemet or Sinemet CR, the proprietary name or established name presentation of your product, or the others colors chosen for strength differentiation within your product line.
2. The color blocking used to highlight the 36.25 mg / 145 mg strength is the [REDACTED] (b) (4) [REDACTED] with colors currently utilized for Sinemet or Sinemet CR, the proprietary name or established name presentation of your product, or the others colors chosen for strength differentiation within your product line.

3. The established name 'Carbidopa and Levodopa' in (b) (4) font is hard to read against the white background and appears less prominent than the proprietary name. Revise the font color of the established name for better contrast and to improve readability of the information.
4. Revise statements that appear in all upper case to title case to improve readability. For example, revise the proprietary name from all upper case (RYTARY) to title case (Rytary).
5. (b) (4)
6. The '/' utilized between the carbidopa and levodopa strength may be misinterpreted as the number '1.' If the health care practitioner focuses on the levodopa component, the '/95 mg' may be misinterpreted as '195 mg.' To prevent confusion between the 95 mg and 195 mg levodopa component, revise the strength statement XX mg/XX mg to include spaces before and after the '/' such as XX mg / XX mg. In order to keep consistency between the presentation of the product strengths and to improve readability, the revised format XX mg / XX mg should be implemented for all strengths.
7. The font for the dosage form 'Extended-release Capsules' should match the font utilized for the presentation of the active ingredient 'Carbidopa and Levodopa' in size, typography, and color.
8. The statement 'Rx Only' appears overly prominent. Debold the 'Rx Only' statement and change the font color to black.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

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JULIE V NESHIEWAT  
09/17/2012

IRENE Z CHAN  
09/17/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

## Memorandum

**Date:** September 17, 2012

**To:** Julie Villanueva Neshiewat, PharmD  
Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

**From:** Quynh-Van Tran, PharmD, BCPP  
Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP)

**cc:** Tracy Peters, PharmD  
Regulatory Project Manager  
Division of Neurology Products (DNP)

Meeta Patel, PharmD  
Regulatory Review Officer  
DCDP

Mathilda Fienkeng, PharmD  
Team Leader, Acting  
DPDP

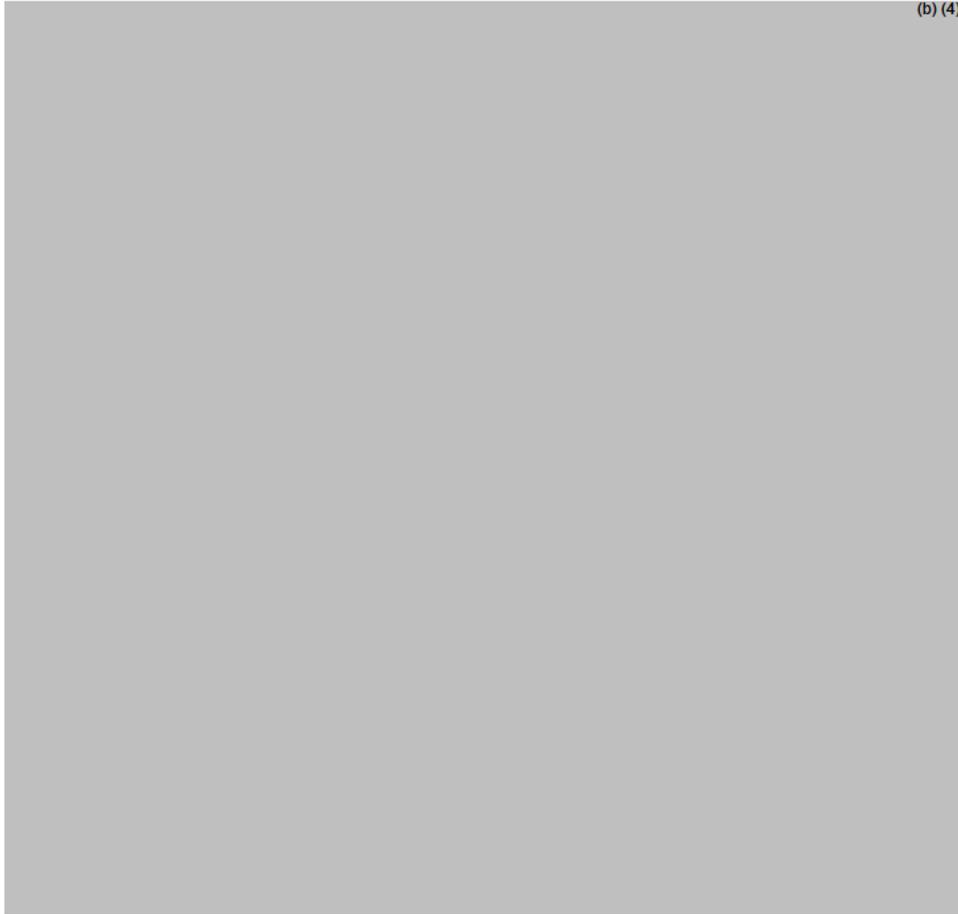
**Subject:** DPDP's comment for NDA 23312  
Rytary™(carbidopa and levodopa) Extended Release Capsules.

---

### Background

This consult is in response to DMEPA's September 17, 2012, request for DPDP's review on carton and container labeling for Rytary™ (carbidopa and levodopa) extended release capsules (Rytary).

(b) (4)



**Consult Response:**

(b) (4)



Thank you for the opportunity to comment on the proposed carton container labeling for Rytary. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185 or [Quynh-Van.Tran@fda.hhs.gov](mailto:Quynh-Van.Tran@fda.hhs.gov).

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/s/  
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QUYNH-VAN TRAN  
09/17/2012

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**CLINICAL INSPECTION SUMMARY**

DATE: August 29, 2012

TO: Tracy Peters, Pharm D., Regulatory Health Project Manager  
Anne Constantino M.D., Medical Officer  
Division of Neurology Products

FROM: Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-312

APPLICANT: Impax Laboratories, Inc.

DRUG: IPX066 (carbidopa-levodopa extended-release capsules)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review  
INDICATION: Treatment of patients with (b) (4) Parkinson's Disease  
CONSULTATION REQUEST DATE: February 9, 2012  
DIVISION ACTION GOAL DATE: August 15, 2012  
PDUFA DATE: October 21, 2012

## **I. BACKGROUND:**

The Applicant, Impax Laboratories Inc., submitted a New Drug Application (NDA) for the use of IPX066 (Carbidopa-Levodopa (CD-LD)) combination extended release (ER) capsules in the treatment of subjects with (b) (4) Parkinson's Disease. Two clinical trials were submitted in support of the application: Study IPX066-B08-05 and Study IPX066-B09-02.

### **Investigational Drug**

IPX066 is an investigational ER CD-LD product intended to produce rapid and sustained concentration of LD over (b) (4) following a single oral dose. The IPX066 formulation contains excipients that are generally regarded as safe. Due to the sustained-release nature of the IPX066 formulation, the peak concentration of LD from IPX066 is approximately 30% relative to the immediate release (IR) LD formulation.

Parkinson's Disease (PD) is characterized by the progressive degeneration of dopamine neurons in substantia nigra. Levodopa (LD) a prodrug of dopamine, when used with CD, is considered most effective in reducing motor symptoms associated with PD.

CD-LD therapy is used as the initial therapy for PD patients who need greater improvement in motor disability and are susceptible to the non-motor adverse effects associated with dopamine agonist such as hallucinations. Currently none of the marketed CD-LD oral products is capable of providing stable therapeutic plasma LD concentrations. The sponsor is seeking approval of a new multiparticulate CD-LD ER capsule product intended to produce an initial increase in LD concentration that is comparable to that of Sinemet, but with the added advantage of a more sustained concentration of LD compared to Sinemet CR. The IPX066 formulation contains CD-LD in a 1:4 ratio. These Phase 3 studies were conducted to assess the efficacy and safety of three daily doses of IPX066 in the treatment of early PD.

The clinical trials submitted in the application had a randomized, double-blind, placebo-controlled design in which subjects were treated for 30 weeks. According to the applicant, the two clinical trials provide evidence that subjects treated with IPX066 for 30 weeks showed significant improvement when compared to subjects treated with placebo.

### **Protocol IPX066-B08-05**

The primary objective of Protocol #IPX066-B08-05 entitled "APEX-PD: A Placebo-Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson's Disease" was to evaluate the safety and efficacy of IPX066 in the treatment of subjects with early PD. An additional objective was to evaluate the impact of IPX066 on the quality of life in subjects with early PD.

The study protocol was designed as a double-blind, placebo-controlled, fixed dose, parallel-arm study evaluating three doses of IPX066 versus placebo for the treatment of subjects with

early PD subjects and were LD-naïve, which was defined as subjects who had not been exposed to LD or CD. Subjects were randomized into one of four treatment groups of IPX066 (145 mg LD, 245 mg LD, 390 mg LD, or placebo) and were administered a dose of IPX066 or placebo 3 times per day. This 30-week double-blind study included a titration period of 4 weeks (3 weeks of dose escalation and 1 week of stabilization), which allowed a safe escalation to the allocated dose, and 26-week maintenance treatment.

According to the Applicant, the new formulation of IPX066 may provide an improved safety profile compared to other products currently approved for the treatment of PD. The duration of the study was 30 weeks.

### **Protocol IPX066-B09-02**

The primary objective of Protocol #IPX066-B09-02 entitled "ADVANCE-PD: A Study to Evaluate the Safety and Efficacy of IPX006 in Advanced Parkinson's Disease" was to evaluate the safety and efficacy of IPX066 in the treatment of advanced PD subjects in comparison to IR CD-LD. This study was a randomized, double-blind, double-dummy, active-control, parallel-group study. Qualified subjects will enter a 3-week IR CD-LD treatment period allowing for dose adjustment followed by a 6-week dose conversion to IPX066. Subjects were randomized equally in a blinded fashion into one of two parallel treatment arms of either IPX066 or IR CD-LD.

According to the Applicant, the new formulation of IPX066 may provide an improved safety profile compared to other products currently approved for the treatment of advanced Parkinson's Disease. The duration of the study was 22 weeks. One domestic site inspection was requested; thus site enrolled subjects in both protocols IPX066-B08-05 and IPX066-B09-02.

The review division requested inspection of three clinical investigators (one domestic site and two foreign sites) for the pivotal protocols Study B-08-05 and B-09-02 because data from the protocols are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects and had a treatment effect that was greater than average, and 2) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations.

**II. RESULTS (by protocol/site):**

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Paul Nausieda, M.D. Wisconsin Institute for Neurologic and Sleep Disorders 945 North 12 <sup>th</sup> Street Suite 4602 Milwaukee, WI 53233 Sites 101 and 126	Protocol B-08-05 Number of subjects: 24  Protocol B-09-02 Number of subjects: 26	3/8-29/2012	VAI
Emmanuelle Pourcher, M.D. Quebec Memory & Motor Skills Disorders Clinic 65 rue Saint Anne Price Building, 3 <sup>rd</sup> Floor Quebec, QC G1R 3X5 Canada Site 108	Protocol B-08-05 Number of subjects: 22	5/28- 6/1/2012	NAI
Lyudmyla Dzyak, M.D. Neurology and Neurosurgery Dept. of Dnipropetrovsk State Medical Academy 14, Oktybrskaya Sq Dnipropetrovsk, 49005 Ukraine Site 205	Protocol B-08-05 Number of subjects: 24	4/23-27/2012	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending.

**Note: Observations noted below for Dr. Dzyak are based on an e-mail communication from the field; the EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

1. **Paul Nausieda, M.D.**  
**Milwaukee, WI, 53233**

**a. What Was Inspected:** This inspection was performed as a data audit for NDA 203312. At this site two protocols were inspected.

Study Protocol IPX066-B-09-02: At this site, a total of 26 subjects were screened, one subject withdrew consent, and three were reported as screen failures. Twenty three (23) subjects were randomized, nineteen subjects completed the study, and three subjects were discontinued due to lack of efficacy. Review of the Informed Consent Documents for some subjects (number reviewed is unknown) verified that subjects signed informed consent prior to enrollment. The medical records/source data for three subjects enrolled were reviewed including drug accountability records, inclusion and exclusion criteria, vital signs, laboratory results, and adverse events. Source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events.

Study Protocol IPX066-B08-05: At this site, a total of 27 subjects were screened and three subjects were reported as screen failures. Twenty four subjects were randomized and completed the study. One subject was discontinued due to lack of efficacy. The medical records/source data for 10 subjects were reviewed in depth, including drug accountability records, consent forms, vital signs, laboratory results, IRB records, ECG readings, study procedures, concomitant medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events.

**b. General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr Nausieda. However, inspectional findings were discussed with the clinical investigator and included:

**Failure to adhere to the protocol:**

Protocol IPX066-B08-05 required Parkinson's Disease Questionnaire-39 and Patient Global Impression to be performed at certain visits. These were not performed at Visit 6 for Subjects 101011 and 101015.

Protocol IPX066-B08-05 states that subjects with a history of infarct WITH atrial fibrillation (Afib) should be excluded from the study. Subject 101012 had a history of hypertension, benign prostatic hyperplasia, paroxysmal atrial fibrillation, ventricular tachycardia, and right bundle branch block. The clinical investigator must determine if the subject's condition/arrhythmia/atrial fibrillation is chronic, well controlled, and unlikely to be aggravated by participation in the study. Subject 101012 was enrolled in the study without documenting the determination that the subjects' condition is in fact well controlled to ensure safety of the subject prior to participation in the study.

**Failure to maintain adequate and accurate case histories:**

The inspectional findings included minor transcription errors in source documents when compared to case report forms and data listings for at least seven subjects at various visits. These findings do not significantly affect efficacy outcome or subject safety. For example, Subject 101001, Visit 2 had an UPDRS score of 14, while the CRF and the data listing showed a score of 13. Similar observations were found in six additional subjects. The clinical investigator agreed that these errors occurred and promised to take appropriate steps to remedy the situation.

The medical records reviewed disclosed no other adverse findings that would negatively impact the reliability of the data. With the exception of the items noted above, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

**c. Assessment of Data Integrity:** Although regulatory violations were noted at Dr. Nausieda’s site, the findings are not likely to significantly affect overall data integrity or subject safety as they are considered isolated in nature. The data from Dr. Nausieda’s site are considered reliable in support of the application.

**2. Emmanuelle Pourcher, M.D.  
Quebec, Canada G1 S-2M5**

**a. What Was Inspected:** At this site, a total of 23 were screened, one subject was reported as a screen failure, 22 subjects were randomized into the study, three subjects were discontinued due to lack of efficacy, and 19 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site. There were no known limitations to the inspection.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Pourcher. However, inspectional findings were discussed with clinical investigator at the conclusion of the inspection. The findings included minor transcription errors in source documents when compared to CRFs. For example, a source document notes for one subject an adverse event related to study drug as “related”, as judged by the clinical investigator; however, the CRF notes “not likely related” The clinical investigator agreed that this was probably a transcription error. In addition, our investigation found that one subject had lost his study drug, but the subject did not miss any medication. The clinical investigator assured the field investigator that the subject received his medication.

The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events. The study appears to have been conducted adequately, and the data generated by this site can be used to support the pending application.

**c. Assessment of Data Integrity:** Although discussion items were noted in the EIR, they are considered minor concerns and discrepancies. Thus, the data in support of clinical efficacy and safety at Dr. Pourcher's site are considered reliable and appear acceptable in support of the pending application.

**3. Lyudmyla Dzyak, M.D.  
Dnipropetrovsk, 49005  
Ukraine**

**a. What Was Inspected:** At this site, a total 24 subjects were screened, 24 subjects were randomized into the study, and 24 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 15 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, including primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Dzyak. The medical records reviewed were found to be in order, organized, and the data verifiable with the exception of numerical values related to PDQ-39 questionnaires could not be verified from the source document. The review team considered that the observation is minor and would have no impact on data acceptability. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

**c. Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr. Dzyak's site are considered reliable and appear acceptable in support of the pending application.

### **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Three clinical investigator sites were inspected in support of this application. The inspection of Drs. Pourcher and Dzyak revealed no regulatory violations. The final classification for Dr. Pourcher is No Action Indicated (NAI). The pending classification for Dr. Dzyak is NAI, pending final review of the establishment inspection report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. While regulatory violations were identified during the inspection of Dr Nausieda, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. The final classification for the inspection of Dr. Nausieda is Voluntary Action Indicated (VAI). Overall, the data submitted from these three sites are considered acceptable in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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Susan Thompson, M.D.  
Acting Branch Chief  
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ANTOINE N EL HAGE  
08/29/2012

SUSAN LEIBENHAUT  
08/29/2012

SUSAN D THOMPSON  
08/29/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: July 11, 2012

Reviewer: Julie Neshiewat, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Rytary (Carbidopa and Levodopa) Extended-release Capsules  
Carbidopa 23.75 mg and Levodopa 95 mg;  
Carbidopa 36.25 mg and Levodopa 145 mg;  
Carbidopa 48.75 mg and Levodopa 195 mg;  
Carbidopa 61.25 mg and Levodopa 245 mg

Application Type/Number: NDA 203312

Applicant/sponsor: Impax Laboratories, Inc.

OSE RCM #: 2012-152

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container labels, carton labeling, and insert labeling for Rytary (Carbidopa and Levodopa) Extended-release Capsules, NDA 203312, for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

This application is a 505(b)(2) application, and the reference listed drugs are Sinemet (Carbidopa and Levodopa) Tablets, NDA 017555, Sinemet CR (Carbidopa and Levodopa) Extended-release Tablets, NDA 019856, Lodosyn (Carbidopa) Tablets, NDA 017830, and Stalevo (Carbidopa, Levodopa, and Entacapone) Tablets, NDA 021485.

The proposed proprietary name, Rytary, was evaluated under separate cover (OSE Review # 2012-175) and was found acceptable.

### 1.2 PRODUCT INFORMATION

During our review of the proprietary name, the Division of Medication Error Prevention and Analysis (DMEPA) sent an information request (IR) to clarify the dosage, frequency of administration, and maximum daily dosage for Rytary. The Applicant submitted an amendment to the request for proprietary name review on February 14, 2012 that indicated a maximum levodopa dosage of (b) (4) mg and carbidopa dosage of (b) (4) mg. Additionally, the Applicant clarified that the dosage and frequency of administration for Rytary is (b) (4) administered three to five times daily.

The following product information is provided in the March 30, 2012 insert labeling submission.

- Active Ingredient: Carbidopa and Levodopa
- Indication of Use: (b) (4) Parkinson's disease, postencephalatic parkinsonism, and (b) (4) parkinsonism following carbon monoxide or manganese intoxication
- Route of Administration: Oral
- Dosage Form: Extended-release Capsules
- Strength: carbidopa 23.75 mg and levodopa 95 mg, carbidopa 36.25 mg and levodopa 145 mg, carbidopa 48.75 mg and levodopa 195 mg, and carbidopa 61.25 mg and levodopa 245 mg
- Dose and Frequency of Administration: (b) (4) given three to five times daily not to exceed a daily dose of carbidopa (b) (4) mg or levodopa (b) (4) mg. For patients who have difficulty swallowing intact capsules, the capsules can be opened and sprinkled on a small amount of (b) (4), such as applesauce. The capsule contents, however, should not be chewed, divided, or crushed.
- How Supplied: 100-count and 240-count bottles for retail; 25-count bottles for professional samples
- Storage: Room temperature

- Container and Closure System: Opaque white high-density polyethylene bottles with matching white (b)(4) closures sealed with an induction inner-seal

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Sinemet and Sinemet CR medication error reports. We also reviewed the Rytary container labels, carton labeling, and insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) using the strategy listed in Table 1.

<b>Table 1: AERS Search Strategy</b>	
Date	April 15, 2012
Drug Names	Sinemet% (trade name) Sinemet% (verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issues (HLGT)

The AERS search identified 181 reports. Each report was reviewed for relevancy and duplication. After individual review, 124 reports were not included in the final analysis for the following reasons:

Product quality issue: decreased drug effect or increased adverse events (n = 63)

Sinemet was a concomitant medication or adverse event unrelated to a medication error (n = 23)

Intentional overdose or abuse (n = 14)

Duplicate report (n = 7)

Undeterminable medication error with Sinemet or Sinemet CR, not otherwise specified (n = 5)

Dose omission (n = 4)

Accidental exposure in pediatric patient (n = 3)

Wrong patient (n = 2)

Extra dose unrelated to labels and labeling (n = 1)

Off label use of Sinemet (n = 1)

Wrong frequency unrelated to labels and labeling: prescribed every 2.5 hours, but administered every 2 hours (n = 1)

## 2.2 LABELS AND LABELING

Using the principals of Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 21, 2011 (Appendix B)
- Carton Labeling submitted December 21, 2011 (Appendix C)
- Insert Labeling submitted March 30, 2012 (No image)

The proposed labels and labeling were also compared to the labels and labeling for the currently marketed Carbidopa and Levodopa products (see Appendix D) to identify potential safety issues.

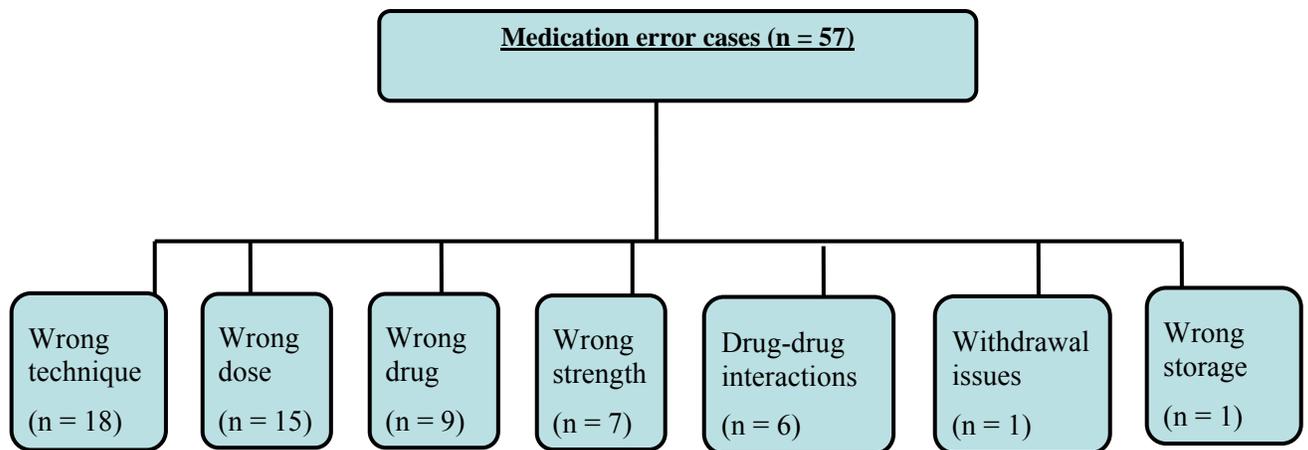
## 3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the Rytary label and labeling.

### 3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, fifty seven Sinemet medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix E provides listings of all ISR numbers for the cases summarized in this review.

**Figure 1: Sinemet medication errors (n = 57) categorized by type of error**



<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

### 3.1.1 Wrong technique (n = 18)

These wrong technique cases describe crushing of tablets, splitting of tablets in half and in fourths, and boiling of tablets to soften the tablets with the immediate-release or extended-release formulation of carbidopa and levodopa. Due to a reformulation of the branded carbidopa and levodopa products, the scoring on the branded immediate-release and extended-release was removed. One case described that the patient was unaware that the reformulated product could not be split. In some of the reported cases, it is unknown if the wrong technique error occurred with the reformulation, which is not scored, versus the original formulation, which was scored. In two of the eighteen cases, the patient was prescribed or instructed to cut the tablet in half. In seven of the cases, the patient had difficulty swallowing or had a feeding tube, in which the tablet was crushed to deliver the medication. The cause for the other wrong technique errors was not reported. Outcomes included hallucination, decreased drug effect, confusion, and lethargy.

Based on the above cases, we considered whether Rytary is vulnerable to wrong technique errors. The proposed carbidopa and levodopa product is a capsule, which contains instructions for opening the capsule and sprinkling the contents (b) (4) in the proposed insert labeling. The proposed insert labeling also states that the contents should not be chewed, divided, or crushed. We find the administration instructions clear; however, the administration instruction of opening the capsule and sprinkling the contents (b) (4) and not chewing is important and should be included in the highlights of the prescribing information. We have included this recommendation in Section 5 below.

### 3.1.2 Wrong dose (n = 15)

Fourteen of the fifteen wrong dose cases were overdoses, in which three of the fourteen cases were considered accidental overdoses, two of the fourteen cases were prescribed overdoses, and eleven of the fourteen cases did not specify if the overdose was accidental or prescribed. Causes of the overdose cases include misinterpreting the physician's order and patients receiving duplicate therapy with combination carbidopa, levodopa, and entacapone and combination carbidopa and levodopa. Outcomes of the overdose cases include hospitalization, syncope, confusion, hallucination, and hypotension. The remaining case describes a wrong dose, not otherwise specified. The wrong dose case stated that the insert labeling suggests a half-tablet of 50 mg/200 mg is bioequivalent to a whole tablet of 25 mg/100 mg, but a publication suggests that there is a 20% greater bioavailability with the half-tablet of 50 mg/200 mg.

The proposed insert labeling for Rytary states that the bioavailability and duration of effect of the proposed product are different compared to other carbidopa and levodopa preparations. The proposed insert labeling also provides a table for converting from immediate-release carbidopa and levodopa to the proposed product. Appropriate dosing and administration instructions are still under development, and DMEPA will provide recommendations during future labeling meetings.

### 3.1.3 Wrong drug (n = 9)

Eight of the nine wrong drug cases occurred between Sinemet and Sinemet CR. The cause for the errors was not reported, but five of the reports describe the error occurring

at dispensing. The outcomes include nausea and lethargy. The remaining case involved Janumet and Sinemet. The cause of the error included look-alike names and achievable strengths. This error was intercepted when the pharmacist paged the physician to clarify the dose.

Rytary has a distinct proprietary name and container labels that appear adequately differentiated from the currently marketed carbidopa and levodopa products, which may minimize wrong drug errors from occurring.

#### **3.1.4 Wrong strength (n = 7)**

Five of the seven wrong strength errors occurred during dispensing, but the cause of the errors were not reported. In one case, the error was intercepted. The other cases describe outcomes of weakness, dehydration, stiffness, and dizziness.

The wrong strength errors prompted us to review the proposed labels for Rytary to determine whether they are vulnerable to selection error. The proposed labels for Rytary were also compared with the labels for the currently marketed Carbidopa and Levodopa products to ensure that all the labels are adequately differentiated. We determined that the strengths within the Rytary product line are not adequately differentiated and thus probably contributing to the wrong strength errors. The proposed labels for Rytary appear to be adequately differentiated from the currently marketed Carbidopa and Levodopa products. Thus, we provide a recommendation in Section 5 below to change the color blocking to four distinct colors to ensure the strengths of Rytary are adequately differentiated.

#### **3.1.5 Drug-drug interaction (n = 6)**

Four cases included drug-drug interactions found in the insert labeling. One of the two other cases reported a suspected drug-drug interaction between Sinemet and Glucosamine. The outcome included an itchy scalp, and thinner and straighter hair. The second case reports a suspected drug-drug interaction between Sinemet and Sildenafil. The outcome included choreoarthetotic movements.

These two drug-drug interactions are not included in the insert labeling, thus will be forwarded to the Division of Pharmacovigilance for further evaluation.

#### **3.1.6 Storage issues (n = 1)**

This case reports medication that was left in the patient's mailbox at 110°F. The proposed labels and labeling clearly state how the product should be stored.

#### **3.1.7 Withdrawal issues (n = 1)**

This case describes a patient who died from Neuroleptic Malignant Syndrome (NMS) after abrupt withdrawal of carbidopa and levodopa. The patient was also erroneously treated with salbutamol and ipratropium. The cause for abruptly withdrawing carbidopa and levodopa was not reported.

The Rytary insert labeling indicates in the dosage and administration section that cases of a symptom complex resembling NMS have been associated with dose reductions and withdrawal of carbidopa and levodopa. Section 17 of the insert labeling should include

patient counseling information to only discontinue the medication under the supervision of a healthcare provider and to not abruptly stop taking the medication.

### **3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT**

Our review of the AERS cases and our label and labeling risk assessment identified deficiencies which we discuss below.

- A. The strengths within the product line are not well differentiated. All four strengths use the same purple color blocking to highlight the strength, which increases the risk of wrong strength selection errors. Four distinct colors should be used to ensure the strengths are adequately differentiated.
- B. The highest strength of the proposed product, carbidopa 61.25 mg and levodopa 245 mg, given at the maximum dose (four capsules) and the maximum frequency of administration (five times daily) exceed the maximum daily dose of carbidopa and levodopa. We note that the higher strength may allow patients to administer fewer capsules less frequently, but in order to prevent overdose errors from occurring, the maximum dosage of carbidopa and levodopa should be clearly stated in the dosage and administration section of the insert labeling, including the highlights.
- C. The insert labeling contains guidelines for converting patients from the marketed immediate-release carbidopa and levodopa product to the proposed product. Factoring in the 70% bioavailability of the proposed product relative to the immediate release product, the total daily dose of immediate release levodopa component is inconsistent with the total daily dose of the proposed levodopa component as presented in Table 1 of the insert labeling. The insert labeling also states that patients treated with carbidopa, levodopa, and entacapone may require an increase in the total daily dose by 30% based on Table 1. However, when the initial total daily dose of levodopa is increased by 30%, it exceeds the maximum daily dose of levodopa. It is unclear how these dosage conversion guidelines were developed. To obtain clarity on this issue, the Review Team sent an information request to the Applicant to provide a justification and the pharmacokinetic/pharmacodynamic data that support the conversion guidelines. The Applicant responded to the information request in a cover letter dated March 27, 2012. This data will be discussed with the Review Team in upcoming labeling meetings to determine the appropriate information that should be included in the insert labeling.

## **4 CONCLUSIONS**

DMEPA concludes that the proposed labels and labeling are unacceptable, as the strengths are not adequately differentiated from one another. Additionally, the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

## 5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

### 5.1 COMMENTS TO THE DIVISION – INSERT LABELING

- A. Throughout the labeling, the dosage is described by the levodopa strength. We recommend revising all dosage to include both the carbidopa and levodopa component. For example, in Section 2 Dosage and Administration, we recommend revising (b) (4) to read “The recommended starting dose of Rytary is one capsule of carbidopa 23.75 mg and levodopa 95 mg three times daily.”
- B. The maximum dosage of a product can be valuable information to provide to all health care providers. The maximum dosage for carbidopa and levodopa naive patients is found in the insert labeling, (b) (4). We recommend that this information also be added to the Highlights Section of the Full Prescribing Information.
- C. We recommend creating subtitles in Section 2 Dosage and Administration to read (b) (4) to help highlight the dosing information for these patient populations.
- D. In Section 2 Dosage and Administration under “Converting Patients from Immediate Release Carbidopa and Levodopa (b) (4) to Rytary,” it states that Rytary should be dosed (b) (4). However, the dosing conversion guideline in Table 1 recommends dosing three times daily. (b) (4). We recommend clarifying when a patient should be titrated from three times daily to every 6 hours (four times daily) administration.
- E. The sentence that reads, (b) (4) lacks clarity with respect to a dosing interval. (b) (4). We suggest providing more definitive guidance concerning the dosing frequency and the circumstances under which an extra dose can be administered.
- F. In Section 2 Dosage and Administration under “Converting Patients from Immediate Release Carbidopa and Levodopa (b) (4) to Rytary,” it states the total daily dosage may be increased or decreased depending on use of entacapone or sustained-release carbidopa and levodopa, but does not indicate the (b) (4). We suggest revising this section to clarify if the total daily dose should be divided into three doses or divided (b) (4) and under what circumstances an additional dose at bedtime can be administered.

- G. (b) (4) states that patients may open the capsule and sprinkle the entire contents on a small amount of (b) (4). This information is important for the health care provider when prescribing the medication. Consider including this information in the Highlights of the Prescribing Information Section 2.
- H. (b) (4) describes cases of a symptom complex resembling Neuroleptic Malignant Syndrome being associated with dose reductions and withdrawal of carbidopa and levodopa. Consider adding a statement in Section 17 to instruct physicians to counsel patients to only discontinue the product under the supervision of a health care provider and to not abruptly stop taking the medication.
- I. Section 16 How Supplied lists the (b) (4), which is not appropriate since this is (b) (4). Remove the (b) (4) information listed under each strength.
- J. In Section 2 Dosage and Administration: Table 1, we recommend deleting the use of overlapping numbers. We also recommend adding a unit of measure immediately following all numbers, as appropriate, and for numbers greater or equal to 1,000, use a comma to prevent the reader from misinterpreting thousands '1000' as hundreds '100.' For example, if clinically appropriate, we recommend the "Total Daily Dose of Immediate Release Levodopa (mg)" found in Table 1 to appear as "400 mg to 549 mg," "550 mg to 749 mg," "750 mg to 949 mg," "950 mg to 1,249 mg," and "1,250 mg or greater." Additionally, replace the abbreviation 't.i.d.' with 'three times daily' to prevent misinterpretation.
- K. The symbol '-' is used in the insert labeling. We recommend that the symbol be substituted with its intended meaning. For example, in Section 2.2 (b) (4) Administration (b) (4), revise the statement '(1-2 tablespoonsful)' to read '(1 to 2 tablespoonsful)' to improve clarity.

## 5.2 COMMENTS TO THE APPLICANT

- A. Container Label (All bottle sizes)
1. All four strengths use the same purple color blocking to highlight the strength, which increases the risk of wrong strength selection errors. Change the color blocking to four distinct colors to ensure the strengths are adequately differentiated. Additionally, ensure that the colors chosen do not overlap with colors currently utilized for Sinemet or Sinemet CR to avoid confusion between the product lines. As an alternative to or in addition to color, you can consider other methods of differentiation, such as boxing or the use of shapes on the proposed container labels.
  2. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and has a prominence commensurate with the prominence with which the proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).

3. As currently presented, the “Rx Only” statement is separated from the other information on the label by a surrounding (b) (4) . (b) (4)  
[REDACTED]
4. Revise the presentation of the active ingredients from “carbidopa-levodopa” to read “carbidopa and levodopa.”
5. Add the finished dosage form of the product as follows: (carbidopa and levodopa) extended-release capsules.
6. Relocate the NDC to appear in the top third portion of the label per 21 CFR 207.35(b)(3)(i), and increase the readability by presenting the NDC in a horizontal orientation.
7. The proposed proprietary name (b) (4) should be replaced with the name Rytary. Additionally, revise the proprietary name from all upper case (RYTARY) to title case (Rytary) to improve readability.
8. The symbol ‘-’ is used on the side panel, which should be substituted with its intended meaning. Revise the statement ‘Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).’ to read ‘Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)’ to improve clarity.
9. [REDACTED] (b) (4)
10. Decrease the size of the Impax logo and consider moving it to the side panel since it competes with the prominence of the proprietary name, established name, and strength.
11. Remove the (b) (4) found on the side panel since this is redundant.

B. Carton Labeling

1. See Recommendations A.1 through A.8
2. Revise the statement (b) (4) on the principal display panel to read “ (b) (4) Bottles, Each Bottle Contains 25 Capsules” for clarity.
3. Remove the statement (b) (4) from the back panel since this is redundant.

4. [REDACTED] (b) (4)

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

## APPENDICES

### APPENDIX A. DATABASE DESCRIPTIONS

#### Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

#### Appendix B: Container Labels

Professional Sample: Manufactured in Hayward and Taiwan



11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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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JULIE V NESHIEWAT  
07/11/2012

IRENE Z CHAN  
07/11/2012

SCOTT M DALLAS  
07/11/2012

CAROL A HOLQUIST  
07/11/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 203312 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Rytary (preliminary approval of name, final review/approval pending) Established/Proper Name: IPX066 (carbidopa/levodopa extended release) Dosage Form: capsules Strengths: 23.75-95mg, 36.25-145mg, 48.75-195mg, 61.25-245mg		
Applicant: Impax Agent for Applicant (if applicable):		
Date of Application: 12/20/11 Date of Receipt: 12/21/11 Date clock started after UN:		
PDUFA Goal Date: 10/21/12		Action Goal Date (if different): 10/19/12
Filing Date: 2/19/12 (2/17/12)		Date of Filing Meeting: 2/1/12
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5-New Formulation or New Manufacturer Proposed indication(s)/Proposed change(s): treatment of <sup>(b) (4)</sup> Parkinson's Disease <sup>(b) (4)</sup> postencephalitic parkinsonism and <sup>(b) (4)</sup> parkonsism which may follow <sup>(b) (4)</sup> <sup>(b) (4)</sup> carbon monoxide intoxication <sup>(b) (4)</sup> or manganese intoxication		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</b></i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> <i><b>and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 102887				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			“Rytary” trade name pending final approval
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>x</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>x</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>x</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		<p>Sinemet-No  Sinemet CR-No  Lodosyn-No  Stalevo-No  exclusivity; yes  patent</p>
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b> 3 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			<p>Impax Laboratories, Inc. here by claims three years exclusivity, under 21 CFR 314.108(b) (4), from the date of approval of NDA 203312 for IPX066 (carbidopa-levodopa extended-release capsules). To the best of Impax Laboratories, Inc. knowledge or belief, no other new drug products containing the combination of carbidopa and levodopa as the active moiety (generic formulations not withstanding) have been approved in the past five years under section 505(b) of the Food, Drug, and Cosmetics Act.</p>
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content	
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<p><input type="checkbox"/> All paper (except for COL)</p> <p><input checked="" type="checkbox"/> All electronic</p> <p><input type="checkbox"/> Mixed (paper/electronic)</p> <p><input checked="" type="checkbox"/> CTD</p> <p><input type="checkbox"/> Non-CTD</p> <p><input type="checkbox"/> Mixed (CTD/non-CTD)</p>
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>	

<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index</b> : Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.				
<b>BLAs only</b> : Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #			X	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>	X			Signed by Arthur Koch, EVP & CFO of Impax

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."  If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			NCT01411137
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].  <i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></i>	X			Correct wording
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)  If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	Electronic submission
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: <b>4/3/12</b></i>				

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC 8/8/12  Documents due 7/30/12
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		Waiver Requested
<p><b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b></p> <p><i>If no, request in 74-day letter</i></p>	X			All subsets of the pediatric population
<p><b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b></p> <p><i>If no, request in 74-day letter</i></p>	X			505B(a)(4)(A)(i); necessary studies are impossible or highly impracticable
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>		x		
<p><b><u>Proprietary Name</u></b></p> <p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	x			Rytary  Goal Due Date: April 16, 2012; preliminary approval
<p><b><u>REMS</u></b></p> <p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i></p>		x		
<p><b><u>Prescription Labeling</u></b></p> <p>Check all types of labeling submitted.</p>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			And WORD
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			

<p><b>If PI not submitted in PLR format</b>, was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b>, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i></p>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			Reviewer Quynh-Van Tran
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	No Patient Labeling; emailed PLT to confirm review not necessary
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of-Phase II Meeting(s)?		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> DNP meeting, August 30, 2011 ONDQA meeting, July 21, 2011	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> meeting May 7, 2009	X			SPA No Agreement letter August 7, 2009
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				SPA Agreement February 27, 2009

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/1/12

BLA/NDA/Supp #: 203312

PROPRIETARY NAME: Rytary (UNDER REVIEW)

ESTABLISHED/PROPER NAME: CARBIDOPA/LEVODOPA EXTENDED RELEASE

DOSAGE FORM/STRENGTH: CAPSULES/ 23.75-95mg, 36.25-145mg, 48.75-195mg, 61.25-245mg

APPLICANT: IMPAX LABORATORIES, INC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of (b) (4) (b) (4) Parkinson's Disease (b) (4) postencephalitic parkinsonism and (b) (4) c parkonsism which may follow (b) (4) carbon monoxide intoxication (b) (4) or manganese intoxication

BACKGROUND: IND 102887

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Tracy Peters	Y
	CPMS/TL:	Robbin Nighswander	N
Cross-Discipline Team Leader (CDTL)	Gerald Dave Podskalny		Y
Clinical	Reviewer:	Anne Constantino	Y
	TL:	G.Dave Podskalny	Y

Clinical Pharmacology	Reviewer:	Jagan Parepally	Y
	TL:	Angela Men	Y
Statistics	Reviewer:	Tristan Massie	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	LuAnn McKinney	Y
	TL:	Lois Freed	Y
Product Quality (CMC) including labeling review	Reviewer:	Charles Jewell	Y
	TL:	Martha Heimann	Y
Facility Review/Inspection (DSI)	Reviewer:	Antoine El Hage	Y
	TL:	Susan Thompson	N
OSE/DMEPA (proprietary name and carton/container)	Reviewer:	Julie Neshiewat	Y
	TL:	Irene Chan	Y

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Primary Reviewer:	Katherine Bonson	N
	Secondary Reviewer:	Silvia Calderon	N
	TL:	Michael Klein	N
Pharmacometrics	Reviewer:	Li Zhang	Y
	TL:	Yaning Wang/ Acting TL Atul Bhattaram	N/N
SEALD		Eric Brodsky	N
Biopharmaceutics	Reviewer:	Sandra Suarez	N
		Albert Chen	Y
	TL:	Angelica Dorantes	N

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b> none</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Efficacy analysis-all information is included and evaluated. Safety-sponsor asked to submit total daily dose; analysis data sets are readable; similar to marketed CD/LD. Need sponsor's justification and the pk/pd data with the analyses to support dose adjustment recommendations listed in label (section 2.3).</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>•</li> <li>•</li> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><b><i>If no, for an original NME or BLA application, include the reason. For example:</i></b></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Bioequivalent w/marketed form. Noted need to review conversion studies from IR product to this product</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed? Product made in Tiwan: Qualified with BE study to product made in California. If used in pivotal Phase 3 trial then no issue, but if never used in P3, then need to inspect site</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> key data well documented; usable format</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments: OMPQ-Timothy Pohlhaus, Shawn Gould</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Division Director  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

	<ul style="list-style-type: none"> <li>notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Tracy Peters

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/  
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TRACY J PETERS  
05/15/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: April 11, 2012

TO: Associate Director  
International Operations Drug Group  
Division of Foreign Field Investigations

Director, Investigations Branch  
Kansas District Office (KAN-DO)  
11630 West 80<sup>th</sup> Street  
Lenexa, KS 66214-3383

From: Sam H. Haidar, R.Ph., Ph.D.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA, Pre-Approval Data  
Validation Inspection** Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 203-312  
DRUG: Carbidopa/levodopa extended release  
capsules  
SPONSOR: Impax Laboratories  
Contact Person: Jeff Mulchahey  
Senior Director, Regulatory Affairs  
30831 Huntwood Avenue  
Hayward, CA 94544  
Tel: 510-240-6426  
Fax: 510-240-6113  
Email: jmulchahey@impaxlab.com

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. **A DBGC, OSI scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspections. The inspections should be completed before July 20, 2012.**

**Study Number:** IPX066-B10-01  
**Study Title:** A randomized, single-center, single-dose, open-label, two-sequence, two-treatment crossover study with a 6-day washout between treatment periods in healthy subjects under fasted conditions with an additional treatment after Period 2

**Clinical Site:**  (b) (4)

**Clinical Investigator:**  (b) (4)

**Contact Person:** Tiffany Nguyen, MBA, CCRA  
Associate Director, Clinical Operations  
TEL: 636-947-1200  
Email: Not Available

Please have the records of all study subjects audited. The subject records in the ANDA submission should be compared to the original documents at the sites. **The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined.** The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings.

**Please check the batch numbers of the test and reference products used in these studies with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and**

320.63<sup>1</sup>. The site conducting the above study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples.

Collect enough of the original containers of reserve samples of the test and reference products used in the study, to meet the "5x quantity" specified in 21 CFR 320.38(c). Mail the collected reserve samples to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
US Courthouse and Custom house Bldg.  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Also, obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letter head, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and ship them to DPA under current program directives. Please see the IOM and/or contact your district for assistance with the Sample Collection Report.

**Analytical Site:**

(b) (4)

**Contact Person:**

(b) (4)

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<sup>1</sup> Please see the Final Rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>) and CDER's guidance document "Handling and Retention of BA and BE Testing Samples" (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>) for more details.

**Methodology:** LC/MS-MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. **The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

**Following the identification of the investigator, background materials will be forwarded directly.**

Headquarters Contact Person: Arindam Dasgupta, Ph.D. (Foreign)  
(301) 796-3326  
Gopa Biswas, Ph.D. (Domestic)  
(301) 796-4167

CC:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Haidar/Biswas/Dasgupta/Patel/Dejernet/CF

HFC-130/ORA HQ DFFI IOB BIMO

KS-DO/HFR-SW350/Bromley/Montgomery

OND/ODEI/DNP/Tracy Peters/Katz

CDER/OCP/DCPI/Parepally

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FACTS: (b) (4)

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/s/  
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GOPA BISWAS  
04/18/2012

SAM H HAIDAR  
04/18/2012