

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217186Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: July 24, 2024

To: Stacy Metz, Regulatory Project Manager,
Division of Neurology (DN1)

Elizabeth Haberfeld, M.D., (DN1)

Tracy Peters, Associate Director for Labeling, (DN1)

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for Crexont (carbidopa and levodopa)
Extended Release Capsules

NDA: 217186

Background:

In response to DN1's consult request dated February 23, 2024, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the NDA submission for Crexont.

PI:

OPDP's review of the proposed PI is based on the draft labeling received by electronic mail from DN1 on July 15, 2024, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the Sponsor to the electronic document room on July 11, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAMUEL A FASANMI
07/24/2024 03:42:21 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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***

Date of This Review:	July 15, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217186
Product Name, Dosage Form, and Strength:	Crexont (carbidopa and levodopa) extended-release capsule, 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg
Applicant Name:	Impax Laboratories, LLC (Impax)
FDA Received Date:	July 11, 2024
TTT ID #:	2022-1261-3
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Impax Laboratories, LLC submitted revised trade and professional sample container labels and carton labeling received on July 11, 2024 for Crexont. The Division of Neurology 1 (DN 1) requested that we review the revised container labels and carton labeling for Crexont (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Impax Laboratories, LLC implemented all of our recommendations and we have no additional recommendations at this time.

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

^a Morris, C. Label and Labeling Review for Crexont (NDA 217186). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2024 JUN 17. TTT ID: 2022-1261-2.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEPHANIE L DEGRAW on behalf of JOHN C MORRIS
07/15/2024 02:25:30 PM

STEPHANIE L DEGRAW
07/15/2024 02:26:02 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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***

Date of This Review:	June 17, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217186
Product Name, Dosage Form, and Strength:	Crexont (carbidopa and levodopa) extended-release capsule, 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Impax Laboratories, LLC (Impax)
FDA Received Date:	February 7, 2024; May 28, 2024
TTT ID #:	2022-1261-2
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 INTRODUCTION

Impax Laboratories, LLC (Impax) submitted a Class 2 resubmission under NDA 218186 for Crexont (carbidopa and levodopa) extended-release capsules. Subsequently, the Division of Neurology 1 (DN 1) requested that we review the proposed prescribing information (PI), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

Crexont (carbidopa and levodopa) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Sinemet tablets (carbidopa and), NDA 017555.

Impax previously submitted NDA 217186 on August 31, 2022. During that review cycle, we reviewed the PI, carton labeling, and container labels, and provided our recommendations to the Division and the Applicant.^a Subsequently, we reviewed revised container label and carton labeling in response to our recommendations, which we found acceptable.^b However, NDA 217186 received a Complete Response letter on June 30, 2023 due to pharmacokinetic bridging and safety deficiencies, and labeling negotiations for the PI did not occur.^c

Thus, Impax submitted a Class 2 Resubmission on February 7, 2024.^d Carton labeling and container labels were received on May 28, 2024.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 217186.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

^a Morris, C. Label and Labeling Review for Crexont (NDA 217186). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 FEB 28. TTT ID No.: 2022-1261.

^b Morris, C. Label and Labeling MEMO for Crexont (NDA 217186). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 APR 27. TTT ID No.: 2022-1261-1.

^c Metz, S. on behalf of Emily Freilich. Complete Response for NDA 217186. Silver Spring (MD): FDA, CDER, OND, Division of Neurology 1 (DN 1) (US); 2023 JUN 30.

^d RESUBMISSION Response to Agency's June 30, 2023 Complete Response Letter NDA 217186 (Seq #0017). Bridgewater (NJ): Impax Laboratories, LLC; 2024 FEB 06. Available from:

<\\CDSESUB1\EVSPROD\nda217186\0017\m1\us\1-2-cover-letter-word-seq-0017-20240206.docx>

3 CONCLUSION

The proposed Crexont PI may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for DN1 in Section 4.

The proposed carton labeling and container labels are nearly identical to those we previously found acceptable. The one difference is the serialization information placeholder is missing from the carton labeling in the current. We also identified a concern with the color schemes used to highlight the professional sample statement on the professional sample carton labeling and container labels. We provide a carton labeling comment regarding the serialization information for Impax in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – Dosage and Administration: Highlights and Section 2			
1.	Dose conversion information for patients taking immediate-release carbidopa-levodopa is presented before recommended dosage information for new levodopa-naïve users.	This presentation is not intuitive and not in alignment with a similar comparator product, Rytary, which we considered when reviewing this PI.	We recommend reorganizing the presentation of dosing information to first describe dosing for levodopa-naïve patients in HL and swapping Sections 2.1 and 2.2.
2.	Use of the phrase (b) (4) in the starting dose statement is unnecessary.	Unnecessary information may detract from important information.	We recommend deleting the phrase (b) (4) and only stating the strength in HL and Section 2.2.
3.	The dose conversion statement “dosages of immediate-release carbidopa-levodopa products are not (b) (4) on a 1:1 basis” is unclear.	Unclear dosing information may increase the risk for wrong dose medication errors.	It appears Crexont is not (b) (4) on an exact 1:1 basis with any carbidopa-levodopa product. If so, then we recommend deleting the term “immediate release” and “1:1” from the dose conversion statement in HL and Section 2.1, similar to language for the comparator

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			product, Rytary. For example, (b) (4)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Table 1 can be improved for clarity and completeness as it does reflect all possible dosing schedules described in the bullet points below the table. For example, a patient taking a most frequent single dose of immediate-release LD of 100 mg or 150 mg who uses less than 500 mg of LD per day means the recommended frequency should be twice daily (b) (4) as indicated in Table 1.	Unclear and incomplete dosage information may increase the risk for confusion or overlooking important dosing information.	We recommend converting the bullets below Table 1 to text within Table 1 with a footnote. See Appendix G for our track changed recommendations.
2.	In Section 2.3, the dose conversion statement is unclear, and should state to convert based on the levodopa component. For example, conversion from 61.25 mg/245 mg Rytary (b) (4) (b) (4) specifying to convert on the levodopa component	Unclear and incomplete conversion information may increase the risk of converting a patient to the wrong strength of Crexont.	We recommend stating to convert on the levodopa component. Additionally, this information may not be suitable for a Rytary to Crexont dose conversion table since it is not an exact 1:1 conversion. If rounding doses is appropriate, this information should be included.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	will result in a Crexont dose of 52.5 mg/210 mg.		
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage statement does not contain unit of measure after each temperature numerical.	This may increase the risk for improper storage medication errors.	We recommend revising the storage statement to read “20°C to 25°C (68°F to 77°F)”.

5 COMMENT FOR IMPAX LABORATORIES, LLC

We note all carton labeling and container labels submitted April 18, 2024 contained a placeholder for serialization information; however, this information is not present on the carton labeling received on May 28, 2024. Please ensure serialization information is added to your proposed intend to market carton labeling.

We note the professional sample carton labeling and container labels contain some overlap and similarity in the color scheme used between strength statements/differentiation and the professional sample statement. (b) (4)

(b) (4). Overlapping or similar color schemes minimize differentiation in the strength, and may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. We recommend revising the color scheme of the professional sample statement such that the professional sample statement and the strength statements appear in their own unique colors that do not overlap or appear similar. (b) (4)

If any additional changes to the carton labeling or container labels are made subsequent to the versions submitted on April 18, 2024, then please submit revised carton labeling or container labels for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Crexont received on February 7, 2024 from Impax Laboratories, LLC, and the Listed Drug (LD).

Table 4. Relevant Product Information for Crexont and the Listed Drug (LD).														
Product Name	Crexont	Sinemet ^e (NDA 017555)												
Initial Approval Date	n/a	May 2, 1975												
Active Ingredient	carbidopa and levodopa													
Indication	treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication													
Dosage Form	extended-release capsule	tablet												
Strength	35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg	10mg/100 mg, 25 mg/100 mg, 25 mg/250 mg												
Route of Administration	oral													
Dose and Frequency	- Converting from Immediate-Release Carbidopa-Levodopa: multiply the most frequent single dose of immediate-release levodopa dose by 2.8 as recommended in Table 1. Table 1: Conversion from Immediate-Release Carbidopa-Levodopa to CREXONT <table> <tr> <th>Most Frequent Immediate-Release Levodopa Single Dose</th><th>Recommended Starting CREXONT Dose of Levodopa</th><th>Recommended Starting CREXONT Dosing Frequency</th></tr> <tr> <td>100 mg</td><td>280 mg</td><td>3 times daily</td></tr> <tr> <td>150 mg</td><td>420 mg</td><td>3 times daily</td></tr> <tr> <td>200 mg</td><td>560 mg</td><td>3 times daily</td></tr> </table> - Levodopa-naïve patients: Starting dose is the lowest dose: 35 mg/140 mg twice daily for 3 days; on the fourth day, dosage may be increased. - Maximum recommended total daily dose: (b) (4) Frequency of administration: 2 to 4 times per day.		Most Frequent Immediate-Release Levodopa Single Dose	Recommended Starting CREXONT Dose of Levodopa	Recommended Starting CREXONT Dosing Frequency	100 mg	280 mg	3 times daily	150 mg	420 mg	3 times daily	200 mg	560 mg	3 times daily
Most Frequent Immediate-Release Levodopa Single Dose	Recommended Starting CREXONT Dose of Levodopa	Recommended Starting CREXONT Dosing Frequency												
100 mg	280 mg	3 times daily												
150 mg	420 mg	3 times daily												
200 mg	560 mg	3 times daily												

Usual Initial Dose

25 mg/100 mg three times a day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight 25 mg/100 mg tablets a day is reached.

Maintenance Dose

Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

^e Sinemet PI accessed May 17, 2023, available at: <http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/9b17b028-964a-473c-823d-81423535bd66/spl-doc?hl=sinemet>

Table 4. Relevant Product Information for Crexont and the Listed Drug (LD).		
Product Name	Crexont	Sinemet® (NDA 017555)
		When a greater proportion of carbidopa is required, one tablet of SINEMET 25-100 may be substituted for each tablet of SINEMET 10-100. When more levodopa is required, SINEMET 25-250 should be substituted for SINEMET 25-100 or SINEMET 10-100. If necessary, the dosage of carbidopa and levodopa 25-250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day.
How Supplied	Each strength is proposed to be supplied in bottles containing 120 capsules.	Bottles containing 100 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.	Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.
Container Closure	HDPE bottles with (b) (4)	high-density polyethylene (HDPE) bottles

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Crexont labels and labeling submitted by Impax Laboratories, LLC.

- Prescribing Information received on February 7, 2024, available from <\\CDSESUB1\EVSPROD\nda217186\0017\m1\us\1-14-1-3-draft-package-insert-word.docx>
- Container labels and carton labeling received on May 28, 2024

B.2 Container Labels and Carton Labeling Images

Container labels – Trade



^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On January 24, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Crexont, IPX203, IND 122793, and NDA 217186. The results of that search are detailed in TTT ID #2022-1261.^g

On May 17, 2024, we performed a gap search to identify any additional reviews finalized since January 24, 2023. Our gap search identified one memo^h, and we did not provide any recommendations at that time.

^g Morris, C. Label and Labeling Review for Crexont (NDA 217186). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 FEB 28. TTT ID No.: 2022-1261.

^h Morris, C. Label and Labeling MEMO for Crexont (NDA 217186). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 APR 27. TTT ID No.: 2022-1261-1.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
06/17/2024 11:01:44 AM

STEPHANIE L DEGRAW
06/17/2024 12:02:05 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217186
Submission Number	17
Submission Date	2/7/2024
Date Consult Received	2/13/2024
Drug Name	CREXONT (carbidopa and levodopa)
Indication	Treatment of Parkinson's disease
Therapeutic Dose	CREXONT is recommended to be dosed 2 to 4 times per day. The maximum recommended total daily dose of CREXONT is (b) (4) (b) (4)
Clinical Division	DN1
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 2/13/2024 regarding the sponsor's QTc evaluation. We reviewed the following materials:

- Previous IRT reviews under NDA 217186 dated [05/25/2023](#) and [09/19/2023](#) in DARRTS;
- Previous IRT review of TQT Study IPX203-102-23 Protocol under IND 122793 dated [11/08/2023](#) in DARRTS;
- Sponsor's cover letter (NDA217186 / SN0017; [link](#));
- Annotated draft label (NDA217186 / SN0017; [link](#));
- TQT Study IPX203-102-23 report (NDA217186 / SN0017; [link](#));
- Clinical Study IPX203-102-23 Report (NDA217186 / SN0017; [link](#));
- Investigator's brochure (Submission / SDN; link if applicable);
- QT evaluation report checklist (NDA217186 / SN0017; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (NDA217186 / SN0017; [link](#)).

1 SUMMARY

Carbidopa did not prolong the QTcF interval in this thorough QT study – see Table 1 for overall results.

The clinical study IPX203-102-23 was a three-way crossover thorough QT/QTc study to evaluate the electrocardiographic effects of a supratherapeutic dose of carbidopa in healthy subjects. The highest dose evaluated was 400 mg which provided 1.1-fold

therapeutic exposure. High clinical exposure scenario for carbidopa has not been reported. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that carbidopa is associated with small mean increases in the QTcF interval (refer to section 4.5). The findings of the primary analysis are further supported by the lack of QTc prolongation in nonclinical data, by-time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: Summary of findings

QT assessment pathway	☒ Thorough QT study ☐ Substitute for thorough QT study (5.1) ☐ Alternative QT study when a thorough QT study is not feasible (6.1)				
Clinical QT study findings	- High clinical exposure scenario for carbidopa is not known (see section 3.1 for Applicant's description) - The highest dose in the thorough QT study provided mean C_{max} that covers steady state exposure of the maximum proposed dosing regimen.				
	ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)
	ΔΔQTcF	Carbidopa 400 mg	1,334	0.4	(-1.0 to 1.8)
In vitro findings	Integrated assessment was not conducted.				
In vivo findings					

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to [SDN 017](#) from the CS-IRT.

Our changes are highlighted ([addition](#), ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting section x, as we do not have any edits to that section. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics
(b) (4)

Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance ([link](#)).

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

We previously disagreed with the sponsor's proposal to not conduct a QT assessment and recommended to conduct a TQT study to assess the QT effects of CREXONT because the new formulation results in significantly higher carbidopa exposure (i.e., C_{max} and AUC) compared to the already approved drugs (ICH E14 section 1.3, prior IRT reviews dated [05/25/2023](#) and [09/19/2023](#) under NDA217186 in DARRTS). We subsequently agreed with the sponsor's proposed TQT Study IPX203-102-23 Protocol (prior IRT review under IND 122793 dated [11/08/2023](#)). In subsequent clarification emails with the sponsor in November and December 2023, we noted that *"the single 400 mg dose of carbidopa in the planned TQT study is a supratherapeutic dose and, based on the information provided in your email, appears to cover the high clinical exposure scenario for IPX203. The adequacy of this dose will be a review issue when data are submitted. We would like to reiterate that the exposures of carbidopa in the TQT study should cover the high clinical exposure scenario of IPX203 Extended-Release capsules"* (sponsor's cover letter pages 13-14 SDN 017; [link](#)).

The maximum recommended total daily dose of CREXONT is (b) (4) carbidopa / (b) (4) mg levodopa. The predicted C_{max,ss} for carbidopa from the proposed maximum total daily dose of carbidopa in IPX203 ((b) (4)) is expected to be (b) (4) under fasting conditions. In the submitted highlights of clinical pharmacology and cardiac safety table, the sponsor does not describe the high clinical exposure scenario and states that such information is not available.

The sponsor is now submitting the TQT study results for review.

3.1.1 Clinical pharmacology

CREXONT (carbidopa and levodopa) (IPX203) extended release (ER) capsules are available 4 strengths: 35 mg / 140 mg, 52.5 mg / 210 mg, 70 mg / 280 mg, and 87.5 mg / 350 mg. The maximum recommended daily dose is (b) (4) carbidopa and (b) (4) taken in (b) (4) doses. The Applicant's proposed labeling recommends that CREXONT can be administered without regard to food.

The Applicant did not explicitly identify the high clinical scenario; however, it appears that based on FDA feedback and the Applicant's cover letter that the high clinical scenario for carbidopa is administration in the fasted state. In Study IPX203-B16-04 (submitted under SDN 1), the Applicant showed that mean C_{max} of carbidopa following IPX203 ER capsules administered to fasted participants was 36% (32% - 40%) of those administered to fed participants. The Applicant also provided simulation results showing that, following a 400 mg single dose of carbidopa (as part of IPX203), the mean C_{max} of carbidopa would be 1402 ng/mL which was about (b) (4) times higher than the mean C_{max} following a (b) (4) of carbidopa.

Due to the available strengths of the capsule formulation, there is no practical way to administer (b) (4) of carbidopa. Following the recommended (b) (4) dosing schedule and staying as close as possible to (b) (4) equal doses would lead to carbidopa doses of (b) (4). While there is no PK data available for a (b) (4) dose, the results from Study IPX203-B16-01 showed that, following multiple 225 mg doses in patients with advanced Parkinson's disease, the fasted mean C_{max} was 862 ng/mL. In the same study, patients who received a 180 mg dose had a fasted mean C_{max} of 768 ng/mL, which is reasonably close to the Applicant's simulated result following a (b) (4). Given that the 400 mg daily dose provides (b) (4) coverage over the (b) (4) dose, it is reasonable to assume that the (b) (4) dose in the high clinical scenario is adequately covered by the carbidopa 400 mg single dose used in the TQT study.

Carbidopa is considered to have low pharmacologic activity and is primarily eliminated in the urine unchanged or as conjugates. The Applicant did not provide data to describe the effect of hepatic or renal impairment on the pharmacokinetics of carbidopa. In general, there are no specific instructions, aside from general caution, or studies to inform use in these settings in the context of pharmacokinetics. Therefore, this evaluation and review has not considered organ impairment as a potential high clinical exposure scenario. This should be addressed in the drug labeling.

Table 2: Summary of dose and exposure assessment

		Mean C _{max}
Highest therapeutic or clinical trial dosing regimen	(b) (4) total daily dose divided into (b) (4) doses (b) (4) (b) (4) fed or fasted, oral capsules	(b) (4) (C _{max,ss}) ¹
Sponsor's High clinical exposure scenario	(b) (4) in fasted state ¹	(b) (4) (C _{max,ss})
Highest dose in QT assessment	400 mg oral capsule	1333.8 ng/mL ²
C_{max} Ratio	1.08	

¹ This is based on observed mean C_{max} of 1022 ng/ml provided by a single dose (b) (4) (n = 5) in study IPX203-B14-02. Based on this data, the mean C_{max} after carbidopa (b) (4) is expected to be (b) (4). However, simulated steady state mean C_{max} based on the observed CD plasma concentrations (N=9) from Study IPX203-B16-04 was estimated to be (b) (4) after (b) (4) QD (b) (4). This dosage isn't possible due to the capsule strength options. Assuming (b) (4) dosing and attempting to keep doses consistent in total strength, a realistic dose would be a (b) (4). For the (b) (4) dose yields a ratio of (b) (4). Assuming a (b) (4) ratio; the (b) (4) dose would yield a C_{max} of (b) (4). This is still adequately covered by the 400 mg dose.

² Observed geometric mean C_{max} in the TQT study

3.1.2 Nonclinical Safety Pharmacology Assessments

The effects of carbidopa on cardiac repolarization were studied in a limited assessment using human induced pluripotent stem cells that differentiated into functional human cardiomyocytes (hiPSC-CM) (Sube and Ertel, 2017). Although CD was not evaluated across a concentration range and the IC₅₀ was not determined, a single concentration was evaluated (1 μM or 26 ng/mL). Carbidopa had no effect on cardiomyocyte beating frequency.

No in vivo cardiovascular assessments have been performed or reported in the literature.

Reviewer's comment: Sube and Ertel 2017 manuscript states carbidopa had no effect on hiPSC-CM rhythm, but they do not comment carbidopa effects on hiPSC-CM repolarization.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The by-time point analysis demonstrated no clinically significant effect of carbidopa 400 mg on QTc in the sponsor's analyses. The LS mean placebo-corrected ΔQTcF (ΔΔQTcF) during carbidopa 400 mg ranged from -0.7 ms. 1.5 hours post-dose to 2.7 ms. 12 hours

post-dose. The 90% 2-sided upper confidence interval (UCI) was < 10 ms. at all time points.

In the by-time point analysis, the LS mean $\Delta\Delta$ HR was below 10 bpm for carbidopa treated subjects across all post-baseline time points.

Reviewer's comment: *The results of the sponsor's analysis are similar to the reviewer's analysis. Please see section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was confirmed by both concentration-QTc modeling and by-time analyses. The slope of the relationship between the placebo-corrected change from baseline for QTcF and the plasma concentration of moxifloxacin was positive and the lower limit of the two-sided 90% confidence interval for the predicted $\Delta\Delta$ QTcF was > 5 ms at the observed mean moxifloxacin plasma concentration, and the lower bound of the 90% CI of mean $\Delta\Delta$ QTcF was above 5 ms at around Tmax of moxifloxacin plasma concentrations.

Reviewer's comment: *Reviewer's analysis agrees with the Applicant's conclusion; assay sensitivity was demonstrated.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<50 or >100 beats/min), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The results of the sponsor's analysis are similar to the reviewer's analysis. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper. The results of the sponsor's analysis show an absence of significant QTc prolongation following 400 mg dose of IPX203 under fasted conditions.

Table 3: Predicted $\Delta\Delta$ QTcF interval at geometric mean peak carbidopa concentration (Concentration-QTc analysis set)

Treatment	Geometric mean Cmax of Carbidopa (ng/mL)	$\Delta\Delta$ Estimate (ms) (90% CI)
Carbidopa 400 mg	1333.8	0.48 (-1.00, 1.97)

Reviewer's comment: *FDA analysis agrees with the Applicant's conclusion of no significant QTc prolongation following a 400 mg dose of IPX203.*

3.2.4 Safety Analysis

There were no deaths nor SAEs reported in this study. There were no TEAEs leading to discontinuation of drug in this study. There were no AEs reported in Cardiac Disorders SCO in this study.

There were four (04) (11.4%) subject discontinuations. The reasons for discontinuation are presented below.

- Subject no. (b) (6) dropped from the study, per Investigator's decision, during period III Day 1 due to abnormal ECG.
 - Subject (b) (6) (male) was discontinued from the study on (b) (6) before dosing on Day 1 of period III (Listing 16.2.1.2) due to repeated pre-dose QTcF values >430 ms.
- Subject no. (b) (6) elected to withdraw from the study due to AE of Pyrexia (fever) in period III Day 1.
- Subject no. (b) (6) dropped from the study, per Investigator's decision, during period II Day 1 due to abnormal ECG.
 - Subject (b) (6) (female) was discontinued from the study on (b) (6) before dosing on Day 1 of Period II (Listing 16.2.1.2) due to repeated pre-dose QTcF values >450 ms.
- Subject no. (b) (6) was dropped from the study, during period III Day- 1 due to positive urine drug screen.

The details of withdrawn/dropped subjects are presented in Listing 16.2.1.2.

Table 4: Discontinued subjects

Subject ID/ Gender/Age	Date of Visit	Day	Visit	Last Treatment Dosed	Discontinuation Date	Reason for Discontinuation
(b) (6) M/45	(b) (6)		Period 3 Day 1	A	(b) (6)	DUE TO ABNORMAL ECG
(b) (6) F/40	(b) (6)		Period 3 Day 1	C	(b) (6)	ADVERSE EVENT
(b) (6) F/44	(b) (6)		Period 2 Day 1	B	(b) (6)	DUE TO ABNORMAL ECG
(b) (6) F/42	(b) (6)		Period 3 Day -1	C	(b) (6)	DUE TO POSITIVE URINE DRUG SCREEN.

Treatment A (blinded): Carbidoa capsule 400 mg (4 × Carbidoa capsule 100 mg (supratherapeutic dose)).
Treatment B (open label): Moxifloxacin Tablets, USP 400 mg (positive control).
Treatment C (blinded): Placebo (negative control).

[Source: CSR – Listing 16.2.1.2; [link](#)]

One subject (Subject no. (b) (6)) withdrew from the study due to a TEAE of Pyrexia (Fever) with moderate severity and possible relationship to the IP. However, it should be noted the AE was reported during the study period with administration of Placebo (negative control).

Reviewer's comment: Discontinuation details for subjects (b) (6) and (b) (6) are described in applicant's [response dated 3/25/2024](#) to our 3/21/2024 IR. Mean predose QTcF values were 446 and 460 msec, for subjects (b) (6) and (b) (6), respectively. None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., $|\text{mean}| > 10$ beats/min) were observed (see section 0).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to treatment. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups. The maximum $\Delta\Delta\text{QTcF}$ values by treatment are shown in Table 5. The largest upper bound of 90% CI of LS mean $\Delta\Delta\text{QTcF}$ for carbidopa was below 10 msec.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time-course (unadjusted CIs).

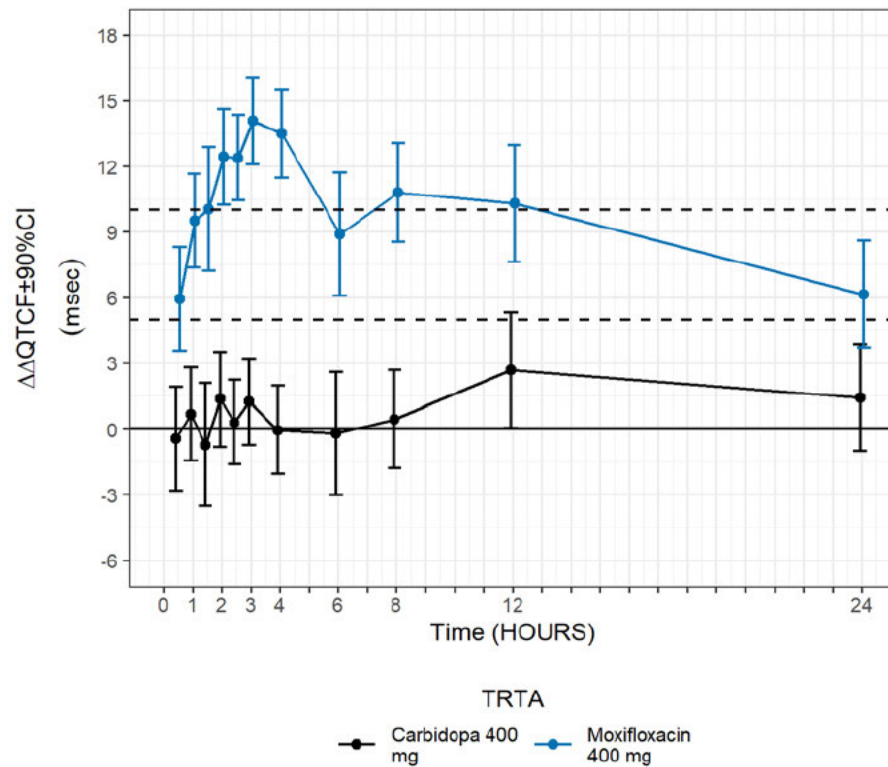


Table 5: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Nact / Npbo	Time (HOURS)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Carbidopa 400 mg	34 / 33	12.0	2.7	(0.0 to 5.3)

4.3.1.1 Assay Sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis—see section 0 for details.

The assay sensitivity was supported by by-time analysis as shown in Figure 1 and Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for $\Delta\Delta\text{QTcF}$

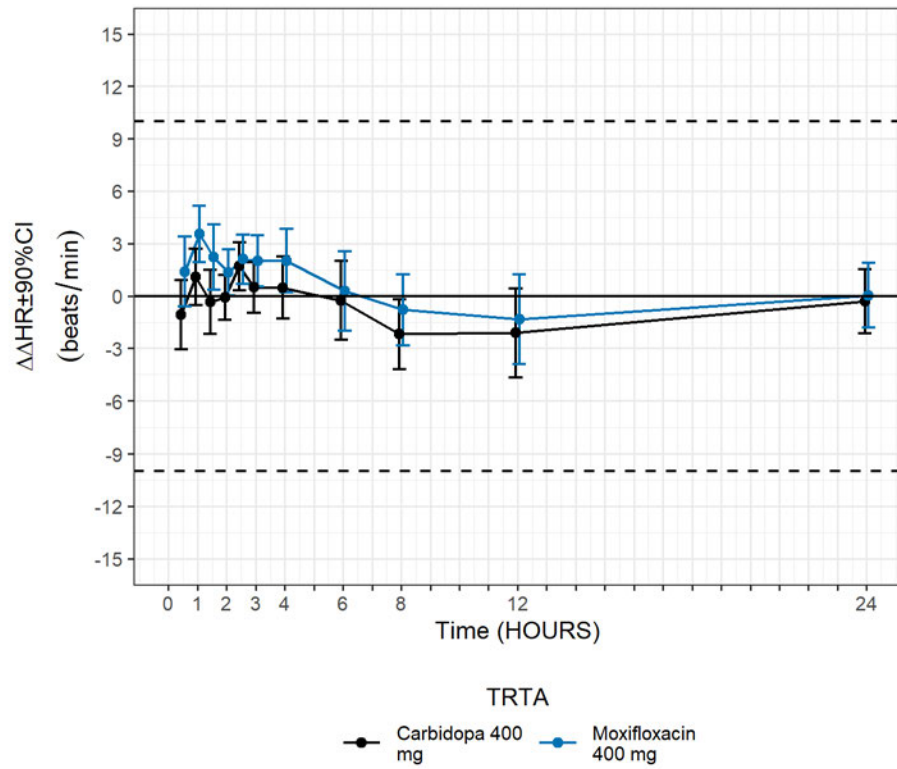
Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Nact / Npbo	Time (HOURS)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	33 / 34	3.0	14.1	(12.1 to 16.1)	(11.4 to 16.8)

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ for different treatment groups.

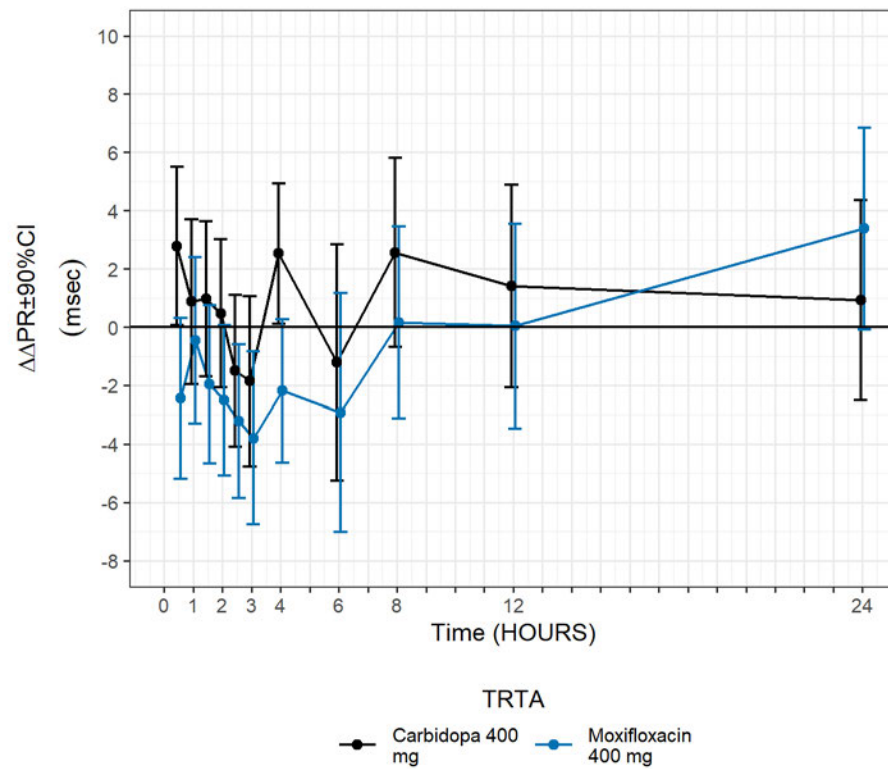
Figure 2: Mean and 90% CI of $\Delta\Delta$ HR Time-course



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta$ PR for different treatment groups.

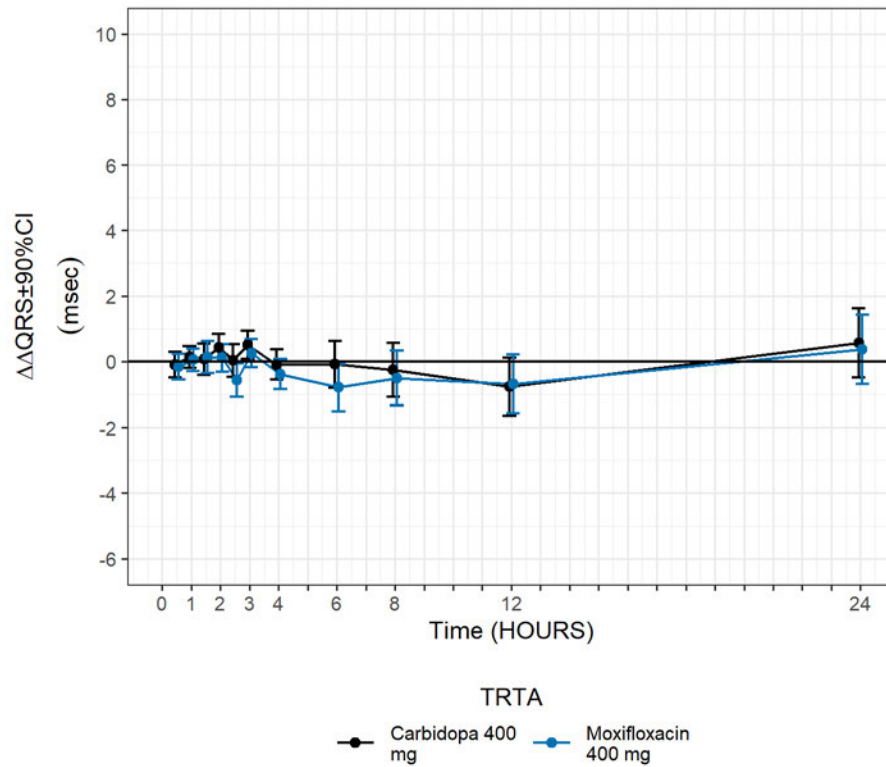
Figure 3: Mean and 90% CI of $\Delta\Delta PR$ Time-course



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta QRS$ for different treatment groups.

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

There were no subjects having observed QTcF above 480 msec or change from baseline above 60 msec in any of the treatment groups.

4.4.2 HR

There were no subjects having observed HR above 100 beats/min in the carbidopa 400 mg treatment group.

4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in any of the treatment groups.

4.5 EXPOSURE-RESPONSE ANALYSIS

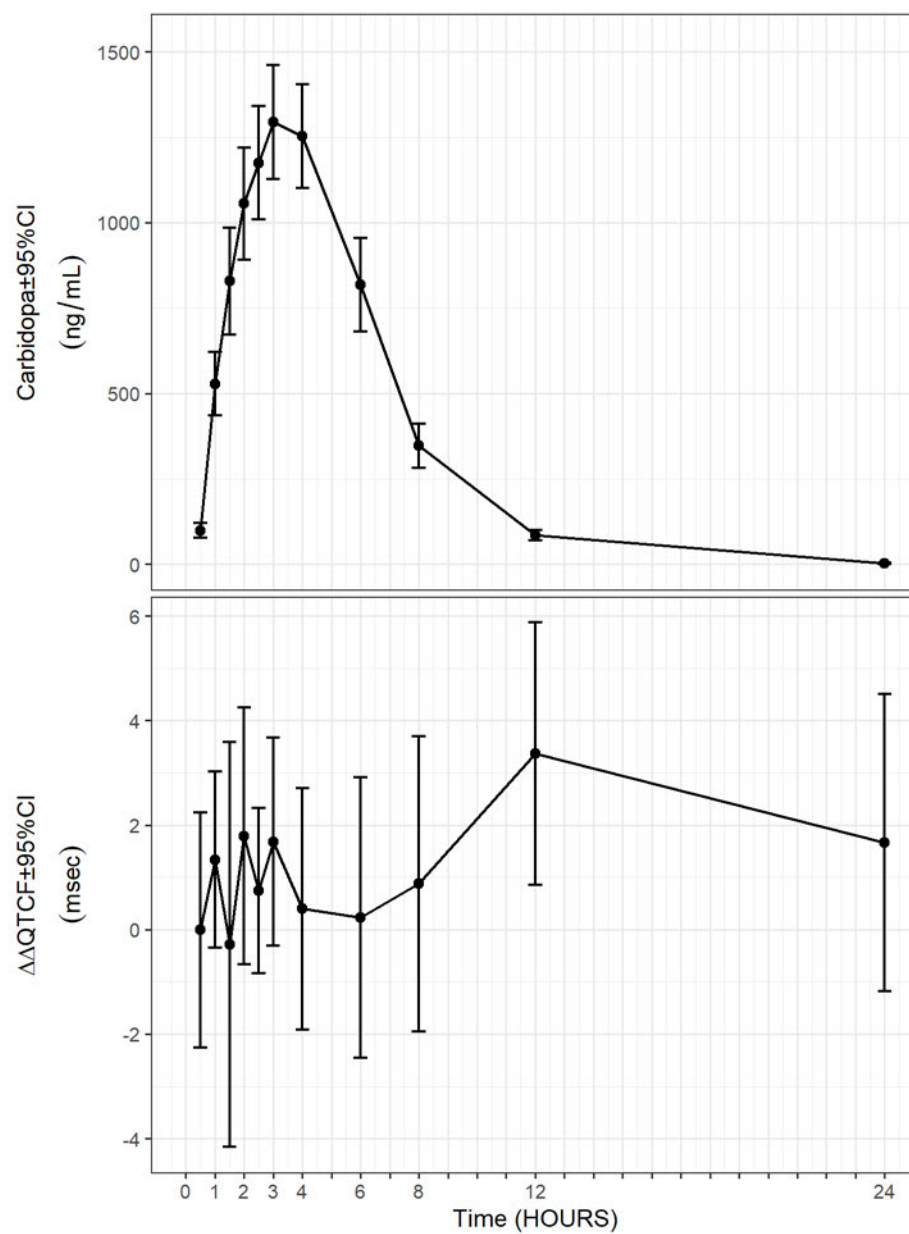
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. The C-QTc dataset included 1046 observations (n = 35) in period 1, 1020 observations (n = 34) in period 2, and 958 observations (n = 32) in period 3.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and $\Delta\Delta\text{QTcF}$; and 3) absence of a nonlinear relationship.

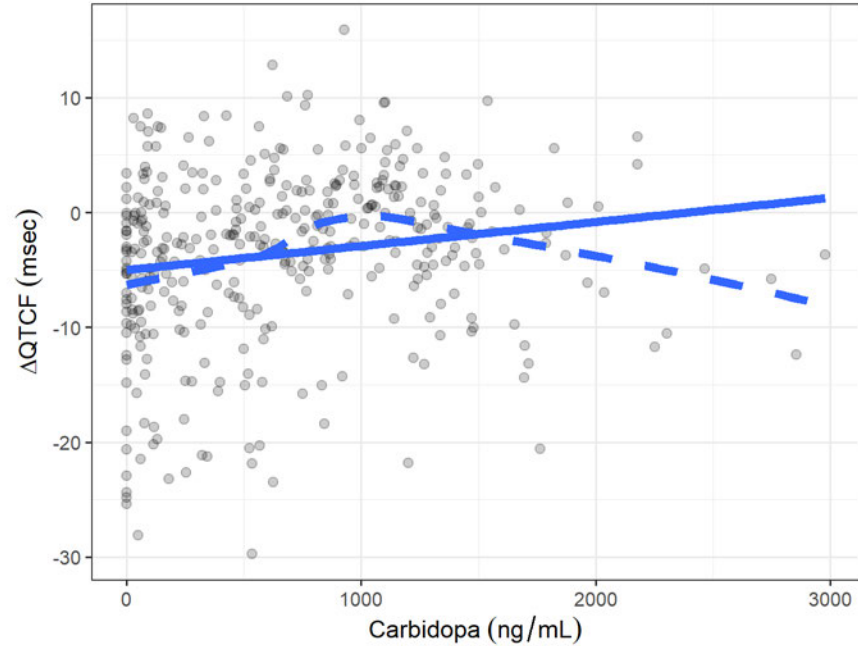
Figure 2 shows the time-course of $\Delta\Delta\text{HR}$, with an absence of significant $\Delta\Delta\text{HR}$ changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and $\Delta\Delta\text{QTcF}$, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)¹



¹ ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 7.

Figure 7: Goodness-of-fit Plot for QTcF

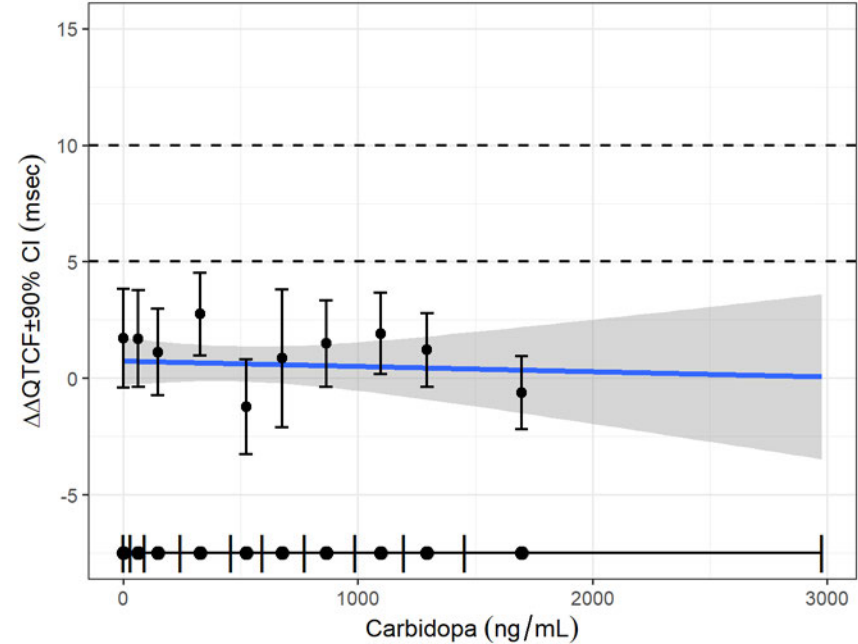


Table 7: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Carbidopa (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Carbidopa 400 mg	1	1,333.8	0.4	(-1.0 to 1.8)

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and $\Delta\Delta\text{QTcF}$ is shown in Figure 8. When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is shown in Figure 9: Goodness-of-fit plot of $\Delta\Delta\text{QTcF}$ for Moxifloxacin, and the predicted QTcF at the geometric mean C_{max} is listed in Table 8. Please see section 0 for additional details.

Figure 8: Time-course of Moxifloxacin Concentration (top) and QTcF (bottom)

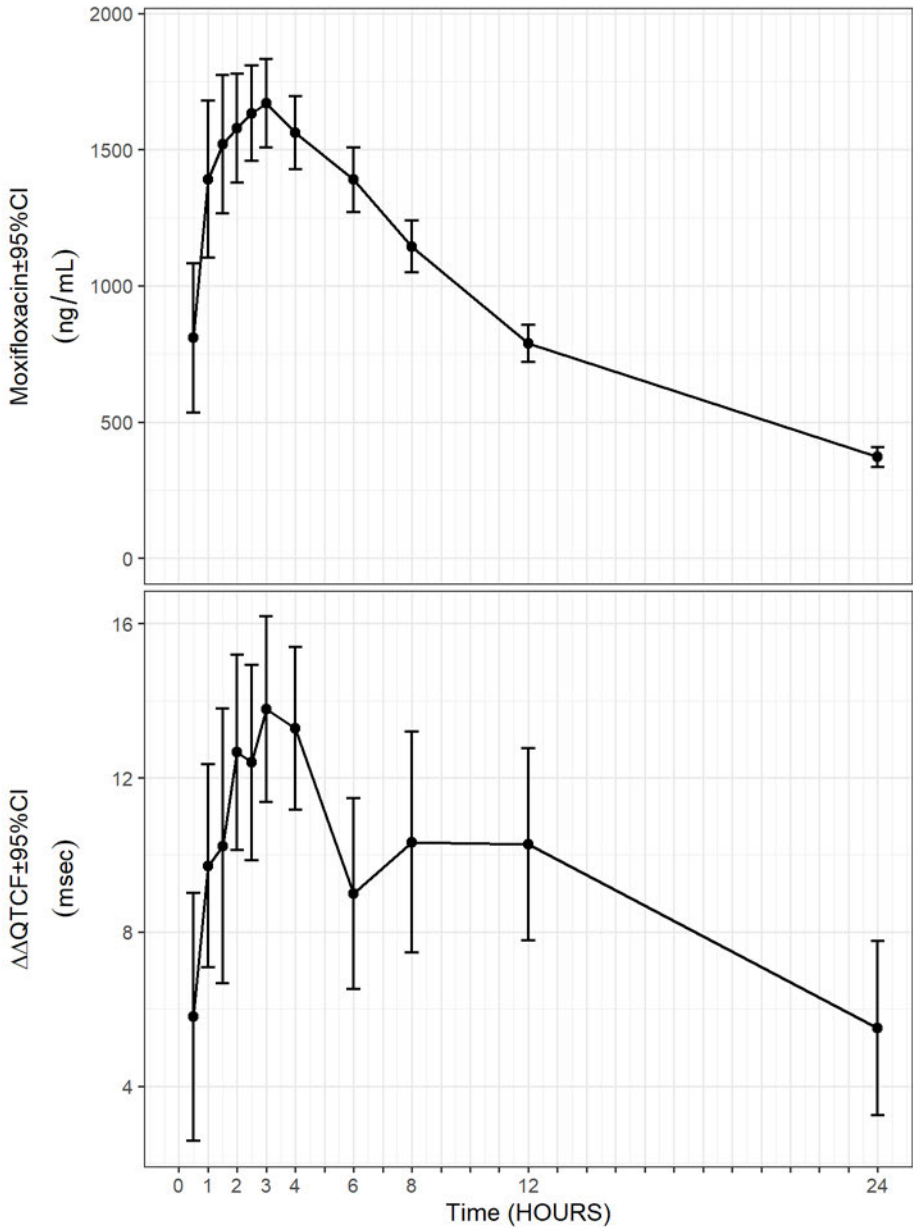


Figure 9: Goodness-of-fit plot of $\Delta\Delta\text{QTcF}$ for Moxifloxacin

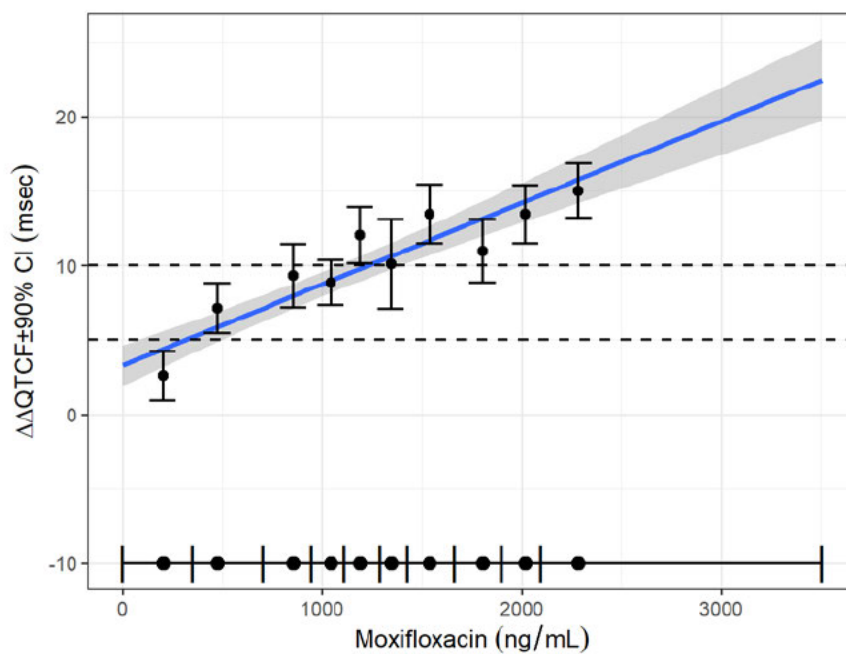


Table 8: Predictions from Concentration- QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	1,902.8	13.7	(12.4 to 14.9)

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE SPONSOR'S CLINICAL QT STUDIES

We have previously reviewed the protocol (DARRTS [05/25/2023](#); [09/19/2023](#); and [11/07/2023](#)).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WEI LIU
04/23/2024 01:52:21 PM

JING SUN
04/23/2024 01:59:09 PM

DALONG HUANG
04/23/2024 03:12:18 PM

JUSTIN S COLLAZO
04/23/2024 03:32:13 PM

ELIFORD N KITABI
04/23/2024 04:22:08 PM

MICHAEL Y LI
04/24/2024 06:55:41 AM

JOSE VICENTE RUIZ
04/24/2024 10:07:15 AM

CHRISTINE E GARNETT
04/24/2024 10:20:21 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 25, 2023

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Natalie Getzoff
DN1

Subject: QT Consult to NDA217186 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 4/28/2023 regarding the Review Division's QT related question. We reviewed the following materials:

- Sponsor's Summary of Clinical Pharmacology Studies ([NDA217186 / SDN001](#));
- Sponsor's proposed CREXONT label ([NDA217186 / SDN001](#)); and
- Investigator's brochure ([NDA217186 / SDN001](#)).

1 Responses for the Sponsor

Question from the Review Division: From clinical pharmacology perspective, NDA 217186 is not approvable due to lack of PK bridging between CREXONT and the reference product, Sinemet. At the proposed maximum daily dose of CREXONT ((b) (4)), carbidopa AUC will be more than 3-fold higher than that of Sinemet, and about 2-fold higher than that of RYTARY. Therefore, CREXONT cannot borrow safety information from Sinemet or Rytary. We are unsure what QT information, if any, would be needed to support the higher exposure of carbidopa in CREXONT.

IRT's response: Per ICH E14 section 1.3, the sponsor should conduct a thorough QT study to assess the QT effects of CREXONT since the new formulation results in significantly higher carbidopa exposure (i.e., Cmax and AUC) compared to the already approved drugs.

2 Internal Comments for the Division

None.

3 BACKGROUND

3.1 Product Information

The sponsor (Impax Laboratories, LLC) is developing IPX203 (CREXONT™), an extended release (ER) formulation of carbidopa and levodopa, for treatment of different forms of Parkinson's disease. Levodopa (LD) is the active component that cross the blood brain barrier (BBB) and increase levels of dopamine in the brain leading to alleviation of symptoms of Parkinson's disease. Carbidopa (CD) inhibits peripheral metabolism of levodopa and thus makes it more available for delivery to the brain. The maximum recommended daily dose of IPX203 is (b) (4) of carbidopa/levodopa.

The drug product is formulated as capsules for oral administration. After oral administration of IPX203, levodopa and carbidopa are rapidly absorbed reaching peak concentration (C_{max}) at median time of 2 and 3 hours respectively. Both drugs exhibit dose proportional increase in C_{max} and AUC and do not accumulate following repeated dosing. The pharmacokinetics of IPX203 is impacted by food, with LD and CD impacted differently ([Summary of clinical pharmacology Section 2.7.2.2.1](#)).

In the current submission (NDA217186) the sponsor is relying on safety profiles of 3 formulations of carbidopa/levodopa marketed in the US (i.e., Sinemet, Sinemet CR, and Rytary) to demonstrate that IPX203 is safe for the intended indication. The sponsor conducted relative bioavailability (RF) studies in healthy subjects and in patients with Parkinson's disease to bridge the PK of IPX203 to that of the reference listed formulations.

Results from the sponsor's RF studies indicate that IPX203 is more bioavailable and results in higher C_{max} for carbidopa compared to the other marketed formulations. According to the sponsor, in healthy subjects (Study IPX203-B16-05), the RF of LD from IPX203 to that from Sinemet and Sinemet CR were 99.02% and 110.41%, respectively, while the RF of CD from IPX203 to that from Sinemet and Sinemet CR were 122.58% and 157.29%, respectively. Similarly, the relative C_{max} of CD from IPX to that from Sinemet and Sinemet CR was 119.62% and 155.64%, respectively.

Similar RF results were observed in patients with advanced Parkinson's disease in a randomized, open-label, rater-blinded, 3-treatment, 3-period, single-dose, crossover, multicenter study (Study IPX203-B14-02). In this study the RF of LD from IPX203 compared to Sinemet and Rytary was 88% and 114%, respectively and the relative C_{max} was 36.67% and 102.87%, respectively; while the RF of CD from IPX203 compared to Sinemet and Rytary was 140% and 192%, respectively and the relative C_{max} was 91.03% and 236.83%, respectively.

On the contrary, in a multiple dose study comparing IPX203 with Sinemet in patients with advance PD, relative bioavailability of LD and CD from IPX203 were comparable to those for Sinemet (Study IPX203-B16-01). In this study, the relative bioavailability of LD from IPX203 in advanced PD patients compared to Sinemet was 89% and the relative C_{max} was 37.23%. The

relative bioavailability of CD from IPX203 compared to Sinemet was 117% and the relative Cmax was 89.87%.

3.2 Sponsor's position related to the question

The sponsor relies on pharmacokinetic bridging of IPX203 to the marketed fixed dose combination products of CD/LD to demonstrate that IPX203 might be as safe as the approved formulations. The sponsor also performed comparative assessment of safety of IPX203 to that of Sinemet, Sinemet CR and Rytary. However, the sponsor did not evaluate the QT effects of the new carbidopa/levodopa formulation (CREXONT). In addition, the sponsor is not proposing any QT labelling for CREXONT. The other approved formulations also do not have any QT labelling either.

3.3 Nonclinical Cardiac Safety

NA

3.4 Clinical Cardiac Safety

NA

3.5 Summary results of prior QTc assessments

No prior QT assessment is available for IPX203

3.6 Relevant details of planned Phase 3 study

No planned Phase 3 study

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELIFORD N KITABI
05/25/2023 10:48:15 AM

CHRISTINE E GARNETT
05/25/2023 10:57:02 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 27, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217186
Product Name, Dosage Form, and Strength:	Crexont (carbidopa and levodopa) extended-release capsule, 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg
Applicant/Sponsor Name:	Impax Laboratories, LLC
TTT ID #:	2022-1261-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 18, 2023 for Crexont. The Division of Neurology 1 (DN 1) requested that we review the revised container labels and carton labeling for Crexont (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Morris, C. Label and Labeling Review for Crexont (NDA 217186). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 FEB 28. TTT ID No.: 2022-1261.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
04/27/2023 09:26:40 AM

STEPHANIE L DEGRAW
04/27/2023 09:55:36 AM

Clinical Inspection Summary

Date	3/15/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Stacy Metz, Pharm.D., Regulatory Project Manager Elizabeth Haberkfeld, M.D., Medical Officer Natalie Getzoff, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #/BLA #	NDA #217186
Applicant	Impax Laboratories, LLC
Drug	Carbidopa and Levodopa extended-release capsules
NME	No
Proposed Indication	Treatment of Parkinson's disease, post-encephalic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Consultation Request Date	11/3/2022
Clinical Inspection Summary Goal Date	4/28/2023
Priority/Standard Review	Standard
Action Goal Date	6/30/2023
PDUFA Date	6/30/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Klos and Fernandez were inspected in support of this NDA and covered Protocol IPX203-B16-02. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Carbidopa and levodopa extended-release capsules were developed under IND #122793 for the treatment of Parkinson's disease (PD), post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. Several carbidopa and levodopa immediate release, controlled-release, and extended-release dosage forms are currently approved and marketed in the US.

The sponsor has submitted the results of Protocol IPX203-B16-02, under NDA #217186, to support the efficacy and safety of carbidopa-levodopa extended-release capsules in the treatment of the proposed indications.

Protocol IPX203-B16-02

Title: “A randomized controlled study to compare the safety and efficacy of IPX203 with immediate-release carbidopa-levodopa in Parkinson’s disease patients with motor fluctuations” [Note: IPX203 is carbidopa-levodopa extended-release]

Subjects: 630

Sites: 105 sites in the United States (55), Western Europe (37), Eastern Europe (13)

Study Initiation and Completion Dates: 11/6/2018 to 6/15/2021

This was a randomized, double-dummy, active-controlled, study in subjects with Parkinson’s disease (PD). Main inclusion criteria included males or females; diagnosed with PD at age ≥ 40 years; PD diagnosis consistent with the United Kingdom Parkinson’s Disease Society Brain Bank Diagnostic Criteria; treated with a stable regimen of carbidopa-levodopa but experiencing motor fluctuations; Hoehn and Yahr Stages 1, 2, 3, 4 in the “on” state (part of Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale [MDS-UPDRS] Part III); Montreal Cognitive Assessment (MoCA) score ≥ 24 at screening visit in “on” state; for the 4 weeks prior to screening, subject experiences daily “wearing-off” episodes with periods of bradykinesia in combination with at least one of rest tremor or rigidity, experiences an “off” state upon awakening on most mornings, and reports an average of at least 2.5 cumulative hours per day of “off” time during waking hours; at Visit 1, review of the 3-day PD diaries confirms that the subject is able to properly complete the diaries with valid entries, and has an average of at least 2.5 hours per day of “off” time during waking hours over the 3 days with at least 1.5 hours of cumulative “off” time each day.

Subjects also had to be responsive to carbidopa-levodopa therapy and currently on a stable regimen for at least 4 weeks prior to Visit 1 and:

- Require at least 100 mg of levodopa from immediate release carbidopa-levodopa for the first morning dose
- Require a total daily dose between 400 and 2400 mg of levodopa, from immediate release carbidopa-levodopa alone or in combination with a single daily bedtime dose of controlled release carbidopa-levodopa
- Dosing frequency of 4 to 9 times daily
- By history, typically experiences an “on” response with the first dose of immediate release carbidopa-levodopa of the day, but the efficacy of this dose typically lasts <4 hours

Subjects could not use the following medications within 4 weeks of Visit 1 or during the study: any doses of controlled release levodopa apart from the single daily bedtime dose; Rytary® (carbidopa-levodopa extended-release capsules); additional carbidopa, benserazide, catechol-O-methyl transferase inhibitors (entacapone, tolcapone), nonselective monoamine oxidase inhibitors, apomorphine, and antidopaminergic medications (including antiemetics). Subjects could not have been treated with dopamine antagonist antipsychotic medications for the purposes of psychosis or bipolar disorder within the last 2 years.

The study was comprised of 4 periods: Screening Period, Immediate Release (IR) Carbidopa-Levodopa Dose Adjustment Period, Dose Conversion to Extended-Release (ER) Carbidopa-Levodopa Period, and Double-Blind Maintenance Period.

Screening Period (4 weeks)

During this period, study eligibility was determined. Study procedures included, but were not limited to, medical history, physical examination, ECG, labs, MoCA, MDS-UPDRS Parts I-IV. During this period, subjects were trained on completion of the PD Diary and PD Diaries were dispensed. Subjects were to complete their PD Diaries on each of the 3 consecutive days immediately prior to Visit 1.

Immediate Release (IR) Carbidopa-Levodopa Dose Adjustment Period (3 weeks [Visit 1])

This was a 3-week, open-label IR carbidopa-levodopa treatment period allowing for dose adjustment. The dosing regimen was adjusted to minimize “off” time without causing troublesome dyskinesia. Dose and regimens of other allowable concomitant PD medications were to remain stable during the study. The subject must be on a stable dosing regimen of IR carbidopa-levodopa for at least 5 days prior to returning for Visit 2.

Study staff called the subjects approximately every 1 to 3 days during this period to ensure timely and appropriate dosing adjustments and to ensure that the subject was able to follow and adhere to dosing instructions.

Dose Conversion to Extended-Release (ER) Carbidopa-Levodopa Period (4 weeks: [Visit 2 /Week 3 to Visit 4/Week 7])

This was a 4 week, open-label period for conversion of IR carbidopa-levodopa to ER carbidopa-levodopa. The initial dosing regimen of ER carbidopa-levodopa was based on the subject’s dosing regimen of IR carbidopa-levodopa at the end of the dose adjustment period (Visit 2) selecting the most frequent dose. ER carbidopa-levodopa was to be dosed approximately every 8 hours. The dosing regimen could be adjusted during this period to achieve the optimal balance of efficacy and tolerability. Subjects must be on a stable dosing regimen of ER carbidopa-levodopa for at least 5 days prior to Visit 4. Subjects were to complete their PD Diaries on each of the 3 consecutive days immediately prior to Visit 4.

Study staff called the subjects approximately every 1 to 3 days during this period to ensure timely and appropriate dosing adjustments and to ensure that the subject was able to follow and adhere to dosing instructions. Randomization occurred during this study period at Visit 4.

Double-Blind Maintenance Period (13 weeks [Visits 5/Week 10 – 7/Week 20])

Subjects were randomized (1:1) to one of the following study arms for 13 weeks:

- ER carbidopa-levodopa capsules with matching IR carbidopa-levodopa placebo tablets
- IR carbidopa-levodopa tablets with matching ER carbidopa-levodopa placebo capsules

The dosing regimen for IR carbidopa-levodopa was the regimen established at the end of the IR carbidopa-levodopa dose adjustment period. The dosing regimen for ER carbidopa-levodopa was the regimen established at the end of the dose conversion to ER carbidopa-levodopa period.

Study visits occurred at Week 10 (Visit 5), Week 15 (Visit 6) and Week 20 (Visit 7). Study staff did not conduct reminder phone calls during this study period. Subjects were to complete their PD Diaries on each of the 3 consecutive days prior to each of these 3 visits.

The *primary efficacy endpoint* was the change from baseline (Visit 4) in “good on” time in hours per day, averaged over the PD Diary days, at the end of the double-blind period (Visit 7 or early termination). “Good on” time was defined as the sum of “on” time without dyskinesia and “on” time with non-troublesome dyskinesia. Key secondary efficacy measures included the Patient Global Impression of Change (PGI-C) scores, and MDS-UPDRS Parts II and III.

Rationale for Site Selection

The clinical sites were chosen based on risk ranking in the BIMO clinical investigator site selection tool (CISST), numbers of enrolled subjects, and prior inspectional history.

III. RESULTS

1. Kevin Klos, M.D.

Site #115

The Movement Disorder Clinic of Oklahoma
7134 S. Yale Avenue
Suite 205
Tulsa, OK 74136

Inspection Dates: 1/3/2023 – 1/5/2023

At this site for Protocol IPX203-B16-02, 18 subjects were screened and enrolled, and 14 subjects were randomized and completed the study. Four subjects discontinued the study during the open-label immediate release carbidopa-levodopa dose adjustment period due to adverse events (n = 3) or lack of efficacy (n = 1). Adverse events that led to study discontinuation during this open-label phase included hypertensive urgency (Subject # (b) (6)), insomnia and nausea (Subject # (b) (6)), and depression (Subject # (b) (6)). Narratives for these discontinuations due to adverse events were included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary and secondary efficacy endpoint data.

The primary efficacy endpoint was the change from baseline in “good on” time defined as “on” time without dyskinesia and “on” time with non-troublesome dyskinesia. Subjects recorded “off” time, “on” time without dyskinesia, “on” time with non-troublesome dyskinesia, and “on” time with troublesome dyskinesia in Parkinson’s disease paper diaries. Primary and secondary efficacy data were verified for all 14 randomized subjects. Primary efficacy data were verified comparing Parkinson’s disease paper diaries against sponsor data line listings; no discrepancies were identified. Key secondary efficacy data, Patient Global Impression of Change (PGI-C) and Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Parts II and III scores, were verified comparing paper source against sponsor data line listings; no discrepancies were identified.

There was no evidence of underreporting of adverse events. No serious adverse events (SAEs) were reported for any subjects at this site.

2. Manuel F. Fernandez, M.D.**Site #163**

Medical Professional Clinical Research Center, Inc.
3850 SW 87 Ave
Suites 201 and 202
Miami, FL 33165

Inspection Dates: 2/9/2023 – 2/17/2023

At this site for Protocol IPX203-B16-02, 40 subjects were screened, 37 subjects were enrolled, 35 subjects were randomized, and 33 subjects completed the study. Two subjects discontinued the study during the open-label immediate release carbidopa-levodopa dose adjustment phase due to “withdrawal by subject” and failure to meet inclusion criterion #10 (≥ 2.5 hours per day of “off” time with at least 1.5 hours of cumulative “off” time on each day). Two subjects discontinued the study during the double-blind phase due to “withdrawal by subject” (n = 1) and noncompliance with the Parkinson’s disease paper diary (n = 1).

Signed informed consent forms, dated prior to participation in the study, were reviewed for 25 of 40 (62.5%) subjects who were screened. An audit of the study records for 25 of 37 (67.6%) enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary and secondary efficacy endpoint data.

The primary efficacy endpoint was the change from baseline in “good on” time defined as “on” time without dyskinesia and “on” time with non-troublesome dyskinesia. Subjects recorded “off” time, “on” time without dyskinesia, “on” time with non-troublesome dyskinesia, and “on” time with troublesome dyskinesia in Parkinson’s disease paper diaries. Primary and secondary efficacy data were verified for 25 of 35 (71.4%) randomized subjects. Primary efficacy data were verified comparing Parkinson’s disease paper diaries against sponsor data line listings; no discrepancies were identified. Key secondary efficacy data, PGI-C and MDS-UPDRS Parts II and III scores, were verified comparing paper source against sponsor data line listings; no discrepancies were identified.

One of the 25 randomized subjects reviewed did not meet inclusion criterion #9. Inclusion criterion #9 states that subjects must be “able to differentiate “on” state from “off” state as determined by at least 75% concordance with a trained rater in “on/off” ratings for 8 ratings over the 4-hour training period. The concordance must include at least 1 “on” and 1 “off” rating and must be achieved within two 4-hour training sessions.” A 50% concordance rate was achieved for Subject # (b) (6) for 8 ratings. This protocol deviation was not included in the sponsor protocol deviation data line listings.

Reviewer comments: The site should have held an additional 4-hour session to achieve the protocol-specified $\geq 75\%$ concordance rate for Subject # (b) (6). This subject, randomized to carbidopa/levodopa ER, discontinued the study approximately one month after randomization due to noncompliance with the Parkinson's disease paper diary. It is unlikely that inclusion of this subject would significantly impact the efficacy analyses.

There was no evidence of underreporting of adverse events. There were nine SAEs occurring in four subjects at this site. All SAEs were reported to the sponsor within the protocol-specified timeframe of 24 hours of knowledge of the event. Narratives for these SAEs were included in the NDA submission.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/NDA #217186
Division of Neurology 1/Division Director/Teresa Buracchio
Division of Neurology 1/(Acting) Deputy Division Director/Emily Freilich
Division of Neurology 1/Medical Team Leader/Natalie Getzoff
Division of Neurology 1/Medical Officer/Elizabeth Haberfeld
Division of Neurology 1/Project Manager/Stacy Metz
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Clinical Analyst/Cara Alfaro
OSI/DCCE/GCPAB Program Analyst/Yolanda Patague
OSI/DCCE/GCPAB Program Analyst/Loreto-Corazon Lim

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARA L ALFARO
03/15/2023 01:52:14 PM

PHILLIP D KRONSTEIN
03/15/2023 02:16:57 PM

JENN W SELLERS
03/15/2023 02:36:55 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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***

Date of This Review:	February 28, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217186
Product Name and Strength:	Crexont (carbidopa and levodopa) extended-release capsule, 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Impax Laboratories, LLC
FDA Received Date:	August 31, 2022
TTT ID #:	2022-1261
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Crexont (carbidopa and levodopa) extended-release capsule, the Division of Neurology 1 (DN 1) requested that we review the proposed Crexont prescribing information (PI), carton labeling and container labels for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 217186 is a 505(b)(2) NDA and the listed drug product is Sinemet tablets, NDA 017555.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, carton labeling, and container labels may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Impax Laboratories, LLC.

4 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – Dosage and Administration: Highlights and Section 2			
1.	Dose conversion information for patients taking immediate-release carbidopa-levodopa is presented before recommended dosage information for new levodopa-naïve users.	This presentation is not intuitive and not in alignment with a similar comparator product, Rytary, which we considered when reviewing this PI.	We recommend reorganizing the presentation of dosing information to first describe dosing for levodopa-naïve patients in HL and swapping Sections 2.1 and 2.2.
2.	Use of the phrase (b) (4) in the starting dose statement is unnecessary.	Unnecessary information may detract from important information.	We recommend deleting the phrase (b) (4) and only stating the strength in HL and Section 2.2.
3.	The dose conversion statement “dosages of immediate-release carbidopa-levodopa products are not (b) (4) on a 1:1 basis” is unclear.	Unclear dosing information may increase the risk for wrong dose medication errors.	It appears Crexont is not (b) (4) on an exact 1:1 basis with any carbidopa-levodopa product. If so, then we recommend deleting the term “immediate release” and “1:1” from the dose conversion statement in HL and Section (b) (4), similar to language for the comparator product, Rytary. For example, (b) (4) (D) (4)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In Section 2.1 the (b) (4)	(b) (4) may increase the risk for confusion.	We recommend (b) (4) (b) (4) “The dosages of immediate-release carbidopa-levodopa (b) (4) products are not

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4) on a 1:1 basis with the dosages of CREXONT.” Alternatively, avoiding use of (b) (4) is acceptable.
2.	Table 1 can be improved for clarity and completeness as it does reflect all possible dosing schedules described in the bullet points below the table. For example, a patient taking a most frequent single dose of immediate-release LD of 100 mg or 150 mg who uses less than 500 mg of LD per day means the recommended frequency should be twice daily (b) (4) as indicated in Table 1.	Unclear and incomplete dosage information may increase the risk for confusion or overlooking important dosing information.	We recommend converting the bullets below Table 1 to text within Table 1. See Appendix G for our track changed recommendations.
3.	In Section 2.3, the dose conversion statement is unclear, and should state to convert based on the levodopa component. For example, conversion from 61.25 mg/245 mg Rytary on the carbidopa component will result in a Crexont dose of 70 mg/280 mg. However, specifying to convert on the levodopa component will result in a Crexont dose of 52.5 mg/210 mg.	Unclear and incomplete conversion information may increase the risk of converting a patient to the wrong strength of Crexont.	We recommend stating to convert on the levodopa component. Additionally, this information may be suitable for a Rytary to Crexont dose conversion table since it is not an exact 1:1 conversion.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The storage statement does not contain unit of measure each temperature numerical.	This may increase the risk for improper storage medication errors.	We recommend revising the storage statement to read “20°C to 25°C (68°F to 77°F)”.

5 RECOMMENDATIONS FOR IMPAX LABORATORIES, LLC

Table 3. Identified Issues and Recommendations for Impax Laboratories, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Trade and Professional Sample Container Labels and Carton Labeling			
1.	The dosage form is not displayed on the principal display panel (PDP).	Critical information for use and product identification should be prominently displayed on the PDP.	Please add the dosage form, “extended-release capsule” to the PDP, directly below the established name.
2.	The (b) (4) statement does not align with language used in the prescribing information (PI).	This can be improved for consistency with the PI.	We recommend revising the (b) (4) statement to read: “Recommended Dosage: See prescribing information.”
3.	The format for the expiration date is not defined.	We are unable to assess the expiration date from a medication error perspective.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the

Table 3. Identified Issues and Recommendations for Impax Laboratories, LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. Please specify whether alphabetical or numerical characters will be used to represent the month.
4.	The established name is not at least half the size of the proprietary name and is less prominent than the strength statement and manufacturer information.	This is not in accordance with 21 CFR 201.10(g)(2).	Ensure the established name is at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2) and revise the established name as needed.
5.	The storage statement does not contain a unit of measure after each temperature numerical.	This may increase the risk for improper storage medication errors.	We recommend you revise the storage statement to read "20°C to 25°C (68°F to 77°F)."
Trade Carton Labeling			
1.	There is a placeholder for serialization information, but it is not clear if this contains the full human-readable product identifier information or a 2D barcode.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the	Please confirm the serialization area contains product identifier information and add a placeholder for the 2D barcode.

Table 3. Identified Issues and Recommendations for Impax Laboratories, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		carton) for tracking and tracing purposes.	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Crexont that Impax Laboratories, LLC submitted on August 31, 2022, and the listed drug (LD), Sinemet.

Table 4. Relevant Product Information for Sinemet and Crexont		
Product Name	Sinemet ^a	Crexont
Initial Approval Date	May 2, 1975	N/A
Active Ingredient	Carbidopa and levodopa	
Indication	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	
Route of Administration	Oral	
Dosage Form	Tablet	Extended-release capsule
Strength	10mg/100 mg, 25 mg/100 mg, 25 mg/250 mg	35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, 87.5 mg/ 350 mg
Dose and Frequency	<u>Usual Initial Dose</u> 25 mg/100 mg three times a day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight 25 mg/100 mg tablets a day is reached. <u>Maintenance Dose</u> Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. Experience with total daily dosages of carbidopa greater than 200 mg is limited.	(b) (4)

^a Sinemet PI accessed January 24, 2023, available at: <http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/9b17b028-964a-473c-823d-81423535bd66/spl-doc?hl=sinemet>

	When a greater proportion of carbidopa is required, one tablet of SINEMET 25-100 may be substituted for each tablet of SINEMET 10-100. When more levodopa is required, SINEMET 25-250 should be substituted for SINEMET 25-100 or SINEMET 10-100. If necessary, the dosage of carbidopa and levodopa 25-250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day.	(b) (4)
How Supplied	Bottles containing 100 tablets	Carton containing 1 bottle of 120 extended-release capsules
Storage	Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.
Container Closure ^b	high-density polyethylene (HDPE) bottles	HDPE bottles with (b) (4)

^b Crexont extended-release capsule container closure specifications available at:
<\\CDSESUB1\EVSPROD\nda217186\0001\m3\32-body-data\32p-drug-prod\jpx203-carbidopa-n-levodopa-er-caps-01\32p7-cont-closure-sys\32p7-container-closure-system.pdf>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 24, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Crexont, IPX203, IND 122793, and NDA 217186. Our search did not identify any previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Crexont labels and labeling submitted by Impax Laboratories, LLC, received on August 31, 2022.

- Container labels
- Carton labeling
- Professional Sample container labels
- Prescribing Information (Image not shown), available from <\\CDSESUB1\EVSPROD\nda217186\0001\m1\us\1-14-1-3-draft-labeling-text.docx>

F.2 Label and Labeling Images

Container labels

Trade



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
02/28/2023 12:52:38 PM

STEPHANIE L DEGRAW
02/28/2023 04:05:57 PM

MEMORANDUM

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

DATE: February 22, 2023

TO: Rigoberto A. Roca, M.D.
Division of Anesthesiology, Addiction Medicine, and
Pain Medicine (DAAP)
Office of Neuroscience (ON)
Office of New Drugs (OND)

Partha Roy, Ph.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

Teresa Buracchio, M.D.
Deputy Director
Division of Neurology (DN-I)
Office of Neuroscience (ON)
Office of New Drugs (OND)

John Sharrets, M.D.
Director
Division of Diabetes, Lipid Disorders and Obesity
(DDLO)
Office of Cardiology, Hematology, Endocrinology and
Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Monica Javidnia, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Julia Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Remote regulatory assessment (RRA) of (b) (4)
(b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portion of Studies (b) (4) and (b) (4)

NON-RESPONSIVE

NON-RESPONSIVE

(NDA 217186, IPX203

[Carbidopa, Levodopa]), and

NON-RESPONSIVE

(b) (4)

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited studies are reliable.

2. Reviewed Studies

NON-RESPONSIVE

Study 190096 (NDA 217186)

Assessment of Dose Proportionality of IPX203 and Bioequivalence of IPX203 Manufactured at Two Sites

Sample Analysis Period: 04/29/2019 - 06/21/2019

NON-RESPONSIVE

3. Scope of RRA

OSIS scientist Monica Javidnia, Ph.D. r
portion of the above studies conducted

(b) (4)

(b) (4)

The RRA included an examination of records and processes for method validation, and study sample analysis. The RRA also included interviews with the firm's management and staff and a facility tour. Additionally, the RRA included a review of study-related SOPs, study-related correspondence, sample receipt, raw study data, audit trails, chromatograms, sample processing forms, select training records for study staff, calibration and maintenance records, and interviews with staff about IT, data security, and archiving processes.

4. RRA Observations

At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

4.1 Note to DDLO/OCHEN/OND

NON-RESPONSIVE

Draft: MJ 02/17/2023; 02/22/2023

Edit: HAI 02/21/2023; MO 02/21/2023; JC 02/22/2023

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/

(b) (4)

(b) (4)

<http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f883b89cf3>

OSIS File #:

(b) (4)

ATTACHMENTS

Attachment 1: Email communication to review division.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MONICA JAVIDNIA
02/22/2023 03:18:13 PM

MEI OU
02/22/2023 04:21:00 PM

SEONGEUN CHO
02/22/2023 04:27:31 PM