CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Memorandum

Date	August 7, 2024
From	Natalie Getzoff, MD Laura Jawidzik, MD
Subject	Summary Memo
NDA/BLA # and Supplement #	217186
Applicant	Impax Laboratories, LLC
Date of Submission	February 7, 2024
PDUFA Goal Date	August 7, 2024
Proprietary Name / Non-Proprietary Name	Crexont (carbidopa and levodopa extended-release)
Dosage Form(s) / Strengths	Extended-release capsules: 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg
Applicant Proposed Indication(s)/Population(s)	*Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication*
Action or Recommended Action:	Approval

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The following was partially extracted from the June 30, 2023, summary memorandum for the original submission. Crexont (IPX203) is a drug being developed to treat Parkinson's disease. IPX203 is an extended-release capsule consisting of carbidopa (CD) and levodopa (LD) in a 1:4 ratio (35/140 mg, 52.3/210 mg, 70/280 mg, 87.5/350 mg). Each capsule consists of immediate release granules (100% of the carbidopa and 25% of the levodopa) and extended-release beads (75% of the levodopa).

Parkinson's disease (PD) is a common, debilitating, progressive disease that leads to disability due to motor and cognitive manifestations. The average age of onset is 55 years of age, and it is estimated to affect at least one million Americans. Core motor symptoms include bradykinesia, rigidity, tremor, and postural instability. Non-motor symptoms are also common. Motor fluctuations, especially periods of OFF time and ON time with troublesome dyskinesia (involuntary movements) often result from therapeutic drug effect on motor symptoms wearing off intermittently. This can occur daily or even with every dosing interval of the patient's regular daily medication. These OFF periods put the patient at an increased risk for a diminished functional status, falls, and disease-related emotional deterioration. There is no cure for Parkinson's disease; however, there are FDA-approved treatments to manage the symptoms of PD, especially the motor deficits.

Treatment options for Parkinson's disease include drugs, such as carbidopa/levodopa (CD/LD) formulations, dopamine agonists, catechol-O-methyltransferase inhibitors, monoamine oxidase inhibitors-B inhibitors, anticholinergics, and amantadine. Deep brain stimulation (DBS) is also an effective, though invasive, treatment option for some motor symptoms of Parkinson's disease in selected patients.

The safety and effectiveness of IPX203 is intended to rely, in part, on prior findings of safety and effectiveness of levodopa and carbidopa from two listed drugs (Sinemet [IR CD/LD] and Rytary [CD/LD-ER]). However, an adequate pharmacokinetic (PK) bridge for carbidopa was not established between IPX203 and Sinemet or Rytary. At the maximum total daily dose of IPX203 proposed in the labeling, the carbidopa AUC was 2x and 3.1x-3.7x greater than the carbidopa AUC following the administration of the maximum recommended total daily doses of CD/LD-ER and IR CD-LD, respectively. Because of the inadequate bridge for carbidopa between IPX203 and the listed and referenced drugs, the Applicant is not able to rely upon the safety of these drugs for carbidopa. The AUCs of levodopa at maximal doses were similar between IPX203, CD/LD-ER, and IR CD-LD; therefore, the Applicant bridged successfully for levodopa, and the Applicant can rely on prior findings of safety and effectiveness of levodopa to support that component of IPX203.

A statistically significant and modestly clinically meaningful smaller decrease in ON time without troublesome dyskinesia time (i.e., ON time

without dyskinesia plus ON time with non-troublesome dyskinesia) and smaller increase in daily OFF time were demonstrated in a single adequate and well-controlled, randomized withdrawal trial in 506 subjects with advanced Parkinson's disease treated with IPX203. The primary efficacy outcome was the change in time (hours) spent ON without troublesome dyskinesia from baseline (Visit 4) to the end of the 13-week double-blind treatment period (Visit 7) based on patient diaries filled out for 3 days prior to each visit. Average ON time without troublesome dyskinesia time was decreased by 0.5 hours in the IPX203 group compared to a decrease of 1.0 hours in the IR CD/LD group (least squares mean difference 0.53 [95% CI 0.09, 0.97]; p=0.0194). This was corroborated by prespecified sensitivity analyses of the primary endpoint. The results for the first key secondary endpoint, the change from baseline to week 13 in hours of average daily OFF time was also statistically significant. There was a smaller increase in daily OFF time for the IPX203 group by 0.48 hours/day (95% CIs = [-0.9021, -0.0603]) with a p-value = 0.0252, compared to the IR CD/LD group. These findings were also supported by the results of the analysis of the Patient Global Impression of Change (PGI-C) scores at the end of double-blind treatment period (Visit 7/ET). Seventy-six (30%) subjects in the IPX203 group had much or very much improved scores, as compared to 47 (19%) in the IR CD/LD group with a p-value = 0.0015.

The results of this adequate and well-controlled trial are supported by existing adequate and well-controlled clinical investigation(s) that demonstrated the effectiveness of immediate-release carbidopa/levodopa and extended-release carbidopa/levodopa, and also from the well-understood mechanism of action of CD/LD. The results of the single positive adequate and well-controlled trial of IPX203 in conjunction with confirmatory evidence from the well-understood mechanism of action of CD/LD and the established efficacy of IR CD/LD in a similar population are adequate to establish substantial evidence of effectiveness of IPX203.

The most commonly observed adverse events in the double-blind period of the clinical trial conducted with IPX203 that occurred with a greater incidence in IPX203-treated subjects than in the IR CD/LD group were in the following categories: gastrointestinal disorders (e.g., nausea), psychiatric disorders (e.g., anxiety), and nervous system (e.g., dyskinesia and dizziness). These events were generally mild to moderate in severity. Serious and/or severe adverse events were relatively uncommon, varied and not specific to any category. Discontinuations due to adverse events during the double-blind period were more frequent in the IPX203 group (5.5%) compared to that in the IR CD/LD group (1.2%), but these incidences were fairly low. Dyskinesia and hallucinations/illusions were adverse events of special interest that occurred more frequently in the IPX203-treated group (2% and 2.7%, respectively) than in the IR CD/LD-treated group (0.4% and 0.2%, respectively), during the double-blind period.

The Agency issued a Complete Response (CR) action for the original submission because, although clinical benefit of IPX203 is established through the determination of effectiveness, the risk of IPX203 could not be fully determined. Specifically, the PK exposures for carbidopa with IPX203 at the maximal dose proposed in the labeling were 1.9x that of Rytary, and 3.1x to 3.7x that of Sinemet (IR CD/LD); therefore, an adequate scientific bridge for carbidopa exposure to the two listed drugs (Sinemet and Rytary) was not established, and the Applicant was not

able to rely on the findings of safety for these drugs to support the safety of IPX203. There was insufficient 12-month exposure of subjects at any dose (n=67) and in particular, at the maximal dose proposed in the labeling (n=0) in the original submission to support safety and there was no characterization of the effects of the higher exposure of carbidopa on the QTc.

The Applicant adequately addressed the clinical deficiencies in the resubmission. The Applicant provided data to support that there were at least 100 subjects were continuously exposed to IPX203 at any dose for at least 12 months (n=179). To support the proposed maximal dose of IPX203 in the labeling ((b) (4)), the Applicant proposed that a "modal dose range" could support the proposed maximal dose, rather than a particular dose. Specifically, the Applicant proposed that a long-term exposure at a modal dose range of (b) (4) LD could support the long-term safety of a maximal dose of (b) (4) LD and identified that there were 45 subjects in this dose range. Use of lower doses to support the safety of a higher dose is not acceptable, and only 11 subjects had 12-month continuous exposure to IPX203 at the proposed maximal dose. Evaluation of the datasets provided by the Applicant identified continuous exposure at a modal dose of ≥2100 mg LD in 32 subjects for at least 12 months, 41 subjects for at least 9 months, and 43 patients for at least 6 months, which is sufficient to support the long-term safety of IPX203 in patients with PD. In addition, the Applicant conducted a thorough QT study that adequately characterized the QTc.

There are no clinical concerns regarding safety or effectiveness that preclude approval. The clinical team has recommended **Approval** for a maximal daily dose of 525 mg/2100 mg.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Parkinson's disease (PD) is a common, debilitating, incurable disease caused by degeneration of the nerve cells that produce the neurochemical dopamine in the brain. The average age of onset is 55 years of age. The prevalence of PD rises with age: 0.5-1% among persons aged 65 to 69 years; 1-3% among persons 80+ years of age. • Core motor symptoms include bradykinesia (a decrease in spontaneity and movement), rigidity, tremor, and postural instability. Other symptoms may include depression and anxiety; cognitive decline; difficulty in swallowing, chewing, and speaking;	Parkinson's disease is a common, progressive, severely-debilitating, degenerative neurological disorder. Over time PD significantly impacts a patient's quality of life, ability to live independently, and functionally perform daily tasks without assistance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	urinary problems or constipation; skin problems; and sleep disruptions. • The control of motor symptoms by anti-Parkinson medication diminishes over time. Motor fluctuations, especially periods of OFF time and ON time with troublesome dyskinesia (involuntary movements) often develop and lead to disability.	
Current Treatment Options	• There is no cure for PD; however, there are FDA approved treatments to manage the symptoms of Parkinson's disease, particularly the motor manifestations. • Pharmacologic treatment options for PD include carbidopa/ levodopa formulations, dopamine agonists, catechol-O-methyltransferase inhibitors, monoamine oxidase-B inhibitors, anticholinergics, and amantadine. • Levodopa gel, introduced directly into the small bowel, and apomorphine available by subcutaneous injection or sublingual film are approved for the treatment of motor fluctuations of PD. • Deep brain stimulation (DBS) is an effective, invasive, therapeutic option for the motor symptoms of Parkinson's disease. DBS may result in significant benefit. Risks include the surgery itself and neuropsychiatric adverse effects. Implantation requires special surgical expertise.	Drug treatments for the motor manifestations of PD are available; however, efficacy is variable and may be associated with side effects that limit benefits. Most patients with moderately advanced PD have multiple daily periods of time when their medication fails to improve their motor function (OFF periods) or leads to side effects (ON time with troublesome dyskinesia). Additionally, the frequency of dosing and route of administration can often be burdensome on patients. Thus, there is a continued need for additional well-tolerated, safe, and effective treatment options.
Benefit	• A single randomized, double-blind, active-controlled study was conducted with IPX203 in subjects with moderate to advanced PD with motor fluctuations. • In Study B16-02, ON time without troublesome dyskinesia time was decreased by 0.5 hours in the ABBV-951 group versus a 1.0 hour decrease in the IR CD/LD group (LS mean difference of 0.53 hours	The mechanism of action for carbidopa and levodopa in treating PD is well-understood. The results of the single positive adequate and well-controlled trial of IPX203, in conjunction with confirmatory evidence from the well-understood mechanism of action of CD/LD and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	[95% CI 0.09, 0.97]; p=0.0194). • The OFF time was reduced, on average, by 0.4 hours in the IPX203 group versus a reduction of 0.9 hours in the IR CD/LD group (difference of -0.48 hours [95% CI -0.9021, -0.0603] p=0.0252). • These findings were supported by the results of the Patient Global Impression of Change (PGI-C) scores: 30% of IPX203-treated subjects reported that they were "much improved" or "very much improved" as compared to 19% of the IR CD/LD-treated subjects (p=0.0015) • The mechanism of action for carbidopa and levodopa in the treatment of PD is well-understood. • CD/LD has previously been shown to be effective in the treatment of motor fluctuations in patients with advanced Parkinson's disease (a very similar population) when administered as an extended-release formulation of CD/LD (Rytary, CD/LD-ER) in a clinical trial, which also provides confirmatory evidence for this application.	the results of a trial of CD/LD-ER in a similar population are adequate to establish substantial evidence of effectiveness of IPX203 in the treatment of advanced PD.
Risk and Risk Management	• At the maximum total daily dose of each product, the ratios of extrapolated $AUC_{0-\infty}$ of carbidopa for IPX203 was 1.9x that of Rytary, and 3.1x to 3.7x that of Sinemet (IR CD/LD). The ratios of extrapolated $AUC_{0-\infty}$ of levodopa of IPX203 to Sinemet and Rytary were similar. • There was insufficient exposure to support the safety of chronic administration of IPX203 to subjects with PD at the proposed maximal dose (b) (4). Only 11 subjects had ≥12-month exposure to IPX203 at proposed maximal dose when exposure was calculated using modal total daily dose. However, there was an adequate number of subjects with 12-month exposure to IPX203 support a maximal daily dose of 525 mg/2100 mg.	A scientific bridge was not established for the carbidopa PK exposure from IPX203 to either Sinemet or Rytary because the exposure of carbidopa from IPX203 is substantially higher than that from Sinemet or Rytary at maximal doses. Therefore, it is not possible to rely on the findings of safety of Sinemet or cross-reference Rytary for the safety of carbidopa to support the approval of IPX203. A scientific bridge to the levodopa component was established based on PK exposures. The safety of IPX203 at doses up to a maximal

Dimension	Evidence and Uncertainties	Conclusions and Reasons

	• Thirteen percent of subjects randomized to IPX203 discontinued Study B16-02 early during the double-blind period compared with 9% of subjects randomized to IR CD/LD. Adverse events were the most common reason (5.5%) subjects discontinued treatment with IPX203.
	• Six subjects died during the development program, one during the controlled trial (during the screening period, not exposed to any treatment). One of the deaths (drowning) was considered related to IPX203, but that causal relationship is not clear, due to other comorbidities.
	• Other potential risks identified during the review include:
	  ○ Dyskinesia
	  ○ Hallucinations/illusions
	• The thorough QT study included in the resubmission adequately characterized the QT effects of IPX203 at the proposed maximal dose.
	• The clinical deficiencies that led the Agency to issue a CR action have been resolved.
		daily dose of 525 mg/2100 mg for the treatment of Parkinson's disease was established based on the results of a double-blind, active-controlled trial comparing a flexible dosing of IPX203 to immediate-release carbidopa/levodopa (Study B16-02), an open-label, long-term safety study during which IPX203 was administered at a flexible dose daily (Study B16-03), and a separate thorough QT study. No unanticipated safety findings were identified during these studies. The safety database was adequate. The known serious risks associated with IPX203 can be mitigated by the following:
		• WARNINGS and PRECAUTIONS in labeling to describe hallucinations/psychosis and dyskinesias, and
		• Warnings for somnolence, impulse control compulsive behaviors, depression and suicidality, withdrawal-emergent hyperpyrexia and confusion, dyskinesia, cardiovascular ischemic events, and glaucoma should be included as they have been reported with other carbidopa/ levodopa products.

2. Background

The Applicant resubmitted a new drug application (NDA) for Crexont (carbidopa [CD] and levodopa [LD]) following a Complete Response (CR) action issued on June 30, 2023. The Applicant is seeking approval through the 505(b)(2) regulatory pathway. The Applicant is relying on the listed drug, Sinemet (immediate release carbidopa/levodopa, IR CD/LD, NDA 017555), for findings of nonclinical toxicology, nonclinical pharmacology, pediatric use, previous findings of effectiveness for all indications, previous findings of safety, pregnancy and lactation, and carcinogenicity, and reproductive and developmental toxicity. In addition, the NDA cross-references information from Rytary (levodopa carbidopa extended-release, CD/LD-ER, NDA 203312) for some information in the Dosage and Administration, Adverse Reactions, Pregnancy and Lactation, Overdosage, Pharmacokinetics, Mutagenesis, Impairment of Fertility, and Patient Counseling Sections of the labeling. In the original submission, the Applicant provided data from bioequivalence/ bioavailability studies in an attempt to establish a PK bridge from IPX203 to IR CD/LD and CD/LD-ER, efficacy and safety data from a single, randomized, double blind, active-controlled trial (Study IPX203-B16-02) and additional safety data from an open-label, long-term safety study (Study IPX203-B16-02).

The Applicant intends to market IPX203 in 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg capsules.

Parkinson's disease (PD) is a common, debilitating, incurable disease that causes degeneration of the nerve cells that produce the neurochemical dopamine. The average age of onset is 55 years of age, and it is estimated to affect at least one million Americans. The diagnosis is made clinically, using established criteria. Core motor symptoms of PD include bradykinesia, rigidity, tremor, and postural instability. Wearing off is a return of the symptoms of PD that were relieved by levodopa (LD) as the effects of the last dose of LD dissipate. Dyskinesias are involuntary, choreiform movements that typically occur at the peak of levodopa's effects in patients with PD. Both dyskinesias and wearing off can be disabling. Non-motor symptoms, such as sleep disturbances, cognitive impairment, fatigue, and constipation, are also common. There is no cure for PD; however, there are treatments approved by FDA to manage the symptoms, especially the motor deficits.

The clinical deficiencies that led to the CR action were related to inadequate data to support clinical safety of IPX203 in the setting of an inadequate bridge to the listed and cross-referenced products, as the PK exposures for carbidopa with IPX203 at the maximal dose proposed in the labeling were 1.9x that of Rytary, and 3.1x to 3.7x that of Sinemet (IR CD/LD). There was insufficient 12-month exposure of subjects at any dose and at the maximal dose proposed in the labeling in the original submission to support safety and there was no characterization of the effects of the higher exposure of carbidopa on the QTc.

In this resubmission, the Applicant provided a reanalysis of the long-term exposure data from Studies B16-02 and B16-03 and results of a thorough QT study. No new efficacy data were included.

3. Product Quality

No new product quality data were included in this resubmission. There were no new issues with the facilities reported since the original submission, as noted in the Office of Product Quality (OPQ) review dated July 22, 2024. See the OPQ review of the original submission dated May 2, 2023, for full details.

OPQ Recommendation: Approval.

4. Nonclinical Pharmacology/Toxicology

No nonclinical data were included in this resubmission. See the Division of Pharm/Tox for Neuroscience review of the original submission dated May 30, 2023, for details.

5. Clinical Pharmacology

See the Office of Clinical Pharmacology (OCP) review of the original submission dated June 28, 2023, for full details of the clinical pharmacology package.

The Applicant provided results of an in vitro alcohol dose dumping study with 0%, 5%, 20%, and 40% ethanol for the lowest (CD/LD 35 mg/140 mg) and the highest (CD/LD 87.5 mg/350 mg) strengths of Crexont. OCP concluded that Crexont has alcohol-induced dose dumping potential for levodopa in the presence of 40% alcohol, but dose dumping was not observed in the presence of lower alcohol concentrations. The clinical significance of this dose dumping is not fully characterized in humans. OCP recommends this information be included in the labeling with a statement that Crexont should not be taken with alcohol.

OCP Recommendation: Approval with the labeling edits above.

6. Clinical/Statistical-Efficacy

No new efficacy information was presented in the NDA resubmission. See the clinical and statistical reviews of the original submission for a detailed discussion of efficacy.

In the original submission the Applicant provided positive results from a single, randomized, double-blind, active-controlled, randomized withdrawal, clinical trial of IPX203 for the treatment of PD. The design of the study and the primary and key secondary efficacy endpoints are consistent with other studies used to support drug approval for other treatment of PD. The statistically significant and clinically meaningful results of this positive adequate and well-

controlled single trial are also supported by FDA's prior finding of effectiveness of carbidopa/levodopa products in the same population, The statistically significant and clinically meaningful results of this positive adequate and well-controlled trial are supported by the effectiveness of immediate-release carbidopa/levodopa (IR CD/LD) in a similar population, as the Applicant was able to bridge to IR CD/LD for the levodopa component of the drug. In addition, these results are supported by the well-understood mechanism of action of CD/LD. The results of the single positive adequate and well-controlled trial of IPX203, in conjunction with confirmatory evidence from the well-understood mechanism of action of CD/LD and the effectiveness of IR CD/LD in a similar population, are adequate to establish substantial evidence of effectiveness of IPX203 in the treatment of PD.

7. Safety

Dr. Haberfeld conducted the safety review of the original NDA submission and this resubmission.

The primary safety analysis was based on review of Study B16-02, a 20-week, multicenter, randomized, double-blind, active-controlled trial in 506 subjects with advanced PD. Additional uncontrolled safety data were analyzed on the uncontrolled safety database, derived from Study B16-03, an open-label safety study for eligible subjects with advanced PD who had been enrolled in Study B16-02. Subjects in Study B16-03 were treated with IPX203 for up to 9 months. For details of the safety analysis of the original submission, see Dr. Haberfeld's clinical review dated June 30, 2023.

The most frequently-reported treatment-emergent adverse events in Study B16-02 are discussed in Section 8.4.4 and summarized in Table 23 in Dr. Haberfeld's clinical review of the original submission.

In the resubmission, the Applicant provided a recalculation of the exposure data from Studies B16-02 and B16-03, and the results of a thorough QT study to address the deficiencies outlined in the June 30, 2023, CR letter.

Reanalysis of Exposure Data to IPX203 during the Phase 3 Studies

In the initial NDA submission, when the Applicant's data were used to calculate exposure of IPX203 using modal daily dose, a total of 299 and 67 subjects had 6- and 12-month exposures, respectively. When exposure duration was assessed by dose category, only 17 subjects had exposures of ≥2400 mg of levodopa (b) (4) (b) (4) for at least 6 months, and no subjects had ≥12-month exposure at the proposed maximal dose (see Table 1).

Table 1: Long-Term Exposure to IPX203 (Pooled Safety Population)

Exposure Duration	Dose Category (mg/day of levodopa)				
	<2000	≥2000	≥2400	≥2600	≥3000
≥ 180 Days	228	71	17	8	2
≥ 360 Days	53	14	0	0	0

Source: Clinical review

Based on this information, there was insufficient long-term exposure to IPX203 at the full range of doses proposed in the labeling. Considering that the Applicant was not able to bridge from IPX203 to either IR CD/LD or CD/LD-ER, the chronic exposure data was considered inadequate to support the safety of IPX203.

The Applicant subsequently identified an error in their approach to calculation of modal for exposure and explained in their Type A briefing package, that they had erroneously included only subjects who had taken exclusively their modal dose for at least 12 months in the original dataset, resulting in an undercount. In both the Type A Meeting package and in the datasets submitted with the resubmission, the Applicant included all subjects who had been exposed to IPX203 at any dose continuously for ≥12 months (n=179). Subjects exposed to IPX203 for ≥12 months consisted of the subjects who had been randomized to IPX203 in the Study B16-02 (4-week open-label conversion to IPX203 followed by 13-week double-blind treatment period) and completed the open-label extension study (9 months).

In the Type A meeting package, the Applicant presented a summary of the distribution of modal doses for these subjects (Table 2).

Table 2: Distribution of Modal Dose for Subjects with Exposure to IPX203 ≥ 12 months

Modal Dose of LD (mg)	Subject Exposure (N = 179) n (%)
560	14 (7.8%)
700	7 (3.9%)
770	1 (0.6%)
840	20 (11.2%)
980	4 (2.2%)
1050	2 (1.1%)
1120	11 (6.1%)
1260	23 (12.8%)
1400	7 (3.9%)
1470	3 (1.7%)
1540	9 (5.0%)
1680	24 (13.4%)
1820	4 (2.2%)
1890	1 (0.6%)
1960	3 (1.7%)

Modal Dose of LD (mg)	Subject Exposure (N = 179) n (%)
2030	1 (0.6%)
2100	15 (8.4%)
2240	9 (5.0%)
2380	11 (6.1%)
2520	5 (2.8%)
2660	1 (0.6%)
2940	1 (0.6%)
3360	2 (1.1%)
5040	1 (0.6%)

Source: Clinical Review of resubmission

As there was still an insufficient number of subjects (n=21) exposed to the highest requested levodopa dose ((b) (4) for at least 12 months, the Applicant proposed to assess exposures in the "highest modal dose range" (highest quartile [(b) (4) levodopa]) rather than using the highest modal dose cutoff to support the proposed maximal dose in the labeling. The Applicant identified 45 subjects who had taken doses of at least 2100 mg for at least 12 months to support the "substantial proportion" requirement. The Agency noted during the meeting that this approach would be a matter of review.

The Applicant submitted the same exposure data from the Type A briefing package in the NDA resubmission. Review of the exposure data included in the resubmission revealed that some subjects who took one dose most frequently (modal dose), but at other times might have taken a higher dose would only be counted as having been exposed to the lower dose based on modal dose calculation.

The Applicant again identified 45 subjects who had received a modal daily carbidopa dose ≥2100 mg levodopa for at least 12 months. However, the clinical reviewer identified 32 subjects exposed at the modal daily dose of at least 525 mg/2100 mg LD, for at least 12 months (Table 3) in the exposure datasets provided by the Applicant. There were 41 subjects with 9-month exposure, and 44 subjects with 6-month exposure at or above 2100 mg. Only 11 subjects had 12-month exposure at the maximal dose proposed in the labeling ((b) (4)), which is insufficient to support the proposed maximum dose.

Table 3: Resubmission Update, Duration of Exposure to IPX203 by Modal Daily Dose Category

	Number of subjects exposed		
Dose	**≥ 6 months**	**≥ 9 months**	**≥ 12 months**
≥ 525 mg/2100 mg	43	41	32
≥ 595 mg/2380 mg	25	21	11

Source: Clinical review of resubmission

Dr. Haberfeld reviewed the adverse events for the subjects with ≥ 12 months exposure and

found no pattern of unusual adverse events compared to the adverse event rates observed in the rest of the safety population.

QT Findings

The Interdisciplinary Review Team for Cardiac Safety Studies (QT-IRT) reviewed the thorough QT study included in the NDA resubmission. Please see the QT-IRT review dated April 24, 2024, for details.

In response to the deficiency in the CR letter and the discussion at the Type A meeting, the Applicant conducted a thorough QT study to characterize the effects of a supramaximal dose of carbidopa on the QT.

Per the QT-IRT review:

> Carbidopa did not prolong the QTcF interval in this thorough QT study.
>
> 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).

The QT-IRT recommended the following edit to the proposed labeling, which was accepted by the Applicant:

> **12.2 Pharmacodynamics**
> Cardiac Electrophysiology
> (b) (4)

Safety Conclusions:

No new safety signals were identified during the review of the resubmission. The requirement for an adequate number of subjects treated for 12 months supports a high dose of 525 mg carbidopa/2100 mg levodopa as the maximum recommended daily dose in the product label.

The clinical deficiencies identified in the CR letter have been adequately addressed.

Safety data were derived primarily from a single active-controlled trial with one open-label safety study providing supportive data. To support the safety of a drug, the Agency generally

requires 100 subjects be exposed for a minimum of at least one year with at least half (or a substantial proportion of) the subjects taking the maximum dose proposed in the labeling. In review of the original NDA submission, 67 subjects had ≥12-month exposure to IPX203 at any dose, and no subjects had ≥12-month exposure to the proposed maximal dose (b) (4) , based on modal dose. Therefore, the Agency determined that there was inadequate exposure to allow for a determination of safety of chronic administration of IPX203.

In the resubmission, the Applicant provided recalculation of the chronic exposure data, which was reviewed and independently evaluated by the clinical reviewer. Based on the information included in the resubmission, there were 179 subjects with any exposure to IPX203 for 12 months and 11 subjects with 12-month exposure at the maximal dose proposed in the labeling (b) (4) which is insufficient to support the proposed maximum dose. There were 32 subjects exposed at the modal daily dose of at least 525 mg/2100 mg, for at least 12 months, 41 subjects with 9-month exposure, and 44 subjects with 6-month exposure at or above 2100 mg. These exposure data are sufficient to support a maximal dose of 525 mg/2100 mg.

The most frequently observed adverse events during the double-blind period that occurred with a greater incidence in IPX203-treated subjects than in subjects taking IR CD/LD were nausea (4.3%), anxiety (2.7%), dizziness (2.3%), and dyskinesia (2%). These events were generally mild to moderate in severity. Of note, during the IPX203 dose conversion period, when all subjects were initially exposed IPX203, the most frequently-reported adverse events were dyskinesia (6.8%), nausea (4.9%), and dry mouth (4.2%).

During the double-blind period, serious adverse events (SAEs) occurred slightly more frequently in IPX203-treated subjects (3.1%) than in IR CD/LD-treated subjects (1.6%). The specific SAEs were varied, occurring in only 1 subject each. Discontinuations due to AEs were more frequently-reported in IPX203-treated subjects (5.5%) than in IR CD/LD-treated subjects (1.2%), and these events were varied in nature. SAEs occurred in a greater proportion of subjects in the open-label safety study (10.3%), but the only SAEs that occurred each in 3 subjects were seizure, confusional state, and COVID-19. The rest of the SAEs occurred in only 1 or 2 subjects, making it difficult to determine any pattern.

There were 5 deaths in in subjects exposed to IPX203; however, because the patients had multiple comorbidities, none of the deaths can reasonably be attributed to IPX203.

The safety profile of IPX203 from the clinical trials is generally acceptable given the seriousness of Parkinson's disease and can be mitigated with warnings and other information in the labeling, consistent with warnings in the labeling of the listed and cross-referenced drugs.

8. Advisory Committee Meeting

An Advisory Committee meeting was not required.

9. Pediatrics

The submission did not include any pediatric data. Because Parkinson's disease generally does not occur in the pediatric population, a full waiver was granted for pediatric studies under Pediatric Research Equity Act (PREA).

10. Labeling

The primary clinical issue with the proposed labeling is that there are insufficient long-term safety data to support the maximal dose proposed in the labeling (b) (4) The long-term safety data supports a maximum recommended total daily dose of 525 mg/2100 mg, based on the exposure data calculated from the resubmission update. The Applicant agreed to the change in the maximal dose of IPX203.

11. Recommendations/Risk-Benefit Assessment

The Applicant has provided substantial evidence of the effectiveness and safety of Crexont (IPX203, carbidopa/levodopa extended-release) based on results of a single, adequate and well-controlled trial and confirmatory evidence. Although the Applicant was not able to establish a PK bridge for carbidopa to either of the referenced drugs, they provided sufficient clinical safety data from the development program to support approval. There were no safety findings in the controlled and uncontrolled clinical trials that cannot be mitigated by labeling. The exposure data support long-term safety of IPX203 at a maximal daily dose of 525 mg/2100 mg.

There are no outstanding unresolved issues.

Specific postmarketing risk management activities are not needed.

Agreement has been reached with the Applicant on product labeling.

We agree with the review team that this NDA should be approved.

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/

NATALIE B GETZOFF
08/07/2024 11:37:18 AM

LAURA A JAWIDZIK
08/07/2024 11:40:25 AM

Summary Memorandum

Date	June 30, 2023
From	Natalie Getzoff, MD Emily Freilich, MD
Subject	Summary Memo
NDA/BLA # and Supplement #	217186
Applicant	Impax Laboratories, LLC
Date of Submission	August 30, 2022
PDUFA Goal Date	June 30, 2023
Proprietary Name / Non-Proprietary Name	Crexont (carbidopa and levodopa extended-release)
Dosage Form(s) / Strengths	Extended-release capsules: 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg
Applicant Proposed Indication(s)/Population(s)	*Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication*
Action or Recommended Action:	Complete Response

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Crexont (IPX203) is a drug being developed to treat Parkinson's disease. IPX203 is an extended-release capsule consisting of carbidopa and levodopa in a 1:4 ratio (35/140 mg, 52.3/210 mg, 70/280 mg, 87.5/350 mg). Each capsule consists of immediate release granules (100% of the carbidopa and 25% of the levodopa) and extended-release beads (75% of the levodopa).

Parkinson's disease (PD) is a common, debilitating, progressive disease that leads to disability due to motor and cognitive manifestations. The average age of onset is 55 years of age, and it is estimated to affect at least one million Americans. Core motor symptoms include bradykinesia, rigidity, tremor, and postural instability. Non-motor symptoms are also common. Motor fluctuations, especially periods of OFF time and ON time with troublesome dyskinesia (involuntary movements) often result from therapeutic drug effect on motor symptoms wearing off intermittently. This can occur daily or even with every dosing interval of the patient's regular daily medication. These OFF periods put the patient at an increased risk for a diminished functional status, falls, and disease-related emotional deterioration. There is no cure for Parkinson's disease; however, there are FDA approved treatments to manage the symptoms of PD, especially the motor deficits.

Treatment options for Parkinson's disease include drugs, such as carbidopa/levodopa (CD/LD) formulations, dopamine agonists, catechol-O-methyltransferase inhibitors, monoamine oxidase inhibitors-B inhibitors, anticholinergics, and amantadine. Deep brain stimulation (DBS) is also an effective, though invasive, treatment option for some motor symptoms of Parkinson's disease in selected patients.

The safety and effectiveness of IPX203 is intended to rely, in part, on prior findings of safety and effectiveness of levodopa and carbidopa from two listed drugs (Sinemet [IR CD/LD] and Rytary [CD/LD-ER]). However, an adequate pharmacokinetic (PK) bridge for carbidopa was not established between IPX203 and Sinemet or Rytary. At the maximum total daily dose of IPX203 proposed in the labeling, the carbidopa AUC was 2x and 3.1x-3.7x greater than the carbidopa AUC following the administration of the maximum recommended total daily doses of CD/LD-ER and IR CD-LD, respectively. Because of the inadequate bridge for carbidopa between IPX203 and the listed and referenced drugs, the Applicant is not able to rely upon the safety of these drugs for carbidopa. The AUCs of levodopa at maximal doses were similar between IPX203, CD/LD-ER, and IR CD-LD; therefore, the Applicant bridged successfully for levodopa, and the Applicant can rely on prior findings of safety and effectiveness of levodopa to support that component of IPX203.

A statistically significant and modestly clinically meaningful smaller decrease in "good" ON time (i.e., ON time without dyskinesia plus ON time with non-troublesome dyskinesia) and smaller increase in daily OFF time were demonstrated in a single adequate and well-controlled,

randomized withdrawal trial in subjects with advanced Parkinson's disease treated with IPX203. The primary efficacy outcome was the change in time (hours) spent ON without troublesome dyskinesia from baseline (Visit 4) to the end of the 13-week double-blind treatment period (Visit 7) based on patient diaries filled out for 3 days prior to each visit. Average "good" ON time was decreased by 0.5 hours in the IPX203 group compared to a decrease of 1.0 hours in the IR CD/LD group (Least Squares mean difference 0.53 [95% CI 0.09, 0.97]; p=0.0194). This was corroborated by prespecified sensitivity analyses of the primary endpoint. The results for the first key secondary endpoint, the change from baseline to week 13 in hours of average daily OFF time was also statistically significant. There was a smaller increase in daily OFF time for the IPX203 group by 0.48 hours/day (95% CIs = [-0.9021, -0.0603]) with a p-value = 0.0252, compared to the IR CD/LD group. These findings were also supported by the results of the analysis of the Patient Global Impression of Change (PGI-C) scores at the end of double-blind treatment period (Visit 7/ET). Seventy-six (30%) subjects in the IPX203 group had much or very much improved scores, as compared to 47 (19%) in the IR CD/LD group with a p-value = 0.0015.

The results of this adequate and well-controlled trial are supported by existing adequate and well-controlled clinical investigation(s) that demonstrated the effectiveness of immediate-release carbidopa/levodopa and extended-release carbidopa/levodopa, and also from the well-understood mechanism of action of CD/LD. The results of the single positive adequate and well-controlled trial of IPX203 in conjunction with confirmatory evidence from the well-understood mechanism of action of CD/LD and the established efficacy IR CD/LD in a similar population are adequate to establish substantial evidence of effectiveness of IPX203.

The most commonly observed adverse events in the double-blind period of the clinical trial conducted with IPX203 that occurred with a greater incidence in IPX203-treated subjects than in the IR CD/LD group were in the following categories: gastrointestinal disorders (e.g., nausea), psychiatric disorders (e.g., anxiety), , and nervous system (e.g., dyskinesia and dizziness). These events were generally mild to moderate in severity. Serious and/or severe adverse events were relatively uncommon, varied and not specific to any category. Discontinuations due to adverse events during the double-blind period were more frequent in the IPX203 group (5.5%) compared to that in the IR CD/LD group (1.2%), but these incidences were fairly low. Dyskinesia and hallucinations/illusions were adverse events of special interest that occurred more frequently in the IPX203-treated group (2% and 2.7%, respectively) than in the IR CD/LD-treated group (0.4% and 0.2%, respectively), during the double-blind period.

Although clinical benefit of IPX203 is established through the determination of effectiveness, the risk of IPX203 cannot be fully determined because of the lack of adequate long-term safety data in the setting of an inadequate bridge to the listed drugs. Specifically, the PK exposures for carbidopa with IPX203 at the maximal dose proposed in the labeling were 1.9x that of Rytary, and 3.1x to 3.7x that of Sinemet (IR CD/LD); therefore, an adequate scientific bridge for carbidopa exposure to the two listed drugs (Sinemet and Rytary) was not established, and the Applicant cannot rely on the findings of safety for these drugs to support the safety of IPX203. In addition, the safety database is inadequate to

characterize the long-term safety of IPX203, as there is insufficient 12-month exposure of subjects at any dose (n=67) and in particular, at the maximal dose proposed in the labeling (n=0). These safety deficiencies cannot be mitigated by labeling or a risk management solution, leading to a determination of a Complete Response.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Parkinson's disease (PD) is a common, debilitating, incurable disease caused by degeneration of the nerve cells that produce the neurochemical dopamine in the brain. The average age of onset is 55 years of age. The prevalence of PD rises with age: 0.5-1% among persons aged 65 to 69 years; 1-3% among persons 80+ years of age. • Core motor symptoms include bradykinesia (a decrease in spontaneity and movement), rigidity, tremor, and postural instability. Other symptoms may include depression and anxiety; cognitive decline; difficulty in swallowing, chewing, and speaking; urinary problems or constipation; skin problems; and sleep disruptions. • The control of motor symptoms by anti-Parkinson medication diminishes over time. Motor fluctuations, especially periods of OFF time and ON time with troublesome dyskinesia (involuntary movements) often develop and lead to disability.	Parkinson's disease is a common, progressive, severely-debilitating, degenerative neurological disorder. Over time PD significantly impacts a patient's quality of life, ability to live independently, and functionally perform daily tasks without assistance.
Current Treatment Options	• There is no cure for PD; however, there are FDA approved treatments to manage the symptoms of Parkinson's disease, particularly the motor manifestations. • Pharmacologic treatment options for PD include carbidopa/ levodopa formulations, dopamine agonists, catechol-O-	Drug treatments for the motor manifestations of PD are available; however, efficacy is variable and may be associated with side effects that limit benefits.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	methyltransferase inhibitors, monoamine oxidase-B inhibitors, anticholinergics, and amantadine. • Levodopa gel, introduced directly into the small bowel, and apomorphine available by subcutaneous injection or sublingual film are approved for the treatment of motor fluctuations of PD. • Deep brain stimulation (DBS) is an effective, invasive, therapeutic option for the motor symptoms of Parkinson's disease. DBS may result in significant benefit. Risks include the surgery itself and neuropsychiatric adverse effects. Implantation requires special surgical expertise.	Most patients with moderately advanced PD have multiple daily periods of time when their medication fails to improve their motor function (OFF periods) or leads to side effects (ON time with troublesome dyskinesia). Additionally, the frequency of dosing and route of administration can often be burdensome on patients. Thus, there is a continued need for additional well-tolerated, safe, and effective treatment options.
Benefit	• A single randomized, double-blind, active-controlled study was conducted with IPX203 in subjects with moderate to advanced PD with motor fluctuations. • In Study B16-02, "good" ON time was decreased by 0.5 hours in the ABBV-951 group versus a 1.0 hour decrease in the IR CD/LD group (LS mean difference of 0.53 hours [95% CI 0.09, 0.97]; p=0.0194). • The OFF time was reduced, on average, by 0.4 hours in the IPX203 group versus a reduction of 0.9 hours in the IR CD/LD group (difference of -0.48 hours [95% CI -0.9021, -0.0603] p=0.0252). • These findings were supported by the results of the Patient Global Impression of Change (PGI-C) scores: 30% of IPX203-treated subjects reported that they were "much improved" or "very much improved" as compared to 19% of the IR CD/LD-treated subjects (p=0.0015) • The mechanism of action for carbidopa and levodopa in the treatment of PD is well-understood.	The mechanism of action for carbidopa and levodopa in treating PD is well-understood. The results of the single positive adequate and well-controlled trial of IPX203, in conjunction with confirmatory evidence from the well-understood mechanism of action of CD/LD and the results of a trial of CD/LD-ER in a similar population are adequate to establish substantial evidence of effectiveness of IPX203 in the treatment of advanced PD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• CD/LD has previously been shown to be effective in the treatment of motor fluctuations in patients with advanced Parkinson's disease (a very similar population) when administered as an extended-release formulation of CD/LD (Rytary, CD/LD-ER) in a clinical trial, which also provides confirmatory evidence for this application.	
Risk and Risk Management	• At the maximum total daily dose of each product, the ratios of extrapolated $AUC_{0-\infty}$ of carbidopa for IPX203 was 1.9x that of Rytary, and 3.1x to 3.7x that of Sinemet (IR CD/LD). The ratios of extrapolated $AUC_{0-\infty}$ of levodopa of IPX203 to Sinemet and Rytary were similar. • There was insufficient exposure to support the safety of chronic administration of IPX203 to subjects with PD, especially at the proposed maximal dose. Only 67 subjects had ≥12-month exposure to IPX203 at any dose, and no subjects had ≥12-month exposure to the proposed maximal dose, when exposure was calculated using modal total daily dose. • Thirteen percent of subjects randomized to IPX203 discontinued Study B16-02 early during the double-blind period compared with 9% of subjects randomized to IR CD/LD. Adverse events were the most common reason (5.5%) subjects discontinued treatment with IPX203. • Six subjects died during the development program, one during the controlled trial (during the screening period, not exposed to any treatment). One of the deaths (drowning) was considered related to IPX203, but that causal relationship is not clear, due to other comorbidities. • Other potential risks identified during the review include: ○ Dyskinesia	The safety of IPX203 cannot be determined, based on the information included in this NDA submission. A scientific bridge was not established for the carbidopa PK exposure from IPX203 to either Sinemet or Rytary because the exposure of carbidopa from IPX203 is substantially higher than that from Sinemet or Rytary at maximal doses. Therefore, it is not possible to rely on the findings of safety of Sinemet or cross-reference Rytary for the safety of carbidopa to support the approval of IPX203. The long-term safety database of IPX203 is inadequate to characterize the chronic safety of IPX203, as there is insufficient 12-month exposure of subjects at any dose or at the maximal dose proposed in the labeling. The lack of adequate long-term safety data in the setting of an inadequate bridge to the listed drugs to support safety cannot be corrected by a risk management solution and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Hallucinations/illusions • No QT studies were performed in the IPX203 development program. The Applicant proposes to rely upon the listed drugs Rytary and Sinemet for safety, including QT information. However, because the Applicant did not bridge successfully between IPX203 and Sinemet or Rytary, it may not rely on either of these products for safety. The Interdisciplinary Review Team for Cardiac Safety Studies (IRT-QT) was consulted and determined that a thorough QT study is needed "to assess the QT effects of CREXONT since the new formulation results in significantly higher carbidopa exposure (i.e., C_{max} and AUC)."	leads to the recommendation of a **Complete Response.**

2. Background

The Applicant has submitted a New Drug Application (NDA) for Crexont (carbidopa [CD] and levodopa [LD]). The Applicant is seeking approval through the 505(b)(2) regulatory pathway. The Applicant is relying on the listed drug, Sinemet (immediate release carbidopa/levodopa, IR CD/LD, NDA 017555), for findings of nonclinical toxicology, nonclinical pharmacology, pediatric use, previous findings of effectiveness for all indications, previous findings of safety, pregnancy and lactation, and carcinogenicity, and reproductive and developmental toxicity. In addition, the NDA cross-references information from Rytary (levodopa carbidopa extended-release, CD/LD-ER, NDA 203312) for some information in the Dosage and Administration, Adverse Reactions, Pregnancy and Lactation, Overdosage, Pharmacokinetics, Mutagenesis, Impairment of Fertility, and Patient Counseling Sections of the labeling. The Applicant provided data from bioequivalence/bioavailability studies in an attempt to establish a PK bridge from IPX203 to IR CD/LD and CD/LD-ER. In addition, this application provides efficacy and safety data from a single, randomized, double blind, active-controlled trial (Study IPX203-B16-02) and additional safety data from an open-label, long-term safety study (Study IPX203-B16-02).

The Applicant intends to market IPX203 in 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg capsules.

Parkinson's disease (PD) is a common, debilitating, incurable disease that causes degeneration of the nerve cells that produce the neurochemical dopamine. The average age of onset is 55 years of age, and it is estimated to affect at least one million Americans. The diagnosis is made clinically, using established criteria. Core motor symptoms of PD include bradykinesia, rigidity, tremor, and postural instability. Wearing off is a return of the symptoms of PD that were relieved by levodopa (LD) as the effects of the last dose of LD dissipate. Dyskinesias are involuntary, choreiform movements that typically occur at the peak of levodopa's effects in patients with PD. Both dyskinesias and wearing off can be disabling. Non-motor symptoms, such as sleep disturbances, cognitive impairment, fatigue, and constipation, are also common. There is no cure for PD; however, there are treatments approved by FDA to manage the symptoms, especially the motor deficits.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for a detailed discussion of the product quality assessment.

According to the OPQ review, the Applicant has provided adequate information to ensure the identity, strength, quality, and purity of the proposed drug product.

The drug product consists of two different contained inside a capsule. The immediate release granules consist of both levodopa and carbidopa with a disintegrant polymer to allow for rapid dissolution. The extended-release beads consist of levodopa, which is coated with a sustained-release polymer, a mucoadhesive polymer, and an enteric coating to control release of levodopa. Within each capsule, 25% of the levodopa and 100% of the carbidopa are included in the immediate=release granules and 75% of the levodopa in the extended-release beads. The applicant plans to market four dosage-proportional strengths of IPX203: 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg. The product is to be supplied in a 120-count HDPE bottle.

Stability and release testing were found to be acceptable for all four dosage strengths. The stability data provides adequate support for a shelf-life of 24 months in the HDPE at USP Controlled Room Temperature. OPQ determined that the manufacturing process for the drug product appears to be satisfactory based on its process selection, in-process controls, final product release test, and executed submission batch records. All manufacturing facilities for this product were found to be acceptable. There were no outstanding issues identified in the OPQ review.

OPQ Recommendation: Approval.

4. Nonclinical Pharmacology/Toxicology

The Division of Pharmacology and Toxicology – Neurology (DPT-N) review was performed by pharmacology/toxicology reviewer Dr. LuAnn McKinney, with Team Leader Dr. David Carbone and Supervisor Dr. Lois Freed.

The following summary of the nonclinical pharmacology/toxicology findings with ABBV-951 is summarized from the DPT-N review.

> Crexont (IPX203) is a 1:4 fixed dose combination of carbidopa (CD) and levodopa (LD) formulated as extended-release capsules intended for the treatment of Parkinson's disease. NDA 217186 was submitted under the 505(b)(2) pathway, with reliance upon the previous findings of safety and effectiveness for the listed drug, Sinemet, to support the NDA. The sponsor was advised during a Pre-NDA meeting (IND 122793; March 4, 2022) that, if an adequate bridge was established to the intended listed drug and that no safety concerns were identified, additional nonclinical studies would not be needed for the NDA.
>
> Based on discussions with the clinical pharmacology team, plasma carbidopa exposure in patients administered the maximum recommended human dose (MRHD) of Crexont (b) (4) exceed that of Sinemet. The safety of the higher CD exposure is to be assessed in clinical trials; therefore, no additional nonclinical data are needed to support the proposed MRHD or the NDA.

DPT-N Recommendation: **Approval** is deferred to the clinical team.

CDTL Comment: There is insufficient long-term safety data to support the safety of IPX203 for chronic administration in the setting of an inadequate scientific bridge to the listed drugs for carbidopa exposure. Therefore, the clinical team is recommending a **Complete Response.**

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewers Dr. Ramakrishna Samala and Dr. Yifei Zhang, with Team Leader Dr. Bilal AbuAsal, and signed by Dr. Mehul Mehta. The primary conclusions of the OCP review are summarized below. Please refer to the OCP review for a more detailed discussion of these findings.

The Applicant provided PK data from five PK studies in NDA 217186:

- Study IPX203-B16-05 evaluated the relative bioavailability of IPX203 compared with IR CD/LD and Sinemet® CR (CR CD/LD).
- Study IPX203-B16-01 assessed the PK, pharmacodynamics/efficacy, and safety of IPX203 in subjects with PD after multiple doses as compared to IR CD/LD.
- Study IPX203-B14-02 assessed the PK, pharmacodynamics/efficacy, and safety of single dose of IPX203 in subjects with PD, compared to IR CD/LD and CD/LD-ER.
- Study IPX203-B16-04 evaluated the effect of food on the PK of CD and LD following IPX203 administration.
- Study IPX203-B16-06 evaluated dose proportionality of IPX203 capsules over the CD/LD dosage strength range of 35 mg/140 mg to 87.5 mg/350 mg and assessed the bioequivalence (BE) between the IPX203 capsules manufactured in New York site (for the commercial product) and (b) (4) (for the Phase 3 clinical trial).

Based on the data included in the NDA, the OCP review team concluded that an adequate PK bridge was not established between IPX203 and FDA approved products (IR CD/LD, CR CD/LD, and CD/LD-ER). At the maximum total daily dose of IPX203 proposed in the labeling, the carbidopa AUC was 2x and 3.1x-3.7x greater than the carbidopa AUC following the administration of the maximum recommended total daily doses of CD/LD-ER and IR CD-LD, respectively. The AUCs of levodopa at maximal doses were similar between IPX203, CD/LD-ER, and IR CD-LD.

The following summary of the general PK findings with IPX203 is extracted from the OCP review.

- Absorption: Based on data from a Phase 1 study in subjects with PD (Study B16-06), dose proportionality was concluded for carbidopa and levodopa at doses between 35-140 mg and 87.5-350 mg. Based on data from studies (B16-01, B16-05, and B14-02), the bioavailability of carbidopa is 103% - 123% relative to IR CD/LD. The bioavailability of levodopa is 88% - 99% relative to IR CD/LD.

- Distribution: Plasma protein binding of carbidopa and levodopa is ~ 36% and 10-30%, respectively.
- Metabolism: Primary metabolites of carbidopa are α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxy-phenylpropionic acid. Levodopa is metabolized to various metabolites. The two major metabolic pathways are decarboxylation by dopa decarboxylase and O-methylation by catechol-O-methyltransferase. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Effect of food on IPX203

Effect of a standardized high-fat meal on the PK of IPX203, and the characterization of the PK of IPX203 after sprinkling the capsule contents on applesauce as a representative soft food was conducted in Study B16-04. When IPX203 is administered with a standard high fat, high calorie breakfast, the exposure of carbidopa (C_{max} and AUC) decreased by 64% and the levodopa exposures were increased by 19% (C_{max}) and 18% (AUC), compared to the fasted state. Following administration of the sprinkled contents of IPX203 capsules on the applesauce to healthy subjects, the geometric mean ratios of carbidopa Cmax and AUC were 86% and 91%, respectively, compared to fasted state. The 90% CI for C_{max} was 78%-97%, which was not contained in the standard BE limits of 80%-125%. Sprinkling the IPX203 capsule contents on applesauce did not affect the levodopa concentration time profile compared to the intact capsule.

Exposure Analysis

Studies B16-01, B16-05, and B14-02 provided the data for the evaluated exposure ratios of carbidopa and levodopa between IPX203 and FDA- approved CD/LD products. Because of the differences in dosing frequencies between the products, dose-normalized $AUC_{0-\infty}$ were extrapolated to the maximum recommended daily dose for each product, to compare the exposures. The OCP reviewer performed an independent analysis of the carbidopa and levodopa exposures after normalizing to the dose conversion ratio and extrapolating to the maximum recommended daily dose for each product.

Study B16-01 was a phase 2 study that compared PK parameters following single and multiple doses of IPX203 and IR CD/LD in patients with advanced PD. The dosing of IPX203 was based in the subject's prestudy regimen of LD. The OCP-generated results are summarized in Table 1 below, revealing that the extrapolated maximum daily exposure of carbidopa in IPX203 is 3.1-fold greater than that of IR CD/LD. The extrapolated maximum exposures of levodopa are similar between IPX203 and IR CD/LD.

Table 1: Dose-Normalized AUC0-∞ of carbidopa and levodopa following first dose on Day 1 extrapolated to maximum total daily dose of respective drug products (Study B16-01)

	Carbidopa		Levodopa	
	IPX203	**IR CD/LD**	**IPX203**	**IR CD/LD**
Normalized dose	70 mg	25 mg	280 mg	100 mg
$AUC_{0-\infty}$ (h* ng/mL)	1038	359	6925	2716

	Carbidopa		Levodopa	
	IPX203	IR CD/LD	IPX203	IR CD/LD
Relative Bioavailability	103%		91%	
Maximum Total Daily Dose (mg)	600	200	2400	2000
Extrapolated $AUC_{0-\infty}$ at Maximum Total Daily Dose	8897	2872	59357	54320
$\frac{IPX203}{IR\ CD-LD}$	3.1		1.1	

(Source: Table 5, OCP review)

Study B16-05 was a Phase 1 comparative PK study, which evaluated the relative bioavailability of IPX203 compared with IR CD/LD and CR CD/LD. The OCP analyses summarized in Table 2 shows that the relative bioavailability of carbidopa in IPX203 and CR CD/LD to IR CD/LD was 123% and 78%, respectively, and the relative levodopa bioavailability was 99% and 90%, respectively. There was a 3.7-fold greater carbidopa exposure at maximum daily dose (extrapolated $AUC_{0-\infty}$) in IPX203 compared to IR CD/LD. Levodopa exposures in subjects taking IPX203 and IR CD/LD were similar.

Table 2: Carbidopa and levodopa exposures, $AUC_{0-\infty}$ extrapolated to maximum total daily dose (Study B16-05)

	Carbidopa			Levodopa		
	IPX203	IR CD/LD	CR CD/LD	IPX203	IR CD/LD	CR CD/LD
Dose (mg)	70	25	25	280	100	100
$AUC_{0-\infty}$ (h * ng/mL)	2247	655	510	7696	2776	2489
Relative Bioavailability	123%	-	78%	99%	-	90%
Maximum Total Daily Dose (mg)	600	200	600*	2400	2000	2400*
Extrapolated $AUC_{0-\infty}$ at Maximum Total Daily Dose	19257	5236	-	65968	55518	59736
$\frac{IPX203}{IR\ CD/LD}$	3.7			1.2		
$\frac{IPX203}{CR\ CD/LD}$	1.6			1.1		

** According to the USPI of SINEMET CR, a dose of 400 to 1600 mg of levodopa per day is effective in most of the patients. Higher doses of SINEMET CR (2400 mg or more of levodopa per day) have been used but are not usually recommended. The CD/LD dose of 600 mg/2400 mg was used as the Maximum Total Daily Dose in this table for the purpose of comparison only.*

(Source: Table 6, OCP review)

Study B14-02 was a Phase 1 study that assessed the PK of single doses of IPX203, IR CD/LD, and CD/LD-ER in subjects with advanced PD. Fifty-one subjects with advanced PD with motor fluctuations who were receiving IR CD/LD at study entry were randomized to one of three dosing sequences of IPX203, IR CD/LD, and CD/LD-ER. As seen in Table 3 below, the relative

bioavailability of carbidopa in IPX203 and CD/LD-ER compared to IR CD/LD was 103% and 53%, respectively, and the relative levodopa bioavailability was 88% and 78%, respectively. There were 3.1-fold and 1.9-fold greater carbidopa exposures at maximum daily dose (extrapolated $AUC_{0-\infty}$) in IPX203 compared to IR CD/LD and CD/LD-ER, respectively. Levodopa exposures in subjects taking IPX203, IR CD/LD, and CD/LD-ER in Study B14-02 were similar.

Table 3: Carbidopa and levodopa exposures, $AUC_{0-\infty}$ extrapolated to maximum total daily dose (Study B14-02)

	Carbidopa			Levodopa		
	IPX 203	**IR CD/LD**	**CD/LD-ER**	**IPX 203**	**IR CD/LD**	**CD/LD-ER**
Normalized dose (mg)	90	25	85	360	100	340
$AUC_{0-\infty}$ (h * ng/mL)	1602	431	770	9800	3108	8275
Relative Bioavailability	103%		53%	88%		78%
Maximum Total Daily Dose (mg)	600	200	612.5	2400	2000	2450
Extrapolated $AUC_{0-\infty}$ at Maximum Total Daily Dose	10680	3448	5549	69176	62160	56315
$\frac{\text{IPX203}}{\text{IR CD/LD}}$	3.1			1.1		
$\frac{\text{IPX203}}{\text{CD/LD ER}}$	1.9			1.1		

(Source: Table 7, OCP review)

In summary, based on the data included in this NDA submission, at the maximum total daily dose of each product, the ratios of extrapolated $AUC_{0-\infty}$ of carbidopa for IPX203 was 1.9x that of CD/LD-ER, and 3.1x to 3.7x that of IR CD/LD. The ratios of extrapolated $AUC_{0-\infty}$ of levodopa of IPX203 to IR CD/LD, CR CD/LD and CD/LD-ER are very similar (~1.1x). Therefore, OCP has determined that the Applicant has established an adequate bridge for levodopa from IPX203 to IR CD/LD and CD/LD-ER; however, the Applicant has not established an adequate bridge for carbidopa exposure from IPX203 to either IR CD/LD or CD/LD-ER and that the comparison of exposures does not support the maximum proposed dose of IPX203.

OCP Recommendation: Inadequate scientific bridging between IPX203 and the listed drugs to support safety of IPX203; OCP defers the evaluation of safety to the nonclinical and clinical teams.

6. Clinical/Statistical-Efficacy

Dr. Elizabeth Haberfeld was the clinical reviewer for this application. Dr. Minjeong Park was the biometrics reviewer, Dr. John Lawrence was the secondary statistical reviewer, and Dr. H.M. James Hung (DBI division director) was the biometrics concurring reviewer.

Study B16-02

The primary evidence of effectiveness for this application is based on the analysis of clinical efficacy endpoints from Study IPX203-B16-02 (Study B16-02). Study B16-02 is Phase 3, randomized, double blind, double dummy trial of IPX203 compared to IR CD/LD in subjects with advanced Parkinson's disease.

Study B16-02 was a study conducted at 105 study centers in the U.S., Western and Eastern Europe. A total of 630 subjects were enrolled into the 3-week oral CD/LD dose adjustment period, 589 in the 4-week IPX203 dose optimization period, and 506 subjects entered the 13-week double-blind period of Study B16-02. The dose adjustment phase was intended to maximize ON time without troublesome dyskinesia and minimize the number of OFF episodes during the day. During the IPX optimization period, subjects were converted from IR CD/LD to equivalent doses of IPX203 at a ratio of 1:2.8. Dosing interval could range from a minimum of 6 to a maximum of 12 hours with the recommended interval being 8 hours. All other drug doses remained stable. Subjects were randomized (1:1) to IPX203 + placebo IR CD/LD or IR CD/LD + placebo IPX203 during visit 4. After randomization, subjects entered the double-blind treatment period (V4 through V7; Study Weeks 7-20). Subjects randomized to the IR CD/LD group were converted back to the stable dose of IR CD/LD established during the dose adjustment phase, and subjects randomized to the IPX203 group continued to take the stable dose of IPX203 established during the IPX203 optimization period. During the double-blind period, the treatment regimens of blinded study drugs, as well as other concomitant medications were maintained as stable. The double-blind period continued through End of Study-Week 20.

Subjects were required to be ≥40 years of age with a diagnosis of levodopa-responsive idiopathic PD and recognizable/identifiable OFF and ON states. Subjects were also required to have a cumulative average of OFF time ≥2.5 hours/day while awake, based on screening diary entries. The total minimum daily baseline dose of levodopa was 400 mg with a maximum of 2400 mg. Subjects had to be on a stable medication regimen with a stable dose of levodopa.

The doses of IR CD/LD and IPX203 in Study B16-02 were individualized. Subjects were titrated to their optimized IR CD/LD and IPX203 doses during the dose adjustment and dose optimization periods, respectively, and were continued on the optimized dose through the double-blind period.

The primary efficacy endpoint was the change from baseline to week 13 (visit 7) of the double-blind treatment period in the mean daily "good" ON time (hours), averaged over the PD diary days, analyzed using mixed model for repeated measures (MMRM) analysis of the modified intent-to-treat analysis set (mITT). The key secondary endpoints were (in hierarchical order):

change from baseline to visit 7 in hours of average daily OFF time, based on patient diary data; proportion of subjects with either “much improved” or “very much improved” in Patient Global Impression of Change (PGI-C) scores at the end of double-blind treatment period; change from baseline to end of double-blind treatment period (visit 7 or ET) in the Movement Disorders Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part III; and change from baseline in the sum of MDS-UPDRS Part II + III at the end of double-blind treatment period (visit 7 or ET). There were several other efficacy endpoints that did not measure change in function or clinical benefit to the subject and were therefore not included in the statistical hierarchy.

Results

Study B16-02 enrolled 630 subjects into the IR CD/LD dose adjustment period, transitioned 589 subjects into the IPX203 dose optimization period, and randomized 506 subjects, 495 of whom entered the double-blind period and had at least one post-treatment efficacy assessment (249 in the IPX203 group, and 246 in the IR CD/LD group).

The demographic characteristics of the mITT population in Study B16-02 were reasonably balanced between the treatment groups, other than a mildly greater proportion of male subjects in the IR CD/LD group (71%) as compared to that in the IPX203 group (61%). There was an overall predominance of male (66%) and White subjects (96%). The imbalances in sex and race are consistent with the demographic features of PD which preferentially affects white males. About half the subjects (50.1%) in the mITT population were recruited from sites located in the U.S. The baseline PD characteristics in the Study B16-02 population were generally balanced between the treatment groups.

A slightly greater proportion of subjects in the IPX203 group discontinued early during the double-blind period of Study B16-02. Thirty-four subjects (13.3%) in the IPX203 group and 23 subjects (9.2%) in the IR CD/LD group discontinued the double-blind period (DBP) prematurely. In the IPX203 treatment group, the most common reason for early discontinuation was adverse event (n=14, 5.5%), while in the IR CD/LD group the most common reason for early discontinuation was “withdrawal by subject” (n=11, 4.4%). Three subjects (1.2%) in the IR CD/LD group exited early due to an adverse event. Five subjects treated with IPX203 withdrew from the trial early because of lack of efficacy compared with 8 in the IR CD/LD group. Of note, 41 subjects (6.5%) discontinued participation during the IR CD/LD dose adjustment period, and 83 (14.1%) subjects discontinued early during the IPX203 dose conversion period, 35 (5.9%) due to adverse events.

As seen in Table 4 below, the LS mean (SE) change in “good” ON time from baseline to week 13 of the double-blind period was -0.5012 (0.1834) hours for the IPX203 group and -1.0305 (0.1828) hours for the IR CD/LD group, indicating a smaller decrease in “good” ON time in the IPX203 group of -0.5293 (0.0859, 0.9727) that was statistically significant (p = 0.0194). The clinical meaningfulness of ~30 minutes less of a reduction in "good” ON time is modest.

Table 4: Primary Efficacy Endpoint Results – Change in "Good" ON Time During the Double-Blind Period (mITT Population)

	Randomized Treatment Group	
Statistics (hour)	**IPX203 (N=249)**	**IR CD-LD (N=246)**
Baseline visit (Week 7)		
N	249	246
Mean (SD)	11.671 (2.943)	11.724 (2.759)
Median (Q1, Q3)	12.0 (10.17, 13.50)	11.67 (9.83, 13.67)
Min., Max.	0.50, 18.83	1.83, 18.0
Visit 7 (Week 20)*		
N	235	241
Mean (SD)	11.349 (3.065)	10.773 (2.775)
Median (Q1, Q3)	11.50 (9.33, 13.50)	10.83 (9.0, 12.67)
Min., Max.	0, 17.67	1.50, 17.0
Change at Visit 7 (Week 13) from baseline		
N	235	241
Mean (SD)	-0.385 (2.706)	-0.968 (3.081)
Median (Q1, Q3)	-0.33 (-1.83, 1.17)	-1.0 (-2.67, 0.83)
Min., Max.	-9.67, 8.50	-9.33, 8.0
LS Mean change (SE) at Week 13 from baseline*	-0.5012 (0.1834)	-1.0305 (0.1828)
LS Mean difference (95% CI) (IPX203 vs. IR CD-LD)	0.5293 (0.0859, 0.9727)	
p-value	0.0194	

*Visit 7 took place at week 13 of the double-blind period, overall study week 20.
Source: modified from Table 5, Statistical Review. Table 5 in the statistical review notes that the LS Mean change (SE) was calculated at Week 12 from baseline; however, the primary efficacy endpoint was analyzed at 13 weeks from baseline. This has been confirmed with Dr. Park.

The sensitivity analyses prespecified by the Applicant in the statistical analysis plan (SAP) supported the primary efficacy analysis and were confirmed by the FDA statistical reviewer.

The results for the first key secondary endpoint, the change from baseline to Week 13 of the double-blind period in hours of average OFF time was also statistically significant. The LS mean change (SE) in OFF time from baseline to Week 13 was 0.3757 (0.1717) hours for the IPX203 group and 0.8568 (0.1713) hours for the IR CD/LD group, indicating a smaller increase in daily OFF time for the IPX203 group by 0.4812 hours/day (95% CIs = [-0.9021, -0.0603]), compared to the IR CD/LD group (p = 0.0252).

The results for the second key secondary endpoint, the proportion of subjects with either "much improved" or "very much improved" in Patient Global Impression of Change (PGI-C) scores at the end of double-blind treatment period (Visit 7/ET), was also statistically significantly in favor of the IPX203 group, supporting the primary efficacy endpoint analysis.

Seventy-six subjects (30%) in the IPX203 group had much or very much improved scores, as compared to 47 subjects (19%) in the IR CD/LD group (p = 0.0015).

The third key secondary endpoint was the difference in the change from baseline to week 12 on the MDS-UPDRS Part III Scale for subjects in the IPX203 group compared to the IR CD/LD group. This endpoint did not achieve statistical significance as the LS mean change in the IPX203 group was 0.7648 (0.7087) as compared to IR CD/LD 0.8110 [0.7153]), p-value = 0.9587.

Study B16-02 was designed as a flexible dose study, so dose-response was not explored.

Efficacy Conclusions

The Applicant has provided positive results from a single, randomized, double-blind, active-controlled clinical trial of IPX203 (carbidopa/levodopa extended-release tablet) for the treatment of advanced PD. The design of the study and the primary and key secondary efficacy endpoints are consistent with other studies used to support drug approval for other treatment of advanced PD. The statistically significant and clinically meaningful results of this positive adequate and well-controlled trial are supported by the effectiveness of immediate-release carbidopa/levodopa (IR CD/LD) in a similar population, as the Applicant was able to bridge to IR CD/LD for the levodopa component of the drug. In addition, these results are supported by the well-understood mechanism of action of CD/LD. The results of the single positive adequate and well-controlled trial of IPX203, in conjunction with confirmatory evidence from the well-understood mechanism of action of CD/LD and the effectiveness of IR CD/LD in a similar population, are adequate to establish substantial evidence of effectiveness of IPX203 in the treatment of advanced PD.

Additionally, the Applicant has proposed labeling for a broader indication than that which was studied, including post-encephalitic parkinsonism and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. Although the efficacy study was completed in patients with advanced PD with motor fluctuations, it may be possible to use the bridge to IR CD/LD for the levodopa component of the drug to support the indication used in both of the listed drugs, Sinemet and Rytary. This is a reasonable approach, given that the efficacy is expected to come from levodopa. However, because of the safety concerns resulting in the Complete Response, this determination will be a matter of review upon resubmission.

7. Safety

Dr. Haberfeld conducted the safety review of this application.

The primary safety analysis was based on review of Study B16-02, a 20-week, multicenter, randomized, double-blind, active-controlled trial in 506 subjects with advanced PD.

Additional uncontrolled safety data were analyzed on the uncontrolled safety database, derived from Study B16-03, an open-label safety study for eligible subjects with advanced PD who had

been enrolled in Study B16-02. The patient population, drug treatment, and measures of safety in Study B16-03 are identical to Study B16-02. Subjects in Study B16-03 were treated with IPX203 for up to 9 months.

Dr. Haberfeld's review indicates that 731 unique subjects were exposed to at least one dose of IPX203. Of these, there were 94 healthy volunteers in Phase 1 studies, 48 subjects with PD in Phase 2 studies, and 589 subjects with PD in Study B16-02, 419 of whom enrolled in the open label safety study.

Exposure to IPX203 during the Phase 3 Studies

In the initial NDA submission, the Applicant used the average maximum daily dose to calculate subject exposure. Based on these calculations, it initially appeared that 179 subjects were exposed to any dose of IPX203 for ≥ 12 months, 43 of whom had 12-month exposure near the maximal dose of IPX203 proposed in the labeling (≥ (b) (4)). No subjects had ≥12-month exposure at or greater than the proposed maximal dose based on average maximum daily dose. Based on these exposure data, it was determined that there was potentially sufficient exposure to support safety in the absence of an adequate bridge to the reference drugs, and the NDA was considered reviewable at the time of filing.

However, modal dose exposure is the preferred method of characterizing exposure in flexible dose trials because it is calculated from the daily dose most frequently reported taken by each subject and best represents each subject's experience. As Studies B16-02 and B16-03 were both flexible dose trials, an IR was sent to the Applicant requesting revised exposure datasets that included modal doses. When exposure of IPX203 was calculated using modal daily dose, a total of 299 and 67 subjects had 6- and 12-month exposures, respectively. When exposure duration was assessed by dose category, only 17 subjects had exposures of ≥2400 mg of levodopa (b) (4) for at least 6 months, and no subjects had ≥12-month exposure at the proposed maximal dose (see Table 5).

Table 5: Long-Term Exposure to IPX203 (Pooled Safety Population)

Exposure Duration	Dose Category (mg/day of levodopa)				
	<2000	**≥2000**	**≥2400**	**≥2600**	**≥3000**
≥ 180 Days	228	71	17	8	2
≥ 360 Days	53	14	0	0	0

Source: Clinical review

As Dr. Haberfeld notes in her review, there is insufficient long-term exposure to IPX203 at the full range of doses proposed in the labeling. Considering that the Applicant was not able to bridge from IPX203 to either IR CD/LD or CD/LD-ER, the chronic exposure data is inadequate to support the safety of IPX203.

The mITT and safety analysis sets are very similar, and the demographic and disease-related characteristics are almost identical for the safety population as for the efficacy population. In

addition, the subjects enrolled in the open-label safety study were similar in demographic and disease related features to the subjects in the controlled period of Study B16-02.

Deaths

There were 6 deaths reported in the Phase 3 studies of IPX203 by the cutoff date for the 120-Day Safety Update. One subject died during the active-controlled Study B16-02, but the death occurred during the screening period. Five deaths occurred in subjects enrolled in Study B16-03. The five deaths were 1) subarachnoid hemorrhage; 2) drowning; 3) lung cancer pulmonary embolism; 4) intestinal volvulus; and 5) sepsis, psychosis, and abdominal distension. None of the deaths had a clear relationship to the use of IPX203. One death (drowning) was adjudicated by the Applicant as related to the study drug; however, the actual causal relationship is not certain.

Adverse Events

Adverse events leading to discontinuation occurred in 0.6% of subjects during the IR CD/LD dose adjustment period and 5.9% of subjects during the IPX203 dose conversion period. During the double-blind period of Study B16-02, 5.5% and 1.2% of subjects in the IPX203 and IR CD/LD groups, respectively, discontinued early due to adverse events. This greater proportion of discontinuations during the IPX203 dose conversion period and in the IPX203-treated group during the double-blind period, as compared to those during the IR CD/LD dose adjustment period and in the IR CD/LD-treated group suggests that IPX203 may be less-well-tolerated than IR CD/LD.

As seen in Table 6 below, 31 subjects (4.9%) experienced 45 treatment emergent serious adverse events (SAEs) during Study B16-02, 7 (1.1%) in subjects during the IR CD/LD dose adjustment period, 12 (2.0%) during the IPX203 conversion period, and 12 (2.4%) during the double-blind period (8 [3.1%] in subjects receiving IPX203 and 4 [1.6%] in subjects in the IR CD/LD group). No treatment emergent SAE occurred in more than one subject except for transient ischemic attack and urinary tract infection, each of which occurred in two subjects.

Table 6: Study IPX203 B16-02 Treatment Emergent Serious Adverse Events

Dictionary-Derived Term	Dose Adjustment	Conversion	Blinded Treatment	
	IR CD/LD (N=630)	IPX203 (N=589)	IPX203 (N=256)	IR CD-LD (N=250)
Any SAE	**7 (1.1)**	**12 (2.0)**	**8 (3.1)**	**4 (1.6)**
Transient ischemic attack	0	2 (0.3)	0	0
Cognitive disorder	1 (0.2)	0	0	0
Dyskinesia	1 (0.2)	0	0	0
Epilepsy	0	0	1 (0.4)	0
Neuralgia	1 (0.2)	0	0	0
On and off phenomenon	1 (0.2)	0	0	0
Syncope	0	0	1 (0.4)	0
Vertebral artery aneurysm	0	0	1 (0.4)	0
Urinary tract infection	0	1 (0.2)	0	1 (0.4)
Cystitis	0	1 (0.2)	0	0

Dictionary-Derived Term	Dose Adjustment	Conversion	Blinded Treatment	
	IR CD/LD (N=630)	IPX203 (N=589)	IPX203 (N=256)	IR CD-LD (N=250)
Epididymitis	1 (0.2)	0	0	0
Influenza	0	1 (0.2)	0	0
Pneumonia	0	1 (0.2)	0	0
Pyelonephritis	0	0	1 (0.4)	0
Sepsis	0	1 (0.2)	0	0
Contusion	0	1 (0.2)	0	0
Hip fracture	0	1 (0.2)	0	0
Radiation neuropathy	1 (0.2)	0	0	0
Skin laceration	0	1 (0.2)	0	0
Subdural hematoma	0	1 (0.2)	0	0
Acute kidney injury	1 (0.2)	0	0	0
Nephrolithiasis	0	1 (0.2)	0	0
Urinary retention	0	1 (0.2)	0	0
Urinary tract obstruction	1 (0.2)	0	0	0
Atrioventricular block complete	0	0	0	1 (0.4)
Bradycardia	0	0	1 (0.4)	0
Cardiac failure	0	0	0	1 (0.4)
Asthenia	0	0	1 (0.4)	0
Chest pain	0	1 (0.2)	0	0
Fatigue	0	0	1 (0.4)	0
Duodenitis	1 (0.2)	0	0	0
Inguinal hernia	1 (0.2)	0	0	0
Hypokalemia	0	1 (0.2)	0	0
Hyponatremia	1 (0.2)	0	0	0
Back pain	0	0	0	1 (0.4)
Osteoarthritis	1 (0.2)	0	0	0
Anemia	0	1 (0.2)	0	0
Ejection fraction decreased	0	0	1 (0.4)	0
Bladder transitional cell carcinoma	0	1 (0.2)	0	0
Hallucinations, mixed	0	0	1 (0.4)	0
Benign prostatic hyperplasia	0	0	0	1 (0.4)
Chronic obstructive pulmonary disease	0	1 (0.2)	0	0
Inguinal hernia repair	0	1 (0.2)	0	0

In Study B16-03, 73 serious TEAEs occurred in 43 patients, or 10.3% of the enrolled population in the open-label study. Nervous system, infectious, and psychiatric serious TEAEs occurred most frequently (3.1%, 2.1%, and 1.9%, respectively) followed by injuries (1.7%). Seizure, confusional state, and COVID-19 each occurred in 3 subjects in the uncontrolled safety population. All other serious TEAEs occurred in 1 or 2 subjects each.

Table 7 summarizes the most frequently reported treatment-emergent adverse events (TEAEs) that occurred in Study B16-02. Nausea (4.3%) and anxiety (2.7%) were the most frequently reported TEAEs in the IPX203 group during the double-blind period. During the IPX203 conversion period, when subjects in Study B16-02 were first exposed to IPX203, the most frequently reported TEAEs were dyskinesia (6.8%), nausea (4.9%), and dry mouth (4.2%). During

the double-blind period, only falls occurred more frequently in subjects in the IR CD/LD group (3.6%) than the IPX203 group (2%).

Table 7: Study B16-02 Treatment Emergent Adverse Events ≥ 2% in Total IPX203

Primary System Organ Class	Preferred Term	Dose Adjustment IR CD-LD N=630 n (%)	Dose Conversion IPX203 N=589 n (%)	Double Blind		Total	
				IPX203 N=256 n (%)	IR CD-LD N=250 n (%)	IPX203 N=589 n (%)	IR CD-LD N=630 n (%)
Nervous system disorders	Dyskinesia	11 (1.7)	40 (6.8)	5 (2.0)	1 (0.4)	45 (7.6)	12 (1.9)
	Dizziness	3 (0.5)	17 (2.9)	6 (2.3)	2 (0.8)	23 (3.9)	5 (0.8)
	Headache	8 (1.3)	9 (1.5)	3 (1.2)	0 (0.0)	12 (2.0)	8 (1.3)
Gastrointestinal disorders	Nausea	7 (1.1)	29 (4.9)	11(4.3)	2 (0.8)	40 (6.8)	9 (1.4)
	Dry mouth	2 (0.3)	25 (4.2)	3 (1.2)	2 (0.8)	28 (4.8)	4 (0.6)
	Constipation	7 (1.1)	12 (2.0)	4 (1.6)	1 (0.4)	16 (2.7)	8 (1.3)
	Vomiting	3 (0.5)	13 (2.2)	3 (1.2)	0 (0.0)	16 (2.7)	3 (0.5)
Psychiatric disorders	Insomnia	6 (1.0)	13 (2.2)	2 (0.8)	1 (0.4)	15 (2.5)	7 (1.1)
	Anxiety	1 (0.2)	9 (1.5)	7 (2.7)	0 (0.0)	16 (2.7)	1 (0.2)
Injury, poisoning and procedural complications	Fall	6 (1.0)	13 (2.2)	5 (2.0)	9 (3.6)	18 (3.1)	15 (2.4)

(Source: Clinical review)

The most frequently reported AEs in the open label safety study by preferred term were dyskinesia, urinary tract infection, and fall (each in 5%), back pain (3.6%), constipation (2.6%), and Covid-19 (2.4%). The rest of the TEAEs each occurred in < 2% of subjects in Study B16-03.

Adverse Events of Special Interest

Dyskinesias are hyperkinetic movements that are related to peak-dose of most drugs used to treat the motor symptoms of PD and, as such, were an adverse event of special interest. Dyskinesia was more frequently reported in the IPX203 group (2%) compared to the IR CD/LD group (0.4%) and was the most frequently-reported adverse event during the IPX203 dose conversion period (6.8%).

Hallucinations and illusions are features of advanced PD, and they may be precipitated or worsened by dopamine replacement therapy. During the blinded period, hallucinations/ illusions were reported more frequently in the IPX203-treated subjects (2.7%) than in the IR CD/LD-treated subjects (0.2%), although the overall frequency was fairly low.

Laboratory and Vital Signs Findings

There were no clinically meaningful changes from baseline in measures of central tendency for hematology, chemistry, or special laboratory parameters observed in either treatment group in Study B16-02. The analysis of hematology and chemistry parameters for the open label studies found no meaningful change from baseline in measures of central tendency. No Hy's law cases were identified in Studies B16-02 or B16-03.

There were no clinically meaningful differences in pulse, systolic or diastolic blood pressure (supine) between subjects treated with IPX203 or IR CD/LD during Studies B16-02 or B16-03.

QT Findings

The measures of central tendency for electrocardiograms (ECG) performed in Study B16-02 did not find meaningful differences in mean heart rate QTcF or the change from baseline in QTcF among subjects treated with IPX203 compared with subjects treated with IR CD/LD. In the open label study, there were no clinically meaningful changes in measures of central tendency for ECG parameters by study visit.

No QT studies were performed in the development program for IPX203, and the Applicant proposed to borrow safety information, including QT information, from Rytary and Sinemet. However, because the Applicant did not bridge successfully between IPX203 and Sinemet or Rytary, they may not rely on either of these products for safety, including an assessment of effect on QT. The Interdisciplinary Review Team for Cardiac Safety Studies (IRT-QT) was consulted and determined that a thorough QT study is needed "to assess the QT effects of CREXONT since the new formulation results in significantly higher carbidopa exposure (i.e., C_{max} and AUC)."

Safety Conclusions:

Safety data were derived primarily from a single active-controlled trial with one open-label safety study providing supportive data. To support the safety of a drug, the Agency generally requires 100 subjects be exposed for a minimum of at least one year with at least half (or a substantial proportion of) the subjects taking the maximum dose proposed in the labeling. Although the exposure of subjects in the pooled dataset from Studies B16-02 and B16-03 was initially considered adequate for review, it was eventually determined that there were insufficient subjects with at least 12-month exposure to IPX203. Specifically, the Applicant reported 179 subjects with at least 12-month exposure to IPX203 at any dose but no subjects with 12-month exposure at the maximal dose proposed in the labeling (b) (4) based on the mean total daily dose. When exposure was calculated using the modal total daily dose, only 67 subjects had ≥12-month exposure to IPX203 at any dose, and again no subjects had ≥12-month exposure to the proposed maximal dose. Therefore, there is inadequate exposure to allow for a determination of safety of chronic administration of IPX203.

The most frequently observed adverse events during the double-blind period that occurred with a greater incidence in IPX203-treated subjects than in subjects taking IR CD/LD were nausea (4.3%), anxiety (2.7%), dizziness (2.3%), and dyskinesia (2%). These events were generally mild to moderate in severity. Of note, during the IPX203 dose conversion period, when all subjects were initially exposed IPX203, the most frequently-reported adverse events were dyskinesia (6.8%), nausea (4.9%), and dry mouth (4.2%).

During the double-blind period, serious adverse events (SAEs) occurred slightly more frequently in IPX203-treated subjects (3.1%) than in IR CD/LD-treated subjects (1.6%). The specific SAEs

were varied, occurring in only 1 subject each. Discontinuations due to AEs were more frequently-reported in IPX203-treated subjects (5.5%) than in IR CD/LD-treated subjects (1.2%), and these events were varied in nature. SAEs occurred in a greater proportion of subjects in the open-label safety study (10.3%), but the only SAEs that occurred each in 3 subjects were seizure, confusional state, and COVID-19. The rest of the SAEs occurred in only 1 or 2 subjects, making it difficult to determine any pattern.

There were 5 deaths in in subjects exposed to IPX203; however, because the patients had multiple comorbidities, none of the deaths can reasonably be attributed to IPX203.

Because the Applicant was not able to establish a PK bridge for carbidopa to either of the referenced drugs, they are not able to rely on the findings of safety for Sinemet or Rytary to support the safety of IPX203. Although the safety profile of IPX203 with respect to adverse events, laboratory findings, and vital signs from the clinical studies appears generally acceptable, the overall safety of IPX203 for chronic use cannot be determined, because there is insufficient long-term exposure of IPX203 in subjects during the development program, both overall (67 subjects with ≥12-month exposure at a single dose) and at the maximal proposed dose in the labeling (0 subjects with ≥12-month exposure).

8. Advisory Committee Meeting

An Advisory Committee meeting was not required.

9. Pediatrics

The submission did not include any pediatric data. Because Parkinson's disease generally does not occur in the pediatric population, a full waiver was granted for pediatric studies under Pediatric Research Equity Act (PREA).

10. Labeling

Deficiencies in the submission preclude labeling discussions.

11. Recommendations/Risk-Benefit Assessment

The Applicant demonstrated that IPX203 was efficacious for treatment of advanced Parkinson's disease. However, because the Applicant was not able to establish a PK bridge for carbidopa to either of the referenced drugs, they are not able to rely on the findings of safety for Sinemet or Rytary to support the safety of IPX203 and must rely on the clinical safety data from the development program to support approval. There is insufficient chronic exposure of subjects to IPX203 to support safe, long-term use in patients. In addition, as no QT studies were performed in the development program for IPX203, and the Applicant is not able to borrow safety

information, including QT information, from Rytary or Sinemet, a thorough QT study is necessary to assess the QT effects of the higher carbidopa exposure in IPX203.

The safety of IPX203 cannot be established based on the comparison to the listed drugs or the results of the Phase 3 clinical studies, and the lack of the safety data cannot be mitigated by risk management solutions; therefore, a Complete Response will be issued.

In the absence of an adequate scientific bridge for carbidopa exposure to Sinemet or Rytary, the Applicant will need to provide adequate long-term safety data, i.e., from 100 patients with continuous exposure to IPX203 for at least 12 months, with a substantial proportion of patients using the highest dose intended for labeling, based on modal dose. In addition, the Applicant will need to conduct a thorough QT study to assess the potential effects of IPX203 on QTc. Alternatively, the Applicant may reformulate the product to reduce the carbidopa exposure to levels that are similar to a listed drug and supported by a bioavailability study. Further clinical studies may also be needed.

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