The Expert Institute for Parkinson's Disease

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CREXONT® (Carbidopa and Levodopa) Extended-Release Capsules in the Evolving PD Landscape

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Since the recognition that Parkinson's disease is fundamentally linked to dopamine deficiency, therapeutic strategies to restore dopaminergic tone have continued to advance over the past several decades. The development of oral carbidopa/levodopa transformed the management of Parkinson's disease, and it remains the cornerstone of treatment. However, treatment with immediate-release carbidopa/levodopa often leads to motor fluctuations that require an increase in the frequency of dosing, prompting the development of more advanced formulations. Designed to optimize oral levodopa absorption, CREXONT® (carbidopa and levodopa) extended-release capsules represent an important advancement in this evolution. Movement disorder specialists and Parkinson's disease experts Drs Sanaz Attaripour Isfahani, Alberto Espay, and Michael Soileau detail the evolution of the Parkinson's disease treatment landscape and how CREXONT's formulation may improve the care of patients with Parkinson's.

Levodopa (LD) was first synthesized in the early 1900s, but its use for the treatment of Parkinson's disease (PD) was not established until FDA approval in 1970.[1,2] Since then, LD has remained the foundation of PD treatment.[1] The American Academy of Neurology guidelines recommend the use of LD for patients with early PD who seek treatment for motor symptoms.[3] Guidelines also caution against waiting to initiate levodopa, as delaying treatment has not been shown to delay dyskinesia and thus does not support the idea of a "levodopa sparing" approach.[3–5]

IMPORTANT SAFETY INFORMATION

Indications and Usage

CREXONT® (carbidopa and levodopa) extended-release capsules for oral use is indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication in adults.

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Since the approval of LD for use in PD, various formulations have been developed to counteract challenges associated with the drug. In 1975, carbidopa (CD) was added to LD to increase the amount of LD reaching the brain.[6] The first formulation of CD/LD was an immediate-release (IR) formulation.[6] While treatment with LD remains effective across the disease course, the therapeutic window narrows and benefit per dose with IR CD/LD becomes shorter and more variable.[7-9] Eventually, many patients on IR CD/LD experience variable symptom control and wearing "Off" phenomena,[10] even after increasing dose strength and frequency. Frequent dosing schedules can significantly impair patient quality of life, hamper adherence, and increase the burden of care, all while offering incomplete symptom control.[11] To address these shortcomings, extended-release (ER) formulations were developed to deliver more stable plasma levels and efficacy with less frequent dosing.[7]

> "When patients take 5-6 doses of IR CD/LD a day, their lives revolve around medication schedules. Fewer doses per day would give my patients more freedom."
>
> – Dr Sanaz Attaripour Isfahani
>
> Movement disorder specialist at the University of California, Irvine

Oral Adjunctive Therapies and CD/LD Pumps

As it becomes more difficult to treat symptoms with IR CD/LD just by increasing the dose or frequency, additional oral strategies are typically employed, such as add-on or adjunctive therapies that complement oral CD/LD therapy, and longer-acting formulations of oral LD (discussed in more detail in the following section).[7,12] Adjunctive agents include inhibitors of monoamine oxidase-B (MAO-B), catechol-O-methyltransferase (COMT), adenosine A2A receptor antagonists, as well as dopamine agonists and amantadine.[12,13] These options can offer further symptomatic control and reduce motor fluctuations, though patients should first be optimized on foundational oral CD/LD therapy before transitioning to other interventions.[3]

IMPORTANT SAFETY INFORMATION (cont'd)
Dosage and Administration

- Evaluate vitamin B6 levels before and during treatment with carbidopa/levodopa therapies
- Levodopa-naïve patients: Starting dose is 35 mg carbidopa/140 mg levodopa taken orally twice daily for the first three days; thereafter, dosage may be increased gradually as needed
- For patients converting to CREXONT from immediate-release carbidopa/levodopa, dosages are not substitutable on a 1:1 basis. See full prescribing information Section 2.2 for instructions
- For patients converting from Rytary® (carbidopa and levodopa) extended-release capsules, initiate CREXONT on an approximately 1:1 mg basis using the levodopa component for conversion

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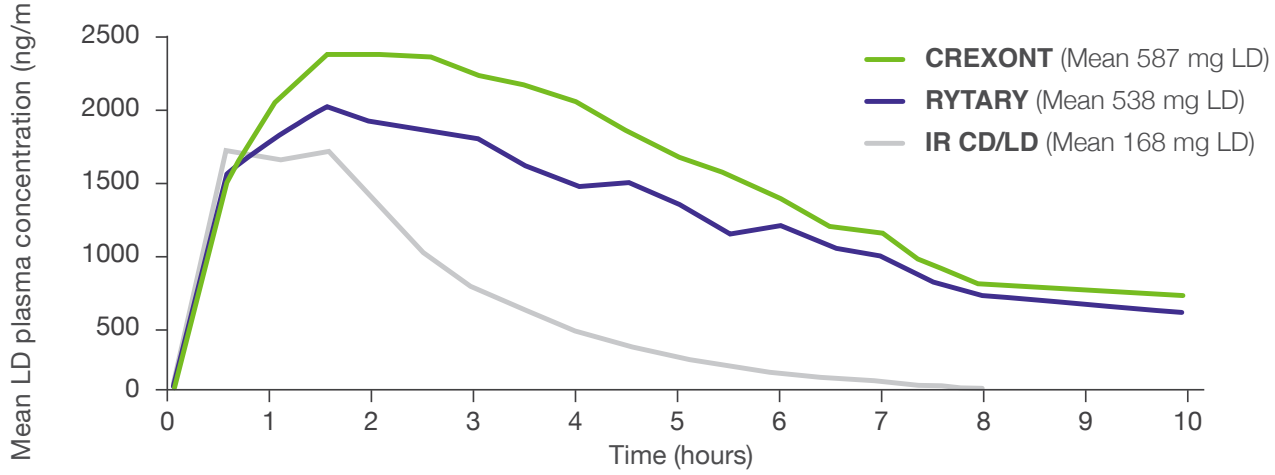
For patients with PD whose symptoms are not being adequately managed with oral CD/LD and adjunctive agents, device-assisted therapies may be considered.[12] These include deep brain stimulation as well as infusion devices that continuously deliver medication subcutaneously or directly into the small intestine via a percutaneous endoscopic gastro-jejunostomy (PEG-J) tube. These methods are typically used later in the disease course once oral therapy can no longer be optimized to keep symptoms manageable.[11-14]

Next-Generation ER CD/LD

Oral ER CD/LD formulations, designed to maximize time when symptoms are controlled and reduce daily dose frequency, offer an opportunity to optimize oral CD/LD therapy and reduce the need for adjunctive and invasive therapies.[7]

RYTARY®, the first-generation ER oral CD/LD, combined an IR component for rapid symptom relief and an ER component to sustain LD levels longer than IR CD/LD.[15] CREXONT, a next-generation oral ER CD/LD, contains IR granules and ER pellets, with a unique design targeted to the proximal small intestine, where LD is best absorbed, by utilizing a mucoadhesive polymer technology.[1,7]

Mean LD plasma concentration-time profiles following a single dose of CREXONT, RYTARY, and IR CD/LD in patients with advanced PD[16,17*†‡]



*Assessment performed on patients in a fasted and "Off" state.[16]

†No plasma concentration values were available after the 8-hour time point in the IR CD/LD group because all patients in that group had been rescued by then.[17]

‡Summary statistics for LD PK parameters are presented by treatment, across all doses of CREXONT, IR CD/LD, and RYTARY, respectively: C_{max} (mean ± SD): 3161 ± 1665 ng/mL, 2492 ± 1459 ng/mL, 2839 ± 1909 ng/mL; t_{max} (median [min–max]): 2.0 h (0.5–7.0); 1.0 h (0.5–2.5); 2.0 h (0.5–6.5); $t_{1/2}$ (mean ± SD): 2.3 ± 0.9 h, 1.4 ± 0.3 h, 2.0 ± 0.7 h; AUC_t (mean ± SD): 13,291 ± 7264 ng h/mL, 4879 ± 2631 ng h/mL, 10,467 ± 6771 ng h/mL; $AUC_{0-\infty}$ (mean ± SD): 16,734 ± 9759 ng h/mL, 5456 ± 2896 ng h/mL, 13,840 ± 8899 ng h/mL.[17]

$AUC_{0-\infty}$=area under the curve extrapolated to Time infinity; AUC_t=area under the curve until the last observation Time t; C_{max}=maximum observed plasma concentration; LS=least squares; PK=pharmacokinetic; SD=standard deviation; $t_{½}$=half-life; t_{max}=time to maximum concentration.

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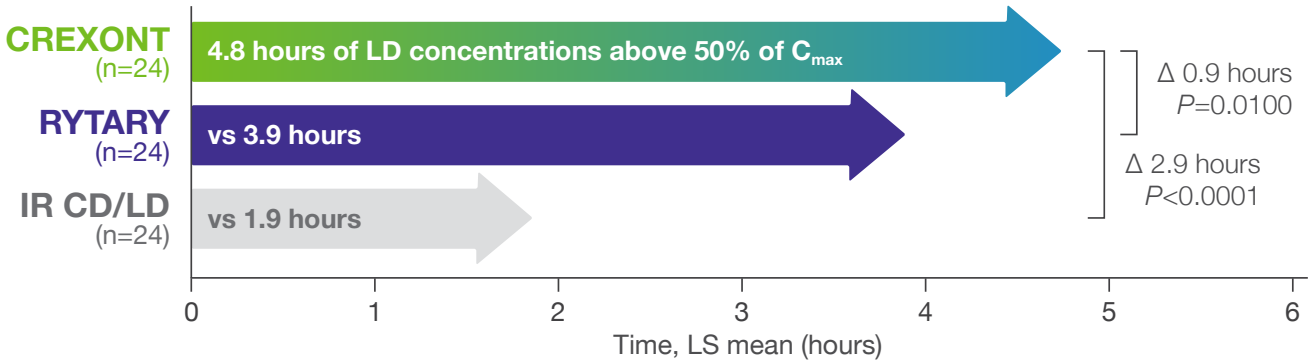
Post hoc analysis of a prespecified secondary PK parameter: duration of LD concentration >50% of C_{max}[16,17]



> "CREXONT represents the next step in ER technology. It provides the longest lasting LD levels of any oral CD/LD available today compared to both IR CD/LD and RYTARY."
>
> – Dr Alberto Espay
>
> Movement disorder specialist at the University of Cincinnati

CREXONT in Parkinson's Disease[18,19]

The efficacy of CREXONT was established in the Phase 3 RISE-PD trial, a multicenter, randomized, double-blind study that compared CREXONT head-to-head with optimized IR CD/LD in patients with Parkinson's disease. In the trial, the dose of IR CD/LD was first optimized in a 3-week open-label optimization period in order to get patients to their maximum "Good On" time on IR CD/LD before conversion to CREXONT. Following this, all patients were converted to CREXONT for four weeks and the dose of CREXONT was optimized. Finally, at Week 7 (which served as the baseline), patients were randomized to continue the optimized dose of CREXONT or to return to their optimized dose of IR CD/LD for a 13-week double-blind maintenance period.

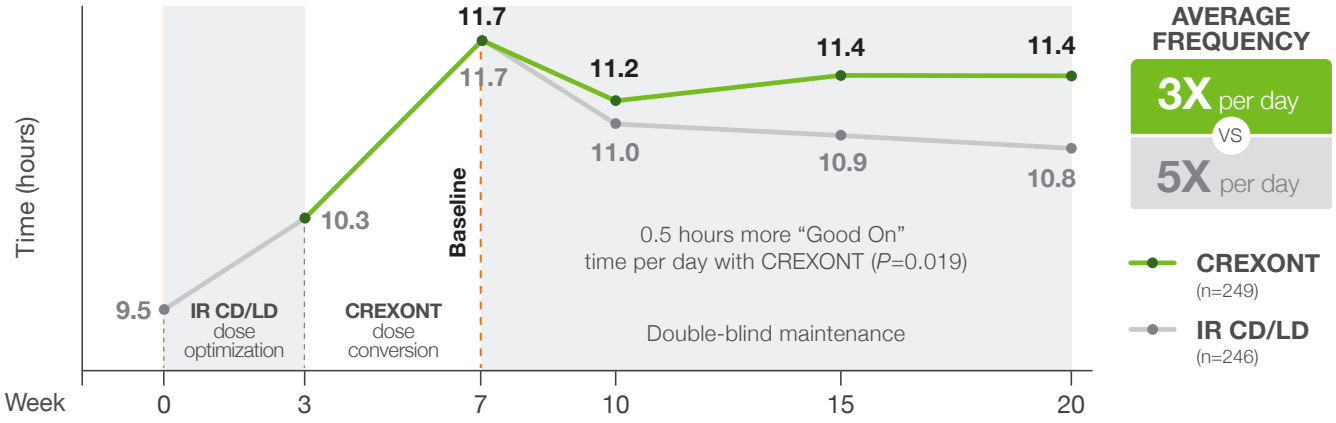
IMPORTANT SAFETY INFORMATION (cont'd)
Dosage and Administration (cont'd)

- CREXONT may be taken up to four times daily. The maximum recommended daily dosage is 525 mg carbidopa/2100 mg levodopa
- CREXONT may be taken with or without food. Capsules should not be chewed, divided or crushed
- CREXONT should not be taken with alcohol

Please see additional Important Safety Information on adjacent pages and accompanying Full Prescribing Information.

The primary endpoint was the mean change in "Good On" time per day, defined as "On" time without troublesome dyskinesia, from baseline to the end of the study or early termination. In a head-to-head study, patients achieved significantly more "Good On" time (0.5 hours per day) with CREXONT at an average dosing frequency of 3 times per day vs an average of 5 times per day with optimized IR CD/LD (P=0.019).[18,19*†]

"Good On" time per day[17–20]



The secondary endpoint of RISE-PD was the mean change in "Off" time, or periods of symptom reemergence, per day from baseline to the end of the study or early termination. Patients on CREXONT had significantly less "Off" time (0.5 hours per day; P=0.025)*†, while taking CREXONT an average of 3 times per day compared to 5 times per day with optimized IR CD/LD.[18,19]

*0.5 hours is LS mean difference.[18]
†P value based on change from end of Week 7 (baseline) to Week 20 (end of study or early termination), as assessed by the patient's PD diary.[18]

IMPORTANT SAFETY INFORMATION (cont'd)

Contraindications

Nonselective MAO inhibitors.

Warnings and Precautions

- CREXONT may cause falling asleep during activities of daily living, somnolence or dizziness. Patients should avoid activities that require alertness such as driving and operating machinery until they know how CREXONT affects them
- It is important to avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal symptoms such as high fever or confusion. Patients who are discontinuing CREXONT should taper off with healthcare provider guidance

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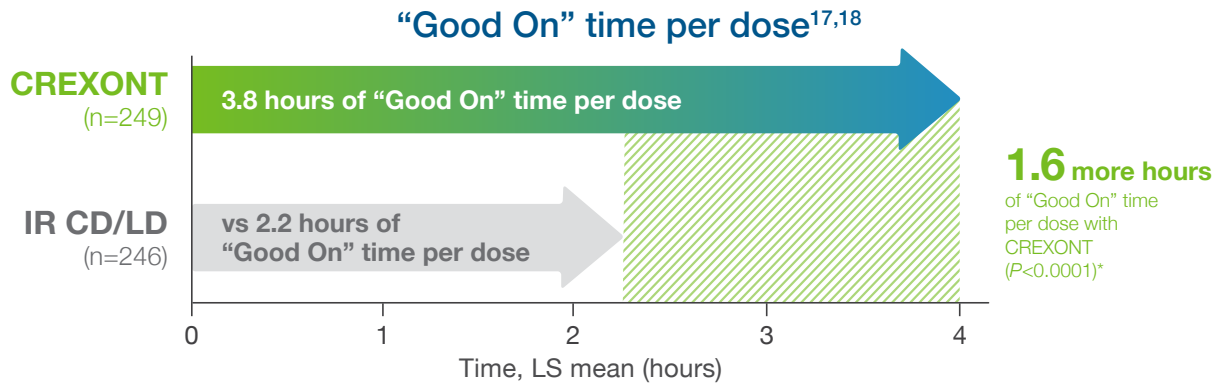
Because of the difference in average daily dose frequency, 3 times per day for CREXONT vs 5 times per day for IR CD/LD, a post-hoc statistical analysis of the primary endpoint was conducted to determine the per-dose "Good On" time. CREXONT provided 3.8 hours of "Good On" time per dose, as opposed to 2.2 hours per optimized IR CD/LD dose, an increase of 1.6 hours (P<0.0001), which represents a 70% increase in "Good On" time per dose.[18]



*P value based on change from end of Week 7 (baseline) to Week 20 (end of study or early termination), as assessed by the patient's PD diary.[18,19]

Safety data from the RISE-PD trial indicate that CREXONT was generally well-tolerated in a head-to-head study when compared to IR CD/LD. Adverse reactions occurring at a higher rate in the CREXONT group than the IR CD/LD group during the double-blind maintenance period (CREXONT vs IR CD/LD) were nausea (4% vs 1%), anxiety (3% vs 0%), dizziness (2% vs 1%), dyskinesia (2% vs 0.4%), constipation (2% vs 0.4%), headache (1% vs 0%), vomiting (1% vs 0%), and insomnia (1% vs 0.4%).[18,19]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

- Consider dose reductions or stopping CREXONT in patients with hallucinations or impulse control disorders (e.g., gambling, sexual urges, or uncontrolled spending)
- Consider dose reduction in patients with dyskinesia
- Treatment with carbidopa/levodopa, including CREXONT, may contribute to reduced vitamin B6 levels. Seizures associated with vitamin B6 deficiency have been reported. Seizures were refractory to traditional anti-seizure medications and were only resolved after vitamin B6 administration. Supplement with vitamin B6 as necessary
- Other symptoms of vitamin B6 deficiency may occur, including depression, confusion, cheilosis, glossitis, dermatitis, anemia, and/or neuropathy. Supplement with vitamin B6 as necessary
- Patients with a major psychotic disorder should not be treated with CREXONT
- Monitor patients with a history of cardiovascular disease for cardiac function
- Monitor patients with a history of peptic ulcer for upper GI hemorrhage
- Monitor patients with glaucoma for increased intraocular pressure

Adverse Reactions

The most common adverse reactions (incidence ≥ 3% and greater than immediate-release CD/LD) are nausea and anxiety.

Please see additional Important Safety Information on adjacent pages and accompanying Full Prescribing Information.

> "I use CREXONT with patients across the PD spectrum—it often spares them from having to increase the IR CD/LD dose or frequency beyond a tolerable level, or having to add other medications. It helps find the 'sweet spot' of symptom control."
>
> – Dr Michael Soileau
>
> Movement disorder specialist at Texas Movement Disorder Specialists

CREXONT is Approved for Treatment Across All Parkinson's Disease Stages

CREXONT provides clinicians with flexibility through its broad label, approved for use in adults with Parkinson's disease across all stages, from early to advanced.[19] Appropriate patients for CREXONT may include PD treatment-naïve patients, those wearing "Off" on IR CD/LD, those intolerant of adjunctive therapies (eg, due to side effects or contraindications), patients seeking to simplify therapy, and patients wishing to delay more invasive options like pumps or surgery.[18,19]

CREXONT can be used either alone or in combination with adjunctive therapies. Patients not appropriate for CREXONT include those on nonselective MAO inhibitors.[19]

For half a century, oral CD/LD has been the foundation of Parkinson's disease treatment. With its novel extended-release formula, CREXONT presents the next step in the advancement of oral CD/LD, designed to better fit the lives of those managing their disease.[1,6,7]

THIS ARTICLE WAS SPONSORED BY AMNEAL PHARMACEUTICALS LLC, AND PARTICIPANTS WERE COMPENSATED FOR THEIR TIME.

IMPORTANT SAFETY INFORMATION (cont'd)

Drug Interactions

Iron salts and dopamine D2 antagonists, including metoclopramide, may reduce the effectiveness of CREXONT.

Use in Specific Populations

Pregnancy: Based on animal data, CREXONT may cause fetal harm. There are no adequate data on the developmental risk associated with the use of CREXONT in pregnant women.

Breastfeeding: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CREXONT.

Geriatric patients: There were no differences in safety outcomes between patients less than 65 years of age, 65-75 years of age, or 75 years and older.

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Global Patient Safety at 1-877-835-5472, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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References: 1. Abbott A. Levodopa: the story so far. Nature. 2010;466(7310):S6-S7. 2. Fahn S. The history of dopamine and levodopa in the treatment of Parkinson's disease. Mov Disord. 2008;23 (Suppl. 3):S497-S508. 3. Pringsheim T, Day GS, Smith DB, et al. Dopaminergic therapy for motor symptoms in early Parkinson disease practice guideline summary. Neurology. 2021;97(20):942-957. 4. Rosinskaya AV, Vasenina EE, Khaybullin TN, Levin OS. Rate of progression of Parkinson's disease in early and late prescription of levodopa. Neurosci Behav Physiol. 2019;49(7):937-941. 5. Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain. 2014;137(Pt 10):2731-2742. 6. Hauser RA. Levodopa: past, present, and future. Eur Neurol. 2009;62(1):1-8. 7. LeWitt P, Ellenbogen A, Burdick D, et al. Improving levodopa delivery: IPX203, a novel extended-release carbidopa-levodopa formulation. Clin Park Relat Disord. 2023;8:100197. 8. Gupta HV, Lyons KE, Wachter N, Pahwa R. Long-term response to levodopa in Parkinson's disease. J Parkinsons Dis. 2019;9(3):525-529. 9. Beckers M, Bloem BR, Verbeek MM. Mechanisms of peripheral levodopa resistance in Parkinson's disease. NPJ Parkinsons Dis. 2022;8(1):56. 10. Rodríguez-Violante M, Ospina-García N, Dávila-Avila NM, Cruz-Fino D, Cruz-Landero A, Cervantes-Arriaga A. Motor and non-motor wearing-off and its impact in the quality of life of patients with Parkinson's disease. Arq Neuropsiquiatr. 2018;76(8):517-521. 11. Soileau MJ, Pagan F, Fasono A, et al. Comparative effectiveness of carbidopa-levodopa enteral suspension and deep brain stimulation on Parkinson's disease-related pill burden reduction in advanced Parkinson's disease: A retrospective real-world cohort study. Neurol Ther. 2022;11(2):851-861. 12. Fabbri M, Rosa MM, Ferreira JJ. Adjunctive therapies in Parkinson's disease: How to choose the best treatment strategy approach. Drugs Aging. 2018;35: 1041-1054. 13. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: A review. JAMA. 2020;323(6):548-560. 14. Olanow CW, Obeso JA, Stocchi F. Drug Insight: continuous dopaminergic stimulation in the treatment of Parkinson's disease. Nat Clin Pract Neurol. 2006;2(7):382-392. 15. Dhall R, Kreitzman DL. Advances in levodopa therapy for Parkinson disease: review of RYTARY (carbidopa and levodopa) clinical efficacy and safety. Neurology. 2016;86 (suppl 1):S13-S24. 16. Modi NB, Mittur A, Rubens R, Khanna S, Gupta S. Single-dose pharmacokinetics and pharmacodynamics of IPX203 in patients with advanced Parkinson disease: a comparison with immediate-release carbidopa-levodopa and with extended-release carbidopa-levodopa capsules. Clin Neuropharmacol. 2019;42(1):4-8. 17. Data on file. Amneal Pharmaceuticals LLC. 18. Hauser RA, Espay AJ, Ellenbogen AL, et al. IPX203 vs immediate-release carbidopa-levodopa for the treatment of motor fluctuations in Parkinson disease: the RISE-PD randomized clinical trial. JAMA Neurol. 2023;80(10):1062-1069. 19. CREXONT [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; 2024. 20. Hauser RA, Espay AJ, LeWitt P, et al. A phase 3 trial of IPX203 vs IR CD-LD in Parkinson's disease patients with motor fluctuations (RISE-PD). Presented at: American Academy of Neurology Annual Meeting; April 2-7, 2022; Seattle, WA, and virtual. S16.010.

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