The Expert Institute for Parkinson's Disease

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Advances in Extended-Release CD/LD Formulations

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Since the first use of immediate-release carbidopa/levodopa 50 years ago, there have been ongoing efforts to improve the consistency of levodopa's therapeutic effect. While advancements in levodopa formulation have sought to reduce motor fluctuations, absorption variability related to delayed gastric emptying in Parkinson's disease has remained a significant challenge. To advance beyond existing formulations and further optimize levodopa absorption, CREXONT® (carbidopa and levodopa) extended-release capsules present another step forward in the evolution of treatment for Parkinson's disease. Movement disorders specialists, Drs Salima Brillman, Justin Martello, and Rajesh Pahwa, detail the limitations of immediate-release, including gastrointestinal absorption challenges, and describe how CREXONT's formulation has transformed innovation into duration for patients with Parkinson's.

Carbidopa/levodopa (CD/LD) has been the gold standard therapy for Parkinson's disease for more than 50 years, marking a major advance in symptom management since its introduction.[1] The initial formulation, immediate release (IR) CD/LD, remains the primary treatment for Parkinson's disease today.[1] However, the short half-life of LD (around 1.5 hours) and its absorption limitations can cause fluctuating plasma levels, leading to variability in symptom control over time.[2]

IMPORTANT SAFETY INFORMATION

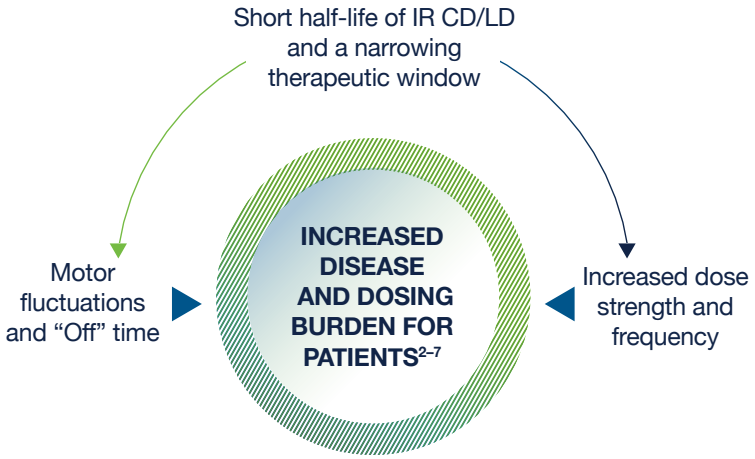
Indications and Usage

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.

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

> *"As Parkinson's disease advances, the therapeutic effect of IR CD/LD doses start to mirror levodopa's half-life—patients may require dosing every 1.5–2 hours, yet symptom relief can remain unpredictable."*
>
> **–Dr Rajesh Pahwa**
>
> *Movement disorder specialist, University of Kansas Medical Center*

The progressive nature of Parkinson's disease creates increasingly complex therapeutic challenges as the condition advances. As the therapeutic window narrows, many patients experience increased "Off" time and motor fluctuations, even after increasing dose and frequency of IR CD/LD.[2-7] Increasing dosing frequency further complicates daily medication routines and may lead to missed or delayed doses as patients try to fit treatment into their lives.[8] Effective disease management requires a careful balance to maintain LD plasma levels high enough to prevent "Off" episodes, while avoiding dyskinesia associated with LD levels that are too high.[2]



CREXONT was designed to help overcome these challenges, with an innovative formulation designed to optimize the absorption of LD.[2] After decades of reliance on IR CD/LD, patients now have an oral ER option that better meets the needs of today's Parkinson's patients, representing another significant step forward in the treatment of Parkinson's disease.

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

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

Challenges With Levodopa Absorption

Achieving and maintaining a therapeutic level of LD in the brain is limited by its short half-life and impacted by gastrointestinal (GI) factors that affect absorption: premature dissolution before reaching the site of LD absorption, and delayed gastric emptying that causes irregular absorption.[9,10] GI symptoms, experienced by 60-80% of patients with Parkinson's disease, can interfere with the absorption of LD, potentially impacting its efficacy.[10]

LD absorption only occurs in a short segment of the proximal small intestine, which creates multiple opportunities for therapeutic failure.[9] Delayed gastric emptying (gastroparesis), present in a wide range of patients (~35-100%), can slow down the transport of LD to the small intestine. This prolonged retention in the stomach allows premature metabolism of LD to dopamine by aromatic L-amino acid decarboxylase (AADC) before reaching the limited absorption site.[9] As a result, much of the ingested LD does not reach the critical site of absorption in the proximal small intestine, reducing effectiveness even when dose and frequency are increased.[2,9]

> ***"Oral levodopa must be adequately absorbed to effectively alleviate symptoms, but many of my patients endure GI issues that compromise their treatment. This is among the often-neglected aspects of caring for individuals with Parkinson's disease."***
>
> **–Dr Salima Brillman**
>
> *Movement disorder specialist, The Parkinson's Disease and Movement Disorder Center of Silicon Valley*

The LD that reaches the proximal small intestine faces a further challenge. LD is a large neutral amino acid (LNAA) and shares a transport system with other LNAAs which compete for absorption and transport by the LNAA transporters. This transport system is potentially saturable, which can reduce LD's absorption.[9]

These GI challenges create limitations in achieving a consistent level of LD in the brain.[2,9] Simply increasing the dose strength or dosing frequency of IR CD/LD as PD progresses is not a viable solution: neither approach addresses irregular LD absorption due to underlying GI factors, and higher dosage is a risk factor for dyskinesia.[2]

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

- 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
- CREXONT may be taken up to four times daily. The maximum recommended daily dosage is 525 mg carbidopa/2100 mg levodopa

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

CREXONT® (carbidopa and levodopa) EXTENDED-RELEASE CAPSULES 35mg/140mg · 52.5mg/210mg 70mg/280mg · 87.5mg/350mg

CREXONT Features a Novel ER Technology

For the first time in Parkinson's disease, a therapy aims to address the absorption challenges and short half-life of LD. CREXONT is designed to extend therapeutic duration and improve clinical outcomes.[11] Previously, controlled release (CR) and extended release (ER) formulations of CD/LD have been developed to try to address complications with IR CD/LD.[12] CR CD/LD was developed to provide sustained release, but studies have shown that it does not significantly reduce "Off" time in patients with moderate to severe motor fluctuations when compared to IR CD/LD.[13,14] The first-generation oral ER CD/LD, RYTARY®, was developed to address the prevalent challenges associated with frequent dosing requirements and persistent "Off" time experienced by patients on IR CD/LD.[14]

RYTARY represented an initial advancement as a first-generation ER CD/LD formulation, incorporating an IR component designed to initiate LD action quickly combined with an ER component that provided sustained LD release for longer than IR CD/LD.[14] This approach addressed some of the limitations of earlier formulations and established the foundation for the development of CREXONT.

> ***"CREXONT represents a significant advancement in Parkinson's treatment, combining extended release with optimized absorption at the key GI tract site. Enhanced absorption may help reduce symptom fluctuations for my patients."***
>
> **–Dr Justin Martello**
>
> *Movement disorder specialist, MedStar Health*

IMPORTANT SAFETY INFORMATION (cont'd)

Dosage and Administration (cont'd)

- CREXONT may be taken with or without food. Capsules should not be chewed, divided or crushed
- CREXONT should not be taken with alcohol

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
- Consider dose reductions or stopping CREXONT in patients with hallucinations or impulse control disorders (e.g., gambling, sexual urges, or uncontrolled spending)

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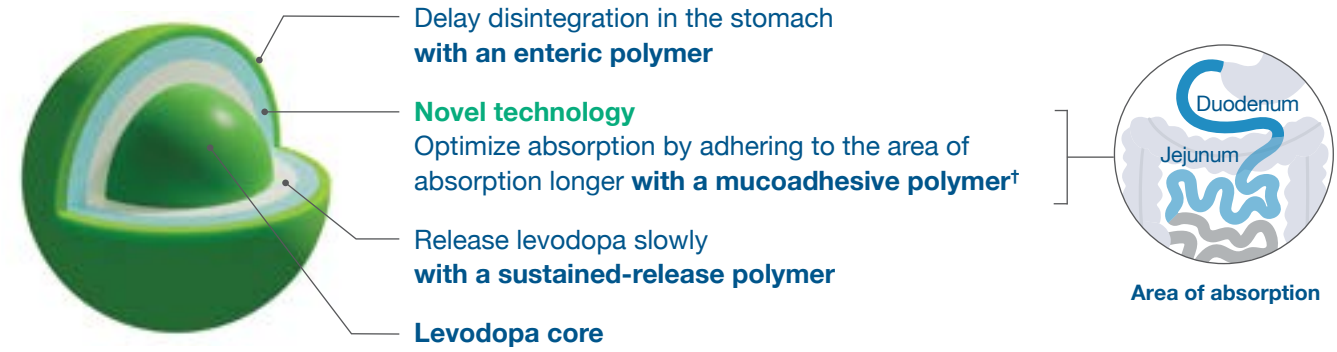
CREXONT represents a unique evolution in ER CD/LD technology beyond RYTARY, as it aims to optimize LD absorption through an innovative formulation designed to adhere to the area of absorption longer.[2] This targeted approach represents a shift from simply extending the duration of LD release to actively optimizing it for the process of absorption itself.

CREXONT contains both IR CD/LD granules and ER LD pellets.[11] The technological innovation of CREXONT lies in its multicomponent polymer system, providing multiple critical functions designed to optimize therapeutic delivery.[11] The outer enteric polymer component delays disintegration in the stomach so that LD can reach the area of absorption, preventing premature gastric degradation, and the sustained-release polymer allows for the slow release of LD.[11] The mucoadhesive polymer is what makes CREXONT truly unique, specifically engineered to optimize absorption by adhering directly to the area of LD absorption in the proximal small intestine.[11] This mucoadhesive polymer approach has been used in other medications, but this is the first time it has been utilized for PD therapy.[11,15]

The ER technology is designed to[11]*:



*Exact mechanism is unknown.
†Exact site and duration of absorption are unknown.

For the first time in Parkinson's disease, we have a treatment that optimizes absorption by targeting the proximal small intestine, where the transporters that absorb LD from the GI tract are localized.[2,9,11] This addresses one of the previous fundamental limitations of conventional oral LD treatment.

IMPORTANT SAFETY INFORMATION (cont'd)
Warnings and Precautions (cont'd)

- 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

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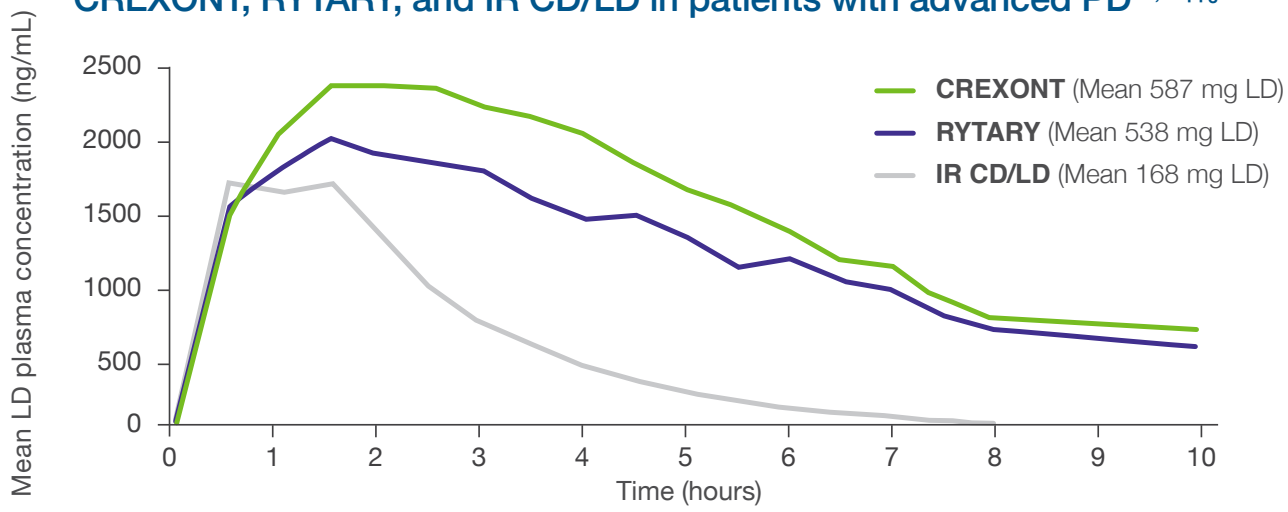
CREXONT Is the Longest-Lasting Oral CD/LD Formulation[16]*

Clinical pharmacokinetic studies have demonstrated that CREXONT LD plasma levels are sustained longer than other available oral CD/LD formulations in patients with Parkinson's disease. Direct comparative analyses show that CREXONT maintains therapeutic LD plasma concentrations for extended periods compared to both RYTARY and conventional IR CD/LD formulations, providing clinicians and patients with a novel technology-driven therapeutic option.

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



*Based on the time that LD plasma levels were maintained above 50% of C_{max}.[16]

†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.

IMPORTANT SAFETY INFORMATION (cont'd)
Warnings and Precautions (cont'd)

- 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

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

CREXONT: The Next Step in ER Technology

CREXONT represents a step forward in ER technology, as the first oral LD formulation specifically designed to target the area of absorption.[2,9,11] This innovative approach moves beyond previous sustained-release strategies to actively optimize absorption itself. CREXONT may offer a solution to levodopa management challenges across the Parkinson's disease spectrum, whether patients are treatment-naïve or have advanced disease.[11,18] The unique mucoadhesive technology in CREXONT helps address previous pharmacokinetic limitations of LD therapy, offering the potential to simplify dosing and improve management.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions

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

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. Hauser RA. Levodopa: past, present, and future. *Eur Neurol*. 2009;62(1):1-8. **2.** 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. **3.** Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA. The effect of a structured medication review on quality of life in Parkinson's disease: the study protocol. *Contemp Clin Trials Commun.* 2019;13:100308. **4.** Calabresi P, Di Filippo M, Ghiglieri V, Tambasco N, Picconi B. Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap. *Lancet Neurol*. 2010;9(11):1106-1117. **5.** 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. **6.** Cenci MA. Presynaptic mechanisms of L-DOPA-induced dyskinesia: the findings, the debate, and the therapeutic implications. *Front Neurol.* 2014;5:242. **7.** Rodríguez-Violante M, Ospina-García N, Dávila-Avila NM, Cruz-Fino D, Cruz-Landero ADL, 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. **8.** Fleisher JE, Stern MB. Medication non-adherence in Parkinson's disease. *Curr Neurol Neurosci Rep.* 2013;13(10):10.1007/s11910-013-0382-z. **9.** Leta V, Klingelhoefer L, Longardner K, et al. Gastrointestinal barriers to levodopa transport and absorption in Parkinson's disease. *Eur J Neurol.* 2023;30(5):1465-1480. **10.** Pfeiffer RF, Isaacson SH, Pahwa R. Clinical implications of gastric complications on levodopa treatment in Parkinson's disease. *Parkinsonism Relat Dis.* 2020;76:63-71. **11.** 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. **12.** Livingston C, Monroe-Duprey L. A review of Levodopa formulations for the treatment of Parkinson's disease available in the United States. *J Pharm Pract.* 2024;37(2):485-494. **13.** SINEMET CR [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2018. **14.** 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. **15.** Kumar R, Islam T, Nurunnabi, M. Mucoadhesive carriers for oral drug delivery. *J Control Release.* 2022;351:504-559. **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.** CREXONT [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; 2024.

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