

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217186Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CREXONT™ safely and effectively. See full prescribing information for CREXONT.

CREXONT™ (carbidopa and levodopa) extended-release capsules, for oral use

Initial U.S. Approval: 1975

INDICATIONS AND USAGE

CREXONT is a combination of carbidopa (an aromatic amino acid decarboxylation inhibitor) and levodopa (an aromatic amino acid) indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication in adults. (1)

DOSAGE AND ADMINISTRATION

- Levodopa-naïve patients: Starting dose is 35 mg carbidopa / 140 mg levodopa taken orally twice daily for the first 3 days; on the fourth day of treatment, dosage may be increased gradually as needed. (2.1)
- Patients converting from immediate-release carbidopa/levodopa: See Table 1 for instructions; dosages are not substitutable on a 1:1 basis. (2.2)
- The maximum recommended daily dosage of CREXONT is 525 mg carbidopa / 2100 mg levodopa. (2.1, 2.2)
- CREXONT may be taken with or without food; do not chew, divide, or crush. (2.4, 12.3)
- CREXONT should not be taken with alcohol. (2.4, 12.3)

DOSAGE FORMS AND STRENGTHS

Extended-Release Capsules: Carbidopa and Levodopa 35 mg / 140 mg, 52.5 mg / 210 mg, 70 mg / 280 mg, 87.5 mg / 350 mg (3)

CONTRAINDICATIONS

Nonselective MAO inhibitors (4)

WARNINGS AND PRECAUTIONS

- May cause falling asleep during activities of daily living. (5.1)
- Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion. (5.2)
- Cardiovascular Events: Monitor patients with a history of cardiovascular disease. (5.3)
- Hallucinations/Psychosis may occur. (5.4)
- Impulse Control Disorders: Consider dose reduction or stopping CREXONT if occurs. (5.5)
- May cause or exacerbate dyskinesia: Consider dose reduction. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 3\%$ and greater than immediate-release CD-LD) are nausea and anxiety. (6.1)

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

DRUG INTERACTIONS

Iron salts and dopamine D2 antagonists, including metoclopramide, may reduce the effectiveness of CREXONT. (7.2, 7.3)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CREXONT 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Patients Naïve to Levodopa Therapy

The recommended starting dosage of CREXONT in levodopa-naïve patients is 35 mg carbidopa / 140 mg levodopa taken orally twice daily for the first three days. Thereafter, dosage may be increased gradually as needed to a maximum daily dosage of 525 mg carbidopa / 2100 mg levodopa divided up to four times daily.

2.2 Dosage in Patients Converting from Immediate-Release Carbidopa-Levodopa to CREXONT

The dosages of immediate-release carbidopa-levodopa products are not substitutable on a 1:1 basis with the dosages of CREXONT.

To convert patients from immediate-release carbidopa-levodopa to CREXONT, follow these steps:

Step 1: Determine the patient's total daily dosage of immediate-release levodopa.

Step 2: Determine the patient's most frequent single dose of immediate-release levodopa. If more than one dose corresponds to the most frequent, use the highest of the doses.

Step 3: Find the values from Step 1 and Step 2 in Table 1 (below) to determine the recommended starting CREXONT dosage of levodopa and dosing frequency.

Step 4: After one to three days, adjust the dose or frequency as needed based on the patient's clinical response and tolerability. Dosage may be increased gradually as needed to a maximum daily dosage of 525 mg carbidopa / 2100 mg levodopa divided up to four times daily.

Table 1: Conversion from Immediate-Release Carbidopa-Levodopa to CREXONT

Total Daily Immediate-Release Levodopa Dosage	Most Frequent Immediate-Release Levodopa Single Dose	Recommended Starting CREXONT Dosage of Levodopa
Less than 500 mg daily	100 mg	280 mg twice daily
	150 mg	420 mg twice daily
	200 mg	560 mg twice daily
Equal to or greater than 500 mg daily	100 mg	280 mg three times daily
	150 mg	420 mg three times daily
	200 mg	560 mg three times daily
	Greater than 200 mg	700 mg three times daily

For patients currently treated with carbidopa and levodopa plus a catechol-O-methyl transferase (COMT) inhibitor (e.g., entacapone or opicapone), the initial total daily dose of levodopa in CREXONT may need to be increased if the COMT inhibitor is discontinued.

Use of CREXONT in combination with other levodopa products has not been studied.

2.3 Dosage for Patients Converting from Extended-Release Carbidopa-Levodopa (Rytary) to CREXONT

For patients converting from RYTARY (extended-release carbidopa-levodopa), initiate CREXONT on an approximately 1:1 mg basis using the levodopa component for conversion.

2.4 Administration Information

Swallow CREXONT whole with or without food. CREXONT should not be taken with alcohol. A high-fat, high-calorie meal may delay the absorption of levodopa to reach the peak plasma concentration by about 2 hours [see *Clinical Pharmacology* (12.3)].

Do not chew, divide, or crush CREXONT capsules.

2.5 Discontinuation of CREXONT

Avoid sudden discontinuation or rapid dose reduction of CREXONT. The daily dose of CREXONT should be tapered at the time of treatment discontinuation [see *Warnings and Precautions* (5.2)].

3 DOSAGE FORMS AND STRENGTHS

CREXONT extended-release capsules contain white to off-white granules and pellets and are available in the following strengths:

- 35 mg carbidopa and 140 mg levodopa: Capsules with white opaque body and yellow opaque cap. Body imprinted with “140” in black ink and cap imprinted with “IPX203” in white ink.
- 52.5 mg carbidopa and 210 mg levodopa: Capsules with white opaque body and green opaque cap. Body imprinted with “210” in black ink and cap imprinted with “IPX203” in white ink.
- 70 mg carbidopa and 280 mg levodopa: Capsules with white opaque body and purple opaque cap. Body imprinted with “280” in black ink and cap imprinted with “IPX203” in white ink.
- 87.5 mg carbidopa and 350 mg levodopa: Capsules with white opaque body and medium orange opaque cap. Body imprinted with “350” in black ink and cap imprinted with “IPX203” in white ink.

4 CONTRAINDICATIONS

CREXONT is contraindicated in patients currently taking a nonselective monoamine oxidase (MAO) inhibitor or have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently [see *Drug Interactions* (7.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Falling Asleep During Activities of Daily Living and Somnolence

Patients treated with levodopa, a component of CREXONT, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on levodopa, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event (sleep attack). Some of these events have been reported more than 1 year after initiation of treatment.

Falling asleep while engaged in activities of daily living usually occurs in patients experiencing preexisting somnolence, although patients may not give such a history. For this reason, prescribers should reassess for drowsiness or sleepiness in CREXONT-treated patients, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with CREXONT, advise patients of the potential to develop drowsiness and specifically ask about factors that may increase the risk for somnolence with CREXONT, such as concomitant sedating medications or the presence of a sleep disorder. Consider discontinuing CREXONT in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.).

If a decision is made to continue CREXONT, patients should be advised not to drive and to avoid other potentially dangerous activities that might result in harm if the patients become somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.2 Withdrawal-Emergent Hyperpyrexia and Confusion

A symptom complex that resembles neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy. Avoid sudden discontinuation or rapid dose reduction in patients taking CREXONT. If the decision is made to discontinue CREXONT, the dose should be tapered to reduce the risk of hyperpyrexia and confusion [*see Dosage and Administration (2.5)*].

5.3 Cardiovascular Ischemic Events

Cardiovascular ischemic events have occurred in patients taking CREXONT. In Study 1 [*see Clinical Studies (14)*], 4/589 (0.7%) of CREXONT-treated patients experienced cardiovascular ischemic adverse reactions compared to 2/630 (0.3%) of oral immediate-release carbidopa-levodopa-treated patients. These patients all had a previous history of ischemic heart disease or risk factors for ischemic heart disease.

In patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias, cardiac function should be monitored in an intensive cardiac care facility during the period of initial dosage adjustment.

5.4 Hallucinations/Psychosis

There is an increased risk for hallucinations in patients taking CREXONT. In Study 1, 17/589 (3%) of CREXONT-treated patients reported hallucinations compared to 2/630 (0.3%) of oral immediate-release carbidopa-levodopa-treated patients.

Hallucinations present shortly after the initiation of therapy and may be responsive to dose reduction in levodopa. Hallucinations may be accompanied by confusion, insomnia, and excessive dreaming. Abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Because of the risk of exacerbating psychosis, patients with a major psychotic disorder should not be treated with CREXONT. In addition, medications that antagonize the effects of dopamine used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of CREXONT [*see Drug Interactions (7.2)*].

5.5 Impulse Control/Compulsive Behaviors

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including CREXONT, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued.

Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with CREXONT. Consider a dose reduction or stopping the medication if a patient develops such urges while taking CREXONT.

5.6 Dyskinesia

CREXONT can cause dyskinesias that may require a dosage reduction of CREXONT or other medications used for the treatment of Parkinson's disease.

5.7 Peptic Ulcer Disease

Treatment with CREXONT may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

5.8 Glaucoma

CREXONT may cause increased intraocular pressure in patients with glaucoma. Monitor intraocular pressure in patients with glaucoma after starting CREXONT.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Falling Asleep During Activities of Daily Living and Somnolence [*see Warnings and Precautions (5.1)*]
- Withdrawal-Emergent Hyperpyrexia and Confusion [*see Warnings and Precautions (5.2)*]
- Cardiovascular Ischemic Events [*see Warnings and Precautions (5.3)*]
- Hallucinations/Psychosis [*see Warnings and Precautions (5.4)*]
- Impulse Control/Compulsive Behaviors [*see Warnings and Precautions (5.5)*]
- Dyskinesia [*see Warnings and Precautions (5.6)*]
- Peptic Ulcer Disease [*see Warnings and Precautions (5.7)*]
- Glaucoma [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

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

The safety population consisted of 589 patients with Parkinson's disease who received CREXONT for up to 76 weeks and had an average duration of exposure of 35 weeks. Study 1 in patients with Parkinson's Disease consisted of a dose adjustment period of immediate-release carbidopa-levodopa treatment prior to a 4-week dose conversion period to CREXONT, which was then followed by a 13-week, double-blind, randomized period comparing CREXONT to immediate-release carbidopa-levodopa [*see Clinical Studies (14)*].

In Study 1, the most common adverse reactions (in at least 3% of patients treated with CREXONT and more frequently than with immediate-release carbidopa-levodopa) that occurred during the double-blind maintenance period were nausea and anxiety.

Table 2 lists adverse reactions occurring in at least 2% of CREXONT-treated patients while converting from immediate-release carbidopa-levodopa and at a higher rate than immediate-release carbidopa-levodopa in the double-blind maintenance period.

Table 2. Adverse Reactions that Occurred in at Least 2% of Patients with Parkinson's Disease who Received CREXONT and at a Higher Rate than Patients who Received Immediate-Release Carbidopa-Levodopa (Study 1)

Adverse Reaction	Dose Conversion Period	Double-Blind Period	
	CREXONT	CREXONT	Immediate-Release Carbidopa-Levodopa
	(N=589) %	(N=256) %	(N= 250) %
Nausea	5	4	1
Anxiety	2	3	0
Dizziness	3	2	1
Dyskinesia	7	2	0.4
Constipation	2	2	0.4
Headache	2	1	0
Vomiting	2	1	0
Insomnia	2	1	0.4

Adverse Reactions Leading to Discontinuation

In Study 1, 6% of patients discontinued treatment because of adverse reactions during conversion to CREXONT. During the double-blind treatment period of Study 1, 5% of patients taking CREXONT and 1% of patients taking immediate-release carbidopa-levodopa discontinued treatment because of adverse events.

The common adverse reactions leading to drug discontinuation during dose conversion were dyskinesia, dizziness, and nausea.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase (MAO) Inhibitors

Nonselective MAO Inhibitors

The use of nonselective MAO inhibitors (e.g., phenelzine and tranylcypromine) with CREXONT is contraindicated [see *Contraindications (4)*]. Discontinue use of any nonselective MAO inhibitors at least two weeks prior to initiating CREXONT.

Selective MAO Inhibitors

The use of selective MAO-B inhibitors (e.g., rasagiline and selegiline) with CREXONT may be associated with orthostatic hypotension. Monitor patients who are taking these drugs concurrently.

7.2 Dopamine D2 Receptor Antagonists and Isoniazid

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce the effectiveness of levodopa. Monitor patients for worsening Parkinson's symptoms.

7.3 Iron Salts

Iron salts or multivitamins containing iron salts can form chelates with levodopa and carbidopa and can cause a reduction in the bioavailability of CREXONT. If iron salts or multivitamins containing iron salts are co-administered with CREXONT, monitor patients for worsening Parkinson's symptoms.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of CREXONT (carbidopa and levodopa) in pregnant women. In animal studies, carbidopa-levodopa has been shown to be developmentally toxic (including teratogenic effects) at clinically relevant doses (*see Data*).

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

When administered to pregnant rabbits throughout organogenesis, carbidopa-levodopa caused both visceral and skeletal malformation in fetuses at all doses and ratios of carbidopa-levodopa tested. No teratogenic effects were observed when carbidopa-levodopa was administered to pregnant mice throughout organogenesis.

There was a decrease in the number of live pups delivered by rats receiving carbidopa-levodopa during organogenesis.

8.2 Lactation

Risk Summary

CREXONT is a combination of carbidopa and levodopa.

Carbidopa

There are no adequate data on the presence of carbidopa in human milk, the effects on the breastfed infant, or the effects on milk production. Carbidopa is excreted in rat milk.

Levodopa

Levodopa has been detected in human milk after administration of carbidopa-levodopa. Levodopa decreases secretion of prolactin in humans, which may inhibit lactation. There are no adequate data on the effects of levodopa on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CREXONT and any potential adverse effects on the breastfed infant from CREXONT or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

There were 282 (45%) patients 65 to less than 74 years of age and 112 (18%) patients 75 years of age and older treated with CREXONT in an active-controlled study for Parkinson's disease (Study 1) [see *Clinical Studies (14)*]. There were no differences in safety outcomes between patients less than 65 years of age, 65 to less than 75 years of age, or 75 years and older.

10 OVERDOSAGE

Based on the limited available information, the acute symptoms of levodopa/carbidopa overdosage can be expected to arise from dopaminergic overstimulation. Doses of a few grams may result in CNS disturbances, with an increasing likelihood of cardiovascular disturbance (e.g., hypotension, tachycardia) and more severe psychiatric problems at higher doses. An isolated report of rhabdomyolysis and another of transient renal insufficiency suggest that levodopa overdosage may give rise to systemic complications, secondary to dopaminergic overstimulation.

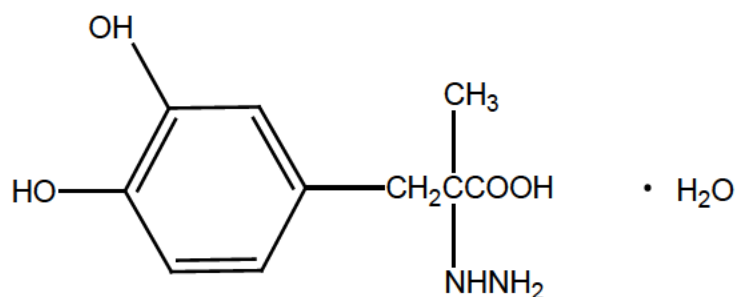
In the event of CREXONT overdosage, monitor patients and provide supportive care. Patients should receive electrocardiographic monitoring for the development of arrhythmias; if needed, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs, increasing the risk of drug interactions (especially catechol-structured drugs) should be taken into consideration.

11 DESCRIPTION

CREXONT is a combination of carbidopa, an inhibitor of aromatic amino acid decarboxylation, and levodopa, an aromatic amino acid, in extended-release capsules for oral use.

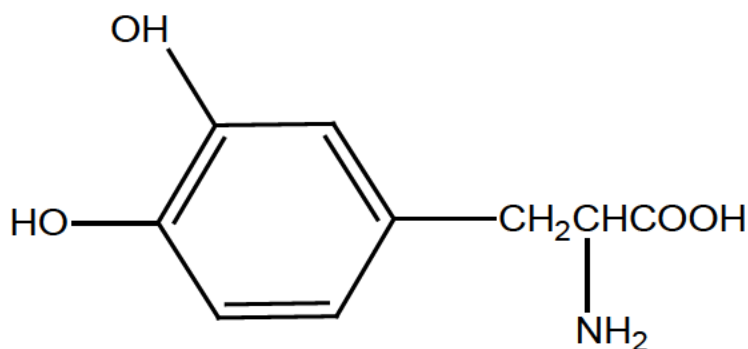
CREXONT contains immediate-release granules consisting of carbidopa and levodopa and extended-release pellets consisting of levodopa.

Carbidopa is a white to off-white powder, crystalline compound, slightly soluble in water, with a molecular weight of 244.24. It is designated chemically as (–)-L- α -hydrazino- α -methyl- β -(3,4-dihydroxy-benzene) propanoic acid monohydrate. Its molecular formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$ and its structural formula is:



Capsule content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (–)-L-α-amino-β-(3,4-dihydroxy-benzene) propanoic acid. Its molecular formula is C₉H₁₁NO₄ and its structural formula is:



Each CREXONT extended-release capsule contains 35 mg carbidopa and 140 mg levodopa, 52.5 mg carbidopa and 210 mg levodopa, 70 mg carbidopa and 280 mg levodopa, or 87.5 mg carbidopa and 350 mg levodopa. The inactive ingredients are amino methacrylate copolymer, cellulose acetate, copovidone, croscarmellose sodium, magnesium stearate, mannitol, methacrylic acid and methyl methacrylate copolymer, microcrystalline cellulose, povidone, sodium lauryl sulfate, talc, and triethyl citrate.

- The 35mg/140 mg capsule shell contains D&C yellow #10, gelatin, Red Iron Oxide, and titanium dioxide.
- The 52.5 mg/210 mg capsule shell contains FD&C Blue #1, gelatin, titanium dioxide, and yellow iron oxide.
- The 70 mg/280 mg capsule shell contains FD&C Blue #1, FD&C Red #3, gelatin, and titanium dioxide.
- The 87.5 mg/350 mg capsule shell contains gelatin, Red Iron Oxide, titanium dioxide, and yellow iron oxide.
- The black imprinting ink contains ammonium hydroxide, ethanol, ferrousferic oxide/black iron oxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze.
- The white imprinting ink contains ethanol, isopropyl alcohol, n-butyl alcohol, povidone, propylene glycol, shellac glaze, sodium hydroxide, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carbidopa

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for delivery to the brain.

Levodopa

Levodopa is the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa treats symptoms of Parkinson's disease.

12.2 Pharmacodynamics

Because its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available to the brain. The addition of carbidopa to levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa.

Patients treated with levodopa therapy for Parkinson's disease may develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia, 'on-off' phenomenon, and akinesia.

Cardiac Electrophysiology

At exposures corresponding to the maximum recommended dose of carbidopa in CREXONT, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

The pharmacokinetics of CREXONT were evaluated following single doses in healthy subjects and following single and multiple doses in patients with Parkinson's disease.

CREXONT shows dose proportional pharmacokinetics for both carbidopa and levodopa over the carbidopa/levodopa dosage strength range of 35 mg/140 mg to 87.5 mg/350 mg.

Absorption

Carbidopa

Following oral dosing of CREXONT, the maximum concentration occurred at approximately 2.5 hours. The bioavailability of carbidopa from CREXONT relative to immediate-release carbidopa-levodopa tablets was approximately 103% to 123%.

Levodopa

The bioavailability of levodopa from CREXONT was approximately 88% to 99% relative to immediate-release carbidopa-levodopa.

For comparable doses, CREXONT results in a levodopa peak concentration ($C_{\max}$) that is 38% that of immediate-release carbidopa-levodopa. Following an initial peak at about one hour, plasma concentrations were maintained for about 6 to 7 hours before declining.

In patients with Parkinson's disease, multiple-dose pharmacokinetics was comparable to single-dose pharmacokinetics, i.e., there was minimal accumulation of levodopa. Variation in levodopa peak to trough plasma concentrations at steady-state defined as $(C_{\max}-C_{\min})/C_{\text{avg}}$ was approximately 1.7 for CREXONT compared to approximately 2.7 for immediate-release carbidopa-levodopa.

Effect of Food

Carbidopa

In healthy adults, oral administration of CREXONT after a high-fat, high-calorie meal decreased both $C_{\max}$ and AUC by approximately 64% for carbidopa compared to administration in the fasted state. The peak plasma concentrations of carbidopa were observed approximately one hour later when CREXONT is taken with a high-fat high-calorie meal.

Levodopa

In healthy adults, oral administration of CREXONT after a high-fat, high-calorie meal increased $C_{\max}$ approximately 19% and $AUC_{0-\infty}$ approximately 18% for levodopa compared to administration in the fasted state [see *Dosage and Administration (2.4)*]. The peak plasma concentrations of levodopa were observed approximately two hours later when CREXONT is taken with a high-fat, high-calorie meal. In addition, absorption of levodopa may be decreased by a high protein meal.

Distribution

Approximately 36% of carbidopa binds to plasma proteins. Approximately 10% to 30% of levodopa binds to plasma proteins.

Metabolism and Elimination

Carbidopa

The terminal phase elimination half-life of carbidopa is approximately 2 hours.

Carbidopa is metabolized to two main metabolites: α -methyl-3-methoxy-4-hydroxyphenylpropionic acid and α -methyl-3,4-dihydroxy-phenylpropionic acid. These two metabolites are primarily eliminated in the urine unchanged or as a glucuronide. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Peripheral dopa-decarboxylase may be saturated by carbidopa in immediate release carbidopa-levodopa products at 70 mg per day to 100 mg per day, which produces similar exposure to 62.5 mg to 89.3 mg per day of carbidopa provided by CREXONT.

Levodopa

The terminal phase elimination half-life of levodopa, the active moiety of antiparkinsonian activity, is approximately 2 hours in the presence of carbidopa.

Levodopa is extensively metabolized to various metabolites. The two major metabolic pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT).

Specific Populations

Geriatric Patients

In pharmacokinetic studies following a single dose of CREXONT, the peak concentrations of carbidopa and levodopa are generally similar between younger (45 to 60 years) and older (60 to 75 years) subjects.

Drug Interaction Studies

In Vitro Studies

Effect of Ethanol

Ethanol-induced dose dumping of CREXONT was observed in the presence of 40% ethanol (80 proof) solution in a dissolution study [see *Dosage and Administration (2.4)*]; however, dose dumping was not observed in the presence of lower ethanol concentrations. The clinical significance of this dose dumping was not fully characterized in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In rats, oral administration of carbidopa-levodopa for two years resulted in no evidence of carcinogenicity.

Mutagenesis

Carbidopa was mutagenic in the *in vitro* Ames test and in the *in vitro* mouse lymphoma *tk* assay but was negative in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

In reproduction studies, no effects on fertility were observed in rats receiving carbidopa-levodopa.

14 CLINICAL STUDIES

The effectiveness of CREXONT for the treatment of Parkinson's disease was established in an active-controlled, multicenter, 20-week clinical trial (Study 1; NCT03670953). Study 1 consisted of a 3-week dose adjustment period of immediate-release carbidopa-levodopa treatment prior to a 4-week conversion period to CREXONT, which was followed by a 13-week, double-blind, double-dummy, randomized, parallel group period comparing CREXONT to immediate-release carbidopa-levodopa. Study 1 enrolled 630 (506

randomized) patients (Hoehn & Yahr Stages I-IV) who had been maintained on a stable regimen of at least 400 mg per day of levodopa prior to entry into the trial and who experienced a minimum of 2.5 hours of “Off” time per day while awake. Patients had a mean age of 67 years and a mean disease duration of 9 years. 96% of the patients were white, 2% were Asian, 1% Black and 63% of the patients were male. At baseline, approximately 73% of patients in the CREXONT group and 63% of patients in the oral IR carbidopa-levodopa group were taking at least 1 or more classes of PD medications other than carbidopa-levodopa. Seventy-four percent of patients were continued on concomitant dopamine agonists (52%), selective monoamine oxidase B (MAO-B) inhibitors (33%), amantadine (19%), and anticholinergics (4%) provided the doses were stable for at least 4 weeks prior to screening. Patients were randomized to receive either immediate-release carbidopa-levodopa or CREXONT at the dose determined during the adjustment or conversion phases. Patients were not allowed to receive supplemental carbidopa-levodopa products or additional carbidopa, any catechol-O-methyl transferase (COMT) inhibitor products, non-selective monoamine oxidase (MAO) inhibitors, selective MAO-A inhibitors, apomorphine, or antidopaminergic agents (including antiemetics) during the trial.

In Study 1, 75% of patients required 2 or fewer titration steps to reach a stable total daily dose of CREXONT.

The mean daily dosage of the levodopa component of CREXONT was 1487 mg.

The primary efficacy measure in Study 1 was the mean change from baseline in “On” time without troublesome dyskinesia in hours per day at the end of the study (Week 20 or at early termination), as assessed by the patient’s Parkinson’s disease diary. “On” time without troublesome dyskinesia was defined as the sum of “On” time without dyskinesia and “On” time with non-troublesome dyskinesia. Patients reported an improvement in “On” time without troublesome dyskinesia with CREXONT compared to immediate-release carbidopa-levodopa which was statistically significant ($p=0.019$) (Table 3). CREXONT-treated patients also reported less “Off” time compared to immediate-release carbidopa-levodopa, which was statistically significant ($p=0.025$) (Table 3).

Table 3. Efficacy Results in Patients with Parkinson’s Disease:

	Week 0 Enrollment	Week 7 Baseline (Randomization)	Week 20 End of Study (or Early Termination)	p-value
Mean “On” time without troublesome dyskinesia (hours)				
CREXONT	9.46	11.67	11.35	0.019*
Immediate-release carbidopa-levodopa	9.61	11.72	10.77	
Mean “Off” time (hours)				
CREXONT	6.15	3.95	4.18	0.025*
Immediate-release carbidopa-levodopa	6.05	4.02	4.75	

* p-value based on change from Week 7 (Baseline) to Week 20 (End of Study or Early Termination)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CREXONT capsules contain white to off-white granules and pellets and are available in bottles of 120 capsules as follows:

Capsule Strength	Description	NDC Number
35 mg Carbidopa and 140 mg Levodopa	Capsules with white opaque body and yellow opaque cap. Body imprinted with “140” in black ink and cap imprinted with “IPX203” in white ink.	64896-967-16
52.5 mg Carbidopa and 210 mg Levodopa	Capsules with white opaque body and green opaque cap. Body imprinted with “210” in black ink and cap imprinted with “IPX203” in white ink.	64896-968-16
70 mg Carbidopa and 280 mg Levodopa	Capsules with white opaque body and purple opaque cap. Body imprinted with “280” in black ink and cap imprinted with “IPX203” in white ink.	64896-969-16
87.5 mg Carbidopa and 350 mg Levodopa	Capsules with white opaque body and medium orange opaque cap. Body imprinted with “350” in black ink and cap imprinted with “IPX203” in white ink.	64896-970-16

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.

Dispense in a tightly closed, light-resistant container.

17 PATIENT COUNSELING INFORMATION

Dosing Instructions

- Advise patients not to take other carbidopa-levodopa preparations with CREXONT without consulting their healthcare provider [see *Dosage and Administration* (2.1)].
- Advise patients to swallow CREXONT whole, without chewing, dividing, or crushing [see *Dosage and Administration* (2.4)].
- CREXONT should not be taken with alcohol [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].
- Inform patients that a high fat, high calorie meal may delay the absorption of levodopa and the onset of action by 2 to 5 hours. For this reason, consideration should be given to taking the first dose of the day about 1 to 2 hours before eating. The patient should also be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

- Advise patients to call their healthcare provider before stopping CREXONT. Discontinue CREXONT slowly. Tell patients to call their healthcare provider if they develop withdrawal symptoms such as fever, confusion, or severe muscle stiffness [*see Dosage and Administration (2.5) and Warnings and Precautions (5.2)*].

Falling Asleep During Activities of Daily Living and Somnolence

Advise patients that certain side effects such as sleepiness and dizziness that have been reported with CREXONT may affect some patients' ability to drive and operate machinery safely [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

Suicidal Ideation and Suicidal Behavior

Instruct patients, family members and caregivers to notify their healthcare provider if suicidal ideation and/or suicidal behavior are experienced by patients using CREXONT [*see Warnings and Precautions (5.2)*].

Hallucinations and Psychosis

Inform patients that hallucinations can occur with levodopa products [*see Warnings and Precautions (5.4)*].

Impulse Control Disorder

Inform patients of the potential for experiencing intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, that are generally used for the treatment of Parkinson's disease [*see Warnings and Precautions (5.5)*].

Dyskinesia

Instruct patients to notify their healthcare provider if abnormal involuntary movements appear or get worse during treatment with CREXONT [*see Warnings and Precautions (5.6)*].

Hypotension and Syncope

Advise patients that they may develop orthostatic hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating [*see Adverse Reactions (6.1)*]. Advise patients to rise slowly after sitting or lying down, especially if they have been doing so for a prolonged period.

Advise patients of the possible additive sedative effects when taking CNS depressants in combination with CREXONT.

Pregnancy and Breastfeeding

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during carbidopa and levodopa extended-release capsule therapy [*see Use in Specific Populations (8.1)*].

Instruct patients to notify their physicians if they intend to breast-feed or are breast-feeding an infant [*see Use in Specific Populations (8.2)*].

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