When your patients taking IR CD/LD begin to experience motor fluctuations

It's time to **MOVE ON** with RYTARY

The patient appearing in this piece was compensated for his services.

Learn how Pat moved on with RYTARY.

Individual results may vary.

INDICATION

RYTARY is a combination of carbidopa and levodopa indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

RYTARY is contraindicated in patients who are currently taking or have recently (within 2 weeks) taken a nonselective monoamine oxidase (MAO) inhibitor (e.g., phenelzine, tranylcypromine). Hypertension can occur if these drugs are used concurrently.

IR CD/LD, immediate-release carbidopa/levodopa.

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

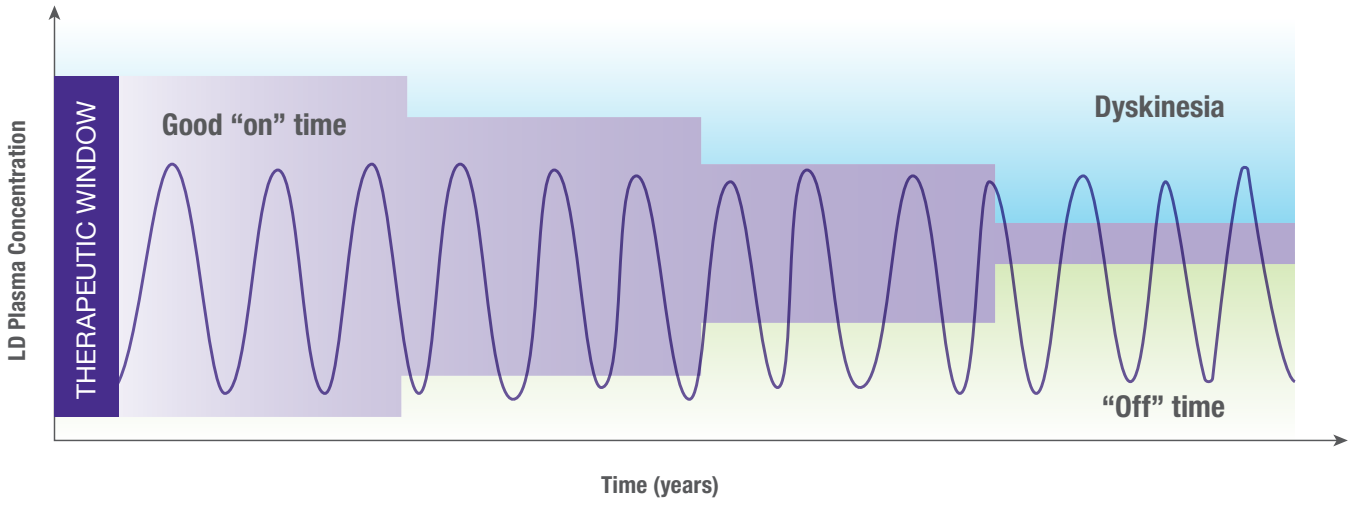
RYTARY®
(carbidopa and levodopa)
EXTENDED-RELEASE CAPSULES
23.75 mg/95 mg • 36.25 mg/145 mg
48.75 mg/195 mg • 61.25 mg/245 mg

PAT'S TREATMENT HISTORY

- **Dopamine agonist**—motor symptoms did not improve; discontinued due to side effects
- **25/100 mg IR CD/LD TID**—after adjusting this initial dose several times, motor symptoms improved; but then dyskinesia and motor fluctuations emerged
- **25/100 mg IR CD/LD QID + COMT inhibitor**—ineffective; discontinued treatment

With 50 years of clinical experience, levodopa remains the most widely used Parkinson's treatment, but it has its limitations[1-3]

As Parkinson's progresses, its therapeutic window narrows, which can lead to the development of motor fluctuations, including "off" time and dyskinesia[1,4]



- Early in Parkinson's disease, patients have a beneficial response to levodopa, allowing them to be in an "on" state without fluctuating in the "off" state[4]
- Over time, the therapeutic window narrows, and achieving an appropriate LD concentration is less attainable, resulting in more "off" time or dyskinesia[4]

Adapted from Goubault E, Nguyen HP, Bogard S, et al. *J Parkinsons Dis.* 2018;8(2):323-331.
COMT, catechol-O-methyl transferase.

A number of medications have been developed over the years to address the limitations of levodopa

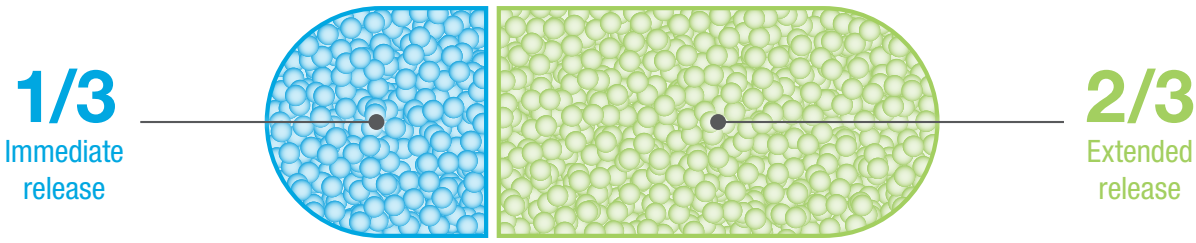
Each new treatment represented an incremental pharmacokinetic improvement[3,5,6]

1975	1991	2003	2015
IR CD/LD	CR CD/LD	CD/LD/entacapone (CLE)	**RYTARY**
DURATION OF SUSTAINED LD PLASMA CONCENTRATION*†:			
1.5 (± 0.7) hours	**2.1 (± 1.0) hours**	**2.1 (± 1.0) hours**	**4.9 (± 2.4) hours**

*Defined as the LD concentration above 50% of C_{max}.[5]
†Based on LD plasma concentration profiles observed after single-dose administration in healthy volunteers.[5]

RYTARY was designed to improve the pharmacokinetics of levodopa over these existing formulations[6]

- Each RYTARY capsule contains multi-beaded technology[7]
  - IR beads provide an immediately available CD/LD dose for fast absorption[7]
  - There are 2 types of ER beads, the first of which exhibits a delayed drug-release profile and the second, a delayed and sustained drug-release profile[7]



After Pat failed on IR CD/LD + a COMT inhibitor, his doctor switched him to RYTARY 36.25/145 mg, 3 capsules QID.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS

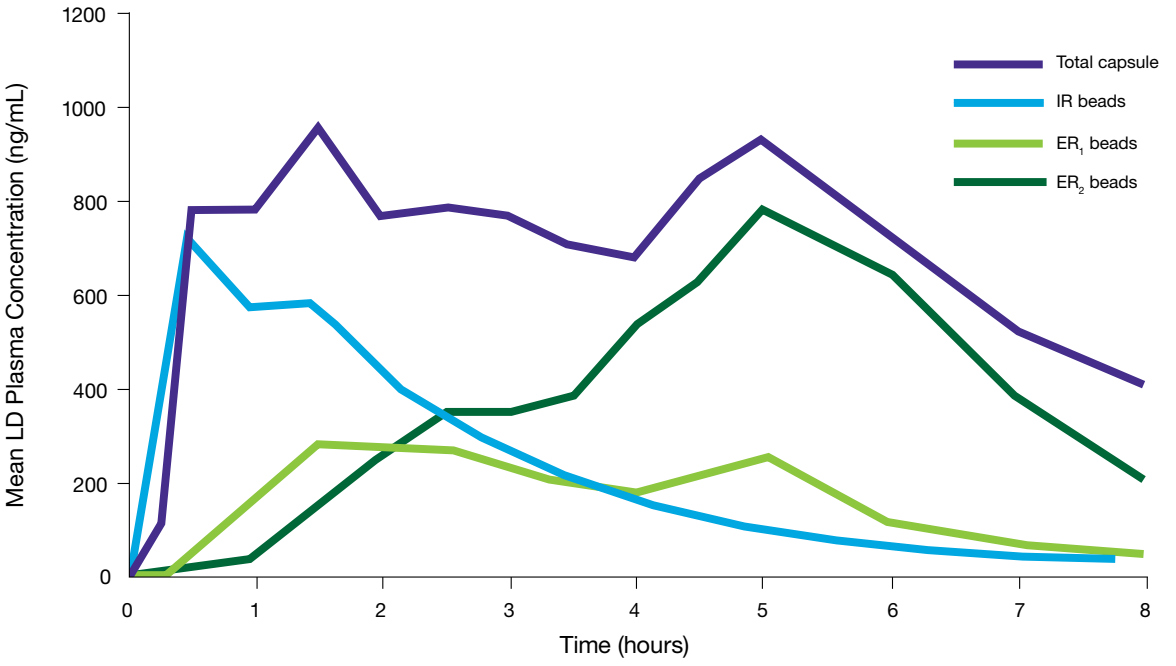
Falling Asleep During Activities of Daily Living and Somnolence: Patients treated with levodopa (a component of RYTARY) have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on levodopa, some perceived that they had no warning signs (sleep attack), such as excessive drowsiness. Some of these events have been reported more than 1 year after initiation of treatment.

CR, controlled release; CLE, carbidopa/levodopa/entacapone; ER, extended release.

RYTARY is formulated to sustain LD plasma concentration with limited fluctuations[8]

After an initial peak at about 1 hour, plasma concentrations are maintained for about 4 to 5 hours[7,9]

Levodopa plasma concentrations of total capsule and individual bead components following a single dose of RYTARY 390 mg[7]



IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

Falling Asleep During Activities of Daily Living and Somnolence (continued): Advise patients of the potential to develop drowsiness and specifically ask about factors that may increase the risk for somnolence with RYTARY, such as concomitant sedating medications or the presence of a sleep disorder. Consider discontinuing RYTARY in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation. If a decision is made to continue RYTARY, patients should be advised not to drive and to avoid other potentially dangerous activities that might result in harm if the patients become somnolent.

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 of, withdrawal of, or changes in dopaminergic therapy. Avoid sudden discontinuation or rapid dose reduction in patients taking RYTARY.

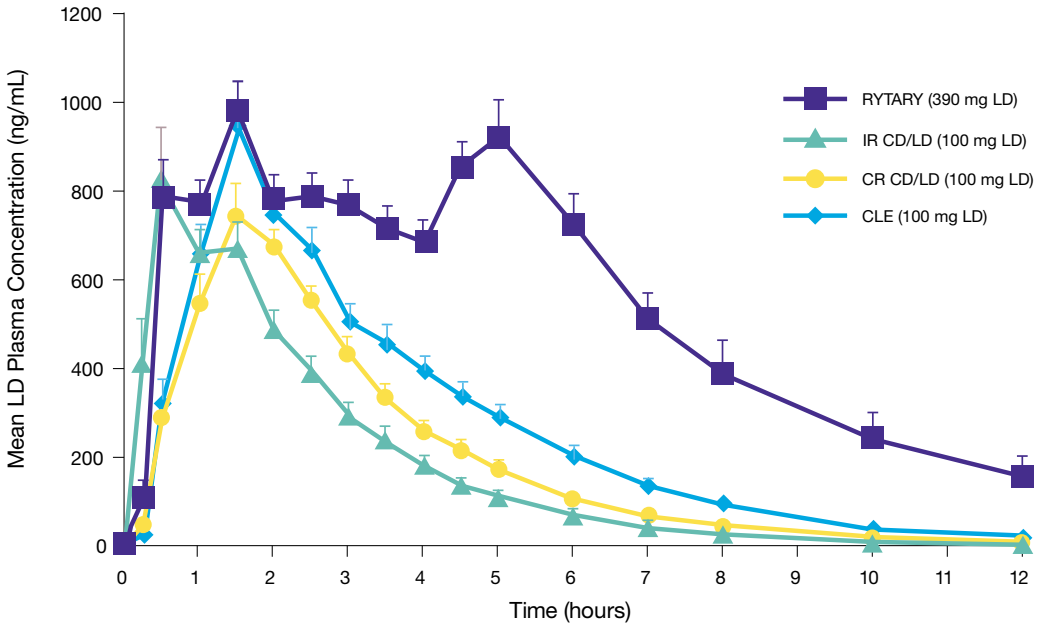
Cardiovascular Ischemic Events: Cardiovascular ischemic events have occurred in patients taking RYTARY. In patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias, cardiac function should be monitored in an intensive cardiac care facility during the period of initial dosage adjustment.

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

RYTARY sustains levodopa levels longer than other CD/LD treatments

Levodopa plasma concentration profiles were collected after a single dose of RYTARY, IR CD/LD, CR CD/LD, and CLE in healthy volunteers[5]

Mean plasma concentration-time profiles of levodopa and carbidopa following a single dose of RYTARY vs IR CD-LD, CR CD-LD, and CLE[5]



Pat's experience with RYTARY:

After making a few adjustments, Pat and his physician found a dose of RYTARY that works for him, (36.25/145 mg, 4 capsules QID) and he is happy with the results.

"With RYTARY, the peaks and valleys that I had been experiencing with IR CD/LD began to smooth out."

Individual results may vary.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

Hallucinations/Psychosis: There is an increased risk for hallucinations and psychosis in patients taking RYTARY. Because of the risk of exacerbating psychosis, patients with a major psychotic disorder should not be treated with RYTARY. 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 RYTARY.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

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 RYTARY, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. Because patients may not recognize these behaviors as abnormal, specifically ask patients or their caregivers about the development of new or increased urges and consider a dose reduction or stopping the medication if a patient develops such urges while taking RYTARY.

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

Peptic Ulcer Disease: Treatment with RYTARY may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Glaucoma: Monitor intraocular pressure in patients with glaucoma after starting RYTARY.

Drug Interactions: Monitor patients taking selective MAO-B inhibitors and RYTARY. The combination may be associated with orthostatic hypotension. Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide), isoniazid, and iron salts or multivitamins containing iron salts may reduce the effectiveness of RYTARY.

The most common adverse reactions (incidence ≥ 5% and greater than placebo) in early Parkinson's disease are nausea, dizziness, headache, insomnia, abnormal dreams, dry mouth, dyskinesia, anxiety, constipation, vomiting, and orthostatic hypotension; and in advanced Parkinson's disease are nausea and headache. Reported adverse reactions identified during post approval use of RYTARY include suicide attempt and ideation.

OVERDOSAGE:

The acute symptoms of levodopa/dopa decarboxylase inhibitor 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.

GENERAL DOSING AND ADMINISTRATION INFORMATION:

See Full Prescribing Information for instructions for starting levodopa-naïve patients on RYTARY and converting patients from immediate-release carbidopa and levodopa to RYTARY (Table 1).

Avoid sudden discontinuation or rapid dose reduction of RYTARY.

The dosages of other carbidopa and levodopa products are not interchangeable on a 1:1 basis with the dosages of RYTARY.

RYTARY should not be chewed, divided, or crushed and should be swallowed whole with or without food. For patients who have difficulty swallowing, the capsule can be opened and the entire contents can be sprinkled on a small amount of applesauce and consumed immediately.

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

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

References: 1. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol.* 2006;5(8):677-687. **2.** Brooks DJ. Optimizing levodopa therapy for Parkinson's disease with levodopa/carbidopa/entacapone: implications from a clinical and patient perspective. *Neuropsychiatr Dis Treat.* 2008;4(1):39-47. **3.** Hauser RA. Levodopa: past, present, and future. *Eur Neurol.* 2009;62(1):1-8. **4.** Goubault E, Nguyen HP, Bogard S, et al. Cardinal motor features of Parkinson's disease coexist with peak-dose choreic-type drug-induced dyskinesia. *J Parkinsons Dis.* 2018;8(2):323-331. **5.** Hsu A, Yao H-M, Gupta S, Modi NB. Comparison of the pharmacokinetics of an oral extended-release capsule formulation of carbidopa-levodopa (IPX066) with immediate-release carbidopa-levodopa (Sinemet®), sustained-release carbidopa-levodopa (Sinemet® CR), and carbidopa-levodopa-entacapone (Stalevo®). *J Clin Pharmacol.* 2015;55(9):995-1003. **6.** Margolesky J, Singer C. Extended-release oral capsule of carbidopa–levodopa in Parkinson disease. *Ther Adv Neurol Disord.* 2017;11:1-12. **7.** Mittur A, Gupta S, Modi NB. Pharmacokinetics of Rytary®, an extended-release capsule formulation of carbidopa-levodopa. *Clin Pharmacokinet.* 2017;56(9):999-1014. **8.** Hauser RA, Ellenbogen AL, Metman LV, et al. Crossover comparison of IPX066 and a standard levodopa formulation in advanced Parkinson's disease. *Mov Disord.* 2011;26(12):2246-2252. **9.** RYTARY [package insert]. Bridgewater, NJ: Amneal Specialty, a division of Amneal Pharmaceuticals LLC; 2019.

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