The Expert Institute for Parkinson's Disease

Powered by amneal

BUILDING A FOUNDATION:

Longer-Lasting "On" Time per Dose

Robert A. Hauser, MD, MBA, FAAN

University of South Florida, College of Medicine, Tampa, FL

John C. Morgan, MD, PhD

Augusta University Medical Center, Augusta, GA

Since its initial conception in the 1960s, levodopa therapy has evolved into different formulations providing longer-lasting benefits for motor symptoms in Parkinson's disease (PD). The development of RYTARY® (carbidopa and levodopa) extended-release capsules has shown that fluctuating PD patients can experience less "off" time and more "on" time with fewer doses per day compared to optimized immediate-release carbidopa/levodopa (IR CD/LD). Most recently, a post hoc analysis showed that RYTARY provides an additional 1.2 hours per dose in "on" time and "on" time without troublesome dyskinesia compared to optimized IR CD/LD. Here, we detail the post hoc analysis with renowned movement disorder specialists Drs Robert A. Hauser and John C. Morgan.

Dopamine replacement therapy with levodopa has long been considered the gold standard therapy for the treatment of Parkinson's disease (PD) motor symptoms.[1] Indeed, various formulations of levodopa accounted for more than half of the prescribed medications for PD in the United States between 2008 and 2016, and the American Academy of Neurology recommends levodopa as first-line therapy for early PD patients with motor symptoms.[2,3]

Over the years, levodopa has been developed into various oral formulations, each with its own unique advantages and limitations, including immediate-release carbidopa/levodopa (IR CD/LD), controlled-release CD/LD (CR CD/LD), carbidopa-levodopa-entacapone (CLE), and most recently, extended-release CD/LD (ER CD/LD).[4,5] While levodopa is highly effective, over time patients commonly develop motor complications such as motor fluctuations and dyskinesia.[6,7] The exact mechanisms that produce motor complications are unclear, but studies suggest levodopa's short half-life is a key factor.[8] As a result, various approaches for extending the duration of therapeutic levodopa levels in oral formulations have been sought.

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.

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

Long-lasting levodopa therapy

"Levodopa provides the foundation for Parkinson's disease treatment. We can add adjunctive therapies, but they need a strong levodopa foundation to be effective," says Dr Robert A. Hauser, Movement Disorder Specialist and Professor of Neurology at the University of South Florida College of Medicine. "The goal in treating Parkinson's is to develop highly effective, long-lasting levodopa formulations. Today, RYTARY represents the longest-lasting oral formulation."

RYTARY is an oral ER CD/LD capsule designed to provide improved pharmacokinetics over earlier oral levodopa formulations.[9,10] Studies have shown that RYTARY sustains plasma levodopa levels longer than IR CD/LD, CR CD/LD, and CLE.[9] Moreover, RYTARY has a smaller fluctuation index than IR CD/LD, meaning that the magnitude of the rise and fall of levodopa levels is less than that seen with IR CD/LD.[10]

The clinical benefits of RYTARY were demonstrated in the pivotal ADVANCE-PD clinical trial, which compared the efficacy and safety of RYTARY to optimized IR CD/LD in Parkinson's patients with motor fluctuations.

> ***"The goal in treating Parkinson's is to develop highly effective, long-lasting levodopa formulations. Today, RYTARY represents the longest-lasting oral formulation."***
>
> - Dr Robert A. Hauser
>
> *Movement Disorder Specialist & Professor of Neurology at the University of South Florida College of Medicine*

IMPORTANT SAFETY INFORMATION (cont'd)

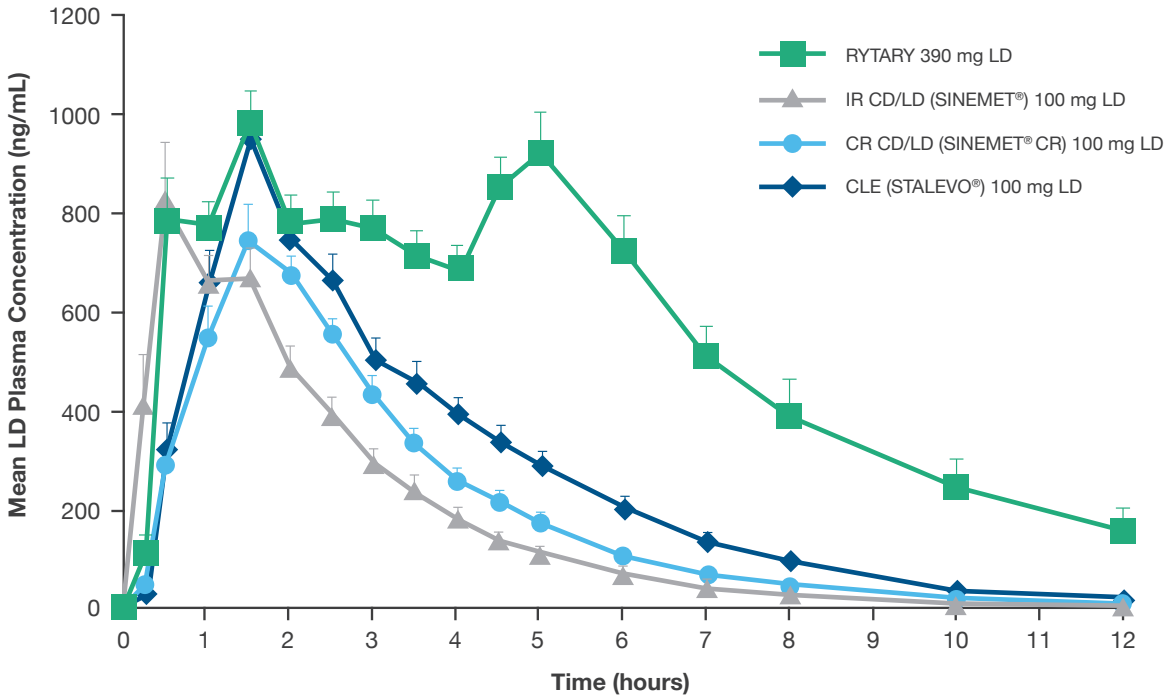
WARNINGS AND PRECAUTIONS

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.

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.

Results from the ADVANCE-PD trial showed that patients on RYTARY experienced a 2X reduction in "off" time during waking hours (13.1% reduction with RYTARY vs 6.2% reduction with optimized IR CD/LD; *P*<0.0001) as well as a 2X increase in "on" time without troublesome dyskinesia (1.8 hours with RYTARY vs 0.8 hours with optimized IR CD/LD; *P*=0.0002).[11] Most impressive was that these results were achieved when RYTARY was given, on average, 3.6 times per day compared to IR CD/LD, which was given, on average, 5 times per day.[11]

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



In a pharmacokinetic study in healthy volunteers, RYTARY was shown to sustain levodopa levels longer than other CD/LD formulations.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

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

> *“The vast majority of my patients praise RYTARY. They tell me how much less ‘off’ time they have and how they can do more of the activities they want to do.”*
>
> - Dr John C. Morgan
>
> *Movement Disorder Specialist & Professor of Neurology at the Augusta University Medical Center*

Dr John C. Morgan, a Movement Disorder Specialist and Professor of Neurology at the Augusta University Medical Center, describes what his patients say about RYTARY: “The vast majority of my patients praise RYTARY. They tell me how much less ‘off’ time they have and how they can do more of the activities they want to do.” In general, RYTARY has been shown to be well tolerated. The most common adverse events associated with taking RYTARY are nausea, dizziness, headache, sleeplessness, abnormal dreams, dry mouth, abnormal involuntary movements, anxiety, constipation, vomiting, and low blood pressure upon rising.[12] Taking RYTARY may also cause individuals to fall asleep while performing routine tasks, even without warning.[12]

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), as hypertension can occur if these drugs are used concurrently.[12] “Because RYTARY is levodopa, it has similar adverse events as other levodopa preparations and is generally well tolerated.”

Increasing “on” time per dose

Healthcare professionals often consider the therapeutic duration of individual levodopa doses when establishing or adjusting a patient’s levodopa regimen; however, clinical trials in Parkinson’s disease often report the reduction in “off” time and increase in “on” time throughout the day rather than per dose.[13-16] To assess the duration of benefit from RYTARY doses and help clinicians appropriately adjust the inter-dose interval for patients, a post hoc analysis of the ADVANCE-PD trial was conducted to determine the mean “on” time per dose of RYTARY.

IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

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.

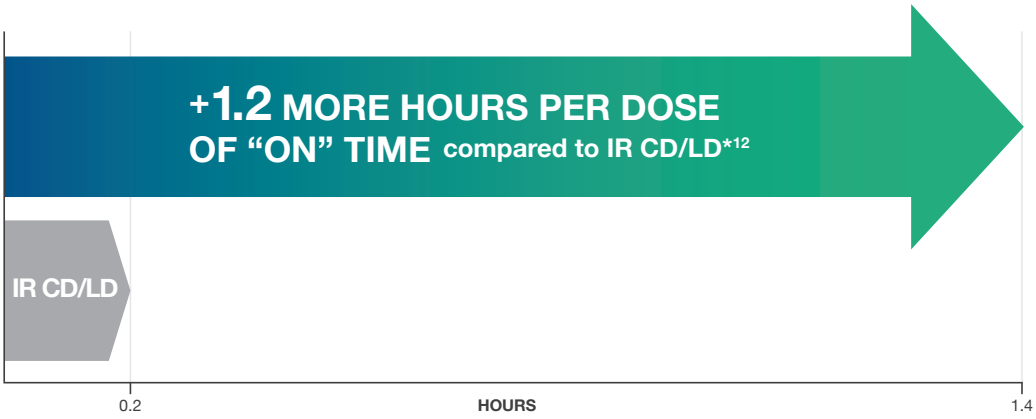
The analysis found that patients taking RYTARY experienced a 1.2 hour increase per dose in "on" time and "on" time without troublesome dyskinesia vs optimized IR CD/LD (*P*<0.0001).[17]

Dr Hauser, who led the post hoc study, explains: "I look at the results of this analysis as providing a blueprint for laying a foundation. We need to know the length of each brick so we can figure out how far apart to space them to avoid gaping holes."

Dr Morgan calls the post hoc analysis "a paradigm shift in thinking about how to best treat fluctuating Parkinson's patients on IR CD/LD," and notes, "the ADVANCE-PD trial showed patients went from an average of 5 doses per day with IR CD/LD to an average of 3.6 with RYTARY, and the post hoc analysis showed more 'on' time per dose with RYTARY. That's an incredible benefit for patients fluctuating on IR CD/LD. As a result of fewer doses, patients have more time during their active day to be at their best and less time to worry about taking medication."

More "On" Time per Dose

After dose optimization of RYTARY, patients experienced an increase of:



Baseline: 2.17 hrs per dose with RYTARY vs 2.24 hrs per dose with IR CD/LD.
End of study: 3.55 hrs per dose with RYTARY vs 2.38 hrs per dose with IR CD/LD.
"On" time per dose was calculated as the number of hours per day spent in the "on" state (regardless of dyskinesia state) divided by the number of LD doses per day.
*The adjusted least square mean difference in increase (from baseline to end of study) in hours of "on" time was calculated using an ANCOVA model.
P<0.0001 vs IR CD/LD.
Data based on a post hoc analysis; study was not powered to evaluate the duration of "on" time per dose as a primary endpoint.

In a post hoc analysis of data from the ADVANCE-PD study, RYTARY provided 1.2 more hours of "on" time per dose compared to optimized IR CD/LD.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

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

Improving medication adherence with fewer doses per day

Often, Parkinson's disease medications require multiple daily doses to control motor symptoms, with some advanced Parkinson's patients requiring dopaminergic medications as often as 6 to 10 doses per day.[18] As a result, timing adherence can be challenging and can lead to missed doses that negatively impact motor symptoms.[19,20] Studies show that Parkinson's patients have difficulty following complicated dosing schedules, with one study finding that nearly 75% of patients struggled with timing adherence.[21]

The most effective approaches to increase compliance are those that simplify dosing.[22] Thus, RYTARY's 1.2 more hours of "on" time per dose over optimized IR CD/LD can provide longer-lasting "on" time at a lower dosing frequency.[17] This reduced dosing frequency regimen may help some patients improve their medication compliance. "Well, if you're not tethered to your pill bottle," Dr Morgan explains, "you can stay out to catch another fish, you can play another hole, you can live your life."

Evolving levodopa therapy

Levodopa therapy has continued to progress ever since its introduction more than 50 years ago.[4,5] Longer-lasting formulations such as RYTARY have become a reality that better sustain levodopa levels with each dose.[8] The recent post hoc analysis has shown that patients can experience more "on" time per dose with RYTARY than with optimized IR CD/LD, and build on a strong levodopa foundation.[17] According to Dr Morgan, "RYTARY should be in every clinician's toolkit when it comes to treating Parkinson's disease, especially in fluctuating patients without contraindications, this is the right choice. In a post hoc analysis of the pivotal study, RYTARY provided patients more 'on' time per dose when compared head-to-head with the gold standard, IR CD/LD. You just can't argue with facts."

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

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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 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

References: 1. Calabresi P, Ghiglieri V, Mazzocchetti P, Corbelli I, Picconi B. Levodopa-induced plasticity: a double-edged sword in Parkinson's disease? *Philos Trans R Soc Lond B Biol Sci*. 2015;370(1672):20140184. **2.** Pringsheim T, Day GS, Smith DB, et al; Guideline Subcommittee of the AAN. Dopaminergic therapy for motor symptoms in early Parkinson disease practice guideline summary: a report of the AAN Guideline Subcommittee. *Neurology*. 2021;97(20):942-957. **3.** Houghton R, Boess F, Verselis L, et al. Treatment patterns in patients with incident Parkinson's disease in the United States. *J Parkinsons Dis*. 2019;9(4):749-759. **4.** Dhall R, Kreitzman DL. Advances in levodopa therapy for Parkinson disease: review of RYTARY (carbidopa and levodopa) clinical efficacy and safety. *Neurology*. 2016;86 (14 Suppl 1):S13-S24. **5.** Hauser RA. Levodopa: past, present, and future. *Eur Neurol*. 2009;62(1):1-8. **6.** Hametner E, Seppi K, Poewe W. The clinical spectrum of levodopa-induced motor complications. *J Neurol.* 2010;257(Suppl 2):S268-S275. **7.** 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. **8.** Thanvi BR, Lo TCN. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad Med J*. 2004;80(946):452-458. **9.** 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. **10.** Mittur A, Gupta S, Modi NB. Pharmacokinetics of Rytary®, an extended-release capsule formulation of carbidopa-levodopa. *Clin Pharmacokinet*. 2017;56(9):999-1014. **11.** Hauser RA, Hsu A, Kell S, et al; IPX066 ADVANCE-PD investigators. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. *Lancet Neurol*. 2013;12(4):346-356. **12.** Amneal Pharmaceuticals. Rytary Health Care Professional Important Safety Information. Published online 2020. **13.** Stalevo [package insert]. East Hanover, NJ: Novartis; 2008. **14.** Gocovri [package insert]. Emeryville, CA: Adamas Pharma; 2017. **15.** Ongentys [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.; 2020. **16.** RYTARY [package insert]. Bridgewater, NJ: Amneal Specialty, a division of Amneal Pharmaceuticals LLC; 2019. **17.** Hauser RA, Zeitlin L, Fisher S, D'Souza R. Duration of benefit per dose: carbidopa-levodopa immediate release vs extended release capsules (Rytary®). *Parkinsonism Relat Disord*. 2021;82:133-137. **18.** Malek N, Grosset DG. Medication adherence in patients with Parkinson's disease. *CNS Drugs*. 2015;29(1):47-53. **19.** Straka I, Minár M, Gažová A, Valkovič P, Kyselovič J. Clinical aspects of adherence to pharmacotherapy in Parkinson disease: a PRISMA-compliant systematic review. *Medicine (Baltimore)*. 2018;97(23):e10962. **20.** Straka I, Minár M, Škorvánek M, et al. Adherence to pharmacotherapy in patients with Parkinson's disease taking three and more daily doses of medication. *Front Neurol*. 2019;10:799. **21.** Grosset D, Antonini A, Canesi M, et al. Adherence to antiparkinson medication in a multicenter European study. *Mov Disord*. 2009;24(6):826-832. **22.** Srivastava K, Arora A, Kataria A, Cappelleri JC, Sadosky A, Peterson AM. Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis. *Patient Prefer Adherence*. 2013;7:419-434.

amneal