When your patients taking immediate-release (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 Phil moved on with the proven efficacy of 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.

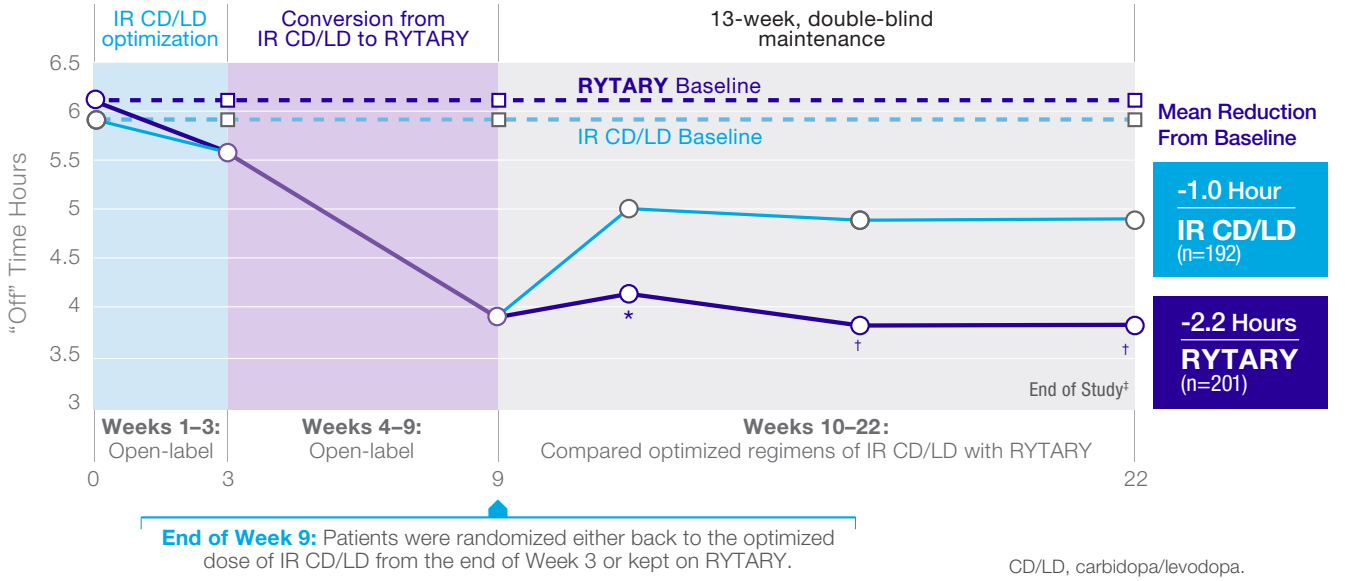
Please see additional Important Safety Information on adjacent pages and accompanying Full Prescribing Information.

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

In a **head-to-head study** vs IR CD/LD,

RYTARY showed a significant reduction in "off" time, following dose optimization[1,2]

STUDY DESIGN **Phase 3, randomized, double-blind study of RYTARY vs IR CD/LD[1,2]**



End of Week 9: Patients were randomized either back to the optimized dose of IR CD/LD from the end of Week 3 or kept on RYTARY.

CD/LD, carbidopa/levodopa.

Weeks 1–3
Open-label IR CD/LD optimization

Weeks 4–9
Open-label conversion from IR CD/LD to RYTARY

Weeks 10–22
Double-blind maintenance comparing optimized regimens of IR CD/LD with RYTARY

*P=0.0004.
†P<0.0001.
‡Week 22 or early termination.

Pivotal trial 2 study design: Data are from a 22-week clinical trial in patients with advanced Parkinson's disease consisting of a 3-week dose adjustment of current levodopa treatment prior to a 6-week conversion to RYTARY, which was followed by a 13-week, randomized, multicenter, double-blind, levodopa-containing active-control, double-dummy, parallel-group trial. RYTARY and optimized IR CD/LD were compared in patients (N=471 enrolled; 393 randomized) on a stable regimen of ≥400 mg of levodopa per day for ≥4 weeks with a 3-day average of ≥2.5 hours of "off" time per day. Concomitant Parkinson's medications (dopamine agonists, selective MAO-B inhibitors, amantadine, and anticholinergics) were continued, provided the doses were stable for ≥4 weeks prior to screening.[1,2]

Phil's treatment history:

- Initially, Phil was treated with **IR CD/LD**, plus pramipexole. The dosage started at 25/100 mg 1 tablet 3 times a day but was then increased to 1.5 tablets 4 times a day due to partial "on" and reduced "on" duration
- Despite the increasing IR CD/LD dose, he still experienced "off" time
- He switched to **RYTARY**, initially at 48.75/195 mg, 2 capsules 4 times a day, and needed a subsequent dose adjustment to 5 times a day, resulting in a reduction of "off" time

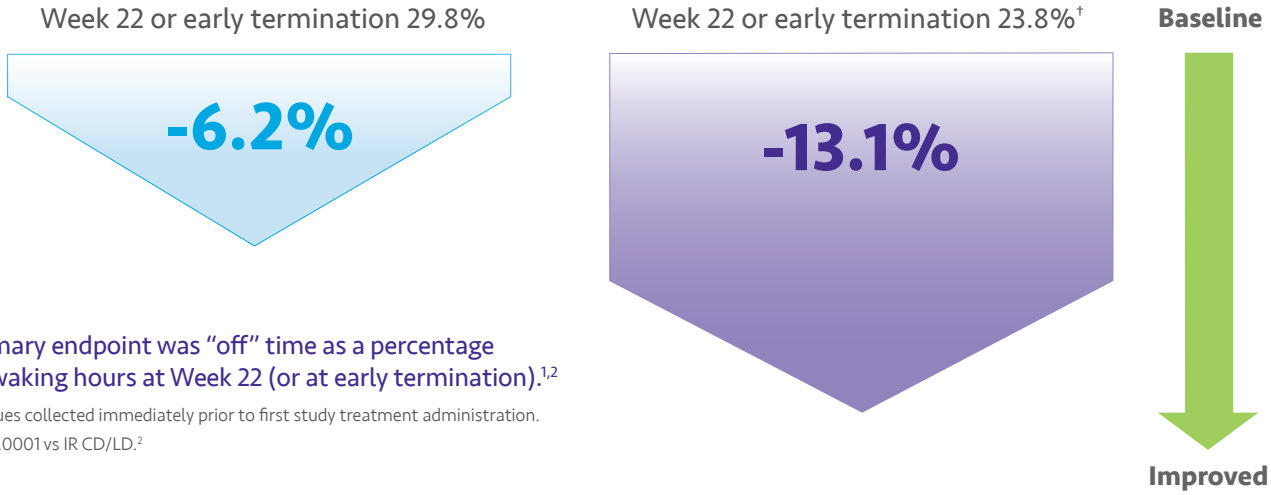
Individual results may vary.

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

Compared with optimized IR CD/LD, RYTARY demonstrated **2X the reduction** in "off" time[1,2]

PRIMARY ENDPOINT RESULTS

Percentage of "off" time during waking hours: head-to-head vs IR CD/LD (N=393)[1,2]



Primary endpoint was "off" time as a percentage of waking hours at Week 22 (or at early termination).[1,2]

* Values collected immediately prior to first study treatment administration.

† *P*<0.0001 vs IR CD/LD.[2]

The term "optimized" refers to the process of adjusting the dose and frequency of IR CD/LD as necessary to achieve optimum motor function.[2]

Phil's current treatment status:

- Following the dose optimization on **RYTARY**, Phil had a reduction in "off" time with no morning or end-of-dose wearing "off"
- Currently, Phil experiences good days at work with **RYTARY**. He reports improvement in motor function with no dyskinesia
- Phil does experience additional symptoms at times, including changes in gait, differences in chewing and swallowing, and dystonia in his legs

Individual results may vary.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

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, and believed that they were alert immediately prior to the event.

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

SECONDARY ENDPOINT RESULTS

In the same head-to-head trial, patients taking RYTARY experienced:

2X REDUCTION IN "OFF" TIME

during waking hours
(2.2 hours* vs 1.0 hour with IR CD/LD)[2]

Baseline: 6.1 hours with RYTARY vs 5.9 hours with IR CD/LD.
Week 22‡: 3.9 hours with RYTARY vs 4.9 hours with IR CD/LD.

2X INCREASE IN "ON" TIME

without troublesome dyskinesia
(1.8 hours† vs 0.8 hour with IR CD/LD)[2]

Baseline: 10 hours with RYTARY vs 10.1 hours with IR CD/LD.
Week 22‡: 11.8 hours with RYTARY vs 10.9 hours with IR CD/LD.

Improved ADL and motor functions measured through UPDRS Parts II and III scores§

Secondary endpoints included the total "off" time during waking hours and the total "on" time without troublesome dyskinesia.

ADL, activities of daily living; UPDRS, Unified Parkinson's Disease Rating Scale.

*$P<0.0001$ vs IR CD/LD, †$P=0.0002$ vs IR CD/LD, ‡Or early termination, §$P<0.0001$ vs IR CD/LD.

Phil began to experience motor fluctuations with IR CD/LD. Switching to RYTARY gave him less "off" time and more "on" time without troublesome dyskinesia.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

Some of these events have been reported more than 1 year after initiation of treatment. Before initiating treatment with RYTARY, 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.

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Comparable adverse event rates vs IR CD/LD[1]

SAFETY Most common adverse reactions in head-to-head pivotal trial[1]

Adverse reaction*	IR CD/LD (n=192)		RYTARY (n=201)	
	Dose Conversion to RYTARY†	IR CD/LD Maintenance	Dose Conversion to RYTARY†	RYTARY Maintenance
Nausea	6%	2%	4%	3%
Headache	3%	2%	5%	1%

*Adverse reactions occurring in at least 5% of patients treated with RYTARY and at a higher rate than optimized IR CD/LD.
†All patients were converted to RYTARY in the open-label Dose Conversion period and then received randomized treatment during maintenance.

- 5% of patients discontinued treatment due to adverse reactions during conversion to RYTARY[1]
- The most common adverse reactions leading to discontinuation during dose conversion were dyskinesia, anxiety, dizziness, and "on-off" phenomenon[1]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

Falling Asleep During Activities of Daily Living and Somnolence (continued): Prescribers should consider discontinuing RYTARY in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating). 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. If the decision is made to discontinue RYTARY, the dose should be tapered to reduce the risk of hyperpyrexia and confusion.

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.

Hallucinations/Psychosis: There is an increased risk for hallucinations and psychosis in patients taking RYTARY. 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 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.

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. 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 RYTARY. Consider a dose reduction or stopping the medication if a patient develops such urges while taking RYTARY.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

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: RYTARY may cause increased intraocular pressure in patients with glaucoma. Monitor intraocular pressure in patients with glaucoma after starting RYTARY.
Melanoma: Patients with Parkinson's disease have a higher risk of developing melanoma than the general population. Patients and providers are advised to monitor for melanoma frequently and on a regular basis when using RYTARY.

ADVERSE REACTIONS:

Clinical Trials Experience:

Early Parkinson's Disease: Most common adverse reactions (incidence ≥ 5 % and greater than placebo) are nausea, dizziness, headache, insomnia, abnormal dreams, dry mouth, dyskinesia, anxiety, constipation, vomiting, and orthostatic hypotension.

Advanced Parkinson's Disease: Most common adverse reactions (incidence ≥ 5 % and greater than oral immediate-release carbidopa-levodopa) are nausea and headache.

Postmarketing Experience: Reported adverse reactions identified during post approval use of RYTARY include suicide attempt and ideation. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to RYTARY exposure.

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. Monitor patients for worsening Parkinson's symptoms.

USE IN SPECIFIC POPULATIONS:

Pregnancy and nursing mothers: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. In animal studies, carbidopa-levodopa has been shown to be developmentally toxic (including teratogenic effects) at clinically relevant doses. RYTARY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Carbidopa is excreted in rat milk. Excretion of levodopa in human milk was reported in one nursing mother. Caution should be exercised when RYTARY is administered to a nursing woman.
Pediatrics: Safety and effectiveness in pediatric populations have not been established.

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). 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. Swallow RYTARY whole with or without food. A high-fat, high-calorie meal may delay the absorption of levodopa by about 2 hours.
For patients who have difficulty swallowing capsules, administer RYTARY by carefully twisting apart both halves of the capsule. Sprinkle the entire contents of both halves of the capsule on a small amount of applesauce (1 to 2 tablespoons) and consume the mixture immediately. Do not store the drug/food mixture for future use.

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 accompanying Full Prescribing Information.

References: 1. RYTARY [package insert]. Hayward, CA: Impax Laboratories, LLC; 2016.
2. 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.

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