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PHARMACY / MEDICAL POLICY – 5.01.651

Pharmacologic Treatment of Parkinson's Disease

Effective Date:	**Oct. 3, 2025***
Last Revised:	Jun. 10, 2025
Replaces:	N/A

*This policy has been revised. Click here to view the current policy.

RELATED MEDICAL POLICIES:
5.01.605 Medical Necessity Criteria for Pharmacy Edits

Select a hyperlink below to be directed to that section.

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Introduction

Parkinson's disease is a progressive neurological disorder that affects movement. It occurs when nerve cells in the brain do not produce enough dopamine, a chemical that helps control movement. Symptoms include tremors, stiffness, and difficulty with balance and coordination. While there is no cure, drugs can help manage symptoms. These drugs include levodopa, which the brain converts to dopamine, and dopamine agonists (e.g., pramipexole, ropinirole) which mimic the effects of dopamine. Other medications, like MAO-B inhibitors, (e.g., selegiline, rasagiline) help prevent the breakdown of dopamine in the brain. Additionally, COMT inhibitors (e.g., entacapone) may be prescribed to prolong the effect of levodopa. Treatment regimens should be tailored to the individual's clinical profile and disease progression. This policy describes when drugs used to treat Parkinson's disease may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Generic apomorphine	**Generic apomorphine may be considered medically necessary for the intermittent treatment of OFF episodes in individuals with Parkinson's disease when:** • Treated with carbidopa/levodopa **AND** • Tried 1 of the following medications before generic apomorphine: ○ Dopamine agonist (e.g., pramipexole, ropinirole) **OR** ○ COMT (catechol-O-methyltransferase) inhibitor (e.g., entacapone) **OR** ○ Monoamine oxidase B inhibitor (e.g., rasagiline, selegiline)
Apokyn (apomorphine)	**Apokyn (apomorphine) may be considered medically necessary for the intermittent treatment of OFF episodes in individuals with Parkinson's disease when:** • Treated with carbidopa/levodopa **AND** • Tried and had an inadequate response or intolerance to 2 generic medications from different drug classes among the following: ○ Dopamine agonist (e.g., pramipexole, ropinirole) ○ COMT (catechol-O-methyltransferase) inhibitor (e.g., entacapone) ○ Monoamine oxidase B inhibitor (e.g., rasagiline, selegiline) **AND** • Has tried and had an inadequate response to generic apomorphine
• **Crexont (carbidopa-levodopa)** • **Dhivy (carbidopa-levodopa)** • **Duopa (carbidopa-levodopa)**	**Crexont (carbidopa-levodopa), Dhivy (carbidopa-levodopa), Duopa (carbidopa-levodopa), Rytary (carbidopa-levodopa), and Sinemet (carbidopa-levodopa) may be considered medically necessary to treat Parkinson's disease when the individual has tried and had an inadequate response or**

Drug	Medical Necessity
• **Rytary (carbidopa-levodopa)** • **Sinemet (carbidopa-levodopa)**	**intolerance to generic carbidopa and generic levodopa used in combination.**

Gocovri (amantadine)	**Gocovri (amantadine) may be considered medically necessary for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy when the individual has:**
	• Tried and had an inadequate response or intolerance to generic amantadine
	AND
	• Dose is limited to 274 mg per day (taken as two 137 mg capsules)
	
	Gocovri (amantadine) may be considered medically necessary as adjunctive treatment to carbidopa/levodopa in individuals with Parkinson's disease experiencing OFF episodes when the individual has:
	• Tried and had an inadequate response or intolerance to 2 generic medications from different drug classes among the following:
	  ○ Dopamine agonist (e.g., pramipexole, ropinirole)
	  ○ COMT (catechol-O-methyltransferase) inhibitor (e.g., entacapone)
	  ○ Monoamine oxidase B inhibitor (e.g., rasagiline, selegiline)
	AND
	• Dose is limited to 274 mg per day (taken as two 137 mg capsules)

Inbrija (levodopa inhalation powder)	**Inbrija (levodopa inhalation powder) may be considered medically necessary for the intermittent treatment of OFF episodes in individuals with Parkinson's disease when:**
	• Treated with carbidopa/levodopa
	AND
	• Tried 1 of the following medications before Inbrija:
	  ○ Dopamine agonist (e.g., pramipexole, ropinirole)
	  OR

Drug	Medical Necessity
	○ COMT (catechol-O-methyltransferase) inhibitor (e.g., entacapone) **OR** ○ Monoamine oxidase B inhibitor (e.g., rasagiline, selegiline)
Lodosyn (carbidopa)	**Lodosyn (carbidopa) may be considered medically necessary to treat Parkinson's disease when the individual has tried and had an inadequate response or intolerance to generic carbidopa.**
Nourianz (istradefylline)	**Nourianz (istradefylline) may be considered medically necessary as adjunctive treatment to carbidopa/levodopa in individuals with Parkinson's disease when the individual has:** • Tried and had an inadequate response or intolerance to 2 generic medications from different drug classes among the following: ○ Dopamine agonist (e.g., pramipexole, ropinirole) ○ COMT (catechol-O-methyltransferase) inhibitor (e.g., entacapone) ○ Monoamine oxidase B inhibitor (e.g., rasagiline, selegiline)
Onapgo (apomorphine)	**Onapgo (apomorphine) may be considered medically necessary for the treatment of motor fluctuations in individuals with advanced Parkinson's disease when:** • The individual is aged 18 years or older **AND** • Diagnosed with idiopathic advanced Parkinson's disease **AND** • Receiving treatment with carbidopa/levodopa therapy **AND** • Experiencing persistent motor fluctuations despite optimized carbidopa /levodopa therapy **AND** • Has a minimum of 3 hours of "off" time per day **AND** • Tried and had an inadequate response or intolerance to 2 generic medications from different drug classes among the following: ○ Dopamine agonist (e.g., pramipexole, ropinirole) ○ COMT (catechol-O-methyltransferase) inhibitor (e.g., entacapone)

Drug	Medical Necessity
	○ Monoamine oxidase B inhibitor (e.g., rasagiline, selegiline) **AND** • Tried and had an inadequate response or intolerance to intermittent apomorphine use **AND** • Medication is prescribed by or in consultation with a neurologist **AND** • Is not currently taking $5HT_3$ antagonists, including antiemetics (e.g., ondansetron, granisetron, palonosetron) and alosetron **AND** • The maximum total daily dosage is limited to 98 mg
Ongentys (opicapone)	**Ongentys (opicapone) may be considered medically necessary as adjunctive treatment to carbidopa/levodopa in individuals with Parkinson's disease experiencing OFF episodes when the individual has:** • Tried and had an inadequate response or intolerance to entacapone or tolcapone
Osmolex ER (amantadine)	**Osmolex ER (amantadine) may be considered medically necessary to treat adult individuals with:** • Parkinson's disease **OR** • Drug-induced extrapyramidal reactions **AND** • The individual has tried and had an inadequate response or intolerance to generic amantadine **AND** • Dose is limited to 322 mg per day (taken as 129 mg tablet and 193 mg tablet)
Stalevo (carbidopa-levodopa-entacapone)	**Stalevo (carbidopa-levodopa-entacapone) may be considered medically necessary to treat individuals with Parkinson's disease when the individual has tried and had an inadequate response or intolerance to generic carbidopa, generic levodopa, and generic entacapone used in combination.**
Vyalev (foscarbidopa and foslevodopa)	**Vyalev (foscarbidopa and foslevodopa) may be considered medically necessary for the treatment of motor fluctuations in individuals with advanced Parkinson's disease when:**

Drug	Medical Necessity
	• The individual is aged 18 years or older **AND** • Diagnosed with idiopathic advanced Parkinson's disease that is levodopa responsive **AND** • Experiencing persistent motor fluctuations despite optimized carbidopa /levodopa therapy **AND** • Taking at least 400 mg of levodopa per day **AND** • Has a minimum of 2.5 hours of "off" time per day **AND** • Tried 1 of the following medications before Vyalev: ○ Dopamine agonist (e.g., pramipexole, ropinirole) **OR** ○ COMT (catechol-O-methyltransferase) inhibitor (e.g., entacapone) **OR** ○ Monoamine oxidase B inhibitor (e.g., rasagiline, selegiline) **OR** ○ Amantadine **AND** • Medication is prescribed by or in consultation with a neurologist **AND** • Not currently taking a nonselective MAO inhibitor (e.g., isocarboxazid, phenelzine, tranylcypromine) or have recently (within 2 weeks) taken a nonselective MAO inhibitor **AND** • The maximum daily dosage is limited to 3,525 mg of the foslevodopa component (equivalent to approximately 2,500 mg levodopa)
Xadago (safinamide)	**Xadago (safinamide) may be considered medically necessary to treat Parkinson's disease when all the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity

	• Is experiencing OFF episodes on carbidopa-levodopa therapy
	AND
	• Use is concomitant with carbidopa-levodopa
	AND
	• Has tried and had an inadequate response or intolerance to **2** of the following:
	  ○ Entacapone
	  ○ Pramipexole
	  ○ Pramipexole ER
	  ○ Rasagiline
	  ○ Ropinirole
	  ○ Ropinirole ER
	  ○ Selegiline
	  ○ Tolcapone

Zelapar (selegiline)	**Zelapar (selegiline) may be considered medically necessary to treat Parkinson's disease when all the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Is experiencing OFF episodes on carbidopa-levodopa therapy
	AND
	• Use is concomitant with carbidopa-levodopa
	AND
	• Has tried and had an inadequate response or intolerance to **2** of the following:
	  ○ Entacapone
	  ○ Pramipexole
	  ○ Pramipexole ER
	  ○ Rasagiline
	  ○ Ropinirole
	  ○ Ropinirole ER
	  ○ Selegiline
	  ○ Tolcapone

Drug	Investigational
As listed	**Use of the drugs for conditions not listed in this policy are considered investigational.** **The drugs listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews for all drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **All other reviews for re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

Code	Description
HCPCS	
J0364	Injection, apomorphine HCl (Apokyn), 1 mg
J3490	Unclassified drugs (used to report: Onapgo)
J7356	Injection, foscarbidopa 0.25 mg/foslevodopa (Vyalev), 5 mg (new code effective 07/01/25)

Related Information

Consideration of Age

Ages stated in this policy for which the drugs are considered medically necessary are based on the FDA labeling for the drug.

Benefit Application

Pharmacy Benefit

Crexont (carbidopa-levodopa), Dhivy (carbidopa-levodopa), Duopa (carbidopa-levodopa), generic apomorphine, Gocovri (amantadine), Inbrija (levodopa inhalation powder), Lodosyn (carbidopa), Nourianz (istradefylline), Ongentys (opicapone), Osmolex ER (amantadine), Rytary (carbidopa-levodopa), Sinemet (carbidopa-levodopa), Stalevo (carbidopa-levodopa-entacapone), Xadago (safinamide), and Zelapar (selegiline) are managed through the pharmacy benefit.

Medical Benefit

Onapgo (apomorphine) and Vyalev (foscarbidopa and foslevodopa) are managed through the medical benefit.

Medical and Pharmacy Benefit

Apokyn (apomorphine) is managed through the medical and pharmacy benefit.

Evidence Review

Background

Parkinson's disease (PD) is an adult-onset, progressive, neurodegenerative disease. In the United States, approximately 1 million people are living with PD, with an anticipated increase to 1.2 million people by 2030. Symptoms develop slowly over time and include both movement (motor)-related and nonmovement symptoms. The cause of PD is multifactorial, with genetic and environmental factors playing key roles in the development of the disease. Patients with PD experience dysfunction and death of dopaminergic neurons in the substantia nigra of the brain, as well as accumulation of the protein alpha-synuclein (Lewy bodies). This leads to imbalances in neurotransmitters and other adverse effects that cause the symptoms of PD. Dopamine is a key neurotransmitter in movement and emotional responses. By the time patients are diagnosed, approximately 60% to 80% of dopaminergic neurons have been lost.

There are no disease-modifying agents for the treatment of PD. Symptomatic treatment is the mainstay of PD management. Pharmacologic treatment is typically delayed until symptoms become bothersome to the patient. In most patients with early PD seeking control of motor symptoms, levodopa (LD) is recommended as initial therapy. In select cases, initial treatment with monoamine oxidase type B (MAO-B) inhibitors, dopamine agonists, or amantadine may be offered as an alternative to early LD. Currently, LD is the most effective treatment for motor symptoms of PD, but it also requires the most frequent dosing and is associated with the highest risk of dopaminergic motor complications (e.g. "wearing off" and dyskinesia). Treatment with LD is more likely to cause dyskinesia than other PD treatment options within the first 5 years, so the minimum effective dose should be used, and patients should be counseled regarding this risk. Controlled-release (CR) formulations of LD and carbidopa (CD)/LD/entacapone have not been shown to be superior for motor benefit in early PD. Immediate-release (IR) CD/LD is the preferred initial formulation. Most neurologists prefer to use a combination of agents rather than increase the dose of a single agent. Good control typically lasts about 5 years with LD, after which motor fluctuations (e.g. "wearing-off" and "on-off" phenomena) and dyskinesia develop.

Summary of Evidence

Gocovri (amantadine)

Gocovri is an extended-release dosage form of amantadine. The efficacy of Gocovri for the treatment of dyskinesia in patients with Parkinson's disease and for the adjunctive treatment to levodopa/carbidopa in patients with Parkinsons's disease experiencing "off" episodes was assessed in two randomized, double-blind, placebo-controlled efficacy trials: Study 1 and Study 2. Key inclusion criteria in both studies included at least 1 hour of troublesome dyskinesia time during the day and at least mild functional impact because of dyskinesia.

Study 1 was conducted in 121 (modified Intention to Treat (mITT) population) Parkinson's disease patients with dyskinesia in the US and Canada. The duration of treatment in Study 1 was up to 25 weeks. Study 2 was conducted in 75 (mITT population) patients with dyskinesia in the US, Germany, France, Spain, and Austria. The duration of treatment was 13 weeks. In both studies, the primary efficacy endpoint was the change in total score of the Unified Dyskinesia Rating Scale (UDysRS) between baseline and Week 12. Key secondary endpoints derived from a Parkinson's disease home diary included changes from baseline to Week 12 in ON time without troublesome dyskinesia and OFF time.

In Study 1 and Study 2, the mean age of patients at the time of Parkinson's disease diagnosis was 55 years (range: 29-75 years). At baseline, patients had a mean UDysRS total score of 40.1 (range: 8-76), a mean duration of ON time without troublesome dyskinesia (Parkinson's disease home diary) of 8.4 hours (range: 0-15.3), and a mean duration of OFF time of 2.8 hours (range: 0-9.5). Patients in Study 1 and Study 2 were treated with a stable dose of levodopa, with 32% of patients on levodopa monotherapy. Patients were also treated with concomitant dopamine agonists (54%) and/or MAO-B inhibitors (44%).

In Study 1 and Study 2, a significant decrease in mean UDysRS total score (reduction in dyskinesia) was observed at Week 12 in patients treated with Gocovri, compared with placebo ($p=0.0009$ and $p=<0.0001$, respectively). In Study 1 and Study 2, there was also a significant increase in ON time without troublesome dyskinesia ($p=<0.0001$ and $p=0.0168$, respectively), and a significant decrease in OFF time ($p=0.0171$ and $p=0.0199$, respectively) between baseline and Week 12 in patients treated with Gocovri, compared with placebo.

The most commonly observed adverse reactions occurring at a frequency of >10% and greater than placebo were hallucination, dizziness, dry mouth, peripheral edema, constipation, fall, and orthostatic hypotension.

Inbrija (levodopa inhalation powder)

Inbrija is an aromatic amino acid indicated for the intermittent treatment of OFF episodes in patients with Parkinson's disease treated with carbidopa/levodopa. The efficacy and safety of Inbrija for the treatment of OFF episodes in patients with Parkinson's disease treated with oral carbidopa/levodopa was evaluated in a 12-week, randomized, placebo-controlled, double-blind study (Study 1; NCT02240030). In Study 1, a total of 114 patients were treated with Inbrija 84 mg (two 42 mg capsules), and 112 patients received placebo. Study medication could be administered up to five times a day. At baseline, patients had at least 2 hours of OFF time per day, and carbidopa/levodopa medication did not exceed 1600 mg levodopa per day. The mean Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores at screening in the ON state were 14.9 for patients randomized to Inbrija 84 mg and 16.1 for patients randomized to placebo. The UPDRS part III is designed to assess the severity of the cardinal motor findings (e.g., tremor, rigidity, bradykinesia, postural instability) in patients with Parkinson's disease. The primary endpoint was the change in UPDRS Part III motor score from pre-dose OFF state to 30 minutes post-dose, measured at Week 12. The average use of Inbrija 84 mg or placebo was approximately 2 doses per day. At Week 12, the reduction in UPDRS Part III motor score for Inbrija 84 mg, compared to placebo at 30 minutes post-dose, were -9.8 and -5.9, respectively. The proportion of patients who returned to an ON state and sustained that ON through 60 minutes post-dose was 58% for INBRIJA 84 mg and 36% for placebo (p=0.003).

The most common adverse reactions (incidence ≥ 5% and higher than placebo) were cough, nausea, upper respiratory tract infection, and sputum discolored.

Nourianz (istradefylline)

Nourianz is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes. The efficacy of Nourianz for the adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes was shown in four randomized, multicenter, double-blind, 12-week, placebo-controlled studies (Study 1, NCT00456586; Study 2, NCT00199407; Study 3, NCT00455507; and Study 4, NCT00955526). The studies enrolled patients with a mean duration of PD of 9 years (range: 1 month to 37 years) that were Hoehn and Yahr Stage II to IV, experiencing at least 2 hours (mean approximately 6 hours) of "off" time per day, and were treated with levodopa for at least one year, with stable dosage for at least 4 weeks before screening (mean total daily dosage range: 416 to 785 mg). Patients continued levodopa treatment with or without concomitant PD medications, including dopamine agonists (85%),

COMT inhibitors (38%), MAO-B inhibitors (40%), anticholinergics (13%), and/or amantadine (33%), provided the medications were stable for at least 4 weeks before screening and throughout the study period. The studies excluded patients who had received a neurosurgical treatment for PD (e.g., pallidotomy, thalamotomy, deep brain stimulation).

The primary efficacy endpoint was the change from baseline in the daily awake percentage of "off" time, or the change from baseline in total daily "off" time, based on 24-hour diaries completed by patients. A change from baseline in "on" time without troublesome dyskinesia (i.e., "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia) was a secondary efficacy endpoint.

Study 1 was conducted in the US and Canada, and Study 2 was conducted in the US In these studies, patients were randomized to once-daily treatment with Nourianz 20 mg, 40 mg, or placebo. Patients treated with Nourianz 20 mg or Nourianz 40 mg once daily experienced a statistically significant decrease from baseline in percentage of daily awake "off" time, compared with patients on placebo. Compared with patients on placebo, patients treated with Nourianz experienced an additional increase from baseline in "on" time without troublesome dyskinesia of 0.96 hours (nominal p=0.026) in Study 1, and of 0.55 hours (nominal p=0.135) in Study 2.

Study 3 and Study 4 were conducted in Japan. In these studies, patients were randomized equally to treatment with Nourianz 20 mg, 40 mg, or placebo. Patients treated with Nourianz 20 mg or Nourianz 40 mg once daily experienced a statistically significant decrease from baseline in "off" time compared with patients on placebo. In Study 3, compared with placebo, an additional increase from baseline in "on" time without troublesome dyskinesia of 0.57 hours (nominal p=0.085) and of 0.65 hours (nominal p=0.048), respectively, were observed in patients treated with Nourianz 20 mg or Nourianz 40 mg. In Study 4, the corresponding increases in "on" time without troublesome dyskinesia were 0.83 hours (nominal p=0.008) for Nourianz 20 mg and 0.81 hours (nominal p=0.008) for Nourianz 40 mg.

The most common adverse reactions (at least 5% and more frequent than placebo) were dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia.

Onapgo (apomorphine)

Onapgo approval was based on results from the Phase 3 TOLEDO study, a randomized, double-blind trial that evaluated the safety and efficacy of Onapgo in patients with PD experiencing motor fluctuations while on carbidopa/levodopa and other PD medications. The 12-week study included 1–4 weeks of dose titration, followed by continued treatment at a stable, individualized dosage. Results showed that at 12 weeks, Onapgo significantly reduced daily off-time (when

medication is not working optimally) compared with placebo. Onapgo-treated patients (n = 53) experienced a 2.6-hour reduction, compared with 0.9 hours in the placebo group (n = 51). This was accompanied by a significant increase in daily on time (when medication is working well), with 2.8 hours for Onapgo-treated patients versus 1.1 hours for the placebo group. Improvements were observed as early as Week 1 and were maintained throughout all measured timepoints.

The most common adverse reactions (incidence ≥10% on Onapgo and at least twice the rate of placebo) were infusion site nodule, nausea, somnolence, infusion site erythema, dyskinesia, headache, and insomnia.

Ongentys (opicapone)

Ongentys is a catechol-O-methyltransferase (COMT) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes. The efficacy of Ongentys for the adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes was evaluated in two double-blind, randomized, parallel-group, placebo- and active-controlled (Study 1, NCT01568073), or placebo-controlled (Study 2, NCT01227655) studies of 14-15 week duration. All patients were treated with levodopa/ DOPA decarboxylase inhibitor (DDCI) (alone or in combination with other PD medications). The double-blind period for each study began with a period for levodopa/DDCI dose adjustment (up to 3 weeks), followed by a stable maintenance period of 12 weeks.

In Study 1, patients (n=600) were randomized to treatment with one of 3 doses of Ongentys. The intention to treat (ITT) population included patients treated with Ongentys 50 mg once daily (n=115) or placebo (n=120). Baseline demographic characteristics were similar across all treatment groups: approximately 60% of patients were male, mean age was 64 years, and all patients were Caucasian. Baseline PD characteristics in the treatment groups were a mean duration of PD of 7 years for Ongentys 50 mg compared to 7.7 years for placebo, and mean onset of motor fluctuations of 2.2 years prior to study enrollment. Eighty-two percent of patients in both groups used concomitant PD medications in addition to levodopa; the most used were dopamine agonists (68%), amantadine (23%), MAO-B inhibitors (20%), and anticholinergics (5%).

The primary efficacy endpoint was the change in mean absolute OFF-time based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. Ongentys 50 mg significantly reduced mean absolute OFF-time compared to placebo (p=0.002).

In Study 2, patients (n=427) were randomized to treatment with either one of two doses of Ongentys once daily (n=283) or placebo (n=144). The ITT study population included patients

treated with Ongentys 50 mg once daily (n=147) or placebo (n=135). Baseline demographic characteristics (Ongentys 50 mg vs. placebo) were: mean age (66 years vs. 62 years), male (61% vs. 53%), Caucasian (78% vs. 66%) and Asian (21% vs. 31%). Baseline PD characteristics were generally similar across treatment groups with a mean duration of PD of 8.2 years, and a mean onset of motor fluctuations of 3.2 years prior to study enrollment. Eighty-five percent of patients treated with Ongentys 50 mg compared to 81% of patients who received placebo used concomitant PD medications in addition to levodopa; the most used were dopamine agonists (70%), amantadine (21%), MAO-B inhibitors (20%), and anticholinergics (12%). The primary efficacy endpoint was the change in mean absolute OFF-time based on 24-hour patient diaries completed 3 days prior to each of the scheduled visits. Ongentys 50 mg significantly reduced mean absolute OFF-time compared to placebo (p=0.008).

The most common adverse reactions (≥4% and > placebo) were dyskinesia, constipation, blood creatine kinase increased, hypotension/syncope, and weight decreased.

Vyalev (foscarbidopa and foslevodopa)

Vyalev injection is a solution that is a combination of foscarbidopa and foslevodopa. Foscarbidopa and foslevodopa are prodrugs that undergo enzymatic bioconversion via intrinsic alkaline phosphatase to carbidopa and levodopa. The Phase 3 randomized, double-blind, double-dummy, active-controlled study (MI5-736) compared the efficacy, safety & tolerability of foscarbidopa/foslevodopa to oral immediate-release carbidopa/levodopa (CD/LD IR), in patients with advanced PD. Participants were provided with a home diary to assess their motor state during the day. The primary endpoint of good "on" time (defined as "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia), was collected & averaged over 3 consecutive days & normalized to a typical 16-hour waking period. Baseline values are defined as the average of normalized good "on" time collected over the 3 PD Diary days before randomization. Approximately 130 adults were enrolled in the study across 80 sites in the U.S. & Australia. Participants were randomized 1:1 to receive either the foscarbidopa/foslevodopa solution as a SC continuous delivery plus oral placebo apsules or oral capsules containing CD/LD IR plus continuous SC delivery of placebo solution for foscarbidopa/foslevodopa. The treatment duration was 12 weeks. The increase in "on" time without troublesome dyskinesia at week 12 was 2.72 hours for foscarbidopa/foslevodopa versus 0.97 hours for oral CD/LD IR (p=0.0083). Improvements in "on" time were observed as early as the first week & persisted throughout the 12 weeks. The most frequent adverse reactions with Vyalev (incidence ≥10% and greater than with CD/LD IR) included infusion site reactions/infections, hallucinations, and dyskinesia.

Xadago (safinamide)

Xadago is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes. Two double-blind, placebo-controlled, multi-national, 24-week studies (Study 1 and Study 2) were conducted in PD patients experiencing "OFF" Time during treatment with carbidopa/levodopa and other PD medications, e.g., dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, anticholinergics, and/or amantadine. In both studies, the primary measure of effectiveness was the change from baseline in total daily "ON" Time without troublesome dyskinesia (i.e., "ON" Time without dyskinesia plus "ON" Time with non-troublesome dyskinesia), based on 18-hour diaries completed by patients for at least 3 days before each of the scheduled visits. Secondary endpoints included "OFF" Time during the diary period and reduction in Unified PD Rating Scale (UPDRS) Part III (motor examination).

In Study 1, patients (n=645) were randomized equally to treatment with Xadago 50 mg/day (n=217 patients), Xadago 100 mg/day (n=216 patients), or placebo (n=212 patients), and had at least one post-baseline assessment of "ON" Time. The percentages of patients taking stable doses of other classes of PD medications, in addition to levodopa/decarboxylase inhibitor, were dopamine agonists (61%), COMT inhibitors (24%), anticholinergics (37%), and amantadine (14%). Use of MAOIs was prohibited. The average daily dosage of levodopa was 630mg. The mean duration of PD was approximately 8 years.

In Study 1, Xadago 50 mg/day and 100 mg/day significantly increased "ON" Time compared to placebo (p=0.0356 and p=0.0238, respectively). The increase in "ON" Time without troublesome dyskinesia was accompanied by a similar significant reduction in "OFF" Time (p=0.0049 and p=0.0037, respectively) and a reduction in Unified PD Rating Scale Part III (UPDRS III) scores assessed during "ON" Time (p=0.0212 and p=0.0011, respectively). Improvement in "ON" Time occurred without an increase in troublesome dyskinesia. Patients who dropped out of the study because of an adverse reaction, lack of efficacy, non-compliance, or withdrawal of consent were treated as treatment failures and assumed to have the smallest change from baseline among all patients. The failure rates are 6.1%, 5.6%, and 6.9% for the placebo group, Xadago 50 mg/day group, and Xadago 100 mg/day group, respectively.

In Study 2, patients (n=549) were randomized to treatment with Xadago 100 mg daily (n=274 patients) or placebo (n=275 patients) for up to 24 weeks. The percentages of patients taking stable doses of other classes of PD medication, in addition to levodopa/decarboxylase inhibitor, were dopamine agonists (74%), COMT inhibitors (18%), anticholinergics (17%), and amantadine (30%). Use of MAOIs was prohibited. The average daily dosage of levodopa was 777 mg. The mean duration of PD was approximately 9 years.

In Study 2, Xadago was significantly better than placebo for increasing "ON" Time ($p < 0.001$). The observed increase in "ON" Time without troublesome dyskinesia was accompanied by a reduction in "OFF" Time of similar magnitude and a reduction in UPDRS III score (assessed during "ON" Time). As in Study 1, the increase in "ON" Time without troublesome dyskinesia was accompanied by a similar significant reduction in "OFF" Time ($p<0.001$) and a reduction in Unified PD Rating Scale Part III (UPDRS III) scores assessed during "ON" Time ($p=0.005$).

The most common adverse reactions (incidence on Xadago 100 mg/day at least 2% greater than placebo) were dyskinesia, fall, nausea, and insomnia.

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History

Date	Comments
03/01/25	New policy, approved February 11, 2025. Add to Prescription Drug section. Moved the Parkinson's disease drugs generic apomorphine, Apokyn (apomorphine), Crexont (carbidopa-levodopa), Dhivy (carbidopa-levodopa), Duopa (carbidopa-levodopa), Rytary (carbidopa-levodopa), Sinemet (carbidopa-levodopa), Gocovri (amantadine), Inbrija (levodopa inhalation powder), Lodosyn (carbidopa), Nourianz (istradefylline), Ongentys (opicapone), Osmolex ER (amantadine), Stalevo (carbidopa-levodopa-entacapone), Xadago (safinamide), and Zelapar (selegiline) from policy 5.01.605 Medical Necessity Criteria for Pharmacy Edits to 5.01.651 Pharmacologic Treatment of Parkinson's Disease with no changes to the coverage criteria.
04/01/25	Interim Review, approved March 11, 2025. Added coverage criteria for Vyalev (foscarbidopa and foslevodopa) for the treatment of motor fluctuations in individuals with advanced Parkinson's disease. Added HCPC code J7799 to report Vyalev.
07/01/25	Interim Review, approved June 10, 2025. Added coverage criteria for Onapgo (apomorphine) for the treatment of motor fluctuations in individuals with advanced Parkinson's disease. Added HCPC code J7356 for Vyalev and J3490 for Onapgo due to criteria update. The following policy changes are effective October 3, 2025 following a 90-day provider notification. Added HCPC code J0364 for Apokyn. Clarified that Apokyn coverage criteria will apply to the medical benefit.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.