LOUISIANA BLUE

Pharmacologic Treatment of Off Episodes in Parkinson Disease

Policy # 00603
Original Effective Date: 01/17/2018
Current Effective Date: 04/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider Xadago®‡ (safinamide), Inbrija™‡ (levodopa), Nourianz™‡ (istradefylline), Apokyn®‡ (apomorphine hydrochloride), generic apomorphine, Ongentys®‡ (opicapone), or Vyalev™‡ (foscarbidopa/ foslevodopa injection) to be **eligible for coverage**** when the patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for Xadago (safinamide), Inbrija (levodopa), Nourianz (istradefylline), Apokyn (apomorphine hydrocholoride), generic apomorphine, Ongentys (opicapone), or Vyalev (foscarbidopa/ foslevodopa injection) will be considered when the following criteria are met:

- For Xadago, Inbrija, Nourianz, or Ongentys requests:
  - Patient has a diagnosis of Parkinson disease; AND
  - Patient is currently being treated with levodopa/carbidopa and is experiencing "off" episodes; AND
  - Patient has tried and failed (e.g. intolerance or inadequate response) TWO of the following alternatives: generic pramipexole, generic ropinirole, generic entacapone, generic selegiline, or generic rasagiline unless there is clinical evidence or patient history that suggests the use of the alternative products will be ineffective or cause an adverse reaction to the patient.
    *(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- For Apokyn or generic apomorphine requests:
    - Patient has a diagnosis of Parkinson disease; AND
    - Patient is currently being treated with levodopa/carbidopa and is experiencing "off" episodes; AND
      *(Note: The requirement that the patient is currently being treated with levodopa/carbidopa is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - Patient has tried and failed (e.g., intolerance or inadequate response) ONE of the following alternatives: generic pramipexole, generic ropinirole, generic entacapone, generic selegiline, or generic rasagiline unless there is clinical evidence or patient history that suggests the use of the alternative products will be ineffective or cause an adverse reaction to the patient; AND
      *(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - If the request is for brand Apokyn, patient has tried and failed (e.g., intolerance or inadequate response) GENERIC apomorphine unless there is clinical evidence or patient history that suggests the use of generic apomorphine will be ineffective or cause an adverse reaction to the patient.
      *(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- For Vyalev requests:
    - Initial
        - Patient is diagnosed with advanced Parkinson's disease; AND
        - Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
        - Patient has tried an oral carbidopa/levodopa therapy and meets ONE of the following:
            - Patient had significant intolerance, according to the prescriber; OR
            - Patient had inadequate efficacy, according to the prescriber; AND

          *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
        - Daily dose does not exceed 3525 mg of the foslevodopa component (equivalent to approximately 2500 mg levodopa).
    - Continuation
        - Patient has received an initial approval for the requested medication; AND

- According to the prescriber, the patient continues to benefit from therapy with Vyalev (e.g., stabilization in clinical signs and symptoms of disease, increase of "on"-time, or decrease in the number of "off" episodes compared to baseline); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Daily dose does not exceed 3525 mg of the foslevodopa component (equivalent to approximately 2500 mg levodopa).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Xadago (safinamide), Inbrija (levodopa), Nourianz (istradefylline), or Ongentys (opicapone) when the patient has not tried and failed at least two alternative products listed in the patient selection criteria to be **not medically necessary.****

Based on review of available data, the Company considers the use of Apokyn (apomorphine hydrochloride) or generic apomorphine, when the patient has not tried and failed at least one alternative product listed in the patient selection criteria to be **not medically necessary.****

Based on review of available data, the Company considers the use of brand Apokyn (apomorphine hydrochloride) when the patient has not tried and failed GENERIC apomorphine to be **not medically necessary.****

Based on review of available data, the Company considers the use of Apokyn (apomorphine hydrochloride) or generic apomorphine when the patient is not currently being treated with levodopa/carbidopa to be **not medically necessary.****

Based on review of available data, the Company considers the use of Vyalev (foscarbidopa/ foslevodopa injection) when the patient has not tried and failed and oral carbidopa/levodopa therapy to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of Vyalev (foscarbidopa/ foslevodopa injection) when the patient has not demonstrated a beneficial response to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers Xadago (safinamide), Inbrija (levodopa), Nourianz (istradefylline), Apokyn (apomorphine hydrochloride), generic apomorphine, Ongentys (opicapone), or Vyalev (foscarbidopa/ foslevodopa injection) for the treatment of any indication other than "off" episodes in Parkinson disease to be **investigational.***

Based on review of available data, the Company considers Xadago (safinamide), Inbrija (levodopa), Nourianz (istradefylline), or Ongentys (opicapone) in patients who are not currently being treated with levodopa/carbidopa to be **investigational.***

Based on the review of available data, the Company considers Vyalev in daily doses that exceed 3525 mg of the foslevodopa component (equivalent to approximately 2500 mg levodopa) to be **investigational.***

Background/Overview

Xadago is a reversible inhibitor of monoamine oxidase B (MAO-B) that is used to prevent the degradation of dopamine and prevent "off" episodes in patients with Parkinson disease managed by levodopa/carbidopa. It is available as a 50 mg and 100 mg tablet and dosed 50 or 100 mg once daily. Unlike the other MAO-B inhibitors, selegiline and rasagiline, Xadago inhibits MAO-B reversibly. It is contraindicated in severe hepatic impairment and when administered concomitantly with any other MAO inhibitor (including linezolid), opioid drugs, serotonin-norepinephrine receptor inhibitors (SNRIs), tricyclic, tetracyclic, or triazolopyridine antidepressants, cyclobenzaprine, methylphenidate, amphetamine derivatives, St. John's Wort, and dextromethorphan.

Inbrija is an inhaled formulation of levodopa and is indicated to treat "off" episodes in patients with Parkinson disease managed by levodopa/carbidopa. The contents of two 42 mg capsules should be inhaled as needed, up to 5 times a day. The maximum dose per "off" period is 84 mg (2 capsules) and the maximum daily dose is 420 mg. Like Xadago, Inbrija is also contraindicated in patients taking nonselective MAO inhibitors.

Nourianz is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson disease experiencing "off" episodes. It is dosed as 20 mg once daily, but the dose can be increased to 40 mg once daily if needed. The safety profile of Nourianz is comparable to other therapies for this indication, but the long-term safety and efficacy has not yet been determined.

Apokyn contains apomorphine, which is a non-ergoline dopamine agonist. Apomorphine is available in injectable form as a generic as well as brand Apokyn which is indicated for the acute, intermittent treatment of hypomobility, "off" episodes associated with advanced Parkinson disease. Apokyn should be initially dosed as 0.1 mL (1 mg) or 0.2 mL (2 mg) subcutaneously as needed with doses increased in 0.1 mL (1 mg) increments every few days on an outpatient basis. Apokyn initiation should be co-administered with trimethobenzamide to control nausea and vomiting and continued only as long as necessary. Doses of Apokyn should be separated by at least 2 hours with a maximum of 5 doses per day. The prescribing information states that the initial dose should be supervised by a healthcare provider.

Ongentys is a catechol-o-methyltransferase (COMT) inhibitor indicated for adjunctive treatment to levodopa/carbidopa in patients with Parkinson disease experiencing "off" episodes. It should be dosed as 50 mg by mouth once daily at bedtime. Generically available COMT inhibitors include entacapone and tolcapone, both of which carry the same indication. The possible advantage of Ongentys over these generic products is that it is dosed less frequently. However, Ongentys has not been studied in comparison to these other products. Additionally, these generically available treatment options may provide a more economical and equally efficacious treatment option.

Vyalev is a combination of foscarbidopa (an aromatic amino acid decarboxylation inhibitor) and foslevodopa (an aromatic amino acid) indicated for the treatment of motor fluctuations in adults with advanced Parkinson's disease. Vyalev is administered as a subcutaneous infusion, preferably in the abdomen, via the Vyafuser™ pump. Patients selected for treatment with Vyalev should be capable of understanding and using the delivery system themselves or with assistance from a caregiver. Vyalev is available as an injection at a concentration of 120 mg foscarbidopa and 2,400 mg foslevodopa per 10 mL (12 mg foscarbidopa and 240 mg foslevodopa per mL). Dosing of Vyalev is determined by the total levodopa dosage (TLD) for the levodopa-containing medication that Vyalev is replacing and the number of hours the patient is typically awake. The maximum recommended daily dosage of Vyalev is 3,525 mg of foslevodopa (approximately 2,500 mg levodopa).

Parkinson disease is a progressive neurodegenerative disease in which dopamine depletion from the basal ganglia results in disruptions in the connections to the thalamus and motor cortex. For most patients, first line therapy involves supplementation of dopamine via levodopa/carbidopa. As the disease progresses, periods of increased symptoms known as "off" episodes can occur when levodopa/carbidopa begins to wear off between doses. Initially, these episodes may be managed by adjusting the levodopa/carbidopa dose and schedule, but this may not be sufficient if the patient is experiencing adverse effects of the levodopa/carbidopa (such as dyskinesia). There are four classes of drugs indicated as adjunctive therapy to manage "off" episodes with levodopa/carbidopa: dopamine agonists, catecholamine-O-methyltransferase (COMT) inhibitors, MAO-B inhibitors, and adenosine receptor antagonists. Dopamine agonists such as pramipexole or ropinirole can be effective at prolonging symptom-free periods, but patients must be monitored for excessive dopaminergic effects (hallucinations, confusion, somnolence). The COMT inhibitors entacapone and tolcapone prolong and potentiate the levodopa effect by preventing its degradation. MAO-B

inhibitors also prevent the degradation of levodopa by blocking its catabolism. There are three available MAO-B inhibitors: rasagiline, safinamide, and selegiline. Both rasagiline and safinamide have demonstrated consistent efficacy in reducing motor complications in combination with levodopa/carbidopa, but the clinical benefit of selegiline appears to be relatively mild. Nourianz is a first-in-class adenosine receptor antagonist that appears to have similar efficacy and safety to other treatment options for this indication. Inbrija provides an additional therapy option of supplemental doses of levodopa when the patient notices an "off" episode beginning.

The American Academy of Neurology guidelines for the treatment of Parkinson disease with motor fluctuations and dyskinesia were published in 2006, prior to the approval of Xadago, Inbrija, Nourianz, or Ongentys. These guidelines recommend that rasagiline, pramipexole, ropinirole, apomorphine (i.e., Apokyn), and tolcapone should be considered to reduce "off" time. It should be noted that tolcapone is associated with liver injury and is therefore rarely used.

Additional guidance was published in 2018 by the International Parkinson and Movement Disorder Society which recommends that treatment approaches be individualized to the patient based on the evaluation of side effect profiles, patient specific characteristics as well as cost and availability. There are currently no studies to suggest superiority of one drug class over another in symptom management. For patients with motor fluctuations, dopamine agonists (pramipexole, ropinirole, apomorphine intermittent injections), levodopa ER, COMT inhibitors (entacapone, Ongentys [opicapone]), and MAO-B inhibitors (rasagiline, zonisamide, Xadago [safinamide]) are considered to be clinically useful. Possibly useful treatments include Nourianz (istradefylline) and tolcapone. For dyskinesia, treatment with amantadine and clozapine is determined to be efficacious and clinically useful. The availability of clinically efficacious generic products in this treatment category lends itself to be a more economical option versus the branded products available on the market.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Xadago, Inbrija, Nourianz, and Ongentys are each indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson disease experiencing "off" episodes. Xadago was approved in March 2017, Inbrija was approved in December 2018, Nourianz was approved in August 2019, and Ongentys was approved in April 2020.

Apokyn was approved in April 2004 for the acute, intermittent treatment of hypomobility, "off" episodes in patients with advanced Parkinson disease.

Vyalev was approved in October 2024 for the treatment of motor fluctuations in adults with advanced Parkinson's disease.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Xadago

Xadago was approved based on two double-blind, placebo-controlled, 24-week studies in patients with Parkinson disease experiencing "off" time during treatment with levodopa/carbidopa. The primary efficacy endpoint in both studies was the change from baseline in total daily "on" time without troublesome dyskinesia.

Study 1 included 669 patients randomized equally to receive Xadago 50 mg/day, Xadago 100 mg/day, or placebo. Patients taking both doses of Xadago had significantly increased "on" time compared to placebo with an increase of 1.37 hours for the 50 mg dose, 1.36 hours for the 100 mg dose and 0.97 hours for the placebo.

Study 2 included 549 patients randomized equally to receive Xadago 100 mg/day or placebo. Patients taking Xadago had significantly increased "on" time compared to placebo with an increase of 1.42 hours for Xadago and 0.57 hours for placebo.

Inbrija

Inbrija was approved based on one 12-week, randomized, placebo-controlled, double-blind study in patients with Parkinson disease treated with oral carbidopa/levodopa. A total of 114 patients were randomized to receive 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 per day of "off" time, 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 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 or placebo was approximately 2 doses per day. At Week 12, the reduction in UPDRS Part III motor score for Inbrija vs placebo was -9.8 and -5.9, respectively. This difference from placebo of -3.92 was statistically significant with a p-value of 0.009.

The effect of Inbrija on pulmonary function was evaluated in patients with Parkinson disease treated with oral carbidopa/levodopa in a 12 month, randomized, controlled, open-labeled study. A total of 271 patients were treated with Inbrija and 127 patients were observed on their regular oral

medication regimen for the treatment of Parkinson disease. Patients with chronic obstructive pulmonary disease (COPD), asthma, or other chronic respiratory disease within the last 5 years were excluded. Pulmonary function was assessed by spirometry every 3 months in both groups. After 12 months, the average reduction in the forced expiratory volume in 1 second (FEV_1) from baseline was the same in both groups (-0.1 L).

Nourianz
The efficacy of Nourianz was demonstrated in four randomized, multicenter, double-blind, 12-week, placebo-controlled studies. The studies enrolled patients with a mean duration of Parkinson disease of 9 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. Patients continued levodopa treatment with or without concomitant Parkinson disease medications, 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 (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.

Study 1 was conducted in the U.S. and Canada, and Study 2 was conducted in the U.S. 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 daily experienced a statistically significant decrease from baseline in percentage of daily awake "off" time compared with patients on placebo. For Study 1, the least squares mean difference (LSMD) between the Nourianz 40 mg group (n=129) and the placebo group (n=66) was a decrease of 6.78% awake "off" hours (p=0.007). For Study 2, the LSMD between the Nourianz 20 mg group (n=112) and the placebo group (n=113) was a decrease of 4.57% awake "off" hours (p=0.025).

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, the LSMD between the Nourianz 20 mg group (n=115) and the placebo group (n=118) was a decrease of 0.65 hours (p=0.028) of "off" time and the LSMD between the Nourianz 40 mg group (n=124) and the placebo group was a decrease of 0.92 hours (p=0.002) of "off" time. In study 4, the LSMD between the Nourianz 20 mg group (n=120) and the placebo group (n=123) was a decrease of 0.76 hours (p=0.006) of "off" time and the LSMD between the Nourianz 40 mg group (n=123) and the placebo group was a decrease of 0.74 hours (p=0.008).

Apokyn
The efficacy of Apokyn for the acute symptomatic treatment of recurring episodes of hypomobility, "off" episodes, in patients with advanced Parkinson disease was established in three randomized, controlled trials of Apokyn. All patients in these trials were using concomitant L-dopa at baseline, 86% were using a concomitant oral dopaminergic agonist, 31% were using a concomitant COMOT inhibitor, and 10% were using a concomitant MAO-B inhibitor. Study 1 was conducted in patients who did not have prior exposure to Apokyn and studies 2 and 3 were conducted in patients with at least 3 months of Apokyn use immediately prior to study enrollment. Almost all patients without prior exposure to Apokyn began taking an antiemetic (trimethobenzamide) three days prior to starting Apokyn and 50% of patients were able to discontinue the concomitant antiemetic, on average two months after initiating Apokyn. The primary endpoint for all three studies was the change from baseline in Part III (Motor Examination) of the UPDRS.

Study 1 was a randomized, double-blind, placebo-controlled, parallel-group trial in 29 patients with advanced Parkinson disease who had at least 2 hours of "off" time per day despite an optimized oral regimen for Parkinson disease including levodopa and an oral dopaminergic agonist. Patients with atypical Parkinson disease, psychosis, dementia, hypotension, or those taking dopamine antagonists were excluded from participation. In an office setting, hypomobility was allowed to occur by withholding the patients' Parkinson disease medications overnight. The following morning, patients (in a hypomobile state) were started on study treatment in a 2:1 ratio (2 mg of Apokyn or placebo given subcutaneously). At least 2 hours after the first dose, patients were given additional doses of study medication until they achieved a therapeutic response (defined as a response similar to the patient's response to their usual dose of levodopa) or until 10 mg of Apokyn or placebo equivalent was given. At each injection re-dosing, the study drug dose was increased in 2 mg increments. Of the 20 patients randomized to Apokyn, 18 achieved a therapeutic response at about 20 minutes. The mean Apokyn dose was 5.4 mg. In contrast, of the 9 placebo-treated patients, none reached a therapeutic response. The mean change from baseline for the UPDRS Part III score for the Apokyn group was -23.9 which was statistically significant compared to that for the placebo (-0.1).

Study 2 was a randomized, placebo-controlled, crossover trial of 17 patients with Parkinson disease who had been using Apokyn for at least 3 months. Patients received their usual morning doses of Parkinson's disease medications and were followed until hypomobility occurred, at which time they received either a single dose of subcutaneous Apokyn (at their usual dose) and placebo on different days in random order. UPDRS Part III scores were evaluated over time. The mean dose of Apokyn was 4 mg. The mean change from baseline UPDRS Part III score for the Apokyn group was -20 which was statistically significant compared to the placebo group (-3).

Study 3 used a randomized withdrawal design in 4 parallel groups from 62 patients (35 Apokyn patients and 27 placebo) with Parkinson disease who had been using Apokyn for at least 3 months. Patients were randomized to one of the following treatments dosed once by subcutaneous administration: Apokyn at the usual dose (mean dose of 4.6 mg), placebo at a volume matching the usual Apokyn dose, Apokyn at the usual dose +2 mg (mean dose 5.8 mg), or placebo at a volume

matching the usual Apokyn dose + 0.2 mL. Patients received their usual morning doses of Parkinson disease medications and were followed until hypomobility occurred; at which time they received the randomized treatment. The mean change from baseline for the Apokyn group for UPDRS Part III scores at 20 minutes post dosing was -24.2 which was statistically significant compared to that for the placebo group (-7.4).

Ongentys
The efficacy of Ongentys for the adjunctive treatment to levodopa/carbidopa in patients with Parkinson disease experiencing "off" episodes was evaluated in two double-blind, randomized, parallel-group studies of 14-15 week duration. Study 1 was placebo- and active-controlled and Study 2 was placebo-controlled. All patients were treated with levodopa/DOPA decarboxylase inhibitor (DDCI) alone or in combination with other Parkinson disease 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 population included patients treated with Ongentys 50 mg once daily (n=115) or placebo (n=120). The majority (82%) of patients in both groups used concomitant Parkinson disease medication in addition to levodopa including 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 with a LS mean change from baseline of -0.93 hours in the placebo group and -1.95 hours in the Ongentys 50 mg group (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 intention to treat study population included patients treated with Ongentys 50 mg once daily (n=147) or placebo (n=135). The majority in both groups used concomitant Parkinson disease medications in addition to levodopa including 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 with a LS mean change from baseline of -1.07 hours in the placebo group and -1.98 hours in the Ongentys 50 mg group (p=0.008).

Vyalev
The efficacy of Vyalev was established in a 12-week, randomized, double-blind, double-dummy, active-controlled, multicenter study which enrolled patients with advanced Parkinson's disease (PD) who were responsive to levodopa treatment, had motor fluctuations inadequately controlled by their current medications, and who experienced a minimum of 2.5 hours of "Off" time per day as assessed by PD diaries. A total of 141 patients were randomized in 1:1 ratio and received either 24-hour/day continuous subcutaneous administration of Vyalev plus oral placebo capsules (N=74) or 24-hour/day

continuous subcutaneous administration of placebo solution plus oral encapsulated carbidopa/levodopa immediate-release (IR) tablets (N=67). The primary clinical outcome measure was the mean change from baseline to Week 12 in the total daily mean "On" time without troublesome dyskinesia (defined as "On" time without dyskinesia plus "On" time with non-troublesome dyskinesia) based on PD diary. The key secondary clinical outcome measure was the mean change from baseline to Week 12 in the total daily mean "Off" time. The "On" and "Off" time were normalized to a daily 16-hour awake period. Daily normalized "Off" and "On" times are averaged over valid PD diary days for each visit to obtain the average daily normalized times. Vyalev demonstrated statistically significant improvements from baseline to Week 12 in "On" time without troublesome dyskinesia compared with the oral IR carbidopa-levodopa group ($p = 0.0083$). Vyalev also demonstrated statistically significant improvements from baseline to Week 12 in "Off" time compared with the oral IR carbidopa-levodopa group ($p = 0.0054$).

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Policy History

Original Effective Date: 01/17/2018
Current Effective Date: 04/01/2025

01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. New policy.
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. Title changed from "Xadago (safinamide)" to "Pharmacologic Treatment of Off Episodes in Parkinson Disease". Added new drug, Inbrija, to policy with relevant background information.

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02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Added new drug, Nourianz, to policy with relevant background information.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Added new drugs Ongentys and Kynmobi to policy with relevant background information.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Added Apokyn to policy with relevant background information.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Updated Apokyn and Kynmobi criteria to allow for trial and failure of only one generic alternative.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2024	Medical Policy Committee review
11/13/2024	Medical Policy Implementation Committee approval. Removed reference to discontinued drug, Kynmobi, and updated background information to include updated treatment guidance. Also, added generic apomorphine to the policy. Criteria updated to require trial and failure of generic apomorphine before brand Apokyn.
03/06/2025	Medical Policy Committee review
03/12/2025	Medical Policy Implementation Committee approval. Added new product, Vyalev, to the policy with relevant criteria and background information.
07/01/2025	Coding update

Next Scheduled Review Date: 03/2026

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J3490, J7799 Code added 7/1/2025 J7356
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.