# Pharmacologic Treatment of Off Episodes in Parkinson Disease

**Policy #** 00603
Original Effective Date: 01/17/2018
Current Effective Date: 03/09/2020

*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), or Nourianz™‡ (istradefylline) to be **eligible for coverage**** when the patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for Xadago (safinamide), Inbrija (levodopa), or Nourianz (istradefylline) will be considered when the following criteria are met:

- 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 criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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# When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Xadago (safinamide), Inbrija (levodopa), or Nourianz (istradefylline) when the patient has not tried and failed at least two alternative products listed in the patient selection criteria 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), or Nourianz (istradefylline) for the treatment of any indication other than "off" episodes with levodopa/carbidopa treatment in Parkinson disease 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

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Nourianz is comparable to other therapies for this indication, but the long-term safety and efficacy has not yet been determined.

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, or Nourianz. These guidelines recommend that rasagiline, pramipexole, ropinirole, 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.

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# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**
Xadago, Inbrija, and Nourianz 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, and Nourianz was approved in August 2019.

# Rationale/Source

**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).

# References

1. Xadago [package insert]. US WorldMeds. Louisville, KY. May 2017
2. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983-995.
3. Inbrija [package insert]. Acorda Therapeutics Inc. Ardsley, NY. January 2019.
4. Nourianz [package insert]. Kyowa Kirin, Inc. Bedminster, NJ. September 2019.

# Policy History

Original Effective Date: 01/17/2018
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| 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". |

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| | Added new drug, Inbrija, to policy with relevant background information. |
| 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. |

Next Scheduled Review Date: 02/2021

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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**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.