

Title: Adjunctive Treatment For Parkinson's Disease

Policy #: Rx.01.219

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **levodopa inhalation (Inbrija™)**, **istradefylline (Nouriaz™)**, and **apomorphine (Apokyn®, Kynmobi™)** as provided under the member's prescription drug benefit.

Description:

Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain. PD is characterized by manifestations of tremor, bradykinesia, and rigidity. PD is a motor condition that includes neuropsychiatric and other nonmotor manifestations.

The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD, however; levodopa-induced complications (eg, motor fluctuations ["wearing off" phenomenon], dyskinesia, dystonia) develop in at least 50% of patients after 5 to 10 years of levodopa treatment. The risk of motor complications increases with higher levodopa doses and younger age of PD onset.

The cause of motor fluctuations is not clear, but it is hypothesized that they evolve as PD progresses because progressive degeneration of the nigrostriatal dopaminergic pathway reduces the ability of nerve terminals to store and release dopamine. The response to exogenous levodopa becomes more pulse-like due to the inability of the nerve terminals to store and release dopamine. Levodopa has a short half-life (90 minutes), rapid cycling pharmacokinetics (PK), and erratic intestinal absorption related to slowed intestinal motility.

The four main drugs or classes of drugs that have anti-parkinson activity are monoamine oxidase type B (MAO B) inhibitors, amantadine, dopamine agonists and levodopa. Initial therapy is individualized and requires a flexible trial-and-error approach. Individuals who exhibit mild symptoms with minimal impact on daily life are good candidates for MAO B inhibitor as initial therapy. For individuals with mild to moderate symptoms that impact daily living, either dopamine agonist or levodopa is recommended in individuals younger than 65; levodopa is preferred in those older than 65 years of age. Levodopa is the drug of choice in individuals with moderate to severe symptoms regardless of age.

Levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier and is presumably converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of PD

Levodopa (Inbrija™) inhalation powder is indicated for the intermittent treatment of OFF episodes in patients with PD treated with carbidopa/levodopa.

Istradefylline (Nouriaz™) is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes. The precise mechanism by which istradefylline exerts its therapeutic effect in PD is unknown.

The mechanism by which apomorphine hydrochloride treats Parkinson Disease is unknown. Apomorphine is a non-ergoline dopamine agonist that has high in-vitro affinity for the dopamine D4 receptor, and moderate affinity for the dopamine D2, D3, D5, and adrenergic α 1D, α 2B, and α 2C receptors. Activity is suspected to be due to stimulation of post-synaptic dopamine D2-type receptors within the caudate-putamen in the brain.

Apomorphine hydrochloride (Kynmobi™) sublingual film is a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of "off" episodes in patients with Parkinson's disease (PD).

Apomorphine hydrochloride (Apokyn®) injection for subcutaneous use is a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease.

Adding a catechol-O-methyltransferase (COMT) inhibitor can prolong and potentiate the levodopa effect and thereby reduce "off" time when used as adjunctive therapy with levodopa.

Policy:

INITIAL CRITERIA: Levodopa inhalation (Inbrija™) or istradefylline (Nourianz™) will be approved when ALL of the following criteria are met:

1. Diagnosis of Parkinson's disease and member is experiencing intermittent off episodes; and
2. Concurrent use of carbidopa/levodopa containing product; and
3. Prescribed by or in consultation with a neurologist; and
4. Member had inadequate response or inability to tolerate TWO of the following:
 - a. MAO-B Inhibitor (e.g., rasagiline, selegiline);
 - b. Dopamine Agonist (e.g., pramipexole, ropinirole);
 - c. COMT inhibitor (e.g., entacapone)

INITIAL CRITERIA: Apomorphine (Apokyn®, Kynmobi™) is approved when ALL of the following are met:

1. Diagnosis of advanced Parkinson's disease and member is experiencing intermittent "off" episodes; and
2. Member is receiving medication in combination with other medications for the treatment of Parkinson's disease (e.g., carbidopa/levodopa, pramipexole, ropinirole, etc...); and
3. Member is not using the medication with any 5-HT3 antagonist (e.g., ondansetron, granisetron, dolasetron, palonosetron, alosetron); and
4. Inadequate response or inability to tolerate apomorphine (Kynmobi™) applies to Apokyn®; and
5. Prescribed by or in consultation with a neurologist

Initial authorization: 2 years

REAUTHORIZATION CRITERIA: Levodopa inhalation (Inbrija®), istradefylline (Nourianz™), or apomorphine (Apokyn®, Kynmobi™) is re-approved with documentation of positive clinical response to therapy.

Reauthorization: 2 years

Black Box Warning as shown in the drug Prescribing Information:

None

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Apokyn® (apomorphine hydrochloride injection) [prescribing information]. Louisville, KY: US WorldMeds, LLC.; April 2020. Available from: https://www.apokyn.com/sites/all/themes/apokyn/content/resources/Apokyn_PI.pdf. Accessed April 01, 2021.

Inbrija™ [package insert]. Ardsley, NY. Acorda Therapeutics, Inc. August 2020. Available at: <https://www.inbrija.com/prescribing-information.pdf>. Accessed February 01, 2021.

Kynmobi™ (apomorphine hydrochloride sublingual film) [prescribing information]. Marlborough, Massachusetts: Sunovion Pharmaceuticals Inc.; May 2020. Available from: <https://www.kynmobi.com/Kynmobi-Prescribing-Information.pdf>. Accessed April 01, 2021.

Nourianz™ [package insert]. Bedminster, NJ. Kyowa Kirin, Inc., August 2020. Available at: <https://www.nourianz.com/assets/pdf/nourianz-full-prescribing-information.pdf>. Accessed April 01, 2021.

Chou KL. Clinical manifestations of Parkinson disease. UpToDate Web site. Updated November 2020. www.uptodate.com. Accessed April 01, 2021.

Fox SH, Katzenschlager R, Lim SY, et al; Movement Disorder Society Evidence-Based Medicine Committee. International Parkinson and Movement Disorder Society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

Grosset DG, Dhall R, Gurevich T, et al. Long-term pulmonary safety of inhaled levodopa in Parkinson's disease subjects with motor fluctuations: a phase 3 open-label randomized study. Poster presented at: 2nd Pan American Parkinson's Disease and Movement Disorders Congress; June 22-24, 2018; Miami, FL.

Jankovic J. Etiology and pathogenesis of Parkinson disease. UpToDate Web site. Updated September 2020. www.uptodate.com. Accessed April 01, 2021.

LeWitt PA, Hauser RA, Grosset DG, et al. A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease. *Mov Disord*. 2016;31(9):1356-65.

LeWitt PA, Hauser RA, Pahwa R, et al; on behalf of the SPAN-PD Study Investigators. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol*. 2019;18:145-54.

Oertel WH, Berardelli A, Bloem BR, et al. Late (complicated) Parkinson's disease. In: Gilhus NE, Barnes MP, Brainin M, eds. *European Handbook of Neurological Management*. West Sussex, United Kingdom: Wiley-Blackwell; 2011:237-267.

Spindler MA, Tarsy D. Initial pharmacologic treatment of Parkinson disease. UpToDate Web site. Updated November 2019. www.uptodate.com. Accessed April 01, 2021.

Tarsy D. Motor fluctuations and dyskinesia in Parkinson disease. UpToDate Web site. Updated January 2021. www.uptodate.com. Accessed April 01, 2021.

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name

Inbrija™
Nourianz™
Apokyn®
Kynmobi™

Generic Name

Levodopa inhalation
Istradefylline
Apomorphine
Apomorphine

Cross References:

Rx.01.33 Off-Label Use

Rx.01.76 Quantity Level Limits for Pharmaceuticals Covered Under the Prescription Drug Benefit

Policy Version Number:	7.00
P&T Approval Date:	March 18, 2021
Policy Effective Date:	July 01, 2021
Next Required Review Date:	March 18, 2022

The Policy Bulletins on this web site were developed to assist the Company in administering the provisions of the respective benefit programs, and do not constitute a contract. If you have coverage through the Company, please refer to your specific benefit program for the terms, conditions, limitations and exclusions of your coverage. Company does not provide health care services, medical advice or treatment, or guarantee the outcome or results of any medical services/treatments. The facility and professional providers are responsible for providing medical advice and treatment. Facility and professional providers are independent contractors and are not employees or agents of the Company. If you have a specific medical condition, please consult with your doctor. The Company reserves the right at any time to change or update its Policy Bulletins.

