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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-2596



Drug Class Update with New Drug Evaluation: Parkinson's Disease Drugs

Date of Review: February 2025

Date of Last Review: October 2020

Generic Name: foscariodopa and foslevodopa

Dates of Literature Search: 12/01/2020 – 11/01/2024

Brand Name (Manufacturer): Vyalev™ (AbbVie, Inc)

Dossier Received: no

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The purpose of this class update is to evaluate new comparative evidence for Parkinson's disease (PD) drugs and evaluate place in therapy of a new drug combination, foscariodopa-foslevodopa, approved by the Food and Drug Administration in 2024 for the treatment of motor fluctuations in adults with advanced PD.

Plain Language Summary:

- Parkinson's disease (PD) is a condition that makes it difficult for a person to control muscle movement, speak, smell, digest food, and complete daily activities of life. People with PD may walk slowly, have muscle stiffness, and shaky body movements at rest.
- About 1 million people in North America have PD, which is about 1% of adults older than 60 years of age.
- There is no cure for PD. PD is treated with medicines that help replace important chemicals that are missing in the body. These medicines may decrease symptoms, but the effects may wear off over time. The medicines also have side effects such as making a person feel tired, sick, or dizzy.
- A new combination medicine called foscariodopa-foslevodopa was approved by the Food and Drug Administration (FDA) to treat patients who have severe PD. In a 12 week study, people taking foscariodopa-foslevodopa had symptoms controlled for a longer time than people taking carbidopa-levodopa by mouth, but how long foscariodopa-foslevodopa will keep working beyond 12 weeks is not clear. The medicine needs a special device for injection under the skin. Common side effects of foscariodopa-foslevodopa include infusion site reactions (pain, swelling, redness, skin infection) and uncontrollable muscle movements.
- We recommend the Oregon Health Authority pay for foscariodopa-foslevodopa when Oregon Health Plan members have advanced symptoms of PD and when they are seeing a specialist in the treatment of PD. Providers must explain why someone needs a special injection form of foscariodopa-foslevodopa before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. Is there new comparative evidence that drugs indicated for treatment of Parkinson's disease (PD) differ in efficacy or effectiveness at improving symptoms, quality of life or in stabilizing disease progression in adults with PD?
2. Is there new comparative evidence that drugs indicated for treatment of PD differ in serious adverse events or tolerability when used to treat adults with PD?
3. What is the efficacy and safety of foscariodopa-foslevodopa for the treatment of people with PD?
4. Are there specific subpopulations based on demographic characteristics (e.g., age, gender, race, disease severity or longevity, disease subtype, functional status, or concomitant therapies) for which one anti-PD drug is better tolerated or more effective than other available drugs used to manage PD?

Conclusions:

- There has been one new guideline, 2 new formulations, 3 safety alerts, and one new drug approval identified since the last drug class review. No new high-quality systematic reviews were identified since the last class review.
- The recent PD guideline from the American Academy of Neurology supports the current preferred drug list (PDL) and prior authorization (PA) criteria.¹
- The FDA-approved 2 new formulations of carbidopa/levodopa: 1) Crexont® which is a combination capsule of immediate-release carbidopa/levodopa granules and extended-release (ER) levodopa and 2) Dhivy®, a combination tablet of carbidopa/levodopa. Both agents are indicated for the treatment of PD, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.^{2,3}
- Labeling for the dopamine agonists (bromocriptine, pramipexole, rotigotine, and ropinirole) was updated to include warnings for increased risk of impulse-control problems and compulsive behaviors and of the potential for adverse effects when tapering off the medication or after discontinuation. Labeling for apomorphine was updated to include a warning that hemolytic anemia requiring hospitalization has been reported with treatment.⁴⁻¹⁰
- There is low quality evidence from one placebo-controlled RCT that at 12 weeks, use of foscariodopa-foslevodopa continuous subcutaneous infusion (CSCI) compared to oral levodopa-carbidopa increased “on” time without troublesome dyskinesia (mean difference (MD) 1.75 h, 95% confidence interval [CI], 0.46 to 3.05; p=0.0083) and also decreased “off” time (MD -1.79 h, 95% CI, -3.03 to -0.54; p=0.0054).^{11,12} There were higher rates of treatment discontinuations in the foslevodopa-foscariodopa treatment group due to adverse events such as infusion-site cellulitis and infusion site bruising, hemorrhage, and edema compared to the oral LD-CD group (22% vs. 2%, respectively) and also higher overall attrition rates (35% vs. 8%, respectively) which limited the ability to draw definitive conclusions about safety and efficacy.^{11,12}
- There is insufficient evidence to evaluate long-term safety of foscariodopa-foslevodopa CSCI. Common adverse events included infusion site adverse events, pain, bruising, hemorrhage, and edema.^{11,12}

Recommendations:

- Implement prior authorization (PA) criteria for foscariodopa-foslevodopa to support use for the treatment of motor fluctuations in adults with advanced Parkinson’s disease.
- After review of costs in executive session, foscariodopa-foslevodopa vial was made nonpreferred and ropinirole HCL tablets were made preferred.

Summary of Prior Reviews and Current Policy

- Treatment options for PD which are currently preferred on the Oregon Health Plan (OHP) Fee-For-Service (FFS) PDL include several formulations of levodopa/carbidopa, and adjunctive therapy such as dopamine agonists (pramipexole), monoamine oxidase B inhibitors (MAOBIs) (selegiline), catechol-O-methyltransferase inhibitors (COMTI) (entacapone), and anticholinergic agents (benztropine, trihexyphenidyl) (see **Appendix 1**).

- Clinical PA criteria limits non-preferred products to funded conditions under the OHP and requires current use of levodopa/carbidopa in patients prescribed safinamide or istradefylline (see **Appendix 4**).
- Guidance from the 2017 National Institute for Health and Care Excellence (NICE) report supports the current PDL and clinical PA criteria.¹³
- From the previous drug class update:
 - Low quality evidence from 4 of 8 RCTs demonstrated that istradefylline, when used as adjunctive treatment to levodopa therapy, reduced “off” time compared to placebo in patients with advanced PD.
 - Low quality evidence from 2 RCTs demonstrated that opicapone reduced “off” time versus placebo in patients with idiopathic PD and motor fluctuations already treated with levodopa therapy.
 - Low quality evidence from 1 RCT demonstrated that apomorphine, sublingual (SL) provided greater reduction in motor complications compared to placebo.¹³
- In an evaluation of paid and denied claims from 4/1/24 to 6/30/24, approximately 220 OHP FFS patients were prescribed therapies within this drug class. Most (76%) prescribed therapy was for preferred agents (primarily bntropine, amantadine, and pramipexole). Only 14 patients (5%) had claims for levodopa therapy. Bromocriptine and ropinirole were the most commonly prescribed non-preferred products. Of patients prescribed a non-preferred drug, 36% had a subsequent prior authorization (PA) request approved for the requested (or similar) agent. Of the patients with no subsequent paid PD therapy, 70% were enrolled in a coordinated care organization, lost eligibility, or had other insurance which may have paid for their medication. Only 12% of patients had a PA denied and 16% of patients had no PA requested by the prescribing provider.

Background:

Parkinson’s disease is a progressive neurodegenerative movement disorder caused by the degeneration of dopamine-secreting neurons in the substantia nigra and other areas of the brain.¹⁴⁻¹⁷ Basal ganglia denervation slowly leads to “parkinsonian” motor symptoms, typically characterized by a combination of bradykinesia, postural instability, resting tremor, and rigidity.¹⁴⁻¹⁷ Generalized non-motor symptoms such as dysphagia, sialorrhea, constipation, confusion, blood pressure dysregulation, and depression may also be present before PD motor symptoms manifest.¹⁴⁻¹⁷ In advanced PD, motor fluctuations are common (cycles of anti-PD drug therapy response followed by recurrence of symptoms and non-response to therapy), and non-motor complications such as autonomic, psychiatric and cognitive impairment are often more prominent, all of which contribute to further functional decline and disability.¹⁴⁻¹⁷

Parkinson’s disease is the most common movement disorder and, after Alzheimer’s disease, is the most common neurodegenerative disorder worldwide.¹⁷ PD develops from a complex interplay of genetic and environmental factors.^{15,17} The greatest risk factor for PD is age, but other established risk factors include male gender and ethnicity with the highest incidence in Hispanic or Latino, Latina or Latino persons, followed by non-Hispanic White, Asian and Black persons.¹⁷ The prevalence of PD is roughly 572 cases per 100,000 persons in populations who are 45 years of age or older.^{14,18} The prevalence and incidence of PD increases with the age and the median age of onset is around 60 years.¹⁴⁻¹⁹ Men are about 1.5 times more likely to develop PD than women.¹⁶ Roughly 1 million people in North America have PD, which is about 1% of the population older than 60 years of age.²⁰

First-line treatment for PD is oral levodopa, a metabolic precursor to dopamine.^{14,15,17} Dopamine is unable to cross the blood-brain barrier (BBB) and has no therapeutic effect in PD when administered peripherally.^{15,17} Levodopa is able to cross the BBB where it is converted into dopamine.^{15,17,19} Levodopa is usually taken in combination with a dopa-decarboxylase inhibitor such as carbidopa to reduce the peripheral degradation of levodopa.^{15,17,19,20} Studies have shown levodopa provides the most symptomatic benefit for PD in the first 2 years of therapy and declines in effectiveness after 3 to 4 years.^{14,19} Roughly 30% of patients have an initial positive response to levodopa/carbidopa that results in less bradykinesia and related disabilities.^{14,19} Other patients either have minimal

response or are unable to tolerate therapy.¹⁴ Common adverse effects of levodopa/carbidopa therapy include cardiovascular effects (e.g. arrhythmias and postural hypotension) and behavioral effects (e.g., depression, agitation, hallucinations, and sleep disturbances).^{14,17,19} Dyskinesias are common after long-term levodopa therapy and are complicated by increased development of motor fluctuations.^{14,17,19} Motor fluctuations are cycles where patients have a long period of drug responsiveness (“on” periods) followed by a return of parkinsonian motor symptoms (“off” episode) before the benefit from the next subsequent dose takes effect.^{14,17,19} The motor fluctuations are largely due to the short half-life of levodopa.^{14,19} Dopamine receptor agonists such as pramipexole and ropinirole are associated with less response fluctuations and dopaminergic complications like dyskinesia but may provide less symptomatic benefit and higher incidence of psychiatric disturbances, somnolence, and edema.¹⁹ Other adjunctive therapies include MAOBIs and COMTIs.^{14,19,20} Guidelines published in 2017 by National Institute for Health and Care Excellence (NICE) evaluated the benefits and harms of PD pharmacological management. It was concluded that: and are summarized in **Table 1**.²¹

Table 1. Comparative Benefits and Harms between PD Drug Categories - Levodopa, DAs and MAO-B Inhibitors (adapted from the NICE guidelines)²¹

| Category | Comparison |
|---|---|
| Motor Symptoms | More improvement with Levodopa |
| Activities of Daily Living | More improvement with Levodopa |
| Motor Complications (i.e. on/off motor fluctuations and dyskinesia) | Fewer motor complications with DAs and MAO-Bs |
| Adverse Events | Fewer specified adverse events with Levodopa and MAO-B Inhibitors |

Abbreviations: DA = dopamine agonists; MAO-B = monoamine oxidase B

*Specified adverse events include excessive sleepiness, hallucinations, and impulse control disorders

NICE recommends against abrupt withdrawal and “drug holidays” with anti-Parkinson’s agents because of risk for neuroleptic malignant syndrome.²¹ NICE recommendations for first-line treatment of motor symptoms associated with PD are summarized in **Table 2**.²¹

Table 2. Recommendations For First-Line Treatment of Motor Symptoms Associated with Parkinson’s Disease²¹

| First Line Treatment Options | Guidance |
|---|---|
| Levodopa/carbidopa | Offer to people in the early stages of PD whose motor symptoms impact their QoL. |
| -Levodopa/carbidopa -Dopamine agonists (e.g. Pramipexole, Ropinirole, Rotigotine) -MAO-B inhibitors (e.g. Selegiline, Rasagiline, Safinamide) | Consider for people in the early stages of PD whose motor symptoms do not impact their QoL. |
| Ergot-derived dopamine agonists (e.g. Cabergoline And Bromocriptine) | Do not offer as first-line treatment for PD. |

Abbreviations: MAO-B = monoamine oxidase B; PD = Parkinson’s disease; QoL = quality of life

Strategies to treat motor fluctuations and reduce “off” time in advanced PD include increasing the dose of dopaminergic medication, adding another dopaminergic medication (e.g., dopamine agonist), dividing the levodopa dose into smaller but more frequent doses, or adding a COMTI or MAOBI to inhibit the breakdown of levodopa and dopamine and prolong their effect.^{14,19} To date, few trials have compared these different strategies. Patients on levodopa therapy often add one of these classes of drug as PD progresses and eventually take drugs from 2 or 3 of these classes in addition to levodopa.^{14,19} The overall benefit of

these adjunctive treatments relative to placebo in decreasing total “off” time ranges from about 0.5 to 2 hours.¹⁴ None of these adjunctive drugs have been shown to be superior to others for treating “off” time.²¹ Re-evaluation of ongoing efficacy and assessment of adverse effects of these adjunctive drugs is important to ensure maximal benefit from individualized patient therapy.²¹ NICE recommendations for adjuvant treatment of motor symptoms associated with PD are summarized in **Table 3**.²¹

Table 3. Adjuvant Treatment of Motor Symptoms Associated with Parkinson’s Disease²¹

| Adjuvant Treatment Options | Guidance |
|---|--|
| -Dopamine agonists *Non-ergot-derived dopamine agonist (Ropinirole, Pramipexole, Rotigotine) **Ergot-derived dopamine agonist (e.g. Cabergoline, Bromocriptine) -MAO-B inhibitors (e.g. Selegiline, Rasagiline, Safinamide) -COMT inhibitors (e.g. Entacapone, Tolcapone) | Adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy after discussing clinical and lifestyle circumstances as well as potential benefits and harms of different drug classes. |
| Amantadine | Consider if dyskinesia is not adequately managed by modifying existing therapy. |
| Anticholinergics | Do not offer to people with PD who have developed dyskinesia and/or motor fluctuations. |

Abbreviations: COMT =Catechol-O-methyltransferase; MAO-B = monoamine oxidase B; PD = Parkinson’s disease

*=Choose over ergot-derived dopamine agonists in most cases because less monitoring is needed

**=Only consider as an adjunct to levodopa for people who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy and whose symptoms are not adequately controlled with a non-ergot-derived dopamine agonist.

A previous review investigated newer FDA-approved anti-PD agents to manage “off” episodes.¹³ Istradefylline was approved by the FDA in August 2019 for adjunctive treatment to levodopa therapy in patients with advanced PD experiencing “off” episodes.²³ Istradefylline is the first adenosine (A_{2A}) receptor antagonist approved for the treatment of motor fluctuations in advanced PD.²³ Opicapone was approved in April 2020 for adjunctive treatment to levodopa therapy in patients with PD experiencing “off” episodes.²⁴ Opicapone is a COMT inhibitor similar to entacapone and tolcapone.^{24,25} Entacapone is the most commonly used COMT inhibitor for the management of “off” episodes, but it needs to be given concomitantly with each levodopa dose; tolcapone is limited by hepatotoxicity and continuous monitoring of liver function.^{24,25} Recently, two treatment options have become available for on-demand, “rescue” management of “off” episodes: subcutaneous apomorphine, a non-ergoline dopamine agonist, and an inhaled dry powder formulation of levodopa.¹⁴ An apomorphine sublingual film formulation was approved by the FDA in May 2020 to address the practical limitations with the SC apomorphine.^{26,27}

There are numerous PD-specific instruments commonly used in clinical trials to evaluate disease progression and treatment efficacy. The 5-point (1 to 5) Hoehn and Yahr (HY) scale is based on bilateral motor involvement and compromised balance and gait. Increasing parkinsonian motor impairment is scaled from unilateral (Stage 1) to bilateral disease without balance difficulties (Stage 2), to the presence of postural instability (Stage 3), loss of physical independence (Stage 4), and being wheelchair- or bed-dependent (Stage 5).²⁸

The Unified Parkinson’s Disease Rating Scale (UPDRS) is another comprehensive assessment tool that continues to be used in research to estimate treatment effects for PD.^{29,30} The UPDRS scale consists of 4 sections: 1) non-motor experiences of daily living (evaluation of mentation, behavior and mood); 2) motor experiences of daily living (e.g., speech, swallowing, handwriting, falling, walking, etc.); 3) motor examination (by clinician); and 4) motor complications.³⁰ Each

item in each section is ranked on a 5-point scale (0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe) and higher scores indicate more severe PD; the total cumulative UPDRS score will range from 0 (no disability) to 199 (total disability).^{30,31} The UPDRS severity cut-off points for each section are estimated to be as follows: Part 1: 10/11 (mild/moderate) and 21/22 (moderate/severe); Part 2: 12/13 (mild/moderate) and 29/30 (moderate/severe); Part 3: 32/33 (mild/moderate) and 58/59 (moderate/severe); and Part 4: 4/5 (mild/moderate) and 12/13 (moderate/severe).³¹ The Movement Disorders Society (MDS) produced a revised version of the UPDRS.³⁴ The minimally clinically important difference (MCID) threshold for improvement in Part 2 of the MDS-UPDRS are estimated to be -3.05 points for clinically relevant improvement and +2.51 points for observing minimal clinically relevant worsening.^{29,32-34}

The Parkinson's Disease Questionnaire (PDQ-39) is a quality of life questionnaire completed by the patient.³⁵ The instrument has been widely used in clinical practice and has been extensively tested for validity and reliability.³⁶ The tool assesses patient difficulties across 8 dimensions of health: mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognitions (4 items), communication (3 items), and bodily discomfort (3 items).³⁵ Scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure).³⁰ MCIDs for the PDQ-39 are estimated to be -4.72 points for improvement and +4.22 points for worsening of PD.³⁶

Assessment of sleep quality and disturbances in subjects with PD may be assessed by the Parkinson's disease Sleep Scale (PDSS).^{37,38} The PDSS is a visual analogue scale that reviews 15 commonly reported symptoms associated with disruptions in sleep.³⁷ The main categories of the PDSS include: overall quality of night's sleep (item 1); sleep onset and maintenance insomnia (items 2 and 3); nocturnal restlessness (items 4 and 5); nocturnal psychosis (items 6 and 7); nocturia (items 8 and 9); nocturnal motor symptoms (items 10–13); sleep refreshment (item 14); and daytime dozing (item 15).³⁷ The PDSS total score ranges from 0 to 150, with lower scores meaning more disability.³⁷ The MCID for the PDSS has not been established.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 10 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

American Academy of Neurology - Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease¹

In 2021, the American Academy of Neurology provided guidance on dopaminergic therapy for motor symptoms in adults with early Parkinson's disease.¹ The systematic review included RCTs of participants with early-stage PD (within 2 years of disease onset or Hoehn & Yahr stages 1 or 2) who had motor symptoms treated with either dopamine agonists, levodopa, MAO-B inhibitors, or COMT inhibitors.¹ Comparative outcomes were based on the UPDRS part 3 (which measures motor symptoms) and comparative risks of adverse effects (dyskinesia, hallucinations, discontinuation due to adverse events, and impulse control disorders).¹ For the recommendations, the Delphi process was employed to assign one of the following three designations based on quality of evidence: A, B, or C. Level A ("must") was the strongest recommendation based on high confidence in the evidence, high magnitude of benefit, and low risk. Level B recommendations ("should") are less stringent but based on the evidence and benefit-risk profile.¹ Level C ("may") was the lowest recommendation and represented a high degree of practice variation. Recommendations with at least a Level A or B designation are highlighted in **Table 4**.¹

Table 4. AAN Guidelines for the Initiation of Pharmacologic Treatment for Motor Symptoms in Early PD¹

| Category | Recommendation | Strength of Recommendation |
|---|---|----------------------------|
| Levodopa vs. Dopamine Agonists vs. MAO-B Inhibitors | Counsel patients on benefits/risks of initial therapy with levodopa, DAs, and MAO-B inhibitors based on disease characteristics to inform treatment decisions. Recommend levodopa as the initial preferential dopaminergic therapy. Do not prescribe DAs to patients with early-stage PD at higher risk of medication-related adverse effects. | Level B |
| Prescribing Levodopa | Initially prescribe IR levodopa rather than CR levodopa or levodopa/carbidopa/entacapone in patients with early PD. Prescribe the lowest effective dose of levodopa to minimize the risk of dyskinesia and other adverse effects. Routinely monitor patients taking levodopa for their motor response to treatment and for the presence of dyskinesia, motor fluctuations, ICDs, EDS, postural hypotension, nausea, and hallucinations, to guide dosage titration over time. Counsel patients taking levodopa that higher dosages are more likely to cause dyskinesia. Counsel patients that in later disease stages, taking levodopa with meals may affect levodopa absorption and efficacy. | Level B |
| Prescribing DAs | Inform the patient and caregiver of important side effects of DAs before prescribing. Screen patients for cognitive impairment, EDS, sudden-onset sleep, hallucinations, orthostatic hypotension, and the presence of risk factors for ICDs before prescribing a DA and repeatedly screen for adverse effects after prescribing a DA. Involve caregivers in assessments. | Level B |
| | Integrate patient preferences concerning formulation, mode of administration, and cost when prescribing a DA. Prescribe the lowest dose of DA required to provide therapeutic benefit. | Level B |
| Tapering and Discontinuing DAs | Recommend tapering or discontinuation of DAs if patients experience disabling medication-related adverse effects including ICDs, EDS, sudden-onset sleep, cognitive impairment, or hallucinations. When DAs must be discontinued due to adverse effects, clinicians should monitor patients for symptoms of DAWS and, when possible, gradually decrease the dosage to minimize symptoms. | Level B |
| Prescribing MAO-B Inhibitors | Counsel patients with early PD on the greater motor benefits of initial therapy with levodopa compared with MAO-B inhibitors to inform treatment decisions. | Level B |

Abbreviations: AAN = American Academy of Neurology; DA = dopamine agonist; DAWS = dopamine agonist withdrawal syndrome; EDS = excessive daytime sleepiness; ICD = impulse control disorder; MAO-B = monoamine oxidase type B; PD = Parkinson’s disease

New Formulations or Indications:

- A new dosage formulation, available as an extended-release (ER) capsule combination product of carbidopa/levodopa (Crexont®) received FDA-approval in August 2024.² The product is a combination of immediate-release carbidopa/levodopa granules and ER levodopa pellets indicated for the treatment of PD, postencephalitic parkinsonism, and parkinsonism associated with carbon monoxide or manganese intoxication.² Approval was based on the results of one study that included a 13-week, double-blind, double-dummy, randomized, parallel group period that compared ER carbidopa/levodopa to immediate-release carbidopa-levodopa.² The trial was preceded by a 3-week dose adjustment period of immediate-release carbidopa-levodopa treatment followed by a 4-week conversion period to the ER product.² The trial enrolled 630 patients (506 randomized) with PD who were taking at least 400 mg/day of levodopa and experiencing motor fluctuations.² The primary efficacy measure was the mean change from baseline in “On” time without troublesome dyskinesia in hours per day at the end of the study (Week 20 or at early termination), as assessed by the patient’s Parkinson’s disease diary.² At 20 weeks, patients treated with Crexont® reported a statistically significant improvement in “On” time without troublesome dyskinesia compared to immediate-release carbidopa levodopa (mean difference 0.53 hours/day; p=0.019).²
- A new formulation of immediate-release carbidopa/levodopa (Dhivy®) was approved in November 2021 for the treatment of Parkinson’s disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.³ Dhivy® contains 25 mg of carbidopa and 100 mg of levodopa and comes in a tablet that has 3 functional scores with each segment containing 6.25 mg of carbidopa and 25 mg of levodopa for more individualized dosing.³

New FDA Safety Alerts:

Table 5. Description of New FDA Safety Alerts⁴⁻¹⁰

| Generic Name | Brand Name | Month / Year of Change | Location of Change (Boxed Warning, Warnings, CI) | Addition or Change and Mitigation Principles (if applicable) |
|---------------|-------------------------|------------------------|--|--|
| apomorphine | Apokyn® | 5/2022 | Warnings and Precautions | Hemolytic anemia requiring hospitalization has been reported with apomorphine treatment in the postmarketing setting. If hemolytic anemia occurs, consider discontinuing APOKYN treatment. |
| bromocriptine | Cycloset® | 7/2021 | Warnings and Precautions | Symptoms including apathy, anxiety, depression, fatigue, insomnia, sweating and pain have been reported during taper or after discontinuation of dopamine agonists. These symptoms generally do not respond to levodopa. |
| pramipexole | Mirapex® Mirapex ER® | | | |
| rotigotine | Neupro® | | | |
| ropinirole | Requip® Requip XL® | | | |
| bromocriptine | Cycloset® | 4/2020 | Warnings and Precautions | Increased risk of impulse-control problems and compulsive behaviors with the use of dopamine agonists. Physicians should consider dose reduction or stopping the medication if a patient develops such urges. |
| pramipexole | Mirapex® Mirapex ER® | | | |

| | | | | |
|------------|-----------------------|--|--|--|
| rotigotine | Neupro® | | | |
| ropinirole | Requip® Requip XL® | | | |

Randomized Controlled Trials:

A total of 41 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Foslevodopa-foscarbidopa (Vyalev™) is a prodrug combination therapy that converts to levodopa and carbidopa in vivo.^{11,12} Foslevodopa-foscarbidopa is administered as a 24-hour continuous subcutaneous infusion that uses an infusion pump.^{11,12} The recommended infusion rate is individualized and dependent upon the patient’s total required levodopa dosage as determined by a clinical specialist (e.g. neurologist) experienced in the treatment of PD.^{11,12}

The efficacy and safety of foslevodopa-foscarbidopa subcutaneous infusion was established in one phase 3 double-blind, double-dummy RCT in patients with motor fluctuations due to advanced PD.^{11,12} Patients were eligible for study enrollment if they had idiopathic PD responsive to levodopa, were at least 30 years of age, had normal cognitive function, and concurrent treatment with PD medications at a total daily dose of 400 mg (typical minimum daily dose) or more levodopa equivalents.^{11,12} Patients also had to have identifiable motor fluctuations with an average “off” time of at least 2.5 hours per day over 3 consecutive days.^{11,12} Key inclusion and exclusion criteria are listed in **Table 8**. Of 270 patients screened, 174 were enrolled and 141 were randomly assigned to either continuous subcutaneous infusion of foslevodopa-foscarbidopa plus oral placebo capsules (n=74) or an optimally-dosed regimen of oral encapsulated levodopa-carbidopa immediate-release (LD-CD IR) plus continuous subcutaneous infusion of placebo solution (n=67).^{11,12} All levodopa-containing medications and COMT inhibitors were converted to an equivalent amount of immediate-release levodopa-carbidopa and then rounded to the closest matching multiple of 100 mg in order to give only full tablets of 100 mg levodopa and 25 mg carbidopa.¹¹ The dose and schedule of treatments were adjusted by the investigator over the first 29 days to optimize control of motor symptoms, defined as maximizing functional on time, minimizing off episodes, and minimizing on time with troublesome dyskinesia. Concomitant non-levodopa-containing Parkinson’s disease medications (eg, dopamine agonists, MAO-B inhibitors, and amantadine) were allowed at a fixed dose throughout the study.¹¹ In the maintenance phase (day 29 to day 85), patients continued with the same treatment regimen for both CSCI and oral therapies until the study conclusion with no dose adjustments.^{11,12}

Patients were mostly male (~70%) and white (93%), with an average age of about 66 years.¹¹ The mean duration since a PD diagnosis was about 8.6 years, and patients had an “off” time of about 6.1 hours (h) per day.¹¹ Most participants had an HY score of 2 (62%) or 3 (24%) indicating bilateral disease without balance difficulties (Stage 2) or presence of postural instability (Stage 3).¹¹ The mean daily dose used in the foslevodopa-foscarbidopa group was higher at 1,667 mg while the oral LD-CD group averaged 1,105 mg/day.¹¹ Overall, almost half (42%) of the patients were on a dopamine agonist.¹¹ 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 patient-reported PD diary.^{11,12} Key secondary clinical outcome measures were tested in a hierarchical order and included the mean change from baseline to Week 12 in the total daily mean “Off” time as assessed by the PD diary, change from baseline in MDS-UPDRS part 2 score, and presence of morning akinesia at week 12 (defined as reporting “off” status as the first morning symptom upon awakening as recorded by the Parkinson disease diary), respectively.¹¹ Other secondary endpoints included the PDQ-39 and PDSS-2.¹¹

Foslevodopa-foscarbidopa increased “on” time without troublesome dyskinesia at week 12 compared with oral levodopa-carbidopa (model-based mean change from baseline 2.72 vs. 0.97 h, respectively; MD 1.75 h; 95% CI 0.46 to 3.05; p=0.0083).^{11,12} Treatment with foslevodopa-foscarbidopa CSCI also demonstrated a decrease in “off” time at week 12 compared to oral levodopa-carbidopa (–2.75 vs. –0.96 h, respectively; MD –1.79 h; 95% CI –3.03 to –0.54; p=0.0054).¹¹ Hierarchical testing for significance was terminated while determining change in MDS-UPDRS part 2 score as statistical significance was not reached (MD –1.58; 95% CI –3.65 to 0.48; p=0.13).¹¹ Other secondary outcomes were considered exploratory. Compared to oral LD-CD IR at 12 weeks, foslevodopa-foscarbidopa improved PDQ-39 summary index (MD –4.10; 95% CI –8.14 to –0.05), PDSS-2 total score (MD –5.40; 95% CI –8.03 to –2.78) and morning akinesia. However, statistical significance was unable to be assessed for these secondary outcomes.¹¹

The trial used adequate randomization methods and there were generally no significant differences between treatment arms for most baseline characteristics with a few exceptions.¹¹ After enrollment, roughly 17% of the participants discontinued the study for adverse events, withdrawn consent, or had difficulty with the drug-delivery system, but most discontinued for unknown reasons.¹¹ The foslevodopa-foscarbidopa group had a higher proportion of participants with prior dopamine agonist use compared to the oral LD-CD group (46% vs. 37%, respectively).¹¹ There was also a disproportionate number of patients in the foslevodopa-foscarbidopa group who discontinued treatment compared to the oral LD-CD group (35% vs. 8%, respectively).¹¹ The impact of these differences on outcomes in this trial is unclear. Differences in infusion-related adverse events such as erythema, pain, cellulitis, and edema may have led to unblinding during the trial, resulting in increased risk of performance and detection bias. Of people enrolled in the study, 93% identified as White and 70% identified as male.¹¹ Non-White races were underrepresented in the study. Long-term efficacy of foslevodopa-foscarbidopa subcutaneous infusion remains unknown.

Clinical Safety:

Adverse events were reported in a larger percentage of patients treated with foslevodopa-foscarbidopa compared to oral LD-CD (85% vs. 63%, respectively).¹¹ The frequency of infusion-site events were higher in the foslevodopa-foscarbidopa group than in the oral LD-CD group (72% vs. 12%, respectively).^{11,12} The most frequent treatment-emergent adverse effects observed in the clinical trial by patients treated with foslevodopa-foscarbidopa CSCI were infusion-site erythema, pain, cellulitis, and edema, while falls were reported at higher rates in the oral LD-CD arm.^{11,12} Foslevodopa-foscarbidopa therapy was associated with a higher frequency of hallucination and/or psychosis compared to oral LD-CD (15% vs. 3%, respectively).¹¹ The foslevodopa-foscarbidopa CSCI group had a higher proportion of patients with an adverse event leading to premature study drug discontinuation compared to the oral LD-CD group (22% vs. 1%, respectively) most commonly due to infusion site adverse events, pain, bruising, hemorrhage, and edema.¹¹ **Table 6** summarizes adverse events with an incidence of at least 2% and higher than oral LD-CD in patients treated with foslevodopa-foscarbidopa CSCI.^{11,12}

Table 6. Adverse Events with An Incidence Of At Least 2% And Higher Than Oral LD-CD In Patients Treated with Foslevodopa-Foscarbidopa CSCI.^{11,12}

| Adverse Event | Foslevodopa-foscarbidopa (n=74) | Oral LD-CD (n=67) |
|------------------------|---------------------------------|-------------------|
| | % | % |
| Infusion-site erythema | 27 | 1 |
| Infusion-site pain | 26 | 1 |

| | | |
|--------------------------|----|----|
| Infusion-site cellulitis | 19 | 0 |
| Infusion-site edema | 12 | 0 |
| Dyskinesia | 11 | 6 |
| Fall | 8 | 18 |
| Infusion site bruising | 8 | 3 |
| Infusion site hemorrhage | 8 | 0 |
| Infusion site nodule | 8 | 0 |
| On and off phenomena | 8 | 0 |
| Hallucination | 7 | 1 |
| Balance disorder | 5 | 0 |
| Constipation | 5 | 0 |
| Hallucination, visual | 5 | 0 |
| Infusion site induration | 5 | 0 |
| Infusion site infection | 5 | 0 |
| Infusion site pruritus | 5 | 0 |
| Peripheral swelling | 5 | 0 |

Abbreviations: LD-CD = levodopa-carbidopa

There were no reported deaths related to foslevodopa-foscarbidopa treatment during participation in clinical trials.^{11,12} The one death that occurred in the oral LD-CD group was preceded by a serious adverse event that was not considered to be treatment related as determined by the investigator.¹¹ Overall, the frequency of serious adverse events was similar across all treatment groups (foslevodopa-foscarbidopa 8%; oral LD-CD, 6%).¹¹ There were no clinically meaningful changes in vital signs, ECG parameters (e.g., QT interval), or laboratory values in patient enrolled in these trials.¹¹

As with many short-term Phase 3 clinical trials, there are gaps in evidence with the safety of long-term use of foslevodopa-foscarbidopa CSCI therapy. The clinical trial was limited to 12 weeks. There is an ongoing, open-label, 96-week continuation study in which patients will receive individualized foslevodopa-foscarbidopa CSCI for 24 hours per day.¹¹ The results of the Foslevodopa/Foscarbidopa Open-label Extension Study have not yet been published.³⁹ Use of foslevodopa-foscarbidopa is contraindicated with concurrent or recent use (within 2 weeks) of a nonselective monoamine oxidase (MAO) inhibitor.¹²

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Motor symptoms (e.g., bradykinesia, rigidity, resting tremor)
- 2) Non-motor symptoms (e.g., autonomic, psychiatric and cognitive impairment)
- 3) Function (disability and impairment)
- 4) Health-related quality of life (e.g., PDQ-39)
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Change in "On" time without troublesome dyskinesia

Table 7. Pharmacology and Pharmacokinetic Properties.¹²

| Parameter | |
|----------------------------------|--|
| Mechanism of Action | Foscarbidopa/foslevodopa is a prodrug combination product that is converted in vivo to carbidopa and levodopa. When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for delivery to the brain. Levodopa is the metabolic precursor of dopamine, does cross the blood-brain barrier, and is converted to dopamine in the brain. |
| Oral Bioavailability | N/A |
| Distribution and Protein Binding | Vd for levodopa is moderately small (partitioning ratio for levodopa between erythrocytes and plasma is approximately 1). Protein binding: Foscarbidopa 26%; Foslevodopa 28% (Carbidopa 36%; Levodopa <10%) |
| Elimination | Carbidopa metabolites are eliminated in the urine unchanged (30%) or as glucuronide conjugates. |
| Half-Life | Carbidopa 2 hours; Levodopa 1.5 hours |
| Metabolism | Foslevodopa and foscarbidopa are prodrugs rapidly converted into levodopa and carbidopa by ubiquitous phosphatases. Carbidopa is metabolized to two main metabolites (α -methyl-3-methoxy-4-hydroxyphenylpropionic acid and α -methyl-3,4-dihydroxyphenylpropionic acid). Levodopa is mainly metabolized by the AADC and the COMT enzymes. Other routes of metabolism are transamination and oxidation. |

Abbreviations: AADC = aromatic amino acid decarboxylase; COMT = Catechol-O-methyltransferase; N/A = not applicable; Vd = volume of distribution

Table 8. Comparative Evidence Table.

| Ref./ Study Design | Drug Regimens/ Duration | Patient Population | N | Efficacy Endpoints | ARR/ NNT | Safety Outcomes | ARR/ NNH | Risk of Bias/ Applicability |
|---|---|---|--|---|-------------|---|--|---|
| 1. Soileau, et al. DB, AC, RCT, MC 12 weeks | 1. Foslevodopa (240 mg/mL) and foscarbidopa (12 mg/mL) solution administered through CSCI over 24 hours per day + placebo to mimic LD-CD IR oral tablets 2. LD-CD (100 mg/25 mg) IR oral tablets + placebo to mimic foslevodopa-foscarbidopa CSCI solution for | <u>Demographics:</u> -Mean age: 66.4 y -Male: 70% -White: 93% -MMSE: 28.77 -MDS-UPDRS part 2 (pre-dose): 14.34 -HY ON score 2 or 3: 86% -On time with troublesome dyskinesia: 9.34 hrs -Off time: 6.13 hrs -Mean LD dose: 1000 mg/d -Dopamine agonist: 42% -Presence morning akinesia: 78% -PDQ-39: 28.53 -PDSS-2 total: 20.09 | <u>ITT:</u> 1. 76 2. 69 <u>PP:</u> 1. 74 2. 67 <u>Attrition:</u> 1. 26 (35%) 2. 5 (8%) | <u>Primary Endpoint:</u> Change from baseline to week 12 in average daily normalized "on" time without troublesome dyskinesia 1. 2.72 hrs 2. 0.97 hrs MD: 1.75 (95% CI 0.46 to 3.05); p = 0.0083 <u>Secondary Endpoints:</u> Change from baseline to week 12 in average daily normalized "off" time: 1. -2.75 hrs 2. -0.96 hrs | N/A for all | TEAE: 1. 70% 2. 22% Serious TEAE: 1. 8% 2. 6% Infusion-site events: 1. 72% 2. 12% Falls/associated injuries: 1. 18% 2. 25% | NA NA NA NA NA | Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (Low) Interactive response technology and stratified by study site to conceal randomized assignment. Baseline characteristics were generally balanced between groups. <u>Performance Bias:</u> (Unclear) Double-dummy design used to preserve blinding for patients and investigators; unblinding possible due to higher frequency of infusion-related adverse events in Foslevodopa-foscarbidopa arm <u>Detection Bias:</u> (Unclear) Study site personnel and patients blinded. Risk for functional unblinding due to infusion reactions. <u>Attrition Bias:</u> (High) Higher proportion of patients in the foslevodopa-foscarbidopa arm discontinued treatment versus oral LD-CD |

| | | | | | | | | |
|--|----------|--|--|---|--|---|----|--|
| | infusion | <p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> -Aged ≥ 30 years -Idiopathic PD responsive to LD-CD <ul style="list-style-type: none"> • Motor symptoms not controlled by current therapy w/ “off” time of ≥ 2.5 hours/day (with ≥ 2 hrs each day) • TDD of ≥ 400 mg/day LD equivalents • Motor fluctuations (“on” and “off”) • Normal cognitive function (MMSE score of 24 or greater) <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> -Received deep brain stimulation, CD-LD suspension, or any PD drug as continuous daily infusion -Previous exposure to FL-FC -Hx of skin conditions or disorders -Hx of drug or alcohol abuse -Suicidal ideation currently or within 1 year or suicide attempts within the last 2 years -Hx or presence of psychotic episodes not controlled by antipsychotics -Unstable medical conditions -Donated or lost 550 mL or more blood volume or received any blood product within 8 weeks prior to screening -Patient has known active Coronavirus-19 infection | | <p>MD: -1.79 (95% CI -3.03 to -0.54); p = 0.0054</p> <p>Change from baseline to week 12 in MDS-UPDRS Part 2 (motor experiences of daily living)</p> <ol style="list-style-type: none"> 1. -2.65 2. -1.06 <p>MD: -1.58 (95% CI -3.65 to 0.48); p = 0.13 (NS)</p> <p>Presence of morning akinesia at week 12*</p> <ol style="list-style-type: none"> 1. 17% 2. 63% <p>PDSS-2*</p> <ol style="list-style-type: none"> 1. -7.92 2. -2.52 <p>MD: -5.40 (95% CI -8.03 to -2.78)</p> <p>PDQ-39 Items*</p> <ol style="list-style-type: none"> 1. -6.38 2. -2.28 <p>MD: -4.10 (95% CI, -8.14 to -0.05)</p> <p>*NS based on pre-specified hierarchal testing plan</p> | | <p>Hallucinations/psychosis:</p> <ol style="list-style-type: none"> 1. 15% 2. 3% <p>Study withdrawal due to TEAE</p> <ol style="list-style-type: none"> 1. 22% 2. 1% <p>p-value and CI not reported</p> | NA | <p>arm (35% and 8%, respectively); Missing data for the primary and key secondary outcomes were imputed using an MMRM, which assumes missing-at-random however, withdrawals were driven largely by TEAEs.</p> <p>Reporting Bias: (Unclear) Potential bias in favor of foslevodopa-foscarbidopa possible in patients with knowledge of treatment assignment as many outcomes were subjective and self-reported in diaries.</p> <p>Other Bias: (High) Authors employed by drug sponsor and participated in the study design, data collection, data management, and data analysis. Manufacturer-funded study.</p> <p>Applicability:</p> <p>Patient: Most patients <10 years duration since PD diagnosis and HY stage 2 or less. All patients took LD and 42% took a dopaminergic agonist both rates are higher than what is currently observed in FFS population. Low rate of enrollment may suggest inclusion into the trial was overly selective.</p> <p>Intervention: Dosing was stabilized and standardized between groups using a conversion factor and then optimized prior to treatment phase.</p> <p>Comparator: Oral LD-CD appropriate to establish efficacy for population studied.</p> <p>Outcomes: Primary outcome appropriate for condition. Study unable to find statistically significant difference between study drug and comparator in MDS-UPDRS, a well-established measure in PD.</p> <p>Setting: 76 sites in Australia and the US</p> |
|--|----------|--|--|---|--|---|----|--|

Abbreviations AC = active comparator; ARR = absolute risk reduction; CD = carbidopa; CI = confidence interval; d= days; DB = double blind; FFS = fee-for-service; FL-FC = foslevodopa-foscarbidopa; hrs= hours; Hx = history; HY = Hoehn & Yale scale; ITT = intention to treat; LD = levodopa; MC = multicentered; MD = mean difference; MDS-UPDRS = Movement Disorder Society-Unified Parkinson’s Disease Rating Scale; mg = milligrams; mL = milliliters; MMRM = mixed model repeated measures; MMSE = Mini-Mental State Examination; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PC = placebo controlled; PD = Parkinson’s Disease; PDQ-39 = Parkinson’s Disease Questionnaire; PDSS = Parkinson’s Disease Sleep Scale; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; susp = suspension; TDD = total daily dose; TEAE = treatment-emergent adverse effects; y = years.

References:

1. Pringsheim T, Day GS, Smith DB, et al. Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary: A Report of the AAN Guideline Subcommittee. *Neurology*. 2021;97(20):942-957.
2. Crexont® (carbidopa and levodopa) extended-release capsules [prescribing information]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; August 2024.
3. Dhivy® (carbidopa/levodopa) tablet [prescribing information]. Alpharetta, GA: Avion Pharmaceuticals LLC; June 2022.
4. Apokyn® (apomorphine for inj) [Prescribing Information]. Durham, NC: Mylan Bertek Pharmaceuticals, Inc; April 2004.
5. Cycloset® (bromocriptine mesylate) [prescribing information]. Tiverton, RI: VeroScience LLC; August 2020.
6. Mirapex® (pramipexole dihydrochloride) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; July 2021.
7. Mirapex ER® (pramipexole dihydrochloride) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; June 2024.
8. Neupro® (rotigotine) [prescribing information]. Smyrna, GA: UCB Inc; July 2021.
9. Requip (ropinirole) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; July 2021.
10. Requip XL (ropinirole) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; July 2021.
11. Soileau MJ, Aldred J, Budur K, et al. Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomized, double-blind, active-controlled, phase 3 trial *Lancet Neurol*. 2022 Dec;21(12):1099-1109. [published correction appears in *Lancet Neurol*. 2023 Mar;22(3):e5]
12. Vyalev™ (foslevodopa/foscarbidopa): 240 mg/mL foslevodopa and 12 mg/mL foscarbidopa solution for subcutaneous infusion [product monograph]. North Chicago, IL: AbbVie Inc. October 2024.
13. Drug Use Research & Management Program. Drug Class Update with New Drug Evaluation: Parkinson's Disease Drugs. https://www.orpdl.org/durm/meetings/meetingdocs/2020_10_01/archives/2020_10_01_ParkinsonDisease_ClassUpdate.pdf. Published October 2020. Accessed 11/1/2024.
14. Tanner CM, Ostrem JL. Parkinson's Disease. *N Engl J Med* 2024 Aug 1;391(5):442-452.
15. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet* 2021 Jun 12;397(10291):2284-2303.
16. Lees AJ, Hardy J, and Revesz T. Parkinson's Disease. *Lancet*. 2009; 373:2055-66.
17. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015;386:896-912.
18. Willis AW, Roberts E, Beck JC, et al. Incidence of Parkinson disease in North America. *NPJ Parkinsons Dis* 2022; 8: 170.
19. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. *JAMA* 2014;311:1670-83.
20. Homayoun H. Parkinson Disease. *Ann Intern Med*. 2018;169(5):ITC33-ITC48.
21. National Institute for Health and Care Excellence (NICE). Parkinson's disease in adults. NICE 2017 Jul:NG71
22. Bega D, Kuo PH, Chalkidou A, et al. Clinical utility of DaTscan in patients with suspected Parkinsonian syndrome: a systematic review and meta-analysis. *NPJ Parkinsons Dis* 2021; 7: 43.
23. Nourianz® tablets (istradefylline) [prescribing information]. Bedminster, NJ: Kyowa Kirin; March 2024.
24. Ogentys® (opicapone) [Prescribing Information]. San Diego, CA: Neurocrine Biosciences, Inc. April 2020.
25. Tasmar® (tolcapone) [Prescribing Information]. Bridgewater, NJ: Valeant Pharmaceuticals. May 2013.
26. Olanow CW, Factor SA, Espay AJ, et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebocontrolled phase 3 study. *Lancet Neurol* 2020;19:135-44.
27. Kynmobi® (apomorphine hydrochloride sublingual film) [Prescribing Information]. Marlborough, MA. Sunovion Pharmaceuticals, Inc: May 2020.
28. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord* 2004;19:1020-8.

29. Sánchez-Ferro Á, Matarazzo M, Martínez-Martín P, et al. Minimal Clinically Important Difference for UPDRS-III in Daily Practice. *Mov Disord Clin Pract*. 2018;5(4):448-450.
30. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008;23:2129-70.
31. Martínez-Martín P, Rodríguez-Blázquez C, Mario A, et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. *Parkinsonism Relat Disord* 2015;21:50-4.
32. Hauser RA, Gordon MF, Mizuno Y, et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. *Parkinsons Dis* 2014;2014:467131.
33. Horvath K, Aschermann Z, Acs P, et al. Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. *Parkinsonism Relat Disord* 2015;21:1421-6.
34. Horváth K, Aschermann Z, Kovács M, et al. Minimal clinically important differences for the experiences of daily living parts of movement disorder society-sponsored unified Parkinson's disease rating scale. *Mov Disord*. 2017;32(5):789-793.
35. Marinus J, Ramaker C, van Hilten JJ, Stiggelbout AM. Health related quality of life in Parkinson's disease: a systematic review of disease specific instruments. *J Neurol Neurosurg Psychiatry*. 2002;72(2):241-248.
36. Horvath K, Aschermann Z, Kovacs M, et al. Changes in Quality of Life in Parkinson's Disease: How Large Must They Be to Be Relevant?
37. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2002;73:629-35.
38. Arnulf I, Konofal E, Merino-Andreu M, et al. Is excessive daytime sleepiness in Parkinson's disease related to poor sleep quality? An objective study of 47 patients [abstract]. *Neurology* 2001;56(suppl 3):A307.
39. Fung VSC, Aldred J, Arroyo MP, et al. Continuous subcutaneous foslevodopa/foscarbidopa infusion for the treatment of motor fluctuations in Parkinson's disease: Considerations for initiation and maintenance. *Clinical Parkinsonism & Related Disorders*. 2024;10:100239.

Appendix 1: Current Preferred Drug List

| <u>Generic</u> | <u>Brand</u> | <u>Form</u> | <u>Route</u> | <u>PDL</u> |
|-------------------------------|-------------------------------|-------------|--------------|------------|
| amantadine HCl | AMANTADINE | CAPSULE | PO | Y |
| amantadine HCl | AMANTADINE | TABLET | PO | Y |
| benztropine mesylate | BENZTROPINE MESYLATE | TABLET | PO | Y |
| carbidopa/levodopa | CARBIDOPA/LEVODOPA | TABLET | PO | Y |
| carbidopa/levodopa | CARBIDOPA-LEVODOPA | TABLET | PO | Y |
| carbidopa/levodopa | DHIVY | TABLET | PO | Y |
| carbidopa/levodopa | SINEMET 10-100 | TABLET | PO | Y |
| carbidopa/levodopa | SINEMET 25-100 | TABLET | PO | Y |
| carbidopa/levodopa | CARBIDOPA-LEVODOPA ER | TABLET ER | PO | Y |
| carbidopa/levodopa/entacapone | CARBIDOPA-LEVODOPA-ENTACAPONE | TABLET | PO | Y |
| carbidopa/levodopa/entacapone | STALEVO 100 | TABLET | PO | Y |
| carbidopa/levodopa/entacapone | STALEVO 125 | TABLET | PO | Y |
| carbidopa/levodopa/entacapone | STALEVO 150 | TABLET | PO | Y |
| carbidopa/levodopa/entacapone | STALEVO 200 | TABLET | PO | Y |
| carbidopa/levodopa/entacapone | STALEVO 50 | TABLET | PO | Y |
| carbidopa/levodopa/entacapone | STALEVO 75 | TABLET | PO | Y |
| entacapone | COMTAN | TABLET | PO | Y |
| entacapone | ENTACAPONE | TABLET | PO | Y |
| pramipexole di-HCl | PRAMIPEXOLE DIHYDROCHLORIDE | TABLET | PO | Y |
| selegiline HCl | SELEGILINE HCL | CAPSULE | PO | Y |
| trihexyphenidyl HCl | TRIHEXYPHENIDYL HCL | SOLUTION | PO | Y |
| trihexyphenidyl HCl | TRIHEXYPHENIDYL HCL | TABLET | PO | Y |
| amantadine HCl | GOCOVRI | CAP ER 24H | PO | N |
| amantadine HCl | AMANTADINE | SOLUTION | PO | N |
| amantadine HCl | OSMOLEX ER | TAB BP 24H | PO | N |
| apomorphine HCl | KYNMOBI | FILM | SL | N |
| bromocriptine mesylate | BROMOCRIPTINE MESYLATE | CAPSULE | PO | N |
| bromocriptine mesylate | BROMOCRIPTINE MESYLATE | TABLET | PO | N |
| carbidopa | CARBIDOPA | TABLET | PO | N |
| carbidopa | LODOSYN | TABLET | PO | N |
| carbidopa/levodopa | CREXONT | CAP IR ER | PO | N |
| carbidopa/levodopa | RYTARY | CAPSULE ER | PO | N |
| carbidopa/levodopa | DUOPA | INT PMP SP | MC | N |
| carbidopa/levodopa | CARBIDOPA-LEVODOPA | TAB RAPDIS | PO | N |
| istradefylline | NOURIANZ | TABLET | PO | N |
| levodopa | INBRIJA | CAP W/DEV | IH | N |
| levodopa | INBRIJA | CAPSULE | IH | N |
| levodopa | LARODOPA | TABLET | PO | N |

| | | | | |
|----------------------|----------------------|------------|----|---|
| opicapone | ONGENTYS | CAPSULE | PO | N |
| pramipexole di-HCl | PRAMIPEXOLE ER | TAB ER 24H | PO | N |
| rasagiline mesylate | AZILECT | TABLET | PO | N |
| rasagiline mesylate | RASAGILINE MESYLATE | TABLET | PO | N |
| ropinirole HCl | ROPINIROLE ER | TAB ER 24H | PO | N |
| ropinirole HCl | ROPINIROLE HCL | TABLET | PO | N |
| rotigotine | NEUPRO | PATCH TD24 | TD | N |
| safinamide mesylate | XADAGO | TABLET | PO | N |
| selegiline HCl | ZELAPAR | TAB RAPDIS | PO | N |
| selegiline HCl | SELEGILINE HCL | TABLET | PO | N |
| tolcapone | TASMAR | TABLET | PO | N |
| tolcapone | TOLCAPONE | TABLET | PO | N |
| apomorphine HCl | APOKYN | CARTRIDGE | SQ | |
| apomorphine HCl | APOMORPHINE HCL | CARTRIDGE | SQ | |
| benztropine mesylate | BENZTROPINE MESYLATE | AMPUL | IJ | |
| benztropine mesylate | BENZTROPINE MESYLATE | VIAL | IJ | |

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 01, 2024

| | | |
|----|---|-------|
| 1 | exp Bantzropine/ | 712 |
| 2 | exp Levodopa/ | 18211 |
| 3 | entacapone.mp. | 794 |
| 4 | exp Pramipexole/ | 1112 |
| 5 | exp Selegiline/ | 2427 |
| 6 | exp Trihexyphenidyl/ | 948 |
| 7 | exp Amantadine/ | 6645 |
| 8 | exp Bromocriptine/ | 7099 |
| 9 | exp Carbidopa/ | 2664 |
| 10 | rasagiline.mp. | 826 |
| 11 | rotigotine.mp. | 678 |
| 12 | ropinirole.mp. | 1068 |
| 13 | safranamide.mp. | 323 |
| 14 | exp Tolcapone/ | 376 |
| 15 | foscarbidopa.mp. | 26 |
| 16 | foslevodopa.mp. | 27 |
| 17 | exp Apomorphine/ | 9133 |
| 18 | opicapone.mp. | 145 |
| 19 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 | 46132 |
| 20 | exp Parkinson Disease/ | 88204 |
| 21 | 19 and 20 | 12242 |
| 22 | limit 21 to (full text and humans and yr="2021 -Current" and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review") and "humans only (removes records about animals)") | 41 |

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYALEV safely and effectively. See full prescribing information for VYALEV.

VYALEV™ (foscariidopa and foslevodopa) injection, for subcutaneous use

Initial U.S. Approval: 1975

INDICATIONS AND USAGE

VYALEV is a combination of foscariidopa (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. (1)

DOSAGE AND ADMINISTRATION

- For subcutaneous administration only, preferably in the abdomen, via the VYAFUSER pump. (2.1, 2.2, 2.3)
- See the Full Prescribing Information for calculation of the base continuous dosage, hourly infusion rate, optional loading dose, and extra dose. (2.2)
- The maximum recommended daily dosage of VYALEV is 3,525 mg of foslevodopa (approximately 2,500 mg levodopa). (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg foscariidopa and 2,400 mg foslevodopa per 10 mL (12 mg foscariidopa and 240 mg foslevodopa per mL). (3)

CONTRAINDICATIONS

VYALEV is contraindicated in patients who are currently taking a nonselective monoamine oxidase (MAO) inhibitor or have recently (within 2 weeks) taken a nonselective MAO inhibitor. (4)

WARNINGS AND PRECAUTIONS

- May cause falling asleep during activities of daily living. (5.1)

- Hallucinations/Psychosis: May respond to dose reduction of VYALEV. (5.2)
- Impulse Control Behaviors: Consider dose reductions or stopping VYALEV. (5.3)
- Infusion Site Reactions and Infections: Monitor for infusion site infections: Following aseptic techniques while using this medication and frequent rotation of the infusion site is recommended to reduce the risk. (5.4)
- Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion. (5.5)
- May cause or exacerbate dyskinesia: Consider dose reduction of VYALEV. (5.6)

ADVERSE REACTIONS

Most common adverse reactions for VYALEV (VYALEV incidence at least 10% and greater than oral carbidopa-levodopa incidence) were infusion/catheter site reactions, infusion/catheter site infections, hallucinations, and dyskinesia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Selective MAO-B inhibitors: May cause orthostatic hypotension. (7.1)
- Antihypertensive drugs: May cause symptomatic postural hypotension. Dosage adjustment of the antihypertensive drug may be needed. (7.2)
- Dopamine D2 receptor antagonists and isoniazid may reduce the effectiveness of VYALEV. (7.3)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2024

Appendix 4: Key Inclusion Criteria

| | |
|---------------------|--|
| Population | Patients with Parkinson's disease diagnosis |
| Intervention | Drugs in Appendix 1 |
| Comparator | Drugs in Appendix 1 |
| Outcomes | Mortality, morbidity, quality of life, functioning or symptoms |
| Setting | Outpatient management |

Appendix 5: Prior Authorization Criteria

Parkinson's Disease Drugs

Goals:

- Promote preferred drugs for Parkinson's disease.
- Restrict use for non-funded conditions (e.g., restless leg syndrome) and support individual review for EPSDT.
- To limit utilization of safinamide to FDA-approved indications.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|--|----------------------|---------------------|
| 1. What diagnosis is being treated? | Record ICD10 code | |
| 2. Is the diagnosis Parkinson's disease or another chronic neurological condition? | Yes: Go to #5 | No: Go to #3 |

| Approval Criteria | | |
|---|--|---|
| <p>3. Is the request for a funded diagnosis?</p> <p>Note: Restless Leg Syndrome is not currently funded.</p> | <p>Yes: Go to #5</p> | <p>No: Not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP</p> <p>Eligible for EPSDT review: go to #4</p> |
| <p>4. Is there documentation of medical appropriateness and medical necessity?</p> <p>Definitions for medical appropriateness include use for an FDA indication AND use, contraindication, or intolerance to preferred agents in the class. Medical necessity includes documentation that the diagnosis impacts the patient's health.</p> | <p>Yes: Go to #5</p> | <p>No: Pass to RPh; deny medical appropriateness or medical necessity</p> |
| <p>5. Is this a request for continuation of therapy?</p> | <p>Yes: Go to Renewal Criteria.</p> | <p>No: Go to #6</p> |
| <p>6. Will the prescriber consider a change to a preferred product?</p> <p><u>Message:</u></p> <ul style="list-style-type: none"> • Preferred products do not require PA. • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. | <p>Yes: Inform prescriber of covered alternatives in class.</p> | <p>No: If for treatment of unfunded condition for patient covered under EPSDT, approve for 1 year.</p> <p>For all other requests: Go to #7</p> |
| <p>7. Is the request for safinamide or istradefylline?</p> | <p>Yes: Go to #12</p> | <p>No: Go to #8</p> |
| <p>8. Is the request for opicapone?</p> | <p>Yes: Go to #9</p> | <p>No: Go to #10</p> |

| Approval Criteria | | |
|---|--|---|
| 9. Is the patient on a non-selective monoamine oxidase (MAO) inhibitor? Note: selective MAO-B inhibitors are permitted (moclobemide; rasagiline; safinamide; selegiline) | Yes: Pass to RPh. Deny; medical appropriateness. | No: Approve for the shorter of 1 year or length of prescription. |
| 10. Is the request for foslevodopa/foscarbidopa? | Yes: Go to #11 | No: Go to #14 |
| 11. Is the agent being prescribed by or in consultation with a neurology specialist? | Yes: Go to #12 | No: Pass to RPh. Deny; medical appropriateness |
| 12. Is the patient currently taking a nonselective monoamine oxidase (MAO) inhibitor or have they recently (within 2 weeks) taken a nonselective MAO inhibitor? | Yes: Pass to RPh. Deny; medical appropriateness. | No: Go to #13 |
| 13. Has the prescriber submitted a calculation of the base continuous dosage, hourly infusion rate, optional loading dose, and extra dose according to FDA prescribing information? | Yes: Approve for requested length of therapy. | No: Pass to RPh. Deny; medical appropriateness. |
| 14. Is the request for apomorphine sublingual film? | Yes: Go to #15 | No: Go to #16 |
| 15. Is the patient on a 5-HT3 antagonist (eg., ondansetron, dolasetron, granisetron, palonosetron, etc.) | Yes: Pass to RPh. Deny; medical appropriateness. | No: Approve for the shorter of 1 year or length of prescription. |
| 16. Is the patient currently taking levodopa/carbidopa? | Yes: Approve for the shorter of 1 year or length of prescription. | No: Pass to RPh. Deny; medical appropriateness. |

| Renewal Criteria | | |
|--|--|--|
| 1. Has the patient's condition progressed slower than expected, stabilized, or improved or as assessed by the prescribing physician and physician attests to patient's status? | Yes: Approve for the shorter of 1 year or length of prescription. | No: Pass to RPh; Deny; medical appropriateness. |

P&T Review: 02/25 (DE); 10/20 (AG); 3/18; 7/16; 9/14; 9/13; 09/10
Implementation: 3/10/25; 11/1/20; 4/16/18; 8/16, 1/1/14, 1/1/11