09-J5000-09

Original Effective Date: 04/01/25

Reviewed: 02/12/25

Revised: 00/00/00

Subject: Foscarbidopa-Foslevodopa (Vyalev) subcutaneous infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Parkinson's disease is a progressive neurodegenerative condition caused by a loss of dopaminergic neurons in the substantia nigra and dopamine depletion, which unbalances oscillatory neural transmission through the basal ganglia, resulting in bradykinesia. Risk factors for Parkinson's disease include older age, genetics (e.g., family history), and environmental factors (e.g., exposure to certain pesticides and solvents). The prevalence of Parkinson's disease is approximately 1% in patients over 65 years of age and 3% in those 80 years of age and older. Its clinical presentation includes motor symptoms such as bradykinesia, resting tremor, and rigidity, along with non-motor symptoms such as cognitive decline, depression, sleep disturbances, and autonomic symptoms. Dopaminergic medications such as oral carbidopa/levodopa are used as initial management of motor symptoms and as effectiveness wanes, alternative or additional agents include dopamine agonists (e.g., pramipexole, ropinirole, rotigotine), catechol-O-methyltransferase (COMT) inhibitors (e.g., entacapone, tolcapone, opicapone), MAO-B inhibitors (e.g., rasagiline, selegiline, safinamide), and amantadine.

On October 17, 2024, the FDA approved foscarbidopa-foslevodopa (Vyalev) subcutaneous infusion for the treatment of motor fluctuations in adults with advanced Parkinson's disease. Foscarbidopa-foslevodopa (Vyalev) is a prodrug combination of foscarbidopa (carbidopa-4′-monophosphate) and foslevodopa (levodopa-4′-monophosphate). Foscarbidopa and foslevodopa are converted in vivo to carbidopa and levodopa, respectively.

As summarized in the prescribing information, the efficacy and safety of foscarbidopa-foslevodopa (Vyalev) was evaluated in a 12-week, randomized, double-blind, double-dummy, active-controlled, multicenter study (Study 1; NCT04380142) in patients with advanced Parkinson's disease. Enrolled patients included those who were responsive to levodopa treatment (i.e., taking ≥ 400 mg/day of

levodopa), had motor fluctuations inadequately controlled by their current medications, and who experienced a minimum of 2.5 hours of “off” time per day as assessed by patient diaries. A total of 141 patients were randomized in 1:1 ratio and received either 24-hour/day continuous subcutaneous administration of foscarbidopa-foslevodopa (Vyalev) plus oral placebo capsules (N=74) or 24-hour/day continuous subcutaneous administration of placebo solution plus oral encapsulated carbidopa-levodopa immediate-release (IR) tablets (N=67). Patients had a mean age of 66.4 years and a mean disease duration of 8.6 years. Most (93%) of the patients were Caucasian, 2% were Asian, 3% African-American and 70% of the patients were male. At baseline, approximately 74% of patients in the foscarbidopa-foslevodopa (Vyalev) group and 66% of patients in the oral immediate release carbidopa-levodopa group were taking at least one or more classes of Parkinson’s disease medications other than carbidopa-levodopa. 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 diary. The key secondary clinical outcome measure was the mean change from baseline to Week 12 in the total daily mean “off” time. The “on” and “off” time were normalized to a daily 16-hour awake period. Daily normalized "off" and "on" times are averaged over valid patient diary days for each visit to obtain the average daily normalized times. Foscarbidopa-foslevodopa (Vyalev) demonstrated improvements from baseline to Week 12 in "on" time without troublesome dyskinesia compared with the oral immediate release carbidopa-levodopa group (p=0.0083; Table 1). Foscarbidopa-foslevodopa (Vyalev) also demonstrated improvements from baseline to Week 12 in “off” time compared with the oral immediate release carbidopa-levodopa group (p=0.0054; Table 1).

Table 1: Change from Baseline to Week 12 in Primary and Key Secondary Measures

	Oral immediate release carbidopa-levodopa[b] (N=67)	Foscarbidopa-foslevodopa (Vyalev) (N=73)
Primary Measure		
“On” time without troublesome dyskinesia (hours)[a]		
Baseline Mean (SD)	9.49 (2.62)	9.20 (2.42)
Change from Baseline to Endpoint Week 12 Mean (SD)	0.85 (3.46)	3.36 (3.62)
LS Mean (SE) of Change	0.97 (0.50)	2.72 (0.52)
LS Mean (SE) of Difference	1.75 (0.65)	
P value	0.0083	
Secondary Measure		
“Off” time (hours)[a]		
Baseline Mean (SD)	5.91 (1.88)	6.34 (2.27)
Change from Baseline to Endpoint Week 12 Mean (SD)	-0.93 (3.31)	-3.41 (3.76)
LS Mean (SE) of Change	-0.96 (0.49)	-2.75 (0.50)
LS Mean (SE) of Difference	-1.79 (0.63)	
P value	0.0054	
LS = least squares; SD = standard deviation; SE = standard error		

[a] Derived from patient diary
[b] Oral immediate release carbidopa-levodopa tablets

The most common adverse reactions for foscarbidopa-foslevodopa (Vyalev) (incidence at least 10% and greater than oral carbidopa-levodopa incidence) were infusion/catheter site reactions, infusion/catheter site infections, hallucinations, and dyskinesia.

POSITION STATEMENT:

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of foscarbidopa-foslevodopa (Vyalev) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria ("1" to "6"):

1. Diagnosis of advanced Parkinson's disease
2. Experiencing persistent motor fluctuations including a minimum of 2.5 hours of "off" time per day while receiving carbidopa/levodopa therapy – documentation must be provided
3. The member is taking at least 400 mg of levodopa daily – documentation must be provided
4. Documentation of an inadequate response, intolerance, or contraindication to at least **TWO** medications from at least **TWO** of the following medication classes - documentation must be provided
    a. COMT inhibitors (e.g., entacapone, tolcapone, opicapone)
    b. MAO-B inhibitors (e.g., rasagiline, selegiline, safinamide)
    c. Dopamine agonists (e.g., pramipexole, ropinirole, rotigotine)
    d. Amantadine
5. Foscarbidopa-foslevodopa (Vyalev) is prescribed by a neurologist or neuromuscular specialist
6. The maximum dose does not exceed 3,525 mg of foslevodopa (approximately 2,500 mg levodopa) daily

Duration of approval: 6 months

Continuation of foscarbidopa-foslevodopa (Vyalev) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria ("1" to "4"):

1. Authorization or reauthorization for foscarbidopa-foslevodopa (Vyalev) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of motor fluctuations associated with advanced Parkinson's disease (if another health plan, documentation of a health plan-paid claim for foscarbidopa-foslevodopa (Vyalev) during the 90 days immediately before the authorization request must be submitted); **OR** the member previously met **ALL** indication-specific initiation criteria

2. The member has had a beneficial response to therapy such as improvement or stabilization in motor fluctuations and/or "off" time per day – documentation must be provided
3. Foscarbidopa-foslevodopa (Vyalev) is prescribed by a neurologist or neuromuscular specialist
4. The maximum dose does not exceed 3,525 mg of foslevodopa (approximately 2,500 mg levodopa) daily

Duration of approval: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Foscarbidopa-foslevodopa (Vyalev) is indicated for the treatment of motor fluctuations in adults with advanced Parkinson's disease with a maximum recommended daily dosage of 3,525 mg of the foslevodopa component (equivalent to approximately 2,500 mg levodopa). Refer to the foscarbidopa-foslevodopa (Vyalev) prescribing information for calculation of the base continuous dosage, hourly infusion rate, optional loading dose, and extra doses.

- Foscarbidopa-foslevodopa (Vyalev) is administered as a subcutaneous infusion with the Vyafuser pump. Patients should be trained on the proper use of the delivery system prior to initiating treatment and, as necessary, thereafter. In preparing foscarbidopa-foslevodopa (Vyalev), use aseptic technique and the sterile, single-patient-use infusion components (syringe, infusion set, and vial adapter) qualified for use with the pump. Do not dilute or mix foscarbidopa-foslevodopa (Vyalev) with other products. Foscarbidopa-foslevodopa (Vyalev) should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Foscarbidopa-foslevodopa (Vyalev) vials are for single dose only, and the entire contents of the vial should be transferred into a syringe for administration. Discard the vial after transfer of the product to the syringe and discard the syringe and any unused medication in the syringe after the product has been in the syringe for 24 hours. Keep the medication vials in the outer carton to protect the vials from breaking and store them refrigerated at 2°C to 8°C (36°F to 46°F). Foscarbidopa-foslevodopa (Vyalev) may be stored at room temperature up to a maximum of 30°C (86°F) for a single period of up to 28 days. Once the product has been stored at room temperature, do not return the product to the refrigerator. If stored at room temperature, discard the product if not used within 28 days. Do not freeze or shake the product.
- Foscarbidopa-foslevodopa (Vyalev) administration is subcutaneously, preferably in the abdomen, avoiding the area with a 2-inch radius from the navel. The infusion set (cannula) can remain in place for up to 3 days when the product is infused continuously. Rotate the infusion site and use a new infusion set at least every 3 days. Select new infusion sites at least 1 inch from sites used within the previous 12 days. Do not infuse the product into areas where the site is tender, bruised, red, or hard to the touch.

- If interruption of foscarbidopa-foslevodopa (Vyalev) therapy occurs, a backup oral carbidopa and levodopa product is recommended, which may result in underdosing. Sudden discontinuation or rapid dose reduction of foscarbidopa-foslevodopa (Vyalev), without administration of alternative dopaminergic therapy, should be generally avoided. Following interruptions of more than 1 hour, a new infusion set (tubing and cannula) should be used and rotated to a different infusion site. If the infusion has been interrupted for longer than 3 hours, the patient may also self-administer a loading dose, if enabled by their healthcare professional.

Dose Adjustments

- None

Drug Availability

- Foscarbidopa-foslevodopa (Vyalev) injection contains 120 mg foscarbidopa and 2,400 mg foslevodopa per 10 mL (12 mg foscarbidopa and 240 mg foslevodopa per mL).
- Each single-dose vial contains 10 mL of a colorless to yellow to brown (may have a purple or red tint) and clear to slightly opalescent solution and is fitted with a grey rubber stopper, aluminum crimp cap, and turquoise plastic flip-off cap. The rubber stopper on the vial does not contain natural rubber latex. Carton of 7 vials: NDC 0074-0501-01.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Foscarbidopa-foslevodopa (Vyalev) is contraindicated in patients who are currently taking a non-selective monoamine oxidase (MAO) inhibitor or have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently.

Precautions/Warnings

- **Falling Asleep During Activities of Daily Living and Somnolence:** Patients treated with levodopa [an active metabolite of foscarbidopa-foslevodopa (Vyalev)] have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on levodopa, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event (sleep attack). Some of these events have been reported more than one year after initiation of treatment. Falling asleep while engaged in activities of daily living usually occurs in patients experiencing preexisting somnolence, although patients may not give such a history. For this reason, prescribers should reassess patients for drowsiness or sleepiness while using foscarbidopa-foslevodopa (Vyalev), especially since some of the events occur well after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients who have already experienced somnolence or an episode of sudden sleep onset should not participate in these activities while taking foscarbidopa-foslevodopa (Vyalev). Before initiating treatment with foscarbidopa-foslevodopa (Vyalev), advise patients about the potential to develop drowsiness and specifically ask about factors that may increase the risk for somnolence such as the use of concomitant sedating medications or the presence of sleep disorders. Consider discontinuing

foscarbidopa-foslevodopa (Vyalev) in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating). If foscarbidopa-foslevodopa (Vyalev) is continued, patients should be advised not to drive and to avoid other potentially dangerous activities that might result in harm if the patient becomes somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

- **Hallucinations/Psychosis:** There is an increased risk for hallucinations and psychosis in patients taking foscarbidopa-foslevodopa (Vyalev). In Study 1, hallucinations occurred in 12.2% of patients treated with foscarbidopa-foslevodopa (Vyalev) compared to 1.5% of patients treated with oral immediate-release carbidopa-levodopa. Psychosis occurred in 4.1% of patients treated with foscarbidopa-foslevodopa (Vyalev) compared to 1.5% of patients treated with oral immediate-release carbidopa-levodopa. Treatment with foscarbidopa-foslevodopa (Vyalev) was discontinued in 1 (1.4%) patient because of hallucinations. Hallucinations associated with levodopa may present shortly after the initiation of therapy and may be responsive to dose reduction of foscarbidopa-foslevodopa (Vyalev) or other concomitantly administered medications. Confusion, insomnia, and excessive dreaming may accompany hallucinations. Abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychosis, disorientation, aggressive behavior, agitation, and delirium. Review of treatment is recommended if these symptoms develop. Because of the risk of exacerbating psychosis, patients with a major psychotic disorder should not be treated with foscarbidopa-foslevodopa (Vyalev). In addition, medications that antagonize the effects of dopamine used to treat psychosis may exacerbate the symptoms of PD and may decrease the effectiveness of foscarbidopa-foslevodopa (Vyalev).
- **Impulse Control/Compulsive Behaviors:** Patients may experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including foscarbidopa-foslevodopa (Vyalev), that increase central dopaminergic tone and that are generally used for the treatment of PD. In some cases, although not all, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with foscarbidopa-foslevodopa (Vyalev). Consider reducing the dose or discontinuing foscarbidopa-foslevodopa (Vyalev) if a patient develops such urges.
- **Infusion Site Reactions and Infections:** Foscarbidopa-foslevodopa (Vyalev) can cause infusion site reactions and infections. In Study 1, one or more infusion site reactions were reported in 62% of patients treated with foscarbidopa-foslevodopa (Vyalev) and 8% of patients who received placebo subcutaneous infusion. Various types of reactions at the infusion site have been reported including: erythema, pain, edema, nodule, bruising, hemorrhage, induration, pruritus, extravasation, inflammation, mass, warmth, hematoma, pallor, rash, and swelling. In Study 1, 8% of patients treated with foscarbidopa-foslevodopa (Vyalev) and no patient who received placebo withdrew from treatment because of an infusion site reaction. In Study 1, infusion site infections occurred in 28% of patients treated with foscarbidopa-foslevodopa (Vyalev) compared to 3% of patients who received placebo subcutaneous infusion. In Study 1, 5% of patients treated with foscarbidopa-foslevodopa (Vyalev) and 2% who received placebo withdrew from treatment because of an infusion site infection. The most frequent infusion site infection reported was cellulitis. If an infection is suspected at the infusion site, the cannula should be removed from the infusion site. If the cannula is removed for an infection, either a new canula should be placed at a new infusion site or, in the event of a prolonged interruption, the patient should be prescribed an oral carbidopa and levodopa product until they are able to resume foscarbidopa-foslevodopa (Vyalev).
- **Withdrawal-Emergent Hyperpyrexia and Confusion:** A symptom complex that resembles neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy. Avoid sudden discontinuation or rapid dose reduction in patients taking foscarbidopa-foslevodopa (Vyalev).

If foscarbidopa-foslevodopa (Vyalev) is discontinued, the dose should be tapered to reduce the risk of hyperpyrexia and confusion.

- **Dyskinesia:** Foscarbidopa-foslevodopa (Vyalev) may cause or exacerbate dyskinesias. In Study 1, dyskinesia occurred in 11% of patients treated with foscarbidopa-foslevodopa (Vyalev) compared to 6% of patients treated with oral immediate-release carbidopa-levodopa. The occurrence of dyskinesias may require a dosage reduction of foscarbidopa-foslevodopa (Vyalev) or other medications used to treat PD.
- **Cardiovascular Ischemic Events:** In clinical studies, myocardial infarction and arrhythmia were reported in patients taking carbidopa-levodopa [the active metabolites of foscarbidopa-foslevodopa (Vyalev)]. Ask patients about symptoms of ischemic heart disease and arrhythmia, especially those with a history of myocardial infarction or cardiac arrhythmias.
- **Glaucoma:** Carbidopa-levodopa [the active metabolites of foscarbidopa-foslevodopa (Vyalev)] may cause increased intraocular pressure in patients with glaucoma. Monitor intraocular pressure in patients with glaucoma after starting foscarbidopa-foslevodopa (Vyalev).

BILLING/CODING INFORMATION:

HCPCS Coding

C9399	Unclassified drugs or biologics [Hospital Outpatient Use ONLY]
J3490	Unclassified drugs

ICD-10 Diagnosis Codes That Support Medical Necessity

G20.A2	Parkinson's disease without dyskinesia, with fluctuations
G20.B2	Parkinson's disease with dyskinesia, with fluctuations

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

REFERENCES:

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4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 2025 Jan 30]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
5. Vyalev (foscarbidopa-foslevodopa) [package insert]. North Chicago, IL: AbbVie Inc., October 2024.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/12/25.

GUIDELINE UPDATE INFORMATION:

04/01/25	New Medical Coverage Guideline: Foscarbidopa-foslevodopa (Vyalev) subcutaneous infusion for the treatment of motor fluctuations in adults with advanced Parkinson's disease.