Foscarbidopa and Foslevopda (VYALEV) in Parkinson's Disease
National Drug Mini-monograph
March 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION[1]

Description / MOA	Foscarbidopa and foslevodopa (FC/FL) are prodrugs converted to carbidopa and levodopa. Carbidopa inhibits peripheral decarboxylation of levodopa making levodopa more available to the brain. Levodopa is converted to dopamine in the brain to treat symptoms of Parkinson's disease (PD).
Indication Under Review	Treatment of motor fluctuations in adults with advanced Parkinson's disease
Dosage Regimen	Infusion rate is calculated based on the patient's current levodopa dose (see prescribing information). FC/FL is administered by a 24h/day continuous subcutaneous infusion. The VYAFUSER pump must be used for administration, this is a Phillips-Medisize portable infusion pump.
Dosage Forms Under Review	120mg foscarbidopa and 2,400mg foslevodopa per 10mL vial

EFFICACY CONSIDERATIONS

Trial	**Soileau et al. phase 3 trial[2]**
Design / Intervention	Double-blind, double-dummy, active-controlled study with 12-week treatment period. For all patients, all levodopa and COMT therapies were converted to an equivalent of carbidopa/levodopa (C/L) 25mg/100mg IR tabs first. Then patients were randomized to either stay on C/L IR tabs or switch to FC/FL subQ infusion. All patients could receive C/L IR tabs if there was rapid deterioration of motor symptoms.
Population	Key inclusion criteria: ≥30 years old, ≥400mg/day of levodopa equivalent, average off time ≥2.5h/day. Average baseline levodopa daily dose was 1,000mg/day.
Results	FC/FL subQ infusion resulted in significantly increased on time without troublesome dyskinesia and decreased off time compared to placebo. Due to hierarchical testing, the remaining secondary outcomes were not significant.

Primary and Key Secondary Efficacy Outcomes

Outcome	C/L IR tabs (n=67)	FC/FL subQ infusion (n=74)	Treatment Difference (95% CI)
On time without troublesome dyskinesia, mean change from baseline, h/day*	0.97	2.72	1.75 (0.46, 3.05)#
Off time, mean change from baseline, h/day^	-0.96	-2.75	-1.79 (-3.03, -0.54)#
MDS-UPDRS part II score, mean change from baseline^	-1.06	-2.65	-1.58 (-3.65, 0.48)
Morning akinesia, n/N (%)^	38/60 (63%)	8/47 (17%)	0.12 (0.04, 0.31)

*primary efficacy outcome; ^key secondary efficacy outcome; #statistically significant, p<0.05

On and off times were subjectively reported from a patient-kept diary, which the authors note is subject to recall bias. The blinding via a double-dummy design may have been hindered by the large difference in infusion site reactions (C/L IR tab 12%; FC/FL subQ infusion 72%) which, as the authors note, is common with subQ administered medications.

Trial	**Aldred et al. phase 3 open label[3]**
Design	52-week, open-label, single-arm. Separate phase 3 trial (i.e., not an extension trial of above)
Population	Key inclusion criteria: ≥30 years old, average off time ≥2.5h/day. No minimum levodopa daily dose identified, but the average was 1,065mg/day
Intervention	Open-label FC/FL subQ infusion. As high frequency of discontinuations during the optimization phase were occurring, various strategies were implemented mid-study to improve tolerance including a different infusion set option, patient- and provider-specific education on aseptic care and management of infusion devices.
Results	At week 52, there was a significant decrease in off time from baseline (-3.5h) and a significant increase in on time without troublesome dyskinesia (3.8h). Of note, on time without dyskinesia drove the on time outcome and supports the theory that a continuous levodopa infusion may decrease peak dose dyskinesias seen with oral C/L. About 50% of patients reported morning akinesia compared to baseline (129/166 at baseline, 25/90 at week 52). Also, significant MDS-UPDRS score improvements were seen in Part II and Part IV (patient subjective assessment of activity capabilities and motor complications), but not Part III (provider-rated PD motor symptoms).
Trial	**Phase 1 trial comparing FC/FL to C/L intestinal gel.[4] This was not the only phase 1 trial, but included here as the only clinical trial that compared FC/FL to C/L intestinal gel.**
Design	Open-label, randomized, 2-period crossover study
Population	Healthy adults 45-75 years old
Intervention	FC/FL loading dose of 4mg/80mg followed by continuous infusion of FC/FL 35mg/700mg at a constant rate for 24 hours
Comparator	C/L intestinal gel loading dose of 12.5mg/50mg followed by continuous infusion of C/L intestinal gel 87.5mg/350mg) at a constant rate for 16 hours, followed by one oral C/L 25mg/100mg at 18h and 21h after start of intestinal gel administration. C/L intestinal gel was administered via NJ tube.
Results	Levodopa exposure measures ($C_{max0-16}$, AUC_{0-16}, and AUC_{∞}) were similar (<8% difference) between intervention and comparator.

SAFETY CONSIDERATIONS

Boxed Warnings[1]	none
Contraindications[1]	Concurrent or recent (within 2 weeks) administration of a nonselective monoamine oxidase inhibitor (MAOI)
Other Warnings[1]	Somnolence and falling asleep during activities of daily living, hallucinations/psychosis, development or worsening of impulse control/compulsive behavior, infusion site reaction, withdrawal-emergent hyperpyrexia and confusion, dyskinesia, ischemic cardiovascular events, glaucoma
AEs in >10% of patients[2,3]	Infusion site reactions/infections, hallucination/psychosis, fall, anxiety, dizziness, dyskinesia
Infusion site reaction - additional information	FC/FL had substantially more AEs than oral C/L in the blinded phase 3 trial (AE leading to premature discontinuation: oral C/L 1%, FC/FL 22%; AE related to study drug: oral C/L 22%, FC/FL 70%)[2]. Infusion site reactions are unique to FC/FL and seem to drive this increase in AEs. In the open label phase 3 trial, the highest discontinuation rate was noted in the first 10 weeks and strategies were implemented mid-study to improve tolerance to subQ infusion[3]. An early post-marketing case series[5] reported: "At our facility, we administered this treatment to 14 patients, and all patients developed redness or nodules." This case series suggests multiple mitigation strategies including topical or subQ steroids, oral NSAIDs, and topical cooling.
Drug Interactions[1]	MAOIs (see contraindications, nonselective may increase blood pressure, selective MAO-B inhibitors may cause orthostatic hypotension), antihypertensive drugs (symptomatic postural hypotension), dopamine D2 antagonists (e.g., risperidone, metoclopramide) and isoniazid may reduce the effectiveness of foslevodopa.

PLACE IN THERAPY – Advanced PD

Drug	VANF	CFU	FDA Indication	Guidelines: 2018 MDS[6] and 2022 EAN[7]
Foscarbidopa/foslevodopa subQ continuous infusion (VYALEV)	Pending review		Treatment of motor fluctuations in adults with advanced PD	Guidelines pre-date approval of FC/FL
Carbidopa/levodopa intestinal gel continuous infusion (DUOPA)	Formulary, PA-F	Yes	Acute, intermittent treatment of hypomobility, "off" episodes associated with advanced PD	MDS: Clinically useful to treat motor fluctuations with optimized oral levodopa. "Acceptable risk with specialized monitoring" EAN: Consider offering if fluctuations are not satisfactorily controlled with medication.
Apomorphine subQ continuous infusion (ONAPGO)	Pending market launch and review		Treatment of motor fluctuations in adults with advanced PD	MDS: Possibly useful to treat motor fluctuations with optimized oral levodopa. "Acceptable risk with specialized monitoring" EAN: Consider offering if fluctuations are not satisfactorily controlled with medication.
Deep Brain Stimulation (DBS): bilateral subthalamic nucleus (STN-DBS) or globus pallidus internus (GPi-DBS)	Nonpharmacologic treatment			MDS: Clinically useful to treat motor fluctuations and/or dyskinesia with optimized oral levodopa. "Acceptable risk with specialized monitoring." EAN: Offer STN-DBS if fluctuations are not satisfactorily controlled with medication or if tremor cannot be controlled with medication. Both STN-DBS and GPi-DBS are effective to treat fluctuations, but dopaminergic medication can be more reduced with STN-DBS.

VHA PLACE IN THERAPY

1. The motor symptoms of advanced PD can be complicated by increased motor fluctuations ("off time"), increased dyskinesias, and decreased on time. Device-assisted and surgical therapies may be considered when oral medications can no longer manage motor fluctuations and dyskinesias.
2. Subcutaneous infusion of FC/FL significantly increased on time without troublesome dyskinesia and decreased off time in two phase 3 trials. Both studies also demonstrated a decreased incidence in morning akinesia with FC/FL. This is unique compared to the other continuous infusion currently available (C/L intestinal gel) which is still associated with morning akinesia[8]. This is likely related to the fact that the intestinal gel infusion is stopped overnight but the FC/FL subcutaneous infusion is not.
3. Compared to oral C/L, the subQ administration of FC/FL led to a high rate of infusion site reactions. Mitigation strategies have been suggested in clinical trials and post-marketing case series[3,5].
4. There are multiple pending studies involving FC/FL including an open label extension trial (NCT04379050), a 96-week trial (NCT04750226), and a three-year observational trial (NCT06107426). There are also other subcutaneous carbidopa/levodopa formulations in clinical trials including: ND0612 and DIZ102.
5. All device-assisted and surgical therapies for advanced PD come with serious safety risks and/or lifestyle changes that need to be considered in the clinical context of the individual patient. Non-motor symptoms of advanced PD like severe dementia, chronic hallucinations, or psychosis may impact decisions of what therapies are a good fit for the patient[9].
6. There is insufficient evidence to broadly support any one of these advanced PD therapies over another. The 2018 MDS guideline notes both surgical and device-assisted therapies have "acceptable risk with specialized monitoring".

References

1. **Foscarbidopa and foslevodopa (VYALEV) injection for subcutaneous use [prescribing information online]. North Chicago, IL: AbbVie October 2024**
2. **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; 21:1099-109**
3. **Aldred J, Freire-Alvarez E, Amelin AV, et al. Continuous subcutaneous foslevodopa/foscarbidopa in Parkinson's Disease: safety and efficacy results from a 12-month, single-arm, open-label, phase 3 study. Neurol Ther. 2023; 12:1937–1958**
4. **Rosebraugh M, Stodtmann S, Liu W, Facheris MF. Foslevodopa/foscarbidopa subcutaneous infusion maintains equivalent levodopa exposure to levodopa-carbidopa intestinal gel delivered to the jejunum. Parkinsonism Relat Disord. 2022 Apr:97:68-72.**
5. **Yoshihara N, Nishikawa N, Watanabe R, Hattori N. Skin inflammatory reactions in patients with continuous subcutaneous injection of foslevodopa-foscarbidopa hydrate: histopathology. Mov Disord. 2024 Nov 19.**
6. **Fox SH, Katzenschlager R, Lim S-Y, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2018 Aug;33(8):1248-1266**
7. **Deuschl G, Antonini A, Costa J, et al. European academy of neurology/movement disorder society – European section guidelines on the treatment of Parkinson's disease: I. Invasive therapies. Mov Disord. 2022 Jul;37(7):1360-1374.**
8. **Slevin JT, Fernandez HH, Zadikoff C, et al. Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients. J Parkinsons Dis. 2015;5(1): 165–174**
9. **Worth PF. When the going gets tough: how to select patients with Parkinson's disease for advanced therapies. Pract Neurol. 2013 Jun;13(3):140-52.**

Prepared March 2025. Contact person: N. Antonovich, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)