Apomorphine Continuous Subcutaneous Infusion (ONAPGO) in Parkinson's Disease
National Drug Mini-monograph
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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 PRESCRIBING INFORMATION[1]	
Description / MOA	Apomorphine is a non-ergoline dopamine agonist with high in vitro binding affinity for the dopamine D4 receptor, and moderate affinity for the dopamine D2, D3, and D5, and adrenergic α1D, α2B, α2C receptors. MOA to treat symptoms of Parkinson's Disease (PD) is believed to be due to stimulation of post-synaptic dopamine D2-type receptors within the caudate-putamen in the brain.
Indication Under Review	Treatment of motor fluctuations in adults with advanced Parkinson's disease
Dosage Regimen	Apomorphine is administered as a continuous SQ infusion (98 mg per 20 mL with Onapgo pump). Initial: 1 mg/hour; adjust dose based on response and tolerability in 0.5 to 1 mg/hour increments at intervals ≥1 day up to a maximum continuous dosage of 6 mg/hour. Maximum total daily dose (including continuous infusion and extra doses): 98 mg/day administered over the waking day (eg, 16 hours).
Dosage Forms Under Review	98 mg/20 mL (4.9 mg/mL) single dose cartridge This is a specialty distribution medicine.
Pretreatment Procedures	Because of the incidence of nausea and vomiting with apomorphine, it is recommended that treatment with trimethobenzamide 300 mg three times a day start 3 days prior to the initial dose of apomorphine (see prescribing information). Alternatively, can start without antiemetics and titrate slowly based upon effectiveness and tolerance.

EFFICACY CONSIDERATIONS	
Trial	**Katzenschlager, et al. TOLEDO phase 3 trial[2]**
Design	A prospective, multicenter, phase 3 study of apomorphine subcutaneous infusion compared with placebo in patients with PD with persistent motor fluctuations despite optimized oral or transdermal medication. The trial included a 12-week, parallel-group, double-blind, placebo-controlled phase (followed by a 52-week open-label phase not included in the results of this study).
Population	N = 106 Key inclusion criteria: ≥30 years old, PD diagnosis > 3 years prior to study, same dose of oral medications for at least 4 weeks prior to enrollment, mean of 3 or more hours of off time per day for 2 days at screening and baseline, with no day recording less than 2 hours of off time.
Intervention	Patients were randomized 1:1 apomorphine subcutaneous infusion to placebo (same pump filled with saline). As the intervention was titrated, other PD medications could be titrated down in a hierarchical order (DA, MAOB inhibitors, COMT inhibitors, levodopa) based on motor symptoms.
Results	Active apomorphine infusions had significantly greater reductions in off times and significantly increased on time without troublesome dyskinesia compared to placebo.

Primary and Key Secondary Efficacy Outcomes

Outcome	Apomorphine (n=53)	Placebo (n=53)	Treatment Difference (95% CI)	P value
Off time (h per day)*	–2.47 (3.70)	–0.58 (2.80)	–1.89 (–3.16 to –0.62)	0.0025
# of patients with ≥ 2 h reduction in off time^	62 (n=33)	29 (n=15)	33.4 (15.5 to 51.4)	0.0008
On time without troublesome dyskinesia (h per day)^	2.77 (3.26)	0.80 (2.93)	1.97 (0.69 to 3.24)	0.0008
Levodopa-equivalent dose (mg)^	-492.1 (618.3)	–163.7 (367.5)	–328.5 (–535.2 to –121.7)	0.0014

*primary efficacy outcome; ^key secondary efficacy outcomes

50 (93%) of patients in the apomorphine group experienced a treatment-emergent adverse event (TEAE). Most commonly skin reactions, nauseas, and somnolence. Neuropsychiatric adverse events also occurred including mild hypersexuality, punding, confusion, hallucinations and psychosis. The placebo group had 30 (57%) incidence of TEAEs.

Trial	**Katzenschlager, et al. TOLEDO open label trial[3]**
Design/Intervention	Open-label extension (OLE) study of participants who completed the TOLEDO double blind placebo (DBP) 12 week trial were offered entry into the open label study to receive apomorphine infusion. The primary focus was

Population	evaluating long term safety. Regular assessments included adverse events, motor status, Patient Global Impression of Change (PGIC), MDS-UPDRS scores.
Results	84 (79%) of patients from the DBP trial continued on in the OLE Mean daily off time reduced from 6.9 hours at DBP baseline to 3.66 hours. Mean daily on time without troublesome dyskinesis improved by 3.31 hours. PGIC hours indicated that 75% of patients felt some level of health improvement by end of the open label study. No significant changes observed in UPDRS motor scores.
Trial	**Isaacson, et al. InfusON phase 3 open label trial[4]**
Design/Intervention	Open-label study enrolled patients with PD experiencing ≥3 hours (h) daily off time despite optimized levodopa and current/prior use of at least one other adjunctive therapy. Continuous subcutaneous apomorphine infusion (CSAI) was initiated with a 1–2 mg bolus followed by 1 mg/h infusion titrated to optimal efficacy and tolerability. Following titration, patients entered a 52-week maintenance period.
Population	Duration of PD was 10 years; duration of PD motor fluctuations was 5.3 years; mean daily off time was 6.6 h. Mean daily on time with troublesome dyskinesia was 0.5 h. Mean baseline levodopa daily dose was 1,063mg/day.
Results	Reduction in off time began at CSAI initiation and reached a mean of 3.0 ± 3.18 h/day by maintenance week 12 (primary efficacy endpoint), with a corresponding increase in on time without troublesome dyskinesias of 3.1 ± 3.35 h/day (key secondary outcome). By maintenance week 12, 68% of patients rated themselves as much or very much improved, 62% had at least a 2-h reduction in daily off time (key secondary outcome) and mean concomitant oral levodopa and levodopa equivalent doses (excluding CSAI) had been reduced by 198 mg/day and 283 mg/day, respectively. Improvements were maintained through week 52.
SAFETY CONSIDERATIONS	
Boxed Warnings[1]	None
Contraindications[1]	Using concomitant 5HT3 antagonists, including antiemetics (e.g., ondansetron) and alosetron. If hypersensitivity/allergic reaction to apomorphine or any of the excipients of apomorphine, including sulfite (i.e., sodium metabisulfite).
Other Warnings[1]	Nausea and vomiting, somnolence and falling asleep during activities of daily living, syncope/hypotension, orthostatic hypotension, falls, infusion site reaction, hallucinations/psychosis, dyskinesia, hemolytic anemia, impulse control disorder/compulsive behaviors, cardiac events, QTc prolongation, hypersensitivity, fibrotic complications, priapism
AEs in > 10% of patients[2,3,4]	Skin nodules at infusion site, nausea, somnolence, infusion site erythema/pruritic, bruising, dyskinesia, headache, insomnia, dizziness, fatigue
Drug Interactions[1]	5HT3 antagonists (hypotension), antihypertensive drugs and vasodilators (hypotension), alcohol (hypotension), dopamine antagonists (diminish efficacy), drugs prolonging QT/QTc interval.
Pregnancy	No adequate data available
Lactation	No data available

THERAPEUTIC ALTERNATIVES – ADVANCED PD				
Drug	**VANF**	**CFU**	**FDA Indication**	**Guidelines: 2018 and 2025 Update MDS[5,6] and 2022 EAN[7]**
Apomorphine SQ Continuous Infusion (ONAPGO)	Pending Review		Treatment of motor fluctuations in adults with advanced PD	MDS: likely efficacious for the treatment of motor fluctuations in PD patients on (attempted) optimal oral levodopa therapy. EAN: Consider offering if fluctuations are not satisfactorily controlled with medication
Foscarbidopa/foslevodopa SQ continuous infusion (VYALEV)	Non-formulary	Yes	Treatment of motor fluctuations in adults with advanced levodopa-responsive PD	MDS: likely efficacious to treat motor fluctuations in PD patients on (attempted) optimal oral levodopa therapy. EAN: Guidelines pre-date approval of Foscarbidopa/foslevodopa
Carbidopa/levodopa intestinal gel continuous infusion (DUOPA)	Non-formulary	Yes	Treatment of motor fluctuations in advanced PD	MDS: Clinically useful to treat motor fluctuations with optimized oral levodopa. 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		Treatment of motor complications not adequately controlled with medication in advanced PD	MDS: Clinically useful to treat motor fluctuations and/or dyskinesia with optimized oral levodopa. 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 OF ADVANCED PD

1. The motor symptoms of advanced PD can be complicated by increased motor fluctuations ("off time"), increased dyskinesias, and decreased on time. Device assisted therapies may be considered when oral medications can no longer manage motor fluctuations and dyskinesias.
2. Continuous subcutaneous apomorphine infusion (CSAI) significantly increased reductions in off times and significantly increased on time without troublesome dyskinesia in 1 RCT and 2 open label trials. Infusion site nodules were the most frequent reason for discontinuation of CSAI. Mitigation strategies to address skin irritations have been suggested in clinical reviews[8].
3. Indirect comparison of off time reduction and on time without troublesome dyskinesia increase appears to be similar between CSAI and foscarbidopa/foslevodopa subcutaneous infusion[9-11].
4. CSAI has been used in Europe for about 30 years. A systematic review (SR) by Kukkle et al. describes similar efficacy outcomes in decreasing off time and increasing on time[12]. They also appear to demonstrate similar adverse events and incidences. Though it should be noted that the vast number of studies reported in this SR were observational. This SR also reported studies that compared CSAI to other interventions, although most were small study populations (<30 participants) and also observational. The only outcome that appeared in multiple comparative studies is that STN-DBS resulted in greater decrease of levodopa equivalent dose, but also greater worsening of neuropsychiatric symptoms than CSAI.
5. One meta-analysis of 5 different interventions (STN-DBS, GPi-DBS, pallidotomy, CSAI, or carbidopa/levodopa intestinal gel) on quality of life (QoL) found that unilateral pallidotomy and CSAI both did not have significant improvement in QoL while the other three interventions did[13].
6. 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[14].
7. There is insufficient evidence to broadly support any one of these advanced PD therapies over another. CSAI may be a good option for those patients who are not candidates for DBS or other invasive devices (i.e. elderly, not surgical candidates, etc.). Individual patient baseline conditions and may influence the decision of one therapy over another. CSAI appears to have higher incidence of somnolence than continuous levodopa-based therapies (subcutaneous or intestinal gel). Both CSAI and carbidopa/levodopa intestinal gel are indicated for use during waking hours, whereas foscarbidopa/foslevodopa subcutaneous infusion is indicated for use 24 hours a day. Some patients may find daytime-only wear of a pump more amenable, but treatment 24 hours a day does appear to prevent morning akinesia[9] (both daytime-only therapies have a bolus function that can be used in the morning).

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