

Carbidopa/ Levodopa Enteral Suspension (Duopa) National Drug Monograph March 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Carbidopa Levodopa enteral suspension (CLES) is a dopaminergic drug indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease (PD). The CLES is administered into the jejunum through a PEG-J using the CADD®-Legacy 1400 portable infusion pump as a continuous daytime (16-hour) infusion
Indication(s) Under Review in this document (may include off label)	Indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease (PD),
Dosage Form(s) Under Review	Enteral Suspension: 4.63 mg carbidopa and 20 mg levodopa per mL
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <input type="checkbox"/> Postmarketing Requirements <i>See Other Considerations for additional REMS information</i>
Pregnancy Rating	Pregnancy Category C

Executive Summary

Efficacy	<ul style="list-style-type: none"> CLES safely and effectively treats motor and some non-motor features of PD leading to improved quality of life and reduced off-time without worsening troublesome dyskinesia Patients who were levodopa-responsive and had persistent motor fluctuations despite optimized treatment with oral carbidopa-levodopa demonstrated improved "Off" time (LSM difference -1.91 hours/day; P=0.0015) with a corresponding increase in "On" time without troublesome dyskinesia (LSM difference 1.86 hours/day, P=0.0059) compared with oral CL-IR from baseline.
Safety	<ul style="list-style-type: none"> The most common adverse reactions for CLES (incidence at least 7% greater than oral immediate-release carbidopa-levodopa) were: complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, atelectasis, and incision site erythema. Peripheral neuropathy is common in Parkinson's disease, and may be worsened with CLES., hyperhomocysteinaemia associated with levodopa therapy may be responsible. This may be due to higher doses of levodopa required due to discontinuation of other dopamine sparing therapies.
Potential Impact	<ul style="list-style-type: none"> In 2001 the VA created six specialized centers known as the Parkinson's Disease Research, Education, and Clinical Centers or "PADRECCs". There are 51,625 unique patients in VA diagnosed with PD. Current pharmacologic management of the disease is based on treating the symptoms of the disorder, in particular the motor symptoms. The mainstay of treatment is based on augmentation of dopamine, which is reduced in the nigrostriatal pathway and is responsible for

the motor symptoms of the disorder. Development of wearing off and other motor fluctuations is a phenomenon of disease progression. As the disease progresses, the plasma half-life of LD becomes more critical in maintaining clinical effects and motor benefit. Doses tend to last for shorter periods as therapy progresses. The aim of CLEs is to “smooth” out these fluctuations by combining immediate and controlled release delivery of levodopa.

- Patients with advanced PD can be considered for therapies such as apomorphine infusion, deep brain stimulation or CLES therapy. Patient characteristics should be applied when making the recommendation for an agent.
- Patients to consider for CLES include those who have been levodopa responsive and are not candidates for deep brain stimulation due to age, cognitive deficits or other medical or psychiatric complications.

Background

Purpose for review

Recent FDA approval of CLES

Issues to be determined:

- ✓ Evidence of need- does CLES provide an alternative for later stages of PD
- ✓ Does CLES offer advantages to currently available alternatives?
- ✓ Does CLES offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does CLES have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
CARBIDOPA/LEVODOPA IR		Treatment Recommendations
CARBIDOPA/LEVODOPA SA		Treatment Recommendations
Non-formulary Alternative (if applicable)	Other Considerations	
CARBIDOPA/LEVODOPA EXTENDED RELEASE CAPSULE		CFU
CARBIDOPA 25MG TAB		Treatment Recommendations
CARBIDOPA /ENTACAPONE /LEVODOPA TAB	Can lessen pill burden	Treatment Recommendations

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2015) using the search terms carbidopa/levodopa immediate release, carbidopa/levodopa sustained release and Duopa. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer’s AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

The available evidence supporting the use of CLES includes open label assessments of safety, tolerability and/or motor efficacy as well as randomized controlled trials, several of which are not blinded and at least one that did include blinding and use of sham infusions.

A randomized, double blind, double dummy, double titration trial of stable advanced PD patients with at least 3 hours of off time daily was conducted in 71 patients.¹² This 12 week trial randomized patients to receive either placebo intestinal gel infusion and treatment with oral immediate release (IR) levodopa carbidopa or placebo IR levodopa-carbidopa and treatment with CLES. The primary outcome was mean change in off-time from baseline to end of the study. This outcome demonstrated a significant reduction favoring CLES over IR levodopa-carbidopa tablets (difference of -1.91 h, $p = 0.0015$). There was a significant increase in on-time without dyskinesia with CLES than the carbidopa-levodopa IR (difference of 1.86 h, $p = 0.0059$). Mean off time reduction observed in the CLES group was 4.04 h, supporting a conclusion that CLES efficacy is similar to open label trials of deep brain stimulation open-label results. A 52 week open label extension trial of this study with 62 patients being enrolled; 33 patients continuing CLES and 29 patients being initiated on CLES.^{13, 14} Throughout the study, continuing CLES patients retained off-time improvements and showed further improvements in the amount of on-time without troublesome dyskinesia (1.0 h, $p < 0.05$). The CLES naïve patients showed significant improvements in off-time (-2.27 h, $p < 0.001$) and on-time without dyskinesia (2.19 h, $p < 0.05$) from baseline to end of study at 52 weeks. There were no significant changes in total UPDRS, quality of life measures or caregiver burden in either group in the open-label study. The majority of patients in both groups were assessed by investigators on Clinical Global Impression scale as “much improved” or “very much improved.”

The largest open-label¹³, prospective trial of CLES demonstrated that of the 354 patients enrolled, 324 completed the nasojejunal test infusion period and went on to long-term CLES therapy. A total of 272 patients (76.8%) completed the study with 7.6% of patients discontinuing therapy due to an adverse event. Efficacy was demonstrated with significant improvements in off time (decreased by 4.4 h/65.6% , $P < 0.001$), on time without troublesome dyskinesia (increased by 4.8 h/62.9% , $P < 0.001$) and on-time with troublesome dyskinesia (decreased by 0.4 h/22.5% , $P=0.023$). Positive outcomes were also reported for other measures such as total UPDRS score, health related quality of life measures and investigator Clinical Global Impression scores.

A post hoc analysis¹⁶ of the studies conducted by Fernandez and Olanow demonstrated that patients with troublesome dyskinesia at baseline experienced a significant reduction in troublesome dyskinesia from baseline to final visit as well as an increase in on time without troublesome dyskinesia. This is likely a result of the a smoother delivery of levodopa with fewer peaks and troughs when using CLES.

Potential Off-Label Use

Based on literature review, potential off-label uses of CLES are unlikely due to invasive nature of the delivery system.

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> • none
Contraindications	<ul style="list-style-type: none"> • CLES is contraindicated in patients taking nonselective monoamine oxidase (MAO) inhibitors
Warnings/Precautions	<ul style="list-style-type: none"> • Gastrointestinal procedure-related complications may result in serious outcomes, such as need for surgery or death • May cause falling asleep during activities of daily living • Monitor patients for orthostatic hypotension, especially after starting CLES or increasing the dose • Hallucinations/Psychosis/Confusion: May respond to dose reduction in levodopa • Impulse Control Disorders: Consider dose reductions or stopping CLES • Monitor patients for depression and suicidality • Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion • May cause or exacerbate dyskinesia: Consider dose reduction • Monitor patients for signs and symptoms of peripheral neuropathy

Adverse Reactions

Common adverse reactions	Most common adverse reactions for CLES are: complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, atelectasis, and incision site erythema.
Death/Serious adverse reactions	In the US Clinical programs for CLES, 2 deaths were considered possibly related to treatment (n=1, intestinal dilation on day 1071 in a patient with a history of pulmonary embolism; n=1, cardiac arrest on day 491 [previously experienced severe adverse event of aspiration following vomiting/pneumonia/respiratory failure within first 2 weeks of treatment
Discontinuations due to adverse reactions	2 main causes leading to CLES withdrawal during the first year postimplant: postsurgical stoma infection and worsening of dyskinesias. The first is a device-related event related to postimplant care and hygiene. Another common cause of withdrawal was dyskinesias.

Drug-Drug Interactions

- Monoamine Oxidase (MAO) Inhibitors-The use of nonselective MAO inhibitors with CLES is contraindicated. Discontinue use of any nonselective MAO inhibitors at least two weeks prior to initiating therapy with CLES
- The use of selective MAO-B inhibitors (e.g., rasagiline and selegiline) with CLES may be associated with orthostatic hypotension. Monitor patients who are taking these drugs concurrently.
- Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce the effectiveness of levodopa. Monitor patients for worsening Parkinson's symptoms.
- Iron salts or multi-vitamins containing iron salts can form chelates with levodopa and carbidopa and can cause a reduction in the bioavailability. If iron salts or multi-vitamins containing iron salts are coadministered with CLES, monitor patients for worsening Parkinson's symptoms.

Risk Evaluation

As of October 1, 2015

	Comments
Sentinel event advisories	<ul style="list-style-type: none"> • None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	<ul style="list-style-type: none"> • None • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Dosing and Administration

The maximum recommended daily dose of CLES is 2000 mg of levodopa (i.e., one cassette per day) administered over 16 hours

- Prior to initiating CLES, convert patients from all forms of levodopa to oral immediate-release carbidopa-levodopa tablets (1:4 ratio)
- Titrate total daily dose based on clinical response for the patient
- Administer CLES into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) with the CADD®-Legacy 1400 portable infusion pump

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • In the controlled clinical trial, 49% of patients were 65 years and older, and 8% were 75 years and older. In patients 65 years and older, there was an increased risk for elevation of BUN and CPK (above the upper limit of the normal reference range) during treatment with CLES compared to the risk for patients less than 65 years.
Pregnancy	<ul style="list-style-type: none"> • Pregnancy Category C. • There are no adequate or well-controlled studies in pregnant women.
Lactation	<ul style="list-style-type: none"> • Carbidopa is excreted in rat milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human milk was reported.
Renal Impairment	<ul style="list-style-type: none"> • No data identified
Hepatic Impairment	<ul style="list-style-type: none"> • No data identified
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting)

- The main indication for moving to CLES is uncontrolled motor fluctuations and/or dyskinesias
- Prior to consideration of CLES, therapy with alternatives such as dopamine agonists, extended release carbidopa/levodopa formulations, and COMT inhibitors should be optimized.
- The initiation of CLES requires placement of a PEG tube. Patients and/or caregivers must be instructed on the care this requires and the potential complications of using a pump based therapy.
- Patients who are not acceptable surgical candidates for deep brain stimulation may be considered for CLES therapy

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.