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Levodopa-Carbidopa Enteral Suspension (e.g., Duopa) for the Treatment of Parkinson Disease

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety

and efficacy has been confirmed in two articles from major peer reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Levodopa-carbidopa enteral suspension (e.g., Duopa®) **may be considered medically necessary** for the treatment of motor fluctuations in individuals with advanced Parkinson's disease (PD), who meet ALL the following criteria:

- Presence of bradykinesia and at least one other cardinal PD feature (tremor, rigidity, postural instability); **AND**
- Levodopa-responsive with clearly defined "On" periods (See **NOTE** 1); **AND**
- Persistent motor complications with disabling "Off" periods (See **NOTE 2**) for a minimum of 3 hours/day despite optimal medical therapy with:
    a) Dopamine agonists; **and**
    b) Oral levodopa and carbidopa; **and**
    c) One agent from the following class;
        1. Catechol-O-methyl transferase (COMT) inhibitors; **or**
        2. Monoamine oxidase (MAO) B inhibitors.

NOTE 1: "On" periods refer to periods of adequate control of PD symptoms.
NOTE 2: "Off" periods refer to periods of the day when the medication is not working well, causing worsening of PD symptoms.

Levodopa-carbidopa enteral suspension **is considered experimental, investigational and/or unproven** for all other indications, including but not limited to individuals with:

- Atypical Parkinson's disease ("Parkinson's Plus" syndrome); **or**
- Secondary Parkinson's disease; **or**
- Concurrent use with nonselective monoamine oxidase (MAO) inhibitors; **or**
- In individuals who are not candidates for percutaneous endoscopic gastrostomy-jejunal (PEGJ) tube placement or in patients where long-term use of a PEG-J is contraindicated; **or**
- When the above initial criteria are not met.

A pump for administering levodopa-carbidopa enteral suspension **may be considered medically necessary** durable medical equipment (DME) for persons who meet the criteria for levodopa-carbidopa enteral suspension.

Policy Guidelines

None.

Description

Parkinson's disease (PD) is a chronic, progressive neurodegenerative condition resulting from the death of the dopamine containing nerve cells in one of the movement control centers of the brain (substantia nigra). (1) Approximately 90,000 Americans are diagnosed with PD each year, and this number does not reflect the thousands of cases that go undetected. An estimated 10 million people worldwide are living with PD. There is a rising prevalence with age and a higher prevalence and incidence of PD in males. (2)

Some forms of PD have genetic or familial risk factors. PD can be either primary or secondary. Primary PD is referred to as idiopathic (having no known cause), while secondary PD is due to sources such as toxins, drugs and conditions. (3)

Parkinsonism is a general term used to describe the group of signs and symptoms similar to PD. Atypical parkinsonism includes a variety of neurological disorders including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), cortico-basal degeneration (CBD), dementia with Lewy bodies (DLB), vascular parkinsonism, parkinsonism with no clear etiology, and parkinsonism-dementia-amyotrophic lateral sclerosis complex. Atypical parkinsonism shares some clinical features of PD, but the symptoms are caused not only by cell loss in the substantia nigra (the brain area most affected in classic PD), but also by additional degeneration of cells in the parts of the nervous system that normally contain dopamine receptors (striatum). Shared PD symptoms may include resting tremors, slowed movement, stiffness, gait difficulty and postural instability, but also include signs and symptoms that are not typically present in PD, hence the term "Parkinsonism plus syndrome." Individuals usually have a poor response or no response to levodopa which is a common feature to all forms of atypical parkinsonism. In contrast to typical PD, in which dopamine receptors are spared, patients with atypical parkinsonian disorders have lost their dopamine receptors and therefore they do not respond to levodopa as well as those with typical PD. Additional imaging studies may be helpful in differentiating parkinsonism from atypical parkinsonism. (3-6)

Making an accurate diagnosis of PD particularly in the early stages of the disease can be difficult as individuals present with the signs and symptoms associated with parkinsonism. Per the International Parkinson and Movement Disorder Society (MDS), to consider a diagnosis of PD the individual must have bradykinesia (slowness of movement) and 1 or more of the following symptoms: shaking or tremor in a limb that occurs while it is at rest, stiffness or rigidity of the arms, legs, or trunk, or trouble with balance and falls. Although PD is predominantly a movement disorder, other impairments frequently develop including psychiatric problems such as depression and dementia. Autonomic disturbances and pain (which is rarely a presenting feature of PD) may later ensue, causing significant disability and handicap with impaired quality of life (QOL) for the affected individual. (1, 7)

Carbidopa/levodopa is the gold-standard medication for the treatment of motor symptoms in PD and is most often taken orally with Sinemet®. (8) As PD advances, carbidopa/levodopa becomes effective for shorter time periods, making it necessary for people to take the drug multiple times a day. Even then, people taking carbidopa/levodopa orally experience periods in which the drug “wears off," meaning levodopa levels in the blood may drop and the patients motor symptoms exacerbate prior to the next dose. These “off times” are particularly problematic in advanced PD because gastrointestinal (GI) issues delay the medication’s ability to reach the small intestine, where the drug is absorbed. (9)

Regulatory Status

On January 09, 2015, Duopa® enteral suspension (AbbVie Inc.) was approved by the United States (U.S.) Food and Drug Administration (FDA) as an orphan drug. Duopa is an enteral suspension combination of levodopa and carbidopa and is indicated for the treatment of motor fluctuations in patients with advanced PD. Duopa is administered as a continuous 16-hour infusion into the jejunum through a percutaneous endoscopic gastrostomy-jejunal tube (PEG-J), using a CADD®-Legacy 1400 portable infusion pump. (10)

Rationale

In 2014, Olanow et al. (11) assessed the safety and efficacy of levodopa-carbidopa intestinal gel (LCIG) delivered continuously through an intrajejunal percutaneous tube in a randomized, double-blind, double-dummy, double-titration trial over a 12-week period. Adults (aged ≥ 30 years) with advanced Parkinson's disease (PD) and motor complications were enrolled throughout 26 centers in Germany, New Zealand, and the United States (U.S.) Eligible participants had jejunal placement of a percutaneous gastrojejunostomy tube and were then randomly allocated (1:1) to treatment with immediate-release oral levodopa-carbidopa plus placebo intestinal gel infusion or LCIG infusion in addition to an oral placebo. Randomization was stratified by site, with a mixed block size of 2 or 4. The primary endpoint was change from baseline to final visit in motor off-time. Change in motor on-time without troublesome dyskinesia as a prespecified key secondary outcome was evaluated. Efficacy in a full-analysis set of participants with data for baseline and at least 1 post-baseline assessment, and imputed missing data with the last observation carried forward approach. Safety was addressed in randomly allocated patients who underwent the percutaneous gastrojejunostomy procedure. From baseline to 12 weeks in the full-analysis set, mean off-time decreased by 4.04 hour(s) (standard error [SE] 0.65) for 35 patients allocated to the LCIG group compared with a decrease of 2.14 hour(s) (0.66) for 31 patients allocated to immediate-release oral levodopa-carbidopa (difference -1.91 hours[s] [95% confidence interval (CI) -3.05 to -0.76]; p=0.0015). Mean on-time without troublesome dyskinesia increased by 4.11 hour(s) (SE 0.75) in the intestinal gel group and 2.24 hour(s) (0.76) in the immediate-release oral group (difference 1.86 [95% CI 0.56 to 3.17]; p=0.0059). In the safety analyses 35 (95%) of 37 patients allocated to the LCIG group had adverse events (AEs; five [14%] serious), as did 34 (100%) of 34 patients allocated to the immediate-release oral levodopa-carbidopa group (seven [21%] serious), mainly associated with the percutaneous gastrojejunostomy tube. The authors concluded that the continuous delivery of LCIG offers a promising option for control of advanced PD with motor complications.

In 2014, Cáceres-Redondo et al. reported on the motor and cognitive outcome of LCIG treatment in advanced PD after a period of at least 24 months. (12) Twenty-nine patients with advanced PD who started LCIG via 1 center between 2007 and 2013 were examined. Motor fluctuations, PD symptoms, activities of daily living and impact on quality of life (QOL) were evaluated as well as cognitive outcome using a battery of neuropsychological tests. All AEs were recorded. Of the 29 PD patients who initiated LCIG, 16 patients reached the follow-up evaluation (24 months), after a mean time-period of 32.2 ± 12.4 months. Six patients did not fulfil the 24-month follow-up visit and were evaluated after a mean time period of 8.6 ± 5.4 months. Seven patients discontinued the treatment before the scheduled visit. "Off" and "On" time dyskinesia duration was significantly reduced. LCIG improved QOL and non-motor symptoms, despite overall unchanged total levodopa doses prior to LCIG beginning. Motor and cognitive decline was detected. A relatively high number of AEs occurred during the follow-up, above all, technical problems with the infusion device and mild problems related with gastrostomy. There were four cases of peripheral neuropathy (PN), 2 of which were considered serious. Data confirmed that LCIG is beneficial in the long-term treatment of advanced PD despite a decline in cognitive functions in a subgroup of patients, probably due to disease progression. PN in patients with LCIG may be more frequent than the published data suggest.

Motor complications in PD are associated with long-term oral levodopa treatment and linked to pulsatile dopaminergic stimulation. LCIG is delivered continuously by percutaneous endoscopic gastrojejunostomy tube (PEG-J), which reduces levodopa-plasma-level fluctuations and can translate to reduced motor complications. In 2015, Fernandez et al. presented the end results of the largest international, prospective, 54-week, open-label LCIG study. (13) PD patients with severe motor fluctuations (>3 h/day "off" time) despite optimized therapy received LCIG monotherapy. Additional PD medications were allowed >28 days post-LCIG initiation. Safety was the primary endpoint measured through AEs, device complications, and number of completers. Secondary endpoints included diary-assessed “off” time, "on" time with and without troublesome dyskinesia, unified Parkinson's disease rating scale (UPDRS), and health-related QOL outcomes. Of 354 enrolled patients, 324 (91.5%) received PEG-J and 272 (76.8%) completed the study. Most AEs were mild/moderate and transient; complication of device insertion (34.9%) was the most common. Twenty-seven (7.6%) patients withdrew because of AEs. Serious AEs occurred in 105 (32.4%), most commonly complication of device insertion (6.5%). Mean daily off time decreased by 4.4 h/65.6% ($P < 0.001$). On time without troublesome dyskinesia increased by 4.8 h/62.9% ($P < 0.001$); on time with troublesome dyskinesia decreased by 0.4 h/22.5% ($P = 0.023$). Improvements persisted from week 4 through study completion. UPDRS and health-related QOL outcomes were also improved throughout. In the advanced PD population, LCIG's safety profile consisted primarily of AEs associated with the device/procedure, levodopa/carbidopa, and advanced PD. LCIG was generally well tolerated and demonstrated clinically significant improvements in motor function, daily activities, and health-related QOL sustained over 54 weeks.

In 2014, Zibetti et al. stated that LCIG infusion is becoming an established therapeutic option for advanced PD patients with fluctuating symptoms unresponsive to conventional oral

treatment. (14) As the implementation of LCIG therapy is increasing, there is a need for safety and efficacy data from current clinical practice. All PD patients treated with LCIG at 1 center over a 7-year period were analyzed to determine the duration of treatment, retention rate, reasons for discontinuation, LCIG efficacy in motor complications, modifications of concomitant therapy and AEs. Of the 59 patients, seven subjects (12%) died of causes unrelated to LCIG infusion and 11 patients (19%) discontinued therapy prior to the cut-off date. Duodopa improved motor complications and over 90% of patients reported an improvement in their QOL, autonomy and clinical global status. The most common AEs were dislocation and kinking of the intestinal tube. The study concluded that LCIG infusion is effective for the long-term treatment of advanced PD patients and exerts a positive and clinically significant effect on motor complications with a relatively low dropout rate.

In 2015, Slevin et al. sought to examine the long-term safety, efficacy and QOL of LCIG. Patients received 52 weeks of open-label LCIG treatment following a 12-week double-blind, double-dummy trial in which they were randomized to either LCIG or immediate-release oral levodopa-carbidopa. (15) Patient cohort designation was by receipt of LCIG in the preceding trial randomization (continuing-LCIG versus LCIG-naïve patients). Sixty-two of 66 subjects in the double-blind proceeded to the open-label extension. Most subjects (95%) reported ≥1 AEs; only 3 subjects (4.8%) discontinued due to AEs. AE incidence declined gradually over 52 weeks. Serious AEs were reported by 23%. LCIG-naïve patients (N=29) showed a decrease in "Off" time and an increase in "On" time without troublesome dyskinesia (change from baseline to final visit in mean [SD] hours = -2.34 [2.78] $P < 0.001$ and 2.19 [3.70] $P = 0.005$, respectively), while continuing-LCIG patients (N=33) showed sustained "Off" time duration and further improvement in "On" time without troublesome dyskinesia (-0.42 [2.67] P=0.377 and 1.00 [2.58] P=0.036, respectively). Most patients in both groups (LCIG-naïve, continuing-LCIG, respectively) were rated 'Much Improved' or 'Very Much Improved' at final visit on the Clinical Global Impression-Improvement scale (69.0%, 69.7%). The authors concluded that LCIG patients continued to derive benefit from LCIG while the magnitude of improvement among LCIG-naïve patients was similar to that observed for patients on LCIG. The overall AE profile was consistent with previous phase 3 clinical trials.

In 2016, Wirdefeldt et al. performed a systematic review of the evidence specific to LCIG therapy. (16) Studies were identified from the PubMed and EMBASE databases through March 2016. Data focused on whether LCIG therapy improved motor and non-motor outcomes as well as QOL in PD patients compared to conventional therapy, apomorphine infusion, or deep brain stimulation. Randomized controlled trials (RCTs) and observational studies, with or without a control group with >10 patients were included and was limited to peer-reviewed articles published in English involving humans. The review indicated that LCIG reduced "off" time, increased "on" time without increasing dyskinesias, and improved QOL in 3 RCTs (one doubleblind). Open-label follow-ups confirm these findings. The data evaluating long-term efficacy and safety are still limited and the quality of evidence that LCIG is effective in reducing fluctuating motor symptoms and improving QOL is moderate. Quality of evidence for reduction of nonmotor symptoms is very low. Safety issues mainly relate to the intestinal infusion system.

The study concluded that LCIG might be a useful treatment option in PD patients with severe motor fluctuations.

In 2017, Timpka et al. reviewed device-aided PD therapies and stated that LCIG infusion is an effective strategy to counteract motor fluctuations and dyskinesia. (17) LCIG therapy, deep brain stimulation (DBS), and subcutaneous infusion of the dopamine agonist apomorphine seem to be similarly effective in reducing "time with PD symptoms (off time)" by at least 60%-65%. The use of advanced therapy also leads to a significant reduction of dyskinesia. Studies indicate that these therapies can improve several nonmotor symptoms in advanced PD which improves health related QOL in most treated patients. LCIG complications are usually related to the infusion equipment and the establishment of the percutaneous endoscopic gastrostomy. LCIG is one device-related therapy indicated for the treatment of motor fluctuations and/or dyskinesia when peroral/transdermal PD medications cannot be further optimized. However, the choice of device-aided therapy is made on basis of indications/contraindications, but also the patients' symptom profile and his/her personal preferences. Therefore, it is important that available treatment options are discussed early prior to the deterioration of motor/nonmotor symptoms.

In 2021, Tsunemi et al. performed a systematic review of intrajejunal infusion of levodopa/ Carbidopa in patients with advanced PD. (18) Advanced PD is inconsistently defined therefore, researchers sought literature specific to LCIG. Retrieved articles were categorized by relevance to identified research questions, including motor complications and symptoms; nonmotor symptoms; functioning, QOL, and caregiver burden; optimal timing of treatment initiation and administration duration; discontinuation; and complications. Most eligible studies (n=56) were open-label, observational studies including relatively small patient numbers. LCIG consistently reduced OFF time and increased ON time without troublesome dyskinesia with varying effects regarding ON time with troublesome dyskinesia and the possibility of diphasic dyskinesia. Recent evidence provides some increased support for the benefits of LCIG in relation to nonmotor symptoms, QOL, activities of daily living, and reduced caregiver burden. Patient age does not appear to significantly impact the effectiveness of LCIG. Discontinuation rates with LCIG (~17%-26%) commonly relate to device-related issues, although the ability to easily discontinue LCIG may represent a potential benefit. LCIG may be a favorable option for patients with advanced Parkinson's disease who show predominant nonmotor symptoms and vulnerability to complications of other advanced therapy modalities. Larger, well-controlled studies would further assist treatment selection.

Professional Guidelines and Position Statements

American Academy of Neurology (AAN)

In 2006, the AAN published guidelines for the treatment of patients with PD with motor fluctuations and dyskinesia. (19) These guidelines were retired without a replacement report from the quality standards subcommittee. The AAN offered the following recommendations:

- Offer entacapone and rasagiline to reduce “off” time (Level A).
- Pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce “off” time (Level B).

- Apokyn (apomorphine subcutaneous injection), cabergoline, and selegiline may be considered to reduce “off” time (Level C).
- Ropinirole may be chosen over bromocriptine for reducing “off” time, but otherwise there is insufficient evidence to recommend one agent over the other (level B).
- Amantadine may be considered to reduce dyskinesia (Level C).

International Parkinson and Movement Disorder Society

In 2018, the International Parkinson and Movement Disorder Society performed an evidence based review regarding the treatments available for motor symptoms in patients with PD. (20) They note that in advanced PD patients, LCIG can reduce OFF time and improve ON time without dyskinesia. The mechanism is likely a combination of both reducing oral levodopa dosing as well as a direct effect on dopamine receptors with a continuous-stimulation approach rather than the intermittent pulsatile dopaminergic stimulation of oral levodopa. Furthermore, percutaneous infusion of LCIG is clinically useful in certain patients with severe motor fluctuations, although it requires appropriate clinical support, restricting use to specialized centers.

Summary of Evidence

Levodopa-carbidopa enteral suspension (e.g., Duopa®) is approved by the United States (U.S.) Food and Drug Administration (FDA) as an orphan drug for advanced Parkinson’s disease (PD). The FDA trial did not include atypical or secondary PD patients; therefore, this drug has only been proven to improve outcomes in advanced PD patients who have failed standard drug therapy to include dopamine agonists, oral levadopa and carbidopa, Catechol-O-methyl transferase (COMT) inhibitors and monoamine oxidase (MAO) B inhibitors. Additionally, levodopa-carbidopa enteral suspension is contraindicated in those who are currently taking or have taken (within 2 weeks) a nonselective MAO inhibitor, as concurrent use can cause hypertension.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member’s benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	E0779, E0781, J7340

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
03/15/2025	Document updated with literature review. Coverage unchanged. Added references 5-7; others removed/updated.
03/15/2024	Reviewed. No changes
07/01/2023	Document updated with literature review. Coverage unchanged. Added references 14, 15; others removed.
01/01/2023	Reviewed. No changes
07/01/2021	Document updated with literature review. The following changes were made in Coverage: 1) Removed term “idiopathic” from the medically necessary statement for levodopa-carbidopa enteral suspension (e.g., Duopa®); 2) Removed note regarding Duopa contraindications and expanded the experimental, investigational and/or unproven statement to include: a) Concurrent use with nonselective monoamine oxidase (MAO) inhibitors, or b) In patients who are not candidates for percutaneous endoscopic gastrostomy-jejunal (PEG-J) tube placement or in patients where long-term use of a PEG-J is contraindicated; or c) when the above initial criteria are not met. 3) Removed asterisks and added “See NOTE 1” and “See Note 2”. Added references 4, 13, 14 and 16; others updated.
03/15/2020	Reviewed. No changes.
07/15/2018	Document updated with literature review. Coverage unchanged. Added references 1, 3-5, 11.

11/01/2016	Reviewed. No changes.
07/15/2015	New medical document. Levodopa-Carbidopa enteral suspension (e.g. Duopa) may be considered medically necessary for the treatment of motor fluctuations in individuals with advanced idiopathic Parkinson's disease (PD), who meet all of the following criteria: 1) Presence of bradykinesia and at least one other cardinal PD feature (tremor, rigidity, postural instability); and 2) Levodopa responsive with clearly defined "On" periods*; and 3) Persistent motor complications with disabling "Off" periods** for a minimum of 3 hours/day despite optimal medical therapy with: a)Dopamine agonists; and b)Oral Levodopa and Carbidopa; and c)One agent from the following class; Catechol-O-methyl transferase (COMT) inhibitors; or Monoamine oxidase (MAO) B inhibitors. Levodopa-Carbidopa enteral suspension is considered experimental, investigational and/or unproven including but not limited to patients with: 1) Atypical Parkinson's disease "Parkinson's Plus" syndrome); or 2) Secondary Parkinson's disease. Note added to reflect the following contraindications: 1) Duopa is contraindicated in patients taking nonselective monoamine oxidase (MAO) inhibitors, 2) in patients that are not candidates for percutaneous endoscopic gastro-jejunal (PEG-J) tube placement, and 3) in patients were long-term use of a PEG-J is contraindicated. A pump for administering Levodopa-Carbidopa enteral suspension may be considered medically necessary durable medical equipment (DME) for persons who meet the criteria for Levodopa-Carbidopa enteral suspension