Therapeutic Class Overview
Carbidopa/Levodopa Agents

INTRODUCTION

- Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain and characterized by the cardinal manifestations of tremor, bradykinesia, and rigidity. Although traditionally recognized as a motor disorder, PD is a complex multifactorial condition that also includes neuropsychiatric and other non-motor manifestations. It is estimated that nearly 1 million people in the United States have PD *(Chou 2020, National Institute of Environmental Health Sciences [NIEHS] 2020)*.
- Current treatment options for PD include levodopa, dopamine agonists (DAs) (eg, bromocriptine, pramipexole, ropinirole), monoamine oxidase (MAO)-B inhibitors, anticholinergic agents, amantadine, and catechol-O-methyl transferase (COMT) inhibitors *(Spindler et al 2021)*.
- The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD and is the first choice if symptoms, especially bradykinesia, become troublesome. Levodopa is combined with the peripheral decarboxylase inhibitor carbidopa to block its conversion to dopamine in the systemic circulation and liver prior to crossing the blood-brain barrier. This prevents nausea, vomiting, and orthostatic hypotension *(Spindler et al 2021)*.
- Levodopa-induced complications develop within several years of starting levodopa in a substantial number of patients; complications include motor fluctuations ("wearing off" phenomenon), dyskinesia, and dystonia. It is estimated that these motor complications occur in 30% to 40% of patients during the first 5 years and 60% or more after 10 years. The risk of motor complications increases with higher levodopa doses and younger age of PD onset *(Spindler et al 2021, Liang et al 2021)*.
- Treatment strategies for managing levodopa-induced dyskinesia include adjusting the levodopa doses and dosing schedule or adding an additional antiparkinson medication. For patients who fail oral and transdermal medical therapies, other options include deep brain stimulation, continuous carbidopa-levodopa intestinal gel infusion, and continuous subcutaneous apomorphine infusion *(Liang et al 2021)*.
- Levodopa combination products are available in several formulations. Immediate-release (IR) tablets, orally disintegrating tablets (ODT), and extended-release (ER) tablets are available in multiple strengths. Rytary, an extended-release (ER) capsule, contains microbeads of carbidopa and levodopa that, after dissolving, are absorbed at different rates. Stalevo tablets include entacapone, a COMT inhibitor, to prolong and potentiate the levodopa effect; this may be useful for patients experiencing end-of-dose "wearing off" periods. Duopa, an enteral suspension, is given as a continuous infusion for patients with motor fluctuations in advanced PD *(Chou et al 2021)*. The newest levodopa product, Inbrija, is an inhalation powder intended to be used as an adjunct to oral carbidopa/levodopa therapy for the intermittent treatment of OFF episodes.
- Medispan class: Antiparkinson Dopaminergics; Levodopa Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
carbidopa/levodopa ODT	✔
Duopa (carbidopa/levodopa) enteral suspension	-
Inbrija (levodopa) inhalation powder	-
Lodosyn (carbidopa) tablets	✔
Rytary (carbidopa/levodopa) ER capsules	-
Sinemet (carbidopa/levodopa) tablets	✔
carbidopa/levodopa ER tablets	✔
Stalevo (carbidopa/levodopa/entacapone) tablets	✔

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	carbidopa/levodopa ODT	Duopa (carbidopa/levodopa)	Inbrija (levodopa)	Lodosyn (carbidopa)	Rytary (carbidopa/levodopa)	Sinemet (carbidopa/levodopa), carbidopa/levodopa ER tablets	Stalevo (carbidopa/levodopa/ entacapone)
Treatment of PD, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	✔				✔	✔	
Treatment of motor fluctuations in patients with advanced PD		✔					
Intermittent treatment of OFF episodes in patients with PD treated with carbidopa/levodopa			✔				
Treatment of PD • Stalevo can be used: ○ To substitute (with equivalent strengths of each of the 3 components) carbidopa/levodopa and entacapone previously administered as individual products ○ To replace carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" and when they have been taking a total daily dose of levodopa ≤ 600 mg and have not been experiencing dyskinesias							✔
For use with carbidopa/levodopa or with levodopa in the treatment of PD, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication • Lodosyn can be used: ○ With carbidopa/levodopa in patients for whom the dosage of carbidopa/levodopa provides less than adequate daily dosage of carbidopa ○ With levodopa in the occasional patient whose dosage requirement of carbidopa and levodopa necessitates separate titration of each medication ○ With carbidopa/levodopa or with levodopa to permit administration of lower doses of levodopa with reduced nausea/vomiting, more rapid dose titration, and with a somewhat smoother response				✔			

(*Prescribing information: carbidopa/levodopa ODT 2016, carbidopa/levodopa ER 2020, Duopa 2020, Inbrija 2020, Lodosyn 2020, Rytary 2019, Sinemet 2020, Stalevo 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Carbidopa/levodopa

- Although the efficacy of levodopa in PD has been widely established in clinical practice, there have been few placebo-controlled (PC) studies evaluating its effects. A systematic review of the available evidence concluded that levodopa is clinically efficacious as monotherapy for symptomatic PD *(Fox et al 2018)*. A Cochrane Review of trials comparing DAs (with or without levodopa) vs placebo and/or levodopa in patients with early PD demonstrated that while patients on a DA were less likely to develop dyskinesia, dystonia, or motor fluctuations, symptomatic control of PD was better with levodopa. Adverse effects (AEs) such as edema, somnolence, constipation, dizziness, and hallucinations were also increased in DA-treated patients vs levodopa-treated patients *(Stowe et al 2008)*.
- ELLDOPA, a multicenter (MC), double-blind (DB), PC, dose-ranging, randomized controlled trial (RCT), evaluated the effect of levodopa on the rate of progression of PD in 361 patients with early PD for 42 weeks. Patients were randomized to either carbidopa/levodopa (3 different doses) or placebo therapy. The primary outcomes were the change in Unified Parkinson Disease Rating Scale (UPDRS) scores and the percent change in the ratio of the specific striatal [^{123}I]β-CIT uptake to the nondisplaceable striatal [^{123}I]β-CIT uptake between the two images (prior to baseline and at week 40). The mean difference between the total score on the UPDRS was 7.8 units in the placebo group, 1.9 units in the groups receiving levodopa at a dose of 150 mg/day and 300 mg/day, and -1.4 units in those receiving 600 mg/day ($p < 0.001$). The mean percent decline in the [^{123}I]β-CIT uptake was significantly greater with levodopa than placebo (-6%, -4%, and -7.2% among those receiving levodopa at 150 mg/day, 300 mg/day, and 600 mg/day, respectively vs -1.4% among those receiving placebo) ($p = 0.036$). The patients receiving the highest dose of levodopa had significantly more dyskinesia, hypertonia, infection, headache, and nausea than those receiving placebo. The authors concluded that from a clinical perspective, the ELLDOPA study did not find that levodopa hastens the progression of PD. Small doses were found to be effective, although less so than higher doses *(The Parkinson Study Group 2004)*.
- A 5-year, MC, DB, parallel-group, RCT compared the long-term clinical and safety effects of IR and controlled release (CR) carbidopa/levodopa in 618 levodopa-naïve PD patients. The mean dose of IR medication after 5 years was 426 ± 205 mg/day and 510 ± 224 mg/day for the bioavailable dose of CR medication ($p = 0.02$). After 5 years, 20.6% of the IR group and 21.8% of the CR group had motor fluctuations or dyskinesia (not statistically significant). The prevalence of AEs did not differ between the treatment arms. The authors concluded that despite the progressive nature of PD, both the IR and CR formulations of carbidopa/levodopa maintained similar control in PD after 5 years. The low incidence of motor fluctuations or dyskinesia was not significantly different between treatment groups and may be partly attributed to the relatively low doses of levodopa used throughout the trial *(Koller et al 1999)*.

Carbidopa/levodopa + entacapone

- The efficacy and safety of adjuvant COMT inhibitor therapy (entacapone or tolcapone) to carbidopa/levodopa therapy were examined in a Cochrane Review of 14 RCTS of PD patients with motor fluctuations (N = 2566). Eight trials examined entacapone 200 mg added to each levodopa dose vs placebo in 1560 patients. Compared with placebo, entacapone significantly reduced levodopa dose (weighted mean difference: 55 mg/day; $p < 0.00001$), reduced OFF-time (difference: 41 minutes; $p = 0.004$), and improved UPDRS activities of daily living and motor scores ($p < 0.05$ for both). Entacapone also significantly increased the risk of dyskinesia, nausea, vomiting, diarrhea, constipation, and dizziness ($p \leq 0.01$ for all). Tolcapone was shown to provide similar benefits in relieving levodopa-induced complications, but also raised liver enzyme levels in some patients *(Deane et al 2004)*.
  - Due to risk of liver toxicity, tolcapone should only be used in PD patients who are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies *(Tolcapone prescribing information 2018)*.

Duopa

- The efficacy and safety of Duopa were evaluated in 3 clinical trials of patients with advanced PD who had persistent motor fluctuations despite optimized treatment with oral carbidopa/levodopa. The primary efficacy measure was mean change in OFF-time from baseline to the end of the study. ON-times with and without dyskinesias were also measured.
  - In a 12-week, DB, PC, RCT, patients (N = 71) were randomized to receive Duopa or placebo per percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). Those who were in the Duopa group received placebo IR carbidopa/levodopa and those in the placebo intestinal gel infusion group received active IR carbidopa/levodopa. Duopa demonstrated a statistically significant reduction in OFF-time compared with IR carbidopa/levodopa (-4.04 hours vs -2.14 hours, respectively; treatment difference: -1.91 hours; $p = 0.0015$). Duopa was associated with a statistically significantly greater improvement than IR carbidopa/levodopa in ON-time without troublesome dyskinesia (4.11 hours vs 2.24 hours, respectively; treatment difference: 1.86 hours; $p = 0.0059$) and in ON-time without

dyskinesia (3.37 hours vs 1.09 hours, respectively; treatment difference: 2.28 hours; p = 0.0142). Significant improvements in the UPDRS II (ability to engage in activities of daily living) score and health-related quality of life (HRQoL), as measured by the Parkinson's Disease Questionnaire (PDQ-39), were also reported in patients receiving Duopa vs IR carbidopa/levodopa *(Olanow et al 2014)*.

- In a 52-week, open-label extension study, all patients received Duopa (N = 62). Those continuing Duopa maintained their improved OFF-time; however, this value was not statistically significant compared to the mean OFF-time at the start of the extension study (mean change in hours/day: -0.42; p = 0.377). Duopa-naïve patients showed a statistically significant improvement in OFF-time from the start of the extension study (mean change in hours/day: −2.34; p < 0.001). Statistically significant improvements in ON-time without troublesome dyskinesia from the start of the extension study were demonstrated in both Duopa-naïve (mean change in hours/day: 2.19; p = 0.005) and Duopa-continuing patients (mean change in hours/day: 1.00; p = 0.036, respectively). In regard to HRQoL, both the Duopa-continuing and Duopa-naïve groups demonstrated statistically significant improvements in the overall UPDRS Part IV score, a measure of motor complications associated with PD *(Slevin et al 2015)*.
- In a 54-week open-label study, all patients received Duopa (N = 354). OFF-time was significantly decreased from baseline to last visit by 4.4 hours/day (p < 0.001). This improvement was sustained throughout all visits from weeks 4 to 54. Similarly, ON-time without troublesome dyskinesia increased by 4.8 hours/day (p < 0.001), and ON-time with troublesome dyskinesia decreased by 0.4 hours/day (p = 0.023). These improvements were sustained at all visits. Statistically significant improvements in UPDRS Parts II and III (activities of daily living and motor examination), UPDRS Part IV dyskinesia items, and HRQoL were observed at the study end compared with baseline *(Fernandez et al 2015)*.

Inbrija

- The efficacy and safety of Inbrija for the treatment of OFF episodes in patients with PD treated with oral carbidopa/levodopa were evaluated in a 12-week, DB, PC, RCT. Patients with at least 2 hours of OFF time per day were randomized to receive Inbrija inhalation powder 60 mg (n = 113), 84 mg (n = 114), or placebo (n = 112) as needed for OFF episodes. The average use of Inbrija or placebo was approximately 2 doses per day. Change in UPDRS Part III (motor) score from pre-dose (OFF state) to 30 minutes post-dose was significantly greater in the Inbrija 84 mg group vs placebo at week 12 (least squares mean change in Inbrija group: -9.83 vs -5.91 in placebo; between-group difference: -3.92; 95% CI, -6.84 to -1.00; p = 0.0088). The proportion of patients who returned to an ON state and sustained the ON state through 60 minutes post-dose was 58% for Inbrija 84 mg and 36% for placebo (p = 0.003) *(LeWitt et al 2019)*.
- The effect of Inbrija on pulmonary function was evaluated in PD patients treated with oral carbidopa/levodopa in a 12-month, open-label, RCT. Patients were randomized to receive Inbrija 84 mg (n = 278) or to an observational cohort receiving oral standard of care therapy (n = 130). There was no significant difference in pulmonary function as assessed by spirometry parameters between the Inbrija and observational cohort groups at 52 weeks. Exploratory endpoints in the Inbrija group included improvements in UPDRS Part III scores, as well as patient-reported measures such as daily OFF time *(Grosset et al 2018a [poster], Grosset et al 2018b [poster], Inbrija prescribing information 2020)*.

Rytary

- The efficacy and safety of Rytary were evaluated in 3 DB, RCTs; 2 trials were conducted in advanced PD patients vs carbidopa/levodopa IR and carbidopa/levodopa + entacapone, and 1 trial was conducted in early PD patients vs placebo.
  - In comparison to IR carbidopa/levodopa (n = 192), Rytary (n = 201) demonstrated a statistically significant improvement in the percentage of OFF-time in advanced PD patients, from a baseline of 36.9% to 23.8% for the Rytary group and from a baseline of 36.0% to 29.8% for the IR carbidopa/levodopa group (p < 0.0001). This translated to the Rytary group experiencing an additional reduction of 1 hour in OFF-time compared to the IR carbidopa/levodopa group (p < 0.0001) *(Hauser et al 2013)*.
  - In a crossover study of advanced PD patients, all patients received either Rytary or carbidopa/levodopa + entacapone (n = 91). Rytary demonstrated a statistically significant improvement in the percentage of OFF-time, from a baseline of 36.3% (both Rytary and carbidopa/levodopa + entacapone patients) to 24.0% vs 32.5% in the carbidopa/levodopa + entacapone group (p < 0.0001). Hence, compared with carbidopa/levodopa + entacapone treatment, Rytary reduced OFF-time by 1.4 hours *(Stocchi et al 2014)*.
  - The PC study randomized 381 levodopa-naïve patients to 3 strengths of Rytary (145 mg, 245 mg, or 390 mg) given 3 times daily or placebo. All dosages demonstrated a statistically significant improvement in UPDRS measures vs placebo throughout the study and at 30 weeks (p < 0.0001). Rytary was well tolerated, with the most commonly reported AEs being nausea, dizziness, and headache; the authors concluded that Rytary 145 mg 3 times daily appeared to provide the best overall balance between efficacy and safety *(Pahwa et al 2014)*.

CLINICAL GUIDELINES

- The American Academy of Neurology (AAN) practice parameter on initiation of treatment for PD *(Miyasaki et al 2002)* recommends that in patients who require the initiation of dopaminergic treatment, levodopa or a DA may be used; the choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with DAs).
  - Treatment of PD patients with cabergoline, ropinirole, and pramipexole results in fewer motor complications (wearing off, dyskinesias, "on/off" motor fluctuations) than levodopa, but is also associated with more frequent adverse events, including hallucinations, somnolence, and edema.
  - Amantadine is noted to have a modest effect on all features of PD with a mild adverse effect profile.

- European Federation of Neurological Societies (EFNS) and Movement Disorders Society (MDS) - European Section (ES) *(Oertel et al 2011)*
  - This joint guideline outlines recommendations for treatment of late (complicated) PD, including treatment of motor complications and the nonmotor symptoms of PD. A summary of the treatment of motor complications is provided.
  - Motor fluctuations: Wearing -" off" (end of dose akinesia, predictable "on"-" off")
    - In the early phase, when motor fluctuations are just becoming apparent, adjustments in frequency of levodopa dosing during the day (4 to 6 daily doses) may attenuate wearing-" off".
    - COMT inhibitors or MAO-B inhibitors may be added: No recommendations can be made on which treatment should be chosen first. On average, all reduce "off" time by about 1 to 1.5 hours per day.
      - No difference has been demonstrated between entacapone and rasagiline. Tolcapone, although more effective than entacapone, is potentially hepatotoxic, and is only recommended in patients who have failed all other available medications.
      - Rasagiline should not be added to selegiline due to cardiovascular (CV) safety issues.
    - DAs may be added: efficacious in reducing "off" time in patients experiencing wearing-"off". Currently, no DA has proven better than another; switching from 1 DA to another can be helpful in some patients.
      - First line: Non-ergot DAs.
      - Second Line: Ergot DAs (association with lung, retroperitoneal, and heart valve fibrosis).
    - Standard levodopa can be switched to a CR formulation:
      - CR formulation of levodopa can improve wearing-" off".
      - CR formulation of levodopa is useful for the treatment of night-time akinesia (nocturnal end-of-dose akinesia).
    - Amantadine or an anticholinergic may be added: In patients with disabling recurrent "off" symptoms that fail to improve further with the aforementioned strategies, the addition of an anticholinergic (in younger patients) or amantadine may improve symptoms in some cases.
  - Dyskinesias: Peak-dose dyskinesia
    - Levodopa dose size may be reduced, with a risk of increasing "off" time; the latter can be compensated for by increasing the number of daily doses of levodopa or increasing the doses of a DA.
    - MAO-B inhibitors or COMT inhibitors may be discontinued or the dose may be reduced, with a risk of worsening of wearing-" off".
    - Amantadine may be added; benefit may last < 8 months.
    - In some cases, discontinuation of oral levodopa for a short period of time (3 days) with simultaneous continuous intravenous infusion of amantadine may temporarily improve dyskinesia.
    - Other interventions that may be considered include deep brain stimulation, internal globus pallidus stimulation, the addition of an atypical antipsychotic (clozapine or quetiapine), apomorphine continuous subcutaneous infusion, and intrajejunal levodopa infusion.

- The International Parkinson and MDS Evidence-Based Medicine Review Update: Treatments for the Motor Symptoms of PD *(Fox et al 2018)* (Refer to Appendix C for definitions of specific recommendations).
  - In patients with early PD, no treatment is considered clinically useful for the prevention or delay of disease progression. In patients requiring symptomatic monotherapy therapy, levodopa preparations (immediate release [IR], controlled release [CR], extended release [ER]), DAs (pramipexole IR and ER, ropinirole IR, rotigotine), MAO-B inhibitors (selegiline, rasagiline) or anticholinergics are considered clinically useful. However, inpatients with early or stable PD on levodopa, adjunct therapy can include DAs, COMT inhibitors, MAO-B inhibitors or surgery.

- In longer term follow-up, the available evidence suggests that there is no clinically relevant difference on motor function, troublesome motor complications, or mortality according to the choice of initial therapy.

- Options for the treatment of motor fluctuations in patients that have been optimized on levodopa therapy, that have demonstrated efficacy and are considered clinically useful include:
  - DAs (pramipexole IR and ER, ropinirole IR and ER, and rotigotine)
  - Levodopa preparations (levodopa ER, levodopa/carbidopa IR, and levodopa/carbidopa/etacapone)
  - COMT inhibitors (entacapone, tolcapone, and opicapone)
  - MAO-B inhibitors (rasagiline, safinamide, and zonisamide)
  - Istradefylline, due to conflicting evidence is considered likely efficacious and possibly useful in patients.
  - For dyskinesia, clinically useful treatments include amantadine, clozapine, and surgery.

SAFETY SUMMARY

Contraindications

- All levodopa products are contraindicated in patients currently taking a nonselective MAO inhibitor or who have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently.
- Sinemet, Stalevo, and generic carbidopa-levodopa formulations are contraindicated in narrow-angle glaucoma.
- Lodosyn is contraindicated in patients with known hypersensitivity to the drug. Since it is used in conjunction with levodopa or carbidopa-levodopa combination products, contraindications for these products may also apply.

Warnings and Precautions

- Warnings and precautions for all of the levodopa products include falling asleep during activities of daily living, hallucinations/exacerbations of psychosis, impulse control disorders, causation or exacerbation of dyskinesia, and increased intraocular pressure in patients with glaucoma.
- Sudden discontinuation or rapid dose reduction should be avoided to reduce the risk of withdrawal-emergent hyperpyrexia and confusion resembling neuroleptic malignant syndrome (NMS).
- Cardiovascular ischemic events and arrhythmia have been reported in patients taking carbidopa/levodopa.
- Patients should be observed carefully for the development of depression with concomitant suicidal tendencies.
- Duopa has warnings for neuropathy and gastrointestinal or gastrointestinal procedure-related risks.
- Inbrija has a warning for bronchospasm in patients with lung disease; use in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended.
- Due to the entacapone component, Stalevo has addition warnings for diarrhea, colitis, and rhabdomyolysis.
- Epidemiological studies have shown that patients with PD have a higher risk of developing melanoma than the general population. Whether the increased risk observed is due to PD or other factors, such as drugs used to treat PD, is unclear.
- Lodosyn has no antiparkinsonian effect when given alone. Lodosyn may decrease the peripheral effects of levodopa (eg, nausea, vomiting), but does not decrease central adverse effects. When Lodosyn is given in combination with levodopa, dyskinesias and other central adverse effects may occur sooner/at lower doses than with levodopa alone. Because Lodosyn is indicated for use with levodopa or carbidopa-levodopa combinations, warnings for these products may also apply.

Key Adverse Effects

- The most common AEs for the carbidopa/levodopa oral formulations include dyskinesias and nausea. Orthostatic hypotension, confusion, dizziness, and hallucinations also occur. Lodosyn has not been demonstrated to have any pharmacodynamic actions at recommended doses; the only AEs that have been observed have been with concomitant use of carbidopa with levodopa or carbidopa-levodopa combinations.
- The most common AEs for Duopa (incidence at least 7% greater than oral carbidopa/levodopa) are complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, atelectasis, and incision site erythema.
- The most common AEs for Inbrija are cough, nausea, upper respiratory tract infection, and discolored sputum.
- The most common AEs for Stalevo are dyskinesias, urine discoloration, diarrhea, nausea, abdominal pain, vomiting, and dry mouth.

DOSING AND ADMINISTRATION

General dosing information

- The optimum daily dosage of the levodopa combination products must be determined by careful titration in each patient.
- Because PD is progressive, periodic clinical evaluations are recommended; adjustment of the carbidopa/levodopa dosage regimen may be required.
- Other antiparkinson medications (eg, anticholinergic agents, dopamine agonists, and amantadine) can be given with the carbidopa/levodopa products. Dosage adjustment of carbidopa/levodopa may be necessary when these agents are added.
- Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
carbidopa/levodopa	ODT	Oral	Usual initial dosage: 3 times daily; dosage may be increased by 1 tablet daily or every other day, as necessary, until a dosage of 8 tablets per day is reached	The ODT should be allowed to dissolve on top of the tongue, then swallowed with saliva; administration with liquid is not necessary.
Duopa (carbidopa/levodopa)	Enteral suspension	PEG-J	Continuous 16-hour infusion period composed of a morning dose, a continuous dose, and extra doses	Duopa must be administered with the CADD-Legacy 1400 portable infusion pump. At the end of the 16-hour infusion, patients will disconnect pump from the PEG-J and take their nighttime dose of oral IR carbidopa-levodopa tablets
Inbrija (levodopa)	Inhalation powder	Inhalation	Inhale 2 capsules as needed for OFF symptoms up to 5 times daily	Capsules for inhalation must be administered with the Inbrija inhaler.
Lodosyn (carbidopa)	Tablet	Oral	Patients receiving carbidopa/levodopa who require additional carbidopa: daily with the first dose of carbidopa/levodopa each day; additional doses may be given throughout the day with each carbidopa/levodopa dose as required for optimal response Patients requiring individual titration of carbidopa and levodopa dosage: 3 to 4 times daily, at the same time as levodopa	
Rytary (carbidopa/levodopa)	ER capsule	Oral	Patients naïve to levodopa therapy: 3 times daily; titrate as needed Converting from IR carbidopa/levodopa to Rytary: follow conversion based on total levodopa dose in prescribing information	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Sinemet (carbidopa/levodopa)	Tablet	Oral	Usual initial dosage: 3 times daily Dosage may be increased by 1 tablet every day or every other day, as necessary, until a dosage of 8 tablets per day is reached	
carbidopa/levodopa ER	ER tablet	Oral	Initial dose in patients not receiving levodopa: twice daily Initial dosage in patients treated with conventional carbidopa/levodopa preparations: carbidopa/levodopa ER should be substituted at an amount that provides ~10% more levodopa per day; the interval between doses should be 4 to 8 hours during the waking day	An interval of at least 3 days between dosage adjustments is recommended.
Stalevo (carbidopa/levodopa/ entacapone)	Tablet	Oral	Converting patients from carbidopa, levodopa, and entacapone to Stalevo: patients taking entacapone 200 mg with each dose of non-ER carbidopa/levodopa can switch to the corresponding strength of Stalevo containing the same amounts of levodopa and carbidopa Converting patients from carbidopa/levodopa products to Stalevo: there is no experience in transferring patients treated with ER formulations of carbidopa/levodopa	Tablets should not be split or fractionated. Patients with hepatic impairment should be treated with caution.

See the current prescribing information for full details

CONCLUSION

- The efficacy of levodopa in the treatment of symptomatic PD has been well established. It is generally the first choice for treatment if symptoms, especially bradykinesia, become troublesome. Levodopa is combined with the peripheral decarboxylase inhibitor carbidopa to block its conversion to dopamine in the systemic circulation and liver prior to crossing the blood-brain barrier.
  - Although highly effective in the treatment of PD symptoms, levodopa-induced complications develop within several years of starting levodopa in a substantial number of patients; complications include motor fluctuations (“wearing off” phenomenon), dyskinesia, and dystonia. Treatment strategies for managing levodopa-induced dyskinesia include adjusting the levodopa dose and dosing schedule or combination therapy.
- Carbidopa/levodopa combination products are available as IR tablets, ER tablets and capsules, and ODTs. Stalevo tablets include entacapone, a COMT inhibitor, to prolong and potentiate the levodopa effect in patients who experience “wearing off”. Duopa, an enteral carbidopa/levodopa suspension, is given as a continuous PEG-J infusion for patients with motor fluctuations in advanced PD. Inbrija is a levodopa inhalation powder intended to be used as an adjunct to carbidopa/levodopa therapy for the intermittent treatment of OFF episodes.
- The optimum daily dosage of the levodopa combination products must be determined by careful titration in each patient.
- Warnings and precautions for all of the levodopa products include falling asleep during activities of daily living, hallucinations/exacerbations of psychosis, impulse control disorders, and causation or exacerbation of dyskinesia. Duopa has additional warnings for gastrointestinal risk and neuropathy. Inbrija has a warning for bronchospasm in

patients with lung disease. Due to the entacapone component, Stalevo has additional warnings for diarrhea, colitis, and rhabdomyolysis. Common AEs for the levodopa products include dyskinesias and nausea.

- Guidelines for the treatment of PD recommend initiation of either a DA or carbidopa/levodopa product; either an IR or an ER product may be considered, as there appears to be no difference in the rate of motor complications. In late PD, motor fluctuations or dyskinesias can be managed by modifying the levodopa dose/schedule or adding an additional antiparkinson medication such as entacapone *(Fox et al 2018, Miyasaki et al 2002, Oertel et al 2011).*

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