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ADIS DRUG EVALUATION

Levodopa/Carbidopa Enteral Suspension: A Review in Advanced Parkinson's Disease

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Abstract

An enteral suspension (ES)/intestinal gel formulation of levodopa/carbidopa (hereafter referred to as levodopa/carbidopa ES) [Duodopa® (EU); Duopa™ (USA)] has been developed to overcome the fluctuating plasma levodopa concentrations associated with oral levodopa/carbidopa formulations. In various countries, including those of the EU (under the Mutual Recognition Procedure), it is approved for the treatment of advanced levodopa-responsive Parkinson's disease (PD) with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results. In several other countries, including the USA, it is approved for the treatment of motor fluctuations in patients with advanced PD. In adults with advanced PD, levodopa/carbidopa ES improved motor fluctuations, activities of daily living and health-related quality of life (HR-QOL) during short-term (12-week) treatment, with the beneficial effects on motor fluctuations largely sustained over the longer term (up to 7 years). Levodopa/carbidopa ES was generally well tolerated in this patient population, with adverse events (AEs) associated with aging, advanced PD-related comorbidities, the procedure/device or dopaminergic therapy. Its safety profile was comparable to that of oral levodopa/carbidopa with respect to non-procedure/device-associated AEs; most procedure/device-associated AEs were consistent in nature and incidence with medically recognised complications of the procedure in non-PD patients. Current evidence indicates that levodopa/carbidopa ES is an effective and generally well tolerated option for the treatment of motor fluctuations in patients with levodopa-responsive advanced PD who are not being effectively managed with non-invasive therapies.

1 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized pathologically by the progressive degeneration or loss of dopaminergic neurons of the substantia nigra pars compacta, and the presence of neuronal Lewy bodies [1, 2]. The subsequent deficiency in dopamine impairs motor function (e.g. bradykinesia, postural instability, rigidity, tremor), with exogenous dopamine replacement with the dopamine precursor levodopa considered the gold standard for PD management [2, 3].

Although oral levodopa is highly effective, its long-term use is often associated with the development of complications (i.e. fluctuations in motor and non-motor symptoms, and dyskinesia) [3, 4]. Such complications likely result from fluctuating plasma levodopa concentrations (which may be caused by changes in various peripheral pharmacokinetic parameters, including impaired gastric emptying resulting in erratic jejunal absorption, and protein competition at intestinal and blood–brain barrier absorption sites) combined with disease progression (as due to the loss of striatal dopamine terminals, fluctuations in plasma dopamine levels are not buffered within the brain, resulting in fluctuating levels of striatal dopamine) [2, 3, 5]. Therefore, striatal dopamine receptors are increasingly exposed to alternating pathologically low and high dopamine levels

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Levodopa/Carbidopa Enteral Suspension: clinical considerations in advanced Parkinson's disease

Continuously infused (over ≈ 16 h) directly into the duodenum or jejunum via a percutaneous endoscopic gastrostomy tube with jejunal extension
Reduces fluctuations and intrasubject variability in plasma levodopa concentrations compared with oral levodopa/carbidopa immediate release
Improves motor fluctuations, activities of daily living and HR-QOL, with motor fluctuation benefits sustained
AEs were mostly drug- or procedure/device-related

following intermittent doses of short-acting oral levodopa; this pulsatile stimulation results in molecular changes in striatal input neurons and neurophysiological changes in basal ganglia output neurons, ultimately leading to the development of motor complications [5]. Thus, over time, levodopa demonstrates a shorter duration of action and slower or failed effects, with patients requiring a higher dosing frequency [3]. Newer oral levodopa formulations, including levodopa/carbidopa extended release, have been developed to provide more constant plasma levodopa concentrations [6]; preparations that provide continuous dopaminergic stimulation may reduce or even avoid the complications associated with oral levodopa therapy [3, 7]. Specifically, the concept is based on the hypothesis that intermittent doses of oral short-acting levodopa/carbidopa do not restore brain dopamine levels in a constant (i.e. physiological) manner and thereby contribute to the development of motor complications [5].

This article discusses pharmacological, therapeutic efficacy and tolerability data relevant to the use of an enteral suspension (ES)/intestinal gel formulation of levodopa/carbidopa (hereafter referred to as levodopa/carbidopa ES) [Duodopa® (EU); Duopa™ (USA)] for the treatment of motor fluctuations in patients with levodopa-responsive advanced PD. The key pharmacological properties of levodopa/carbidopa ES are summarized in Table 1.

2 Therapeutic Efficacy of Levodopa/Carbidopa ES

The short-term (12 weeks) efficacy of levodopa/carbidopa ES in patients with advanced PD and motor complications despite optimised treatment with oral levodopa/carbidopa and other anti-parkinsonian therapies has been evaluated in two identical, randomized, double-blind, double-dummy, multinational, phase III studies in a predominately Caucasian population [8] and a noncomparative, multinational, phase III study in an Asian (Japanese, Korean and Taiwanese) population [9] (Sect. 2.1). The protocols and statistical analysis plans of the two identical studies were modified before database lock in order to combine the results of the studies, with a single analysis subsequently conducted [8, 10]. Longer-term (up to 7 years) efficacy data from open-label, multinational, phase III, clinical extension [11–13] and safety [14] studies (Sect. 2.2) and real-world studies [15–21] (Sect. 2.2.1) are also discussed.

Levodopa/carbidopa (20/5 mg/mL) ES was administered as a morning bolus followed by a continuous dose [infused over ≈ 16 h (i.e. over the patient's waking day)] via a percutaneous endoscopic gastrostomy tube with jejunal extension (PEG-J) [8, 9, 11–14]. Each patient's starting dose was based on their previous total daily dose of oral levodopa [8, 9, 14] or oral levodopa/carbidopa [11–13].

2.1 Short-Term Outcomes

Levodopa-responsive patients (aged ≥ 30 years) who were experiencing ≥ 3 h/day 'off' time underwent PEG-J placement and received levodopa/carbidopa ES [8, 9] or levodopa/carbidopa (100/25 mg) immediate release (IR) [administered as divided doses over ≈ 16 h] [8]. In the study in the predominately Caucasian population [8], the mean time required to titrate to a stable dose was 7 and 8 days in the levodopa/carbidopa ES and levodopa/carbidopa IR groups, with 90% of patients titrated to a stable dose in ≤ 9 days. Moreover, in the respective treatment groups, baseline characteristics did not significantly differ, the mean daily baseline levodopa dose was 1005.4 mg and 1123.5 mg, and 40.5–59.5% and 17.6–76.5% of patients had previously received a catechol-*O*-methyltransferase inhibitor, dopamine agonist and monoamine oxidase B inhibitor therapy. Patients in this study experiencing persistent 'off' episodes were permitted to receive levodopa/carbidopa IR as rescue medication [8]. In the study in the Asian population [9], the mean time required to titrate to a stable dose was 6 days and the mean total daily levodopa dose at the final visit was 1227.6 mg.

A continuous infusion of levodopa/carbidopa ES was effective in reducing motor complications in adults with advanced PD [8]. Relative to levodopa/carbidopa IR, it demonstrated a statistically significant and clinically meaningful difference in the least-squares mean (LSM) change from baseline to week 12 in daily normalised (to a 16-h waking day) 'off' time (primary endpoint) and a statistically significant difference in daily normalised 'on' time without troublesome dyskinesia (key secondary endpoint) (Table 2). A sensitivity analysis supported the findings of the primary analysis. Significant ($p < 0.05$) improvements in the respective endpoints were seen in a consistent manner from week 8 and maintained over the study. Levodopa/carbidopa ES also

Table 1 Overview of the key pharmacological properties of levodopa/carbidopa enteral suspension

Pharmacodynamic properties	
Levodopa	Metabolic precursor of dopamine able to cross the blood–brain barrier; following administration, it is decarboxylated to form dopamine, which relieves PD symptoms [10, 26]
Carbidopa	An aromatic amino acid decarboxylation inhibitor unable to cross the blood–brain barrier; inhibits the extracerebral decarboxylation of levodopa, thereby increasing the availability of levodopa for transportation to the brain, and reducing dopamine-related peripheral, but not central, adverse events (e.g. nausea, vomiting) [10, 26]
Levodopa/carbidopa ES	Suspension of levodopa 20 mg/mL and carbidopa 5 mg/mL in a carboxymethylcellulose gel delivered by a portable infusion pump into the duodenum or jejunum via a percutaneous endoscopic gastrostomy tube [3, 10, 26]
	Associated with a stable rise in striatal dopamine levels (as assessed by dopamine receptor availability) in pts with advanced PD [43]
	Maintains plasma levodopa concentrations at steady levels within individual therapeutic windows, thereby reducing motor fluctuations and decreasing 'off' time in pts with advanced PD; motor fluctuation and hyperkinesia/dyskinesia effects often achieved during the first day of therapy [10]
	Not associated with the development of tolerance over time [10]
Pharmacokinetic properties	
Levodopa	Estimated levodopa bioavailability with levodopa/carbidopa ES relative to oral levodopa/carbidopa IR of 97% [37]
	Therapeutic plasma concentrations rapidly achieved (t_{max} of 2.85 h) and maintained (degree of fluctuation of 0.52 and intrasubject variability of 13% from 2 h onwards)[a] [44]; intrasubject variability in plasma concentrations was 3.2-fold lower (21 vs. 67%) with levodopa/carbidopa ES relative to oral levodopa/carbidopa IR [45]
	In Japanese pts with advanced PD, bioavailability was comparable and intrasubject variability in plasma concentrations was low compared with oral levodopa/carbidopa IR therapy [46]
	As levodopa competes with certain amino acids for transport across the intestinal wall, its absorption may be reduced in pts on a high-protein diet [26]
	Approximately 10–30% bound to plasma proteins [26]
	Predominately metabolized by the aromatic amino acid decarboxylase and COMT (the primary pathway when levodopa is coadministered with carbidopa) enzymes and eliminated as metabolites, mostly in the urine [10, 26]; estimated elimination half-life of 1.5 h[a] [44]
Carbidopa	Compared with levodopa, it has a slower (t_{max} of 5.70 h) and more variable (degree of fluctuation of 0.96 and intrasubject variability of 19% from 2 h onwards) absorption[a] [44]
	Approximately 36% bound to plasma proteins [26]
	Metabolized to two primary metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid), which are primarily eliminated (unchanged or as glucuronide conjugates) in the urine, with unchanged carbidopa accounting for 30% of the total urinary excretion; estimated elimination half-life of ≈ 2 h [10]
Levodopa/carbidopa ES	Mean absorption time was rapid (7 min) compared with oral levodopa/carbidopa IR (25 min) [37]
Potential drug interactions	
No interaction studies have been performed with levodopa/carbidopa ES [10]; however, caution is advised with the coadministration of levodopa/carbidopa ES and antihypertensives, dopamine receptor antagonists, iron and MAO type B inhibitors, among others [10, 26]	
Concomitant administration with non-selective MAO inhibitors [10, 26] and selective MAO type A inhibitors [10] is contraindicated[b]	

COMT catechol-*O*-methyltransferase, *ES* enteral suspension, *IR* immediate release, *MAO* monoamine oxidase, *PD* Parkinson's disease, *pts* patients, t_{max} time to maximum concentration

[a]In 18 pts with advanced PD receiving levodopa/carbidopa ES [administered as a morning bolus followed by a continuous dose (infused over ≈ 16 h)] in an open-label, multicentre study [44]

[b]Consult local prescribing information for detailed information

significantly ($p = 0.0142$) improved 'on' time without dyskinesia (LSM change from baseline to week 12 of 3.37 vs. 1.09; between-group difference of 2.28), but not 'on' time with non-troublesome dyskinesia or 'on' time with troublesome dyskinesia, compared with levodopa/carbidopa IR. Of note, these three endpoints were not included in the hierarchical testing procedure [8].

With regard to other secondary endpoints (in hierarchical order), levodopa/carbidopa ES was associated with significant ($p < 0.05$) differences relative to levodopa/carbidopa IR in the LSM change from baseline to week 12 in the Parkinson Disease Questionnaire (PDQ)-39 summary index score [− 10.9 vs. − 3.9 (baseline scores of 35.1 vs. 38.6); between-group difference of − 7.0], the mean investigator-rated clinical global impression (CGI) score at week 12 (2.3 vs. 3.0; between-group difference of − 0.7) and the LSM change from baseline to week 12 in the Unified Parkinson Disease Rating Scale (UPDRS) Part II (activities of daily living) score [− 1.8 vs. + 1.3 (mean baseline scores of 11.6 vs. 11.8); between-group difference of − 3.0] [8]. The LSM change from baseline to week 12 in the UPDRS Part III (motor) score did not significantly differ between the levodopa/carbidopa ES and levodopa/carbidopa IR groups [− 1.5 vs. − 2.9 (mean baseline scores of 18.1 vs. 22.5); between-group difference of 1.4]. Statistical significance was thus not tested for the subsequent endpoints [EuroQol-5 Dimension

Table 2 Efficacy of levodopa/carbidopa enteral suspension in adults with advanced Parkinson's disease and motor complications

Treatment (no. of full analysis set pts)	Daily 'off' time (h)		Daily 'on' time without troublesome dyskinesia (h)	
	LSM change from BL[a] (BL value)	BGD in LSM change from BL	LSM change from BL (BL value)	BGD in LSM change from BL
Levodopa/carbidopa ES (35)	− 4.04 (6.3)	− 1.91**[b]	4.11 (8.7)	1.86*
Levodopa/carbidopa IR (31)	− 2.14 (7.0)		2.24 (7.8)	

Results at week 12 from a multinational, phase III study [8]. Additional information obtained from the UK summary of product characteristics [10]

BGD between-group difference, *BL* baseline, *ES* enteral suspension, *IR* immediate release, *LSM* least-squares mean, *pts* patients

*$p = 0.0059$, **$p = 0.0015$ vs. levodopa/carbidopa IR

[a]Primary endpoint

[b]Considered clinically meaningful as the BGD in the LSM change from BL is ≥ 1 h [47]

(EQ-5D) score, Zarit caregiver burden interview score, total levodopa daily dose and levodopa rescue dose]. The mean change from baseline to week 12 in the total levodopa daily dose was + 91.7 mg in the levodopa/carbidopa ES group and + 249.7 mg in the levodopa/carbidopa IR group, and the mean overall levodopa rescue doses were 139.8 mg and 180.6 mg [8].

It is worth noting that the two studies were not designed to determine whether levodopa/carbidopa ES exerted a beneficial effect on dyskinesia [8]. At baseline, patients were experiencing a mean 'on' time with troublesome dyskinesia of approximately 1 h [8]. In a post hoc analysis of data from patients with ≥ 1 h of 'on' time with troublesome dyskinesia at baseline, both levodopa/carbidopa ES ($n = 11$) and levodopa/carbidopa IR ($n = 12$) were associated with significant ($p < 0.05$) reductions from baseline in 'on' time with troublesome dyskinesia and 'off' time, and a significant increase from baseline in 'on' time without troublesome dyskinesia [22]. There were no significant between-group differences in these endpoints. An increase in the dose of levodopa/carbidopa ES was not significantly correlated with an increase in 'on' time with troublesome dyskinesia [22].

The beneficial effects of levodopa/carbidopa ES on reducing motor complications have also been seen over the short term (12 weeks) in Asian patients with advanced PD [9]. Levodopa/carbidopa ES was associated with a significant ($p < 0.001$) mean change from baseline (mean baseline value of 7.4 h) to week 12 in daily normalised (to a 16-h waking day) 'off' time of − 4.6 h (primary endpoint; $n = 29$). Significant ($p \leq 0.001$) improvements in this endpoint were seen early (from week 2) and maintained over the study. With respect to secondary endpoints (in hierarchical order), at week 12, levodopa/carbidopa ES was associated with significant ($p \leq 0.05$) LSM improvements from baseline in daily normalised 'on' time without troublesome dyskinesia and daily normalised 'on' time with troublesome dyskinesia, significant ($p < 0.001$) mean improvements from baseline in the PDQ-39 summary index score and significant ($p < 0.001$) mean improvements relative to a null hypothesis of no change in patient- and investigator-rated CGI scores. Moreover, at week 12, almost four-fifths (79.3%) of 29 patients rated the change in their HR-QOL (as assessed by the patient-rated CGI scale) as 'very much improved' or 'much improved'. The mean change from baseline to week 12 in the UPDRS Part II (activities of daily living) score was not statistically significant; thus, statistical significance was not tested for the subsequent endpoints [9].

2.2 Longer-Term Outcomes

In adults with advanced PD and motor complications despite optimised PD treatment, the beneficial effects of levodopa/carbidopa ES on motor complications were largely maintained over the longer-term (up to 7 years) in several open-label, multinational, phase III, safety studies [11–14]. Where reported, the starting levodopa/carbidopa ES dose was based on the previous dose of oral levodopa/carbidopa [11, 13] or oral levodopa [14].

In eligible patients ($n = 33$ [11] and 28 [12] receiving levodopa/carbidopa ES throughout the core and extension studies) participating in two ≥ 52-week studies (one [11] of which is an extension of the two identical 12-week studies in predominately Caucasian patients [8], the other [12] an ongoing extension of the 12-week study in Asian patients [9]), the mean [11] and LSM [12] improvements in daily normalised 'off' time observed with levodopa/carbidopa ES therapy in the core studies were sustained at the last visit (where reported [12], the median exposure to levodopa/carbidopa ES was 408 days). Moreover, at this timepoint, there was a significant ($p < 0.05$) mean improvement from baseline of the extension study in daily normalised 'on' time without troublesome dyskinesia in the extension in a predominately Caucasian population [11], whilst the LSM improvements

in daily normalised 'on' time without troublesome dyskinesia and 'on' time with troublesome dyskinesia observed in the core study were maintained in the extension in Asian patients [12]. Patients ($n=29$) who switched from levodopa/carbidopa IR in the two identical core studies to levodopa/carbidopa ES in the extension study experienced significant ($p<0.05$) mean changes from baseline (of the extension study) at the last visit in daily normalised 'off' time and daily normalised 'on' time without troublesome dyskinesia [11]. Significant ($p<0.05$) improvements in these endpoints were seen early (from week 4) and maintained over the extension study [11].

Likewise, in 316 efficacy–evaluable patients participating in a 54-week safety study, significant ($p<0.05$) mean changes from baseline (baseline values of 6.75, 7.65 and 1.61 h, respectively) at the last visit were seen in mean daily normalised 'off' time [4.4 h (65.6%)], 'on' time without troublesome dyskinesia [4.8 h (62.9%)] and 'on' time with troublesome dyskinesia [− 0.4 h (− 22.5%)] [14]. Therapy with levodopa/carbidopa ES was also associated with significant ($p<0.001$) mean improvements from baseline to the last visit in the UPDRS total, Part II and Part III scores, the UPDRS Part IV dyskinesia subscore and the EQ-5D summary index score, and from screening to the last visit in the PDQ-39 summary index score. Significant ($p<0.001$) improvements from baseline/screening in these endpoints were seen early (from week 4) and maintained over the study. Almost four-fifths (77.9%) of patients were assessed (using the investigator-rated CGI scale) as having 'very much improved' or 'much improved' at the end of the treatment. This study enrolled patients aged ≥ 30 years who were levodopa responsive and who were experiencing ≥ 3 h/day of 'off' time. The mean time required to titrate to a stable dose was 5 days and the mean total daily levodopa dose at the final visit was 1572.4 mg [14].

In a post hoc analysis of data from patients in the safety study with ≥ 1 h of 'on' time with troublesome dyskinesia at baseline, levodopa/carbidopa ES ($n=144$) was associated with significant ($p<0.001$) mean improvements from baseline to last visit in 'off' time, 'on' time without troublesome dyskinesia and 'on' time with troublesome dyskinesia [22]. Of note, there was no significant correlation between an increase in the dose of levodopa/carbidopa ES and an increase in 'on' time with troublesome dyskinesia [22].

Preliminary results from the efficacy cohort (comprising patients who were enrolled in the USA; $n=86$) of an ongoing study [13], which included patients who had completed either one of the two identical 12-week studies [8] and their 52-week extension [11] or the 54-week safety study [14], suggest that reductions in motor complications were mostly sustained during up to 7 years' levodopa/carbidopa ES therapy [13]. From baseline (i.e. the last assessment of the previous study) to the data cut-off date, the benefits of levodopa/carbidopa ES therapy (median total exposure of 4.3 years) on daily normalised 'off' time [mean change from baseline of nearly 4 h (baseline value of ≈ 6 h estimated from a graph)] and daily normalised 'on' time without troublesome dyskinesia [mean change from baseline of ≈ 4 h (baseline value of ≈ 9 h estimated from a graph)] were maintained. However, the benefits on other endpoints (daily normalised 'on' time with troublesome dyskinesia, the UPDRS total, Part II and Part III scores, and PDQ-39 summary index score) deteriorated from the last assessment in the previous study ($p<0.05$) [13]. Over the treatment period of this study, the mean total daily levodopa dose increased from 1588 to 1783 mg ($n=71$); 30 (42.3%) patients were using an extra levodopa/carbidopa ES dose (average of 141 mg/day) at the data cut-off date [13].

2.2.1 In Real-World Studies

Results from several observational and retrospective studies [15–21] generally support the longer-term efficacy of levodopa/carbidopa ES in the real-world setting. For instance, in GLORIA (a 24-month, non-interventional, multinational registry) [15], the largest of these, patients with advanced PD and motor complications underwent PEG-J placement and received levodopa/carbidopa ES [15]. Clinical observations for the ≤ 12 months prior to the day of registry enrolment in patients previously treated with levodopa/carbidopa ES were collected retrospectively; from the day of registry enrolment, clinical observations in all patients were collected prospectively [15].

Levodopa/carbidopa ES therapy was associated with significant ($p<0.001$) mean changes from baseline (mean values of 6.0 and 4.3 h) to last visit of − 3.9 h in daily 'off' time (as assessed by the modified UPDRS Part IV Item 39; $n=207$) and − 1.1 h in daily 'on' time with dyskinesia (as assessed by the modified UPDRS Part IV Item 32; $n=211$) [15]. Significant ($p<0.01$) improvements in these endpoints were seen early (from day 1) and maintained over the study. There were also significant ($p<0.05$) mean changes from baseline of − 2.0 in the activities of daily living (UPDRS Part II score) and − 2.2 in the motor examination (UPDRS Part III score) at month 18 ($n=162$ and 190) [mean baseline values of 16.5 and 24.6] and of − 1.9 in the motor examination at month 24 ($n=190$). The mean change of − 1.3 in the activities of daily living at month 24 ($n=165$) was not significant compared with baseline. Significant ($p<0.01$) improvements in these endpoints were seen early (from day 1) and maintained to month 18. QOL (as assessed by the short-form, eight-item PDQ total score) was significantly ($p<0.001$) improved from baseline at every study visit to the last visit (mean change from baseline of − 5.3; mean baseline score of 46.8) [$n=205$] [15].

Over 18 months of therapy, the mean daily levodopa dose significantly ($p < 0.001$) increased to 1795 mg in patients receiving levodopa/carbidopa ES monotherapy (from 1509 mg on day 1; $n = 98$) and 1998 mg in those receiving levodopa/carbidopa ES in combination with other medications (most commonly oral levodopa and dopamine agonists) [from 1960 mg on day 1; $n = 89$] [15]. Interestingly, a post hoc analysis [23] of GLORIA suggests that levodopa/carbidopa ES as monotherapy may be effective in patients with advanced PD undergoing routine clinical care. Further data would be of interest.

3 Safety and Tolerability of Levodopa/Carbidopa ES

Levodopa/carbidopa ES was generally well tolerated in adults with advanced PD participating in the short- and longer-term (up to 7 years) clinical and real-world studies discussed in Sect. 2, with its safety profile consistent between Japanese, Korean and Taiwanese patients and Caucasian patients, and between real-world and clinical studies. Adverse events (AEs) were generally mild or moderate in severity and associated with aging, advanced PD-related comorbidities, the procedure/device or dopaminergic therapy. Indeed, very common (incidence ≥ 1/10) adverse reactions reported in clinical studies or post-marketing experience with levodopa/carbidopa ES were either related to the drug (anxiety, constipation, depression, dyskinesia, fall, insomnia, nausea, orthostatic hypotension, PD and weight loss) or the procedure/device (abdominal pain, complications of device insertion, excessive granulation tissue, incision-site erythema, postoperative wound infection, post-procedural discharge, procedural pain and procedural site reaction) [10]. Of note, the majority of these adverse reactions occurred within the first 28 days of therapy, subsequent to PEG-J placement [10].

In an integrated analysis [24] of four multinational, phase III studies (the two identical 12-week studies [8] and their 52-week extension [11], the 54-week safety study [14] and the ongoing up to 7 years' study [13]), 17% of 412 levodopa/carbidopa ES recipients discontinued therapy because of an AE (regardless of whether or not it was associated with the procedure/device), with the rate of discontinuation because of an AE remaining stable following the titration period [24]. Procedure/device-associated AEs were the most common cause of discontinuation, with complication of device insertion, the most frequently reported AE, resulting in discontinuation in 2.4% of patients. Most (94%) of the 34 deaths reported in the integrated analysis were considered by the study investigators to be unrelated or unlikely to be related to the treatment system; rather, they were associated with the mortality profile of the patient population. However, two deaths (cardiac arrest and intestinal dilatation) were considered to be possibly related, with the intestinal dilatation likely related to the mode of delivery [24].

In terms of non-procedure/device-associated AEs, the safety profile of levodopa/carbidopa ES was comparable to that of oral levodopa/carbidopa [24]. Moreover, the most frequently reported of these AEs were consistent with common events seen in an older patient population, or events related to the disease itself or known to be associated with dopaminergic therapy [24].

Polyneuropathy was one of the common (incidence ≥ 1/100 to < 1/10) adverse reactions reported in clinical studies or post-marketing experience with levodopa/carbidopa ES [10]. In the integrated analysis, 20 (5%) of 412 patients experienced polyneuropathy considered possibly or probably related to therapy [24]. As the monitoring of vitamin B_6 and B_{12} levels and other laboratory tests were not required at baseline, there is insufficient information to establish the causality of polyneuropathy with the enteral suspension of levodopa/carbidopa [24].

Impulse control disorder (ICD) is a recognised AE associated with the use of levodopa [10], and patients with an ICD (e.g. binge eating and compulsive eating, compulsive spending or buying, increased libido and hypersexuality, and pathological gambling [10]) considered significant by the study investigators were excluded from the clinical studies comprising the integrated analysis [24]. At the data cut-off date of the integrated analysis, 6% of patients had ≥ 1 compulsive behaviour reported in the Minnesota Impulsive Disorders Interview (MIDI), with the most common being pathological gambling (in six patients) [24].

The procedure/device-associated AEs reported in the integrated analysis were expected, given the known risks associated with PEG-J placement, and most were consistent in nature and incidence with medically recognised complications of the procedure in non-PD patients [24]. The majority of procedure/device-associated AEs and serious AEs resolved within the first 28 days of treatment; they persisted in only 17% and 2% of patients. At the end of the first and second years of treatment, 92% and 82% of patients retained the original PEG-J; patients had a mean of 0.3 PEG-J replacements [24].

4 Dosage and Administration of Levodopa/Carbidopa ES

In various countries, including those of the EU (under the Mutual Recognition Procedure) [25], levodopa/carbidopa ES is approved for the treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results. In several

other countries, including the USA [26], it is approved for the treatment of motor fluctuations in patients with advanced PD. This section focuses on the US prescribing information [26] and the UK summary of product characteristics [10].

Levodopa/carbidopa ES is administered into the duodenum [10] or jejunum [10, 26] via either a temporary nasoduodenal [10] or nasojejunal [10, 26] tube (over the short term), or directly via a PEG-J using a portable pump (over the long term) [10, 26]. The total daily dose comprises three individually adjusted doses: the morning bolus dose (infused over 10–30 min); the continuous maintenance dose (infused over 16 h); and the extra bolus dose(s) [to manage acute 'off' symptoms].

Local prescribing information should be consulted for detailed information regarding dose recommendations and adjustments, administration procedures, discontinuation, contraindications, potential drug interactions, use in special patient populations, and warnings and precautions.

5 Place of Levodopa/Carbidopa ES in the Management of Advanced PD

The search for a therapy that can change the course of PD (by slowing or halting the underlying neurodegenerative process) continues [2, 27]. Until such a treatment is identified, clinicians rely on symptomatic management, which mostly involves increasing intracerebral dopamine levels (with the dopamine precursor levodopa) or stimulating dopamine receptors (with dopamine agonists) [2]. PD progression is characterized by a worsening of motor symptoms, which are complicated by the development of fluctuations in the control of motor and non-motor symptoms, dyskinesia and psychosis arising from long-term symptomatic management [2]. Indeed, randomized, double-blind, multicentre studies indicate that wearing off and dyskinesia affect over half of patients after up to 4 years [4, 28], with long-term studies suggesting that motor complications eventually develop in almost all levodopa-treated patients [29, 30].

Early on in the development of motor fluctuations, treatments are usually oral (or transdermal) agents (e.g. dopaminergics, enzyme inhibitors or non-dopaminergics), with parenteral therapies and surgical techniques introduced for more advanced patients [31]. Insufficient motor complication control is the most common reason why patients are moved from non-invasive to device-aided therapies [32]. The 2010 European Federation of Neurological Societies/Movement Disorder Society–European Section evidence-based treatment recommendations [33] proposed deep brain stimulation (DBS) of the subthalamic nucleus or posteroventral pallidum (Level A), subcutaneous apomorphine as penject (Level A) or pump (Level C), and levodopa/carbidopa ES (Level C) for the treatment of motor complications in PD, although DBS was only recommended for patients aged < 70 years who did not have major psychiatric or cognitive problems (because of the risk of AEs). DBS was also recommended by the UK National Institute for Health and Care Excellence 2017 guidelines for patients with advanced PD whose symptoms were not adequately controlled by best medical therapy (which may include intermittent apomorphine injection and/or continuous subcutaneous apomorphine infusion) [34]. A recent (2018) evidence-based medicine review update on treatments for the motor symptoms of PD by the International Parkinson and Movement Disorder Society [31] listed injection/infusion therapies or surgery as options for bothersome motor fluctuations and to reduce dyskinesia in suitable patients with advanced PD. Although the review predated fully published data on the efficacy of continuous subcutaneous apomorphine infusion, it considered intermittent apomorphine injections (particularly for 'off' periods that require rapid reversal), DBS (in carefully selected patients with PD) and levodopa/carbidopa ES (in certain patients with severe motor fluctuations) 'clinically useful'. An expert consensus opinion [32] concluded that continuous subcutaneous apomorphine infusion, DBS or levodopa/carbidopa ES should be considered for the treatment of patients aged < 70 years with motor fluctuations or dyskinesia who are otherwise healthy; continuous subcutaneous apomorphine infusion or levodopa/carbidopa ES should be considered a first-line treatment and DBS a second-line treatment for patients aged > 70 years; and continuous subcutaneous apomorphine infusion or levodopa/carbidopa ES should be considered (alongside a reduction or cessation of oral therapy) for the treatment of patients aged > 70 years with mildly or moderately impaired cognition (or other contraindications to DBS). The magnitude of the benefits observed with levodopa/carbidopa ES (Sect. 2) was similar to those reported with DBS [8, 35, 36], suggesting a therapeutic alternative that avoids the risks associated with intracranial surgery. Direct comparisons of these interventions would be of interest.

The ES formulation of levodopa/carbidopa was developed to overcome the fluctuating plasma levodopa concentrations associated with oral levodopa/carbidopa formulations [37] (Sect. 1). Of note, while PEG-J placement requires hospital admission, the titration (including customization of therapeutic regimens) of levodopa/carbidopa ES can be successfully performed in an outpatient setting [38]. Compared with oral levodopa/carbidopa IR, levodopa/carbidopa ES is absorbed more quickly (reflective of its direct delivery into the duodenum or jejunum) and results in similar levodopa bioavailability but reduced fluctuations and intrasubject variability in plasma levodopa concentrations (Table 1). The 2018 evidence-based medicine review update conclusion on levodopa/carbidopa ES as 'clinically useful' is consistent with the findings of the clinical and real-world studies in levodopa-responsive patients with

advanced PD and motor complications discussed in Sect. 2. A continuous infusion of levodopa/carbidopa ES significantly improved daily normalised 'off' time and daily normalised 'on' time without troublesome dyskinesia over the short-term (12 weeks) in two identical phase III studies in predominately Caucasian patients (Sect. 2.1). Although these two studies were not designed to determine whether levodopa/carbidopa ES exerted a beneficial effect on dyskinesia, a post hoc analysis of data from patients with a baseline 'on' time with troublesome dyskinesia of ≥ 1 h suggests that patients with a higher burden of troublesome dyskinesia at baseline derive a beneficial effect from levodopa/carbidopa ES therapy. Activities of daily living and HR-QOL benefits (assessed using the UPDRS Part II score and the PDQ-39 summary index score) were also demonstrated with short-term levodopa/carbidopa ES therapy in the two identical phase III studies, with the beneficial effects of levodopa/carbidopa ES on motor complications also seen over 12 weeks in Asian patients (Sect. 2.1). Over the longer-term (up to 7 years), levodopa/carbidopa ES was largely associated with consistent benefits in motor complications, with sustained improvements observed in daily normalised 'off' time and daily normalised 'on' time without troublesome dyskinesia (Sect. 2.2). It is worth noting that a retrospective analysis [39] of the two identical phase III studies [8] and the 54-week safety study [14] determined that levodopa/carbidopa ES can be successfully initiated with or without a nasojejunal tube.

Levodopa/carbidopa ES was generally well tolerated over the longer term in adults with advanced PD, with its safety profile consistent between Asian patients and Caucasian patients, and between real-world and clinical studies (Sect. 3). AEs were generally mild or moderate in severity and associated with aging, advanced PD-related comorbidities, the procedure/device or dopaminergic therapy. In terms of non-procedure/device-associated AEs, the safety profile of levodopa/carbidopa ES was comparable to that of oral levodopa/carbidopa. In terms of procedure/device-associated AEs, the reported AEs were expected given the known risks associated with PEG-J placement; indeed, most were consistent in nature and incidence with medically recognised complications of the procedure in non-PD patients, with the majority resolving within the first 28 days of treatment. It is worth noting that although polyneuropathy has been reported with the infusion of levodopa/carbidopa ES, there is currently insufficient information to establish causality (Sect. 3).

PD progression is associated with increasing costs and decreasing HR-QOL [40]. In a recent cost-utility analysis using a Markov model with a lifetime horizon (20 years) and conducted from a National Health Service and Personal Social Services perspective, levodopa/carbidopa ES was cost-effective relative to standard of care in patients with advanced PD unsuitable for apomorphine or DBS in 22% of simulations at a willingness-to-pay (WTP) threshold of £30,000 per quality-adjusted life-year (QALY) gained and in 44% of simulations at a WTP threshold of £50,000/QALY [incremental cost effectiveness ratio (ICER) of £52,110/QALY] (2017 values; costs and benefits discounted at 3.5%) [41]. Moreover, according to a scenario analysis, a patient access scheme discount of 15% results in an ICER below the willingness-to-pay threshold [41]. In another cost-utility analysis using a Markov model with a lifetime horizon (20 years), levodopa/carbidopa ES had a 76% probability of being cost effective relative to standard of care in patients with advanced PD, based on an Irish healthcare payer WTP threshold of €45,000/QALY (ICER of €26,944/QALY) [2013 values; costs and outcomes discounted at 4%] [42].

In conclusion, current evidence indicates that levodopa/carbidopa ES is an effective and generally well tolerated option for the treatment of motor fluctuations in patients with levodopa-responsive advanced PD who are not being effectively managed with non-invasive therapies.

Data Selection Levodopa/Carbidopa Enteral Suspension: 689 records identified	
Duplicates removed	253
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	168
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	221
Cited efficacy/tolerability articles	16
Cited articles not efficacy/tolerability	31
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Duodopa, Duopa, levodopa, carbidopa, ABT-SLV187, enteral, intestinal, intraduodenal, intrajejunal, Parkinson. Records were limited to those in English language. Searches last updated 16 September 2019	

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Compliance with Ethical Standards

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