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REVIEW ARTICLE

Pharmacokinetics of Rytary®, An Extended-Release Capsule Formulation of Carbidopa–Levodopa

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Abstract Parkinson's disease (PD) is a chronic progressive neurological disorder characterized by resting tremor, rigidity, bradykinesia, gait disturbance, and postural instability. Levodopa, the precursor to dopamine, coadministered with carbidopa or benserazide, aromatic amino acid decarboxylase inhibitors, is the most effective and widely used therapeutic agent in the treatment of PD. With continued levodopa treatment, a majority of patients develop motor complications such as dyskinesia and motor 'on-off' fluctuations, which are, in part, related to the fluctuations in plasma concentrations of levodopa. A new extended-release (ER) carbidopa–levodopa capsule product (also referred to as IPX066) was developed and approved in the US as Rytary® and in the EU as Numient®. The capsule formulation is designed to provide an initial rapid absorption of levodopa comparable to immediate-release (IR) carbidopa–levodopa, and to subsequently provide stable levodopa concentrations with reduced peak-to-trough excursions in plasma concentrations in order to reduce motor fluctuations associated with pulsatile stimulation of dopamine receptors and to minimize dyskinesia. Phase III studies of this ER carbidopa–levodopa capsule formulation in patients with PD have shown a significant reduction in 'off' time compared with IR carbidopa–levodopa and carbidopa–levodopa–entacapone. We present a review of the clinical pharmacokinetics and pharmacodynamics of this ER product of carbidopa–levodopa in healthy subjects and in patients with PD.

Key Points

Rytary® (Numient®, IPX066) is an extended-release (ER) capsule formulation of carbidopa–levodopa that combines immediate-release (IR) and ER beads to provide a rapid onset of effect that is then sustained for a longer duration than standard formulations of carbidopa–levodopa.

For comparable doses of levodopa, Rytary® results in 30% maximum observed plasma concentration and 70% area under the concentration–time curve compared with IR levodopa.

Rytary® and IR carbidopa–levodopa have a similar concentration–effect relationship based on the Unified Parkinson's Disease Rating Scale Part III, and finger tapping rate.

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1 Introduction

Parkinson's disease (PD) is characterized by the progressive degeneration of nigrostriatal dopaminergic neurons. Levodopa (L-3,4-dihydroxyphenylalanine), the metabolic precursor of dopamine, in combination with aromatic amino acid decarboxylase (AADC) inhibitors such as carbidopa or benserazide, is considered the most effective treatment for management of the loss of mobility associated with PD.

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The oral absorption, central nervous system (CNS) penetration, and distribution of levodopa are mediated by active transporters. Levodopa is actively absorbed and transported across the intestinal mucosa and blood–brain barrier (BBB). L- and B(0,+)-type amino acid transporters (LAT1, LAT2, rBAT, and their oligomers with the heterologous proteins 4F2hc, TAT1, and OCT) have been implicated in the oral and CNS absorption of levodopa [1–4]. The absorption of levodopa is restricted to the upper small intestine. Once absorbed, levodopa is converted to dopamine by AADC and is metabolized to 3-O-methyldopa (3-OMD) by catechol-O-methyltransferase (COMT), among other metabolites. Inhibitors of AADC and COMT are coadministered with levodopa to suppress the peripheral formation of dopamine, reduce the exogenous dose of levodopa by maximizing the amount of levodopa transported across the BBB, and reduce adverse effects of peripheral dopamine, such as nausea and hypotension.

Continuous stimulation of striatal dopaminergic receptors remains the goal and is a current unmet need of oral pharmacotherapy for PD. With progression of PD and chronic therapy, levodopa is often associated with the development of involuntary motor function complications such as 'on-off' phenomena, 'wearing-off', and dyskinetic movements. The most common form of dyskinesia, termed 'peak-dose dyskinesia', coincides with peak plasma levels of levodopa. Although a number of factors contribute to the development of motor complications in levodopa therapy, pulsatile levodopa administration and high levodopa doses are considered key factors [5–7].

Multiple therapeutic strategies, including oral controlled-release (CR) formulations and intestinal/jejunal infusion, have been attempted to provide continuous and sustained oral delivery of levodopa in an effort to reduce or delay the development of dyskinesias. Current oral CR products such Sinemet® CR, which is absorbed over 4–6 h, are associated with erratic absorption and variable levodopa plasma concentrations. The absorption of Sinemet® CR is less predictable than that of Sinemet® immediate-release (IR) and may require supplemental doses of IR carbidopa–levodopa [8]. The effect of Sinemet® CR on dyskinesias is also often difficult to predict. Continuous controlled oral delivery of levodopa has been a challenge due to its short plasma half-life, unreliable absorption due to delayed and/or variable gastric emptying, variable in vivo dissolution of levodopa products, and absorption being limited to the small intestine where the transporters for levodopa are located. Gastrointestinal dysfunction is a key non-motor symptom in PD across all stages of PD, with studies reporting impaired gastric emptying and constipation. Gastroparesis is observed in 70–100% of subjects [9, 10] and can lead to response fluctuations, including delayed 'on' or lack of an 'on' (no 'on' phenomenon), and

there is a clear relationship between gastric emptying and levodopa absorption [11].

Although dopamine agonists have longer plasma half-lives than levodopa, cause less pulsatile stimulation of dopamine receptors, and are used for therapy in the earlier stages of PD, they are not as efficacious as levodopa and suffer from common side effects. The use of COMT inhibitors, such as entacapone, with carbidopa–levodopa reduces 'off' time but large fluctuations in levodopa plasma concentrations still occur in their presence [12, 13]. Entacapone also adversely affects the rate at which dyskinesias develop on carbidopa–levodopa treatment when started early in disease [14]. Levodopa remains indispensable in the treatment of PD, especially in the later stages of the disease, and there is a clinical need for an improved oral carbidopa–levodopa product that can consistently deliver stable levodopa plasma concentrations.

The development program for this new extended-release (ER) capsule formulation of carbidopa–levodopa (also referred to as IPX066) included studies to characterize the pharmacokinetics in healthy volunteers and patients with PD, and to evaluate dose proportionality, and the effect of food and intrinsic factors on the pharmacokinetics. Both the safety and efficacy of this ER carbidopa–levodopa product have been reported previously [15–17]. This review focuses on the integrated pharmacokinetic and pharmacodynamic properties of this ER capsule formulation of carbidopa–levodopa.

2 Drug Formulation

IPX066, an ER capsule formulation of carbidopa–levodopa (Rytary® in the US and Numient® in the EU), is designed to provide a plasma profile characterized by an initial rapid increase in levodopa concentrations followed by sustained levodopa concentrations with minimal peak-to-trough fluctuations. This profile provides a rapid onset of effect and reduces 'off' time in PD subjects. The formulation is a combination of levodopa and carbidopa at a ratio of 4:1 and is available in four strengths: 23.75/95, 36.25/145, 48.75/195, and 61.25/245 mg carbidopa–levodopa. The formulation contains four components: an IR component, ER component 1, ER component 2, and a functional excipient component. The IR component, ER component 1, and ER component 2 contain both levodopa and carbidopa as active ingredients, while the fourth component does not contain levodopa or carbidopa but includes tartaric acid as a functional excipient serving as an acidifying agent designed to facilitate the absorption of levodopa. The four components of the ER carbidopa–levodopa formulation exhibit different individual drug-release characteristics and are designed to deliver the initial increase in levodopa
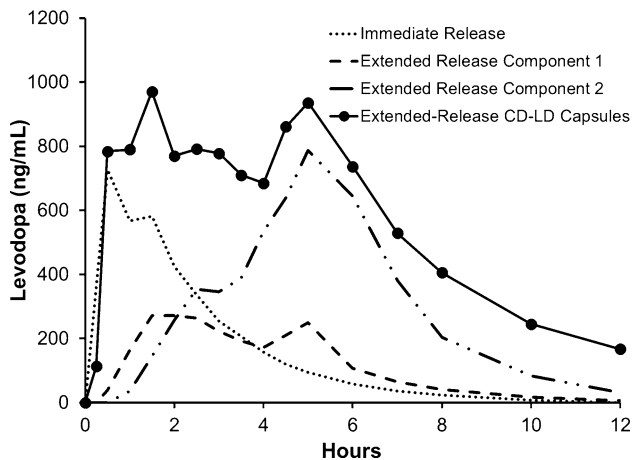
Fig. 1 Pharmacokinetic profile for immediate-release CD-LD, individual extended-release components and intact capsules of Rytary®. Data presented are LD concentrations from different studies that evaluated the performance of individual components and the pharmacokinetics of extended-release CD-LD capsules. *CD* carbidopa, *LD* levodopa

concentrations and provide the sustained plasma profile. Early in development, pharmacokinetic studies were conducted in healthy volunteers to evaluate various combinations of IR and formulations designed to release levodopa over a range of durations to allow selection of the desired in vivo levodopa profile. Figure 1 presents the plasma concentration profile for IR levodopa, ER component 1 beads, and ER component 2 beads at levodopa doses from the individual components that would correspond to a total dose of 390 mg. Also presented is the pharmacokinetic profile for a single dose of 390 mg ER carbidopa–levodopa intact capsule (two capsules of levodopa 195 mg). The combination of the IR and two ER formulation components allows achievement of the desired levodopa pharmacokinetic profile characterized by a rapid initial increase following by sustained levodopa plasma concentrations.

3 Pharmacokinetics

The clinical development program to characterize the pharmacokinetics and pharmacodynamics of ER carbidopa–levodopa included the following goals:

- characterize the single and multiple dose pharmacokinetics and pharmacodynamics relative to IR carbidopa–levodopa in patients with PD;
- characterize the single dose pharmacokinetics and pharmacodynamics relative to CR carbidopa–levodopa and relative to carbidopa–levodopa–entacapone in patients with PD;

- study the single-dose pharmacokinetics relative to other marketed carbidopa–levodopa formulations in healthy volunteers;
- evaluate the effect of food and of emptying the capsule contents onto soft foods such as applesauce;
- study the dose proportionality of the pharmacokinetics;
- characterize the effects of intrinsic factors such as age, gender, and weight on the pharmacokinetics

3.1 Single-Dose Pharmacokinetics in Healthy Adults

The single-dose pharmacokinetics of ER carbidopa–levodopa capsules was compared with the pharmacokinetics of other currently available formulations of carbidopa–levodopa in healthy subjects in an open-label, randomized, crossover study [18]. Subjects received a single oral dose of ER carbidopa–levodopa (two capsules of 48.75/195 mg carbidopa–levodopa), IR carbidopa–levodopa (25/100 mg Sinemet®), CR carbidopa–levodopa (25/100 mg Sinemet® CR) or carbidopa–levodopa–entacapone (25/100/200 mg Stalevo®) under fasting conditions. The levodopa dose of ER carbidopa–levodopa (390 mg) was chosen to approximately match the expected peak levodopa concentrations for IR carbidopa–levodopa [18]. With ER carbidopa–levodopa capsules, levodopa plasma concentrations increased rapidly, reaching an initial peak at approximately 1 h, with mean time to maximum concentration (t_{max}) occurring at approximately 4.5 h, after which levodopa concentrations decreased slowly and were <10% of peak at approximately 10 h. The pharmacokinetics of levodopa from the different formulations are summarized in Table 1. In spite of a 3.9-fold higher levodopa dose with ER carbidopa–levodopa compared with the other treatments, peak levodopa concentrations were approximately 1.2- to 1.6-fold higher. As expected, area under the concentration–time curve (AUC) values were approximately 2.2- to 3-fold higher. The bioavailability of levodopa from ER carbidopa–levodopa capsules relative to IR carbidopa–levodopa, CR carbidopa–levodopa, and carbidopa–levodopa–entacapone was 83.5, 78.3, and 58.8%, respectively. In comparison, on a dose-normalized basis, peak plasma concentrations of levodopa from ER carbidopa–levodopa relative to IR carbidopa–levodopa, CR carbidopa–levodopa, and carbidopa–levodopa–entacapone were 31.3, 40.0, and 33.4%, respectively. The absolute bioavailability of levodopa from IR carbidopa–levodopa has been reported to be 84% [19]. Hence, the absolute bioavailability of levodopa from ER carbidopa–levodopa capsules is approximately 70% (the 83.5% bioavailability of levodopa from ER carbidopa–levodopa relative to IR carbidopa–levodopa multiplied by 0.84).

Table 1 Single-dose pharmacokinetic parameters for levodopa in healthy subjects ($n = 22$) Adapted from Hsu et al. [18]

Product[a]	C_{max} (ng/mL)	t_{max} (h)[b]	AUC_∞ (ng h/mL)	$t_{1/2}$ (h)	C_{max} ratio	F (%)
ER CD-LD 390 mg	1326 ± 268	4.5 (0.5–8.0)	7244 ± 2553	1.9 ± 0.7	–	–
IR CD-LD 100 mg	1094 ± 401	1.0 (0.5–2.0)	2251 ± 664	1.6 ± 0.2	0.34 ± 0.10	83.5 ± 21
CR CD-LD 100 mg	855 ± 299	1.5 (1.0–2.0)	2403 ± 680	1.6 ± 0.2	0.43 ± 0.16	78.3 ± 20
CD-LD-Entacapone 100 mg	1027 ± 284	1.5 (1.0–2.0)	3291 ± 1149	1.6 ± 0.2	0.35 ± 0.11	58.8 ± 18

ER extended-release, *IR* immediate-release, *CR* sustained release, *LD* levodopa, *CD* carbidopa; C_{max} maximum observed plasma concentration, t_{max} time to maximum concentration, $t_{1/2}$ half-life, C_{max} *ratio* dose-normalized ratio of ER CD-LD C_{max} to reference product, AUC_∞ area under the concentration–time curve extrapolated to infinity, *F* relative bioavailability

[a] The doses listed are for levodopa

[b] Median (range)

3.2 Single-Dose Pharmacokinetics in Patients with Parkinson's Disease (PD)

The single-dose pharmacokinetics of ER carbidopa–levodopa capsules in patients with PD was investigated relative to IR carbidopa–levodopa (Sinemet®), CR carbidopa–levodopa (Sinemet® CR), and carbidopa–levodopa–entacapone (Stalevo®), each in a separate crossover study [17, 20]. In these studies, patients took a single dose of their typical pre-study IR carbidopa–levodopa regimen following an overnight fast on one occasion, and ER carbidopa–levodopa on a separate occasion. The dose of ER carbidopa–levodopa was based on a conversion designed to achieve similar peak levodopa concentrations as the comparator treatments. Based on pharmacokinetic data in healthy volunteers that ER carbidopa–levodopa results in dose-adjusted levodopa maximum observed plasma concentrations (C_{max}) that are approximately 31.3% on IR carbidopa–levodopa, it was expected that the ER levodopa doses would be at least twofold higher. Figure 2 presents the levodopa plasma concentration–time profile following single doses of IR carbidopa–levodopa and ER carbidopa–levodopa capsules. As noted in healthy subjects, levodopa concentrations peaked within approximately 1 h and then decreased rapidly following IR carbidopa–levodopa. With ER carbidopa–levodopa capsules, the initial increase in levodopa concentrations was similar to that noted with IR levodopa, but levodopa concentrations were sustained for 4–5 h following the peak. In addition, in spite of an approximate two- to five-fold higher levodopa dose with ER carbidopa–levodopa, peak levodopa concentrations were comparable to IR dosing. The single-dose pharmacokinetics of ER carbidopa–levodopa and the other carbidopa–levodopa products in patients are presented in Table 2. On a dose-normalized basis, the levodopa C_{max} from ER carbidopa–levodopa compared with IR carbidopa–levodopa, CR carbidopa–levodopa, and carbidopa–levodopa–entacapone were 30.5, 52.2, and 29.7%, respectively. The bioavailability of levodopa from ER carbidopa–
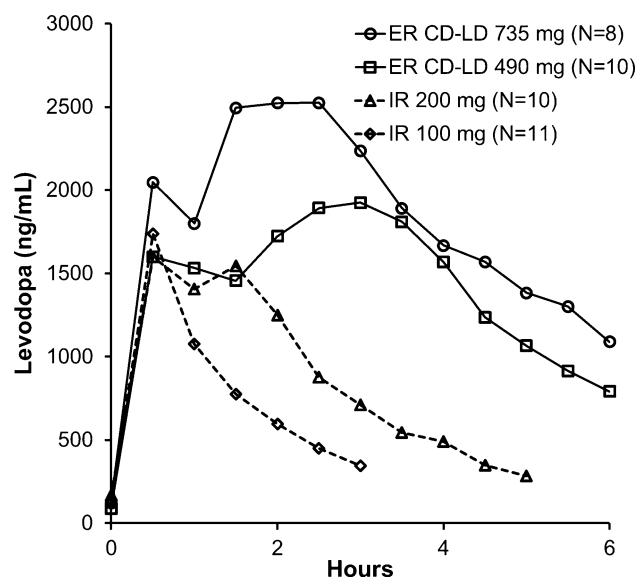

Fig. 2 Single-dose pharmacokinetics of IR and ER CD-LD in patients with Parkinson's disease. *ER* extended-release, *IR* immediate-release, *CD* carbidopa, *LD* levodopa

levodopa relative to IR carbidopa–levodopa and carbidopa–levodopa–entacapone was 69 ± 23 and 47 ± 16, respectively. Due to the short sampling duration in the pharmacokinetic study, the bioavailability of levodopa from ER carbidopa–levodopa relative to CR carbidopa–levodopa was not estimated.

3.3 Multiple-Dose Pharmacokinetics in Patients with PD

Multiple-dose pharmacokinetics of ER carbidopa–levodopa compared with IR carbidopa–levodopa was characterized in patients with advanced PD [20]. Patients received an individualized dosing regimen of ER carbidopa–levodopa and IR carbidopa–levodopa for 8 days in a crossover fashion, with multiple-dose pharmacokinetic assessment carried out over 12 h on the last day of each treatment

Table 2 Single-dose pharmacokinetics of ER CD-LD in patients with PD compared with other CD-LD products

Product	C_{max} (ng/mL)	t_{max} (h)[a]	AUC_∞ (ng h/mL)	$t_{1/2}$ (h)
ER CD-LD capsules				
LD 435 mg ($n = 12$)	1686 ± 970	1.5 (1–6)	–	–
LD 490 mg ($n = 16$)	2424 ± 763	2.5 (0.5–4)	11291 ± 3945	1.6 ± 0.5
LD 585 mg ($n = 7$)	2936 ± 1360	1.5 (0.5–2.5)	15210 ± 8905	2.4 ± 0.9
LD 735 mg ($n = 14$)	3058 ± 701	1.5 (0.5–3)	13221 ± 3756	1.5 ± 0.2
LD 780 mg ($n = 3$)	3703 ± 1220	2 (0.5–2.5)	18424 ± 4093	2.2 ± 1
LD 980 mg ($n = 6$)	4967 ± 1040	2 (0.5–4.5)	20479 ± 3257	1.7 ± 0.1
IR CD-LD				
LD 100 mg ($n = 11$)	1870 ± 697	0.5 (0.5–1.5)	3173 ± 1090	1.5 ± 0.4
LD 200 mg ($n = 10$)	2331 ± 769	1.3 (0.5–2)	5978 ± 1830	1.5 ± 0.2
LD 250 mg ($n = 4$)	3935 ± 1570	0.5 (0.5–1)	7690 ± 1090	1.6 ± 0.1
CR CD-LD				
LD 200 mg ($n = 12$)	1453 ± 814	2 (1–4)	5000 ± 3070[b]	–
CD-LD-Entacapone				
LD 100 mg ($n = 10$)	2105 ± 897	1 (0.5–1.5)	7223 ± 3640	1.8 ± 0.3
LD 150 mg ($n = 6$)	2493 ± 837	1 (0.5–2)	8655 ± 5320	1.8 ± 0.2
LD 200 mg ($n = 4$)	3038 ± 756	1.3 (1–2)	10936 ± 3924	1.7 ± 0.4

The pharmacokinetics for ER CD-LD capsules are based on data integrated from three studies

C_{max} maximum observed plasma concentration, t_{max} time to maximum concentration, $t_{1/2}$ half-life, AUC_∞ area under the concentration–time curve extrapolated to infinity, *CD* carbidopa, *LD* levodopa, *ER* extended-release, *IR* immediate-release, *CR* controlled-release, *PD* Parkinson's disease

[a] Median (range)

[b] AUC_t reported

period. During the first 3 days of each treatment period, the dosing regimen (dose and frequency) was adjusted as necessary to achieve optimal efficacy with reduced adverse effects. For the ER carbidopa–levodopa capsule treatment, 89% of patients took one or two doses, and 11% took three doses over the 12-h assessment period, with no subject taking more than four doses. In contrast, during the IR carbidopa–levodopa treatment, 37% of patients took one or two doses, 26% took three doses, and 37% took four or more doses over the 12-h assessment period. Figure 3 presents the multiple-dose levodopa concentration–time profile for ER carbidopa–levodopa and IR carbidopa–levodopa over the 12-h assessment period. Multiple dose pharmacokinetics of ER and IR carbidopa–levodopa are summarized in Table 3. The magnitude of rise and fall of levodopa plasma concentrations relative to the average concentration (i.e. the fluctuation index) may be of particular interest for an ER formulation. The lower the fluctuation index, the more likely the C_{max} is blunted relative to the trough, thus improving the pharmacodynamic profile and minimizing C_{max}-related adverse effects [21]. The fluctuation index measured as $(C_{max} - C_{min})/C_{ave}$ was 1.5 and 3.2 for ER carbidopa–levodopa and IR carbidopa–levodopa, respectively. Both treatments had a similar accumulation ratio indicating that the ER formulation does not result in accumulation of levodopa when administered
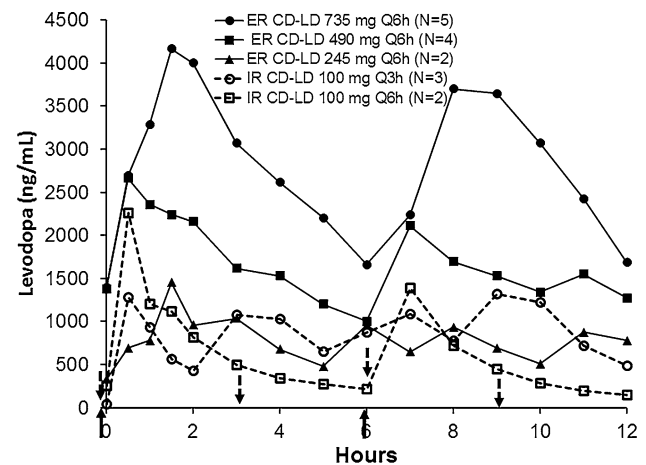

Fig. 3 Multiple-dose pharmacokinetics of IR and ER CD-LD in patients with Parkinson's disease. *Arrows* represent oral dose administrations every 3 or 6 h. *ER* extended-release, *IR* immediate-release, *CD* carbidopa, *LD* levodopa, *Qxh* every *x* hours

approximately every 6 h in accordance with the prescribing guidelines.

3.4 Dose Proportionality

The dose proportionality of ER carbidopa–levodopa capsules was evaluated in a single-dose, open-label,

Table 3 Multiple-dose pharmacokinetics of ER CD-LD and IR CD-LD in patients with PD

Product	C_{max} (ng/mL)	C_{ave} (ng/mL)	Accumulation	Fluctuation
ER CD-LD capsules				
LD 490 mg ($n = 7$)	3227 ± 1089	1623 ± 518	1.3 ± 0.4	1.7 ± 0.4
LD 735 mg ($n = 11$)	4166 ± 1787	2316 ± 777	1.3 ± 0.8	1.4 ± 0.4
IR CD-LD				
LD 100 mg ($n = 11$)	2209 ± 744	741 ± 203	1.1 ± 0.3	3.0 ± 1.1
LD 200 mg ($n = 9$)	3057 ± 1108	969 ± 384	1.1 ± 0.3	3.3 ± 1.0

C_{max} maximum observed plasma concentration, C_{ave} average concentration over 12 h, *Accumulation* drug accumulation, *Fluctuation* fluctuation calculated as $(C_{max} - C_{min})/C_{ave}$, *ER* extended-release, *IR* immediate-release, *CD* carbidopa, *LD* levodopa, *PD* Parkinson's disease

randomized, crossover study in healthy subjects [22]. ER carbidopa–levodopa was provided as one capsule of each dose strength (levodopa 95, 145, 195, 245 mg), and each subject received a single dose of each treatment with 240 mL of room-temperature water under fasted conditions in a randomized sequence. Dose proportionality was assessed using a power model ($Y = \alpha \times [Dose]^\beta$), as described by Gough et al. [23], with the modification by Smith et al. [24] Dose proportionality was to be concluded if the proportionality exponent estimate (β) for levodopa C_{max} and AUC was close to unity and the 90% confidence intervals (CIs) were within the acceptance interval (0.7645–1.2355).

A total of 31 healthy subjects were enrolled; 28 subjects received all four treatments and were included in the statistical analysis. Online Resource Table 1 presents the pharmacokinetic and dose-proportionality analysis. ER carbidopa–levodopa showed dose-proportional pharmacokinetics over the capsule strength range of 95/245 mg of levodopa. The power-model analysis confirmed that the 90% CI for the proportionality exponent estimate (β) for C_{max}, AUC_t, and AUC_∞ were within the acceptance interval, indicating dose proportional pharmacokinetics.

Dose proportionality of the ER carbidopa–levodopa capsules was also examined using the pooled single-dose pharmacokinetic data in patients with advanced PD from the pharmacokinetic cohort enrolled in the efficacy studies. Levodopa C_{max} and AUC_∞ increased in an approximate dose-proportional fashion over the broad range of doses administered (Fig. 4).

3.5 Comparison of Pharmacokinetics in Healthy Subjects and Patients with PD

The pharmacokinetics of ER carbidopa–levodopa capsules has been studied in multiple studies in healthy volunteers [18, 22] and in patients with advanced PD [17, 20]. Table 4 summarizes the levodopa pharmacokinetics in healthy subjects and in patients following normalization to a levodopa dose of 245 mg. Modest differences were noted
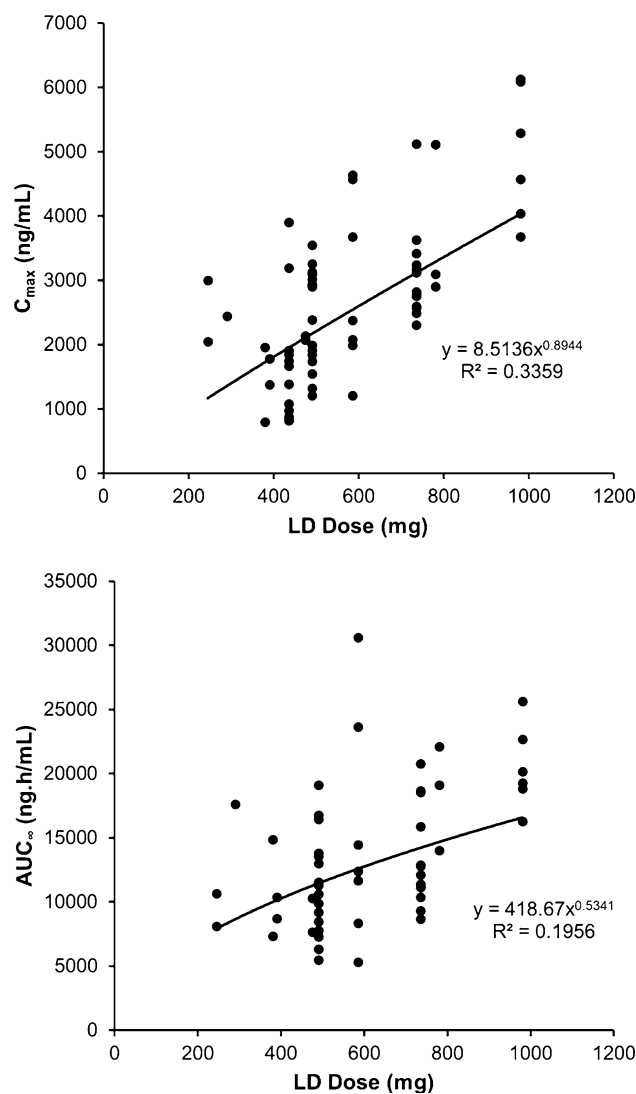

Fig. 4 Relationship between LD dose and LD pharmacokinetics in patients with Parkinson's disease. C_{max} maximum observed plasma concentration, AUC_∞ area under the concentration–time curve extrapolated to infinity, *LD* levodopa

in the levodopa pharmacokinetics of ER carbidopa–levodopa between healthy subjects and patients with PD. Mean dose-normalized levodopa AUC_∞ and C_{max} were higher

Table 4 Summary of dose-normalized levodopa pharmacokinetics in healthy subjects and patients with PD following ER CD-LD

	C_{max} (ng/mL)	t_{max} (h)[a]	AUC_∞ (ng h/mL)	$t_{1/2}$ (h)
Healthy subjects (N = 184)	822 ± 259	4.0 (0.3–8.0)	3884 ± 1285	1.7 ± 0.7
PD patients (N = 72)	1130 ± 484	2.0 (0.5–6.0)	5579 ± 2465	1.9 ± 0.7[b]

C_{max} and AUC_∞ are dose-normalized to 245 mg

C_{max} maximum observed plasma concentration, t_{max} time to maximum concentration, AUC_∞ area under the concentration–time curve extrapolated to infinity, $t_{1/2}$ half-life, *ER* extended-release, *CD* carbidopa, *LD* levodopa, *PD* Parkinson's disease

[a] Median (range)

[b] N = 59

(approximately 44 and 38% for AUC_∞ and C_{max}, respectively) in subjects with PD compared with healthy subjects. The elimination half-life for levodopa was comparable in the two populations.

3.6 Maintenance of Levodopa Plasma Concentrations

The ER carbidopa–levodopa capsule formulation is designed to provide an initial increase in levodopa concentrations that are comparable to IR carbidopa–levodopa and subsequently maintain the levodopa concentration for an extended period of time. Table 5 summarizes the duration of time levodopa plasma concentrations are sustained above 50% of C_{max} in both healthy subjects and patients with PD for ER carbidopa–levodopa and other marketed carbidopa–levodopa products following a single dose.

ER carbidopa–levodopa sustains levodopa plasma concentrations above 50% of C_{max} for a longer duration (4–5 h) than IR carbidopa–levodopa (approximately 1.5 h), CR carbidopa–levodopa (2–3 h), and carbidopa–levodopa–entacapone (2–2.5 h) in healthy subjects and subjects with PD. Notably, the estimated duration that concentrations are sustained above 50% C_{max} was consistent across the studies and in both healthy volunteers and patients with

PD. Consistent with the sustained levodopa concentrations, the duration of pharmacodynamic effect following ER carbidopa–levodopa capsules is approximately 2 h longer than that for IR carbidopa–levodopa or carbidopa–levodopa–entacapone for both tapping and Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor function) scores [17, 20].

3.7 Low Variability in Pharmacokinetics

Variability (percentage of coefficient of variation) in levodopa pharmacokinetics may be estimated as a ratio of the standard deviation (SD) and mean. Table 6 summarizes the variability in levodopa pharmacokinetics for ER carbidopa–levodopa capsules compared with other levodopa products from the study in healthy volunteers [18]. Intersubject variability in C_{max} was lower, and for AUC_t was lower or comparable for ER carbidopa–levodopa capsules than for other carbidopa–levodopa products.

Several studies conducted in healthy volunteers as part of the development of ER carbidopa–levodopa capsules involved a crossover design that allowed estimation of intersubject (between subject) and intrasubject (within subject) variability. Natural logarithmically-transformed dose-normalized C_{max} and AUC_∞ were analyzed by analysis of variance using a linear mixed model to obtain

Table 5 Comparison of duration of time (hours) the LD concentrations are sustained above 50% of C_{max} by CD-LD products following a single dose. Data presented are Mean ± SD

Product	Healthy subjects	PD patients		
	Hsu et al. [18] (N = 22)	Study 1 (N = 27)	Study 2 (N = 32)	Study 3 (N = 12)
ER CD-LD	4.9 ± 2.4	4.0 ± 2.0	4.1 ± 1.5	4.1 ± 1.3
IR CD-LD	1.5 ± 0.7	1.4 ± 0.7	NA	NA
CR CD-LD	2.1 ± 1.0	NA	NA	3.1 ± 1.0
CD-LD-Entacapone	2.1 ± 1.0	NA	2.5 ± 1.1	NA

NA not applicable, *ER* extended-release, *IR* immediate-release, *CR* sustained release, *LD* levodopa, *CD* carbidopa, C_{max} maximum observed plasma concentration, *SD* standard deviation

Table 6 Intersubject variability (% CV) in LD pharmacokinetics from ER CD-LD capsules and other CD-LD products

	ER CD-LD	IR CD-LD	CR CD-LD	CD-LD-Entacapone
C_{max}	20.2	36.7	35.0	27.7
AUC_t	30.9	30.0	28.8	34.9

C_{max} maximum observed plasma concentration, AUC_t area under the concentration–time curve from time zero to the last measured concentration, *ER* extended-release, *IR* immediate-release, *CR* sustained release, *LD* levodopa, *CD* carbidopa, *CV* coefficient of variation

estimates of intra- and intersubject variabilities for these parameters using pooled data from the crossover studies. Intrasubject variability was 17.2% for log AUC_∞ and 18.8% for log C_{max}, whereas intersubject variability was 22.2% for log AUC_∞ and 19.8% for log C_{max}. These intrasubject variabilities would be considered low according to the commonly used regulatory definition that drugs that exhibit intrasubject variability of >30% are considered highly variable [26–28].

The multiple-dose pharmacokinetics of ER carbidopa-levodopa and IR carbidopa–levodopa was compared in patients [20]. Over the 12-h assessment period, the average interindividual coefficient of variation for plasma concentrations of levodopa after ER carbidopa–levodopa treatment was 33.2%, significantly lower than during IR carbidopa–levodopa administered every 6 h (75.2%) or IR carbidopa–levodopa administered every 3 h (43.0%) ($p < 0.05$, Bartlett's test).

3.8 Effect of Food on the Pharmacokinetics of Extended-Release (ER) Carbidopa–Levodopa Capsules

The sustained-release beads in the ER carbidopa–levodopa capsule formulation are designed to exhibit lower drug release below pH 7. The effect of two representative soft-food products [Jell-O (pH 6.5) and Kozy-Shack Flan Crème Caramel Pudding (pH 6.1)] with pH values above 6 was investigated to evaluate the in vitro release of levodopa. Approximately 10 mL of each food was mixed with ER component 2 beads and allowed to stand at ambient temperature for 30 min. The beads were washed with water until no food residue was visible and the amounts (%) of levodopa and carbidopa remaining in the beads were determined. Mixing ER carbidopa–levodopa with selected soft foods with a pH of approximately 6.0 for up to 30 min resulted in <4.5% levodopa release and did not affect the integrity of the formulation, as demonstrated by the insignificant amount of levodopa released upon mixing.

The effect of a high-fat meal on the pharmacokinetics of single-dose ER carbidopa–levodopa was also investigated in healthy volunteers [22]. In a three-period, randomized,

crossover study, subjects received two capsules of ER carbidopa–levodopa 61.25/245 mg under fasting conditions, and then, after an appropriate washout of at least 6 days, received two capsules of ER carbidopa–levodopa 61.25/245 mg after consuming a high-fat, high-calorie breakfast as recommended by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance [29, 30]. On a separate occasion, subjects received the contents of carbidopa–levodopa capsules sprinkled over a tablespoon of applesauce under fasting conditions. Administration of ER carbidopa–levodopa with a high-fat, high-calorie breakfast delayed the initial increase in levodopa concentration by approximately 2 h, reduced C_{max} by 21%, and increased AUC_∞ by 13% compared with the fasted state. Sprinkling the ER carbidopa–levodopa capsule contents on applesauce did not affect the pharmacokinetics [22].

4 Effect of Intrinsic Factors on the Pharmacokinetics of ER Carbidopa–Levodopa Capsules

The effect of various intrinsic factors, including race, gender, age, body weight, and renal function, on the pharmacokinetics of ER carbidopa–levodopa was evaluated using dose-normalized data from studies in healthy volunteers and patients.

4.1 Effect of Race

The vast majority (95%) of patients with PD in whom pharmacokinetic data were available were White; therefore, no assessments of race on levodopa pharmacokinetics were conducted in patients with PD. In the healthy population, levodopa C_{max} and AUC_∞ values were 10–17% higher in Black versus White subjects. Median time to peak levodopa concentration and terminal half-life were comparable in the two groups (Table 7).

4.2 Effect of Gender

Plasma concentrations of levodopa were higher in women compared with men, in both healthy subjects and patients with PD. In healthy subjects, mean dose-normalized levodopa C_{max} values were approximately 25% greater and AUC_∞ values approximately 38% higher in females than in males, while in patients with PD, mean dose-normalized C_{max} was 35% greater and AUC_∞ was 37% higher in females than in males. Median time to peak levodopa concentration and terminal plasma half-life of levodopa were comparable in men and women for both healthy subjects and patients with PD (Table 8).

Table 7 LD pharmacokinetics for ER CD-LD capsules in healthy subjects categorized by race (mean ± SD)

	White ($N = 121$)	Black ($N = 61$)	Ratio (Black/White)
C_{max} (ng/mL)	793 ± 269	873 ± 224	1.10
t_{max} (h)[a]	4.0 (0.3–7.0)	4.5 (0.5–8.0)	–
$t_{1/2}$ (h)	1.7 ± 0.9	1.7 ± 0.5	1.0
AUC_∞ (ng h/mL)	3679 ± 1252	4294 ± 1284	1.17

AUC_∞ and C_{max} are dose-normalized to 245 mg

C_{max} maximum observed plasma concentration, t_{max} time to maximum concentration, $t_{1/2}$ half-life, AUC_∞ area under the concentration–time curve extrapolated to infinity, *SD* standard deviation, *ER* extended-release, *CD* carbidopa, *LD* levodopa

[a] Median (range)

4.3 Effect of Age

Patients with PD in whom pharmacokinetic data were available were significantly older than healthy subjects; 93% of patients with PD were older than 50 years of age, while 98% of healthy subjects were younger than 50 years of age.

Dose-normalized levodopa AUC_∞ increased with increasing age in healthy subjects and patients with PD. Age accounted for approximately 4% and 15% of the variability in levodopa AUC_∞ in healthy volunteers and patients with PD, respectively (Online Resource Fig. 1), and mean dose-normalized C_{max} and AUC_∞ were 27 and 52% higher, respectively, in patients with PD older than 65 years of age compared with patients younger than 50 years of age.

4.4 Effect of Body Weight

Table 9 summarizes levodopa pharmacokinetics in healthy subjects and patients with PD, by weight. Dose-normalized C_{max} and AUC_∞ of levodopa from ER carbidopa–levodopa were negatively correlated with body weight in healthy

subjects and patients with PD. Body weight accounted for approximately 18 and 31% of the observed variability in dose-normalized C_{max} and AUC_∞ of levodopa, respectively, in patients with PD (Online Resource Fig. 2). As expected, no difference in t_{max} and $t_{1/2}$ was observed between the weight groups.

4.5 Effect of Renal Function

The relationship between estimated creatinine clearance, a measure of renal function, and levodopa pharmacokinetics was evaluated using the pooled dose-normalized pharmacokinetic data from studies in healthy volunteers and patients with PD. Dose-normalized AUC_∞ values tended to increase with decreasing creatinine clearance in both healthy subjects and patients with PD (Online Resource Fig. 3). Estimated creatinine clearance explained approximately 14 and 18% of the variability in AUC_∞ in healthy subjects and patients with PD, respectively, and accounted for approximately 13 and 14% of the variability in levodopa C_{max} in healthy subjects and patients with PD, respectively.

Table 8 LD pharmacokinetics for ER CD-LD capsules in healthy subjects and patients with PD categorized by gender (mean ± SD)

	C_{max} (ng/mL)[a]	t_{max} (h)[b]	$t_{1/2}$ (h)	AUC_∞ (ng h/mL)[a]
Healthy subjects				
Males ($N = 97$)	734 ± 211	4.0 (0.3–6.0)	1.7 ± 0.30	3291 ± 874
Females ($N = 87$)	920 ± 273	3.5 (0.3–8.0)	1.7 ± 0.78	4545 ± 1351
Subjects with PD				
Males ($N = 52$)	1029 ± 405	1.5 (0.5–6.0)	1.9 ± 0.7[c]	5103 ± 2218[c]
Females ($N = 20$)	1390 ± 580	2.0 (0.5–3.0)	1.9 ± 0.9[d]	6975 ± 2695[d]

PD Parkinson's disease, C_{max} maximum observed plasma concentration, t_{max} time to maximum concentration, $t_{1/2}$ half-life, AUC_∞ area under the concentration–time curve extrapolated to infinity, *ER* extended-release, *CD* carbidopa, *LD* levodopa, *SD* standard deviation

[a] Dose normalized to 245 mg

[b] Median (range)

[c] $N = 45$

[d] $N = 15$

Table 9 Pharmacokinetics of ER LD capsule in healthy subjects and subjects with PD categorized by body weight

	C_{max} (ng/mL)[a]	t_{max} (h)[b]	$t_{1/2}$ (h)	AUC_{∞} (ng h/mL)[a]
Healthy subjects				
40 to <65 kg (N = 42)	991 ± 279	4.5 (0.5–8.0)	1.7 ± 0.77	4911 ± 1504
65–91 kg (N = 119)	799 ± 224	3.5 (0.3–7.0)	1.7 ± 0.72	3744 ± 1012
≥91 kg (N = 23)	631 ± 218	3.5 (0.3–6.0)	1.7 ± 0.30	2730 ± 722
Subjects with PD				
40 to <65 kg (N = 8)	1509 ± 649[c]	1.5 (0.5–3.0)[c]	2.1 ± 1.1	8781 ± 2330
65–91 kg (N = 34)	1148 ± 439[c]	2.0 (0.5–6.0)[c]	1.8 ± 0.5	5457 ± 2352
≥91 kg (N = 18)	917 ± 347[c]	2.0 (0.5–3.5)[c]	1.9 ± 0.8	4380 ± 1307

C_{max} maximum observed plasma concentration, t_{max} time to maximum concentration, $t_{1/2}$ half-life, AUC_{∞} area under the concentration–time curve extrapolated to infinity, *PD* Parkinson's disease, *ER* extended-release, *LD* levodopa

[a] Dose normalized to 245 mg

[b] Median (range)

5 Pharmacodynamics

The pharmacokinetic/pharmacodynamic relationship for ER carbidopa–levodopa capsules has been characterized in patients with PD using finger tapping, UPDRS Part III score, and the incidence of dyskinesia [25]. The pharmacodynamic models included a biophase effect site equilibration with a sigmoid maximum effect (E_{max}) transduction for tapping and UPDRS Part III score, and an ordered categorical model for dyskinesia. Pharmacodynamic parameters for tapping and UPDRS Part III scores are presented in Online Resource Table 2. The estimated half maximal effective concentration (EC_{50}) for tapping was 1590 ng/mL, with an equilibrium half-life of 36 min, while the EC_{50} for the UPDRS Part III score was 812 ng/mL, with an equilibrium half-life of 23 min, and the EC_{50} for dyskinesia was 601 ng/mL, with an equilibrium half-life of 27 min [25].

In addition, a dose-response relationship for UPDRS Part II plus Part III was established in levodopa-naïve PD patients using a disease progression model [31]. The model comprised three components: a linear function describing natural disease progression, a component describing placebo (or non-levodopa) effects, and a component describing the levodopa-specific effect. Natural disease progression in early PD was 11.6 units/year and the half maximal effective dose (ED_{50}) for the total daily dose of levodopa was 450 mg [31].

6 Discussion

Oral levodopa is rapidly absorbed across the intestinal mucosa by amino acid transporters expressed in the proximal small intestine. Therefore, oral absorption of levodopa is largely limited to the intestinal region where these transporters are expressed and the extent of absorption depends on the rate at which levodopa transits through the upper small intestine. The absolute oral bioavailability of levodopa is dose-dependent due to capacity-limited absorption via the active transporters. In practice, doses of levodopa are carefully titrated in each patient to achieve optimal efficacy. Low concentrations of levodopa in plasma (and in the brain) can result in the reappearance of the core symptoms of PD; however, side effects such as motor fluctuations, occur when levels of levodopa exceed a patient-specific threshold. Furthermore, uncontrolled and unpredictable fluctuations in plasma and striatal concentrations of levodopa are thought to contribute to the development of 'on-off' fluctuations, including dyskinesias. Therefore, the treatment of motor symptoms in PD is most effective when plasma concentrations of levodopa are maintained within a therapeutic range, which progressively narrows as the disease progresses.

Although several controlled-release (CR) formulations of levodopa (with carbidopa or benserazide) have been developed, these formulations are associated with erratic absorption and variable levodopa plasma concentrations [32, 33]. In addition, the latency to onset of motor improvement is typically 60–180 min with the CR formulation due to the slower absorption. Thus, CR formulations are commonly administered with IR carbidopa–levodopa in patients, particularly for the first dose in the morning [34, 35]. Various methods, including oral CR formulations and duodenal infusion of levodopa, have sought to provide continuous and sustained oral delivery of levodopa in an effort to reduce or delay the development of motor complications. With the exception of invasive and often impractical continuous intraduodenal infusion of levodopa by a pump, current regimens of oral levodopa are beset by a limited window of effect, requiring frequent administrations and/or unpredictable pharmacokinetics.

The development of improved oral CR products of levodopa has been hindered by its unfavorable properties, including poor solubility, short plasma half-life, inconsistent absorption due to slow or variable gastric emptying, and its absorption being limited to the proximal small intestine.

ER carbidopa–levodopa is a new capsule formulation that provides immediate delivery of a fraction of the levodopa dose followed by CR from beads that provide the remainder of the levodopa dose over an extended duration. The pharmacokinetic profile of ER carbidopa–levodopa capsules is characterized by an initial increase in levodopa plasma concentrations that is comparable to IR carbidopa–levodopa, to provide a rapid initial onset of effect. Following an initial plateau in levodopa concentrations at approximately 1 h, concentrations are maintained for 4–5 h before declining. This plasma profile provides an extended duration of effect with a lower fluctuation in plasma levodopa concentrations (1.5 for ER carbidopa–levodopa capsules compared with 3.2 for IR carbidopa–levodopa). The magnitude of rise and fall of levodopa plasma concentrations relative to the average concentration (i.e. the fluctuation index) may be of particular interest for an ER formulation. The lower the fluctuation index, the more likely the C_{max} is blunted relative to the trough, thus improving symptom control and minimizing C_{max}-related adverse effects [21]. An ideal carbidopa–levodopa product would have minimal fluctuation and maintain steady levodopa concentrations over the dosing interval. Fluctuations in levodopa concentrations are of particular concern since the short duration response for levodopa is correlated with the short peripheral pharmacokinetics. Although it may be expected that CR formulations would have a reduced fluctuation index, that does not always appear to be the case for carbidopa–levodopa products. In a study comparing multiple-dose pharmacokinetics of conventional Sinemet® tablets and Sinemet® CR formulations CR3 and CR4 in healthy volunteers, the fluctuation index was 2.45, 2.06, and 1.86, respectively [36]. The use of selective COMT inhibitors, such as entacapone and tolcapone, is also reported to prolong the effect of a levodopa dose. However, this does not seem to result in an improved fluctuation index. LeWitt and colleagues [13] compared CR carbidopa–levodopa and combined entacapone with carbidopa–levodopa in subjects with PD. The mean fluctuation index was 2.35 for carbidopa–levodopa–entacapone and 1.96 for CR carbidopa–levodopa. Similarly, Nyholm et al. noted a fluctuation of 2.23 for carbidopa–levodopa–entacapone and 1.26 for carbidopa–levodopa microtablets in healthy subjects [37].

A detailed discussion of the potential mechanisms by which ER carbidopa–levodopa improves the pharmacokinetic profile of levodopa is beyond the scope of this review; However, some features of the formulation are worth noting. The ER carbidopa–levodopa capsule formulation is not designed to affect the intestinal transit characteristics of levodopa. The formulation includes tartaric acid, an organic acid, to modulate the drug release rate and act as an acidifying excipient. The presence of tartaric acid in the core of the formulation may govern the prolonged and slow release of levodopa by interfering with the dissolution of the enteric coat. In intestinal epithelial cell lines (Caco-2, IEC-6), an acidic medium has been shown to stimulate the transport of levodopa [2]. Tartaric acid inhibits P-glycoprotein (P-gp) and the efflux of P-gp substrates from the serosal to mucosal side in epithelial cells. Furthermore, it may be noted that levodopa is a substrate for P-gp. Salicylic acid has been shown to facilitate the absorption of levodopa after rectal administration in rats by a mechanism that requires its presence in the rectal membrane [38]. Studies have shown that exogenous administration of ascorbic acid improves levodopa absorption (C_{max} and AUC) in PD patients with poor levodopa bioavailability [39, 40]. Therefore, one may speculate that tartaric acid cumulatively extends the window of levodopa absorption in the gastrointestinal tract by promoting an acidic milieu in regions of the intestine where levodopa is a substrate for pH-sensitive amino acid transporters or exchangers, by inhibiting P-gp-mediated efflux from the more distal regions of the intestine or by enhancing its mucosal permeation via paracellular pathways. Although previous studies have looked into the role an acid may play in levodopa formulations, there is uncertainty whether the addition of an acid aids in extending the absorption of oral levodopa, and the exact mechanism of action of tartaric acid in the ER carbidopa–levodopa formulation has not been completely elucidated.

On a dose-normalized basis, levodopa C_{max} values for ER carbidopa–levodopa capsules are approximately 30% and AUC values are approximately 70% compared with IR carbidopa–levodopa. Following oral administration of ER carbidopa–levodopa capsules, levodopa concentrations are maintained above 50% C_{max} for a longer duration than with other carbidopa–levodopa formulations. ER carbidopa–levodopa also exhibits low (approximately 20%) intrasubject variability in levodopa C_{max} and AUC_∞, and the intersubject variability is lower or comparable with other carbidopa–levodopa products. These pharmacokinetic characteristics mean that when patients are converted to ER carbidopa–levodopa from their current levodopa regimen, the total daily dose of levodopa from ER carbidopa–levodopa will be approximately twofold higher compared with the current levodopa dose. The total daily dose of ER carbidopa–levodopa capsules is administered using a combination of the available dose strengths as three to five divided doses based on patient characteristics (e.g. disease stage, total dose, and patient propensity to experience

dyskinesia). In spite of the higher total levodopa dose with ER carbidopa–levodopa capsules, peak levodopa concentrations are not expected to be higher than following the patient's typical IR carbidopa–levodopa dose.

The effect of food on the pharmacokinetics of single-dose ER carbidopa–levodopa capsules was investigated in healthy subjects [22]. In the phase III clinical trials, patients with PD were advised to take their ER carbidopa–levodopa capsules in the same way as they would take their usual levodopa medication with respect to food intake. Administration of the ER carbidopa–levodopa capsules with a high-fat breakfast in healthy subjects did not result in dose dumping and there was no effect on the overall extent of absorption of levodopa (AUC). A high-fat breakfast delayed the absorption of levodopa: t_{max} was 1–2 h later and levodopa C_{max} decreased by approximately 21% [22]. Although there was a slower rate of absorption with a high-fat meal, the overall duration of time that levodopa concentrations were maintained above 50% C_{max} was longer (7.0 h) compared with the fasting state (4.4 h). Administration of the ER carbidopa–levodopa capsule contents sprinkled onto a small quantity of applesauce did not compromise the rate or extent of absorption of levodopa versus ER carbidopa–levodopa capsules swallowed whole in a fasted state [22]. In addition, in vitro assessments with representative foods at a pH value of approximately 6 indicated that the capsule formulation is robust and does not result in dose dumping. Swallowing difficulties are not uncommon in subjects with PD [41, 42] and, in these patients, the ability to sprinkle the contents of ER carbidopa–levodopa capsules onto a small quantity of soft food, such as applesauce or pudding, to facilitate dosing may be advantageous.

Results of the effect of food on levodopa pharmacokinetics from standard and CR formulations have been mixed. Baruzzi and colleagues examined the effect of standardized meals on the pharmacokinetic of levodopa (50/200 mg) in PD patients taking Sinemet® (carbidopa:levodopa 1:10) [43]. When levodopa was administered after meals, levodopa t_{max} increased threefold (from 45 to 134 min) compared with that in the fasted state. The extent of levodopa absorption (AUC$_6$) and C_{max} in the fed state were lower by an average of 15% and 30%, respectively [43]. In mild to moderately severe PD patients, levodopa C_{max} and AUC$_4$ after administration of a single carbidopa–levodopa CR (50/200 mg carbidopa–levodopa) tablet in the fasted state were, on average, 16–17% higher relative to that following a protein-rich meal [44]. Contin et al. reported that the intake of a single dose of Sinemet® CR (50/200 mg carbidopa–levodopa) by patients with mild to moderately severe PD after a standard low-protein meal reduced levodopa AUC$_6$ by 24%, C_{max} was unchanged, and t_{max} was delayed [45]. These confounding effects of food

on the levodopa pharmacokinetics of IR and CR carbidopa–levodopa may be attributed to various factors, including differences in formulations, different ratios of carbidopa:levodopa, study designs, and specific compositions of food in each study.

High-protein meals have been reported to impair the absorption and clinical response to levodopa, while low-protein diets have been associated with enhanced clinical response [46]. Because there is no impact on the pharmacokinetics of levodopa when it is administered with a high- or low-protein meal compared with the fasted state [47], the mechanism of the interaction is believed to be via competition through an amino acid transport system at the BBB rather than at the gastrointestinal tract. This observation is supported by a positron emission tomography (PET) study conducted with [^{18}F]fluorodopa which showed that elevating large neutral amino acids in plasma two- to threefold reduced the entry of [^{18}F]fluorodopa into the brain [48]. Since this interaction between levodopa and amino acids occurs at the BBB, a similar interaction would be expected with ER carbidopa–levodopa capsules. In summary, a high-fat, high-calorie meal may delay levodopa absorption and decrease levodopa C_{max}. Sprinkling the ER carbidopa–levodopa capsule contents on applesauce did not affect levodopa pharmacokinetics compared with the intact capsule. Similar to other carbidopa–levodopa products, patients should be cautioned that taking ER carbidopa–levodopa with foods rich in proteins or amino acids may interfere with the clinical effects of levodopa.

Based on a pooled analysis of pharmacokinetic data in healthy volunteers and patients with PD, levodopa exposure after administration of ER carbidopa–levodopa capsules was higher in PD patients compared with healthy subjects (37% for C_{max} and 44% for AUC), likely because the PD patients were older (mean 62.8 years) compared with the healthy cohort (mean 30.9 years). Rainero and colleagues studied the pharmacokinetics of standard carbidopa–levodopa in 11 healthy volunteers (mean 58.3 years) and 16 patients with PD (mean 63.1 years) [49], and noted that the AUC$_\infty$ was 3.38 µg h/mL in PD patients and 3.06 µg h/mL in healthy subjects, while C_{max} values were 1.35 µg/mL in PD patients and 1.07 µg/mL in healthy subjects. These findings are similar to those noted in the current analysis with ER carbidopa–levodopa capsules.

Dose-normalized levodopa C_{max} and AUC$_\infty$ following administration of ER carbidopa–levodopa capsules were higher in females (25–35% for C_{max}, 37–38% for AUC$_\infty$) than in males in healthy subjects and patients with PD. These results are consistent with other carbidopa–levodopa formulations [50–53]. Published studies demonstrate a significant effect of gender on levodopa exposure (higher concentrations in females), even after correction for body

weight. Kompoliti and colleagues examined the effects of gender on the pharmacokinetics of levodopa following a single dose of carbidopa–levodopa (25/100 mg) in fasted PD subjects [53]. The mean age in their study was 69.3 years for women and 68.9 years for men, and all weighed within ±15% of the predicted ideal weight. The results of this study showed that women had significantly higher mean body-weight-normalized levodopa AUC_6 (82%) and higher mean C_{max} (58%), but comparable median t_{max}, compared with men. In fed PD subjects administered an oral dose of levodopa 100 or 250 mg with an AADC inhibitor, body-weight-normalized levodopa AUC, but not C_{max}, was significantly ($p < 0.003$) greater in women than in men [52, 54], while in fasted PD subjects administered oral carbidopa–levodopa 25/250 mg, levodopa AUC and C_{max} were significantly higher in females (31% and 28%, respectively) than in males [52]. The authors noted that women were significantly lighter and more dyskinetic than men. By comparison, a population analysis of fasted subjects with mild to severe PD (age 34–78 years, disease duration of 0.8–24 years) administered a single oral dose of benserazide-levodopa (25/100 mg) reported that the pharmacokinetics of levodopa (apparent volume of distribution [V/F], absorption rate constant [k_a], and elimination rate constant [k_{el}]) were independent of patient characteristics, including gender [55]. The pharmacokinetic data with ER carbidopa–levodopa capsules indicate that women exhibit an approximately 33% higher levodopa C_{max} and AUC_∞ compared with men, similar to several other reports in the literature. Since dosing for PD patients is accomplished by careful individual titration, these differences are likely of minor relevance in treating PD patients.

Consistent with our observations with ER carbidopa–levodopa capsules, the AUC of levodopa was negatively correlated with body weight in male and female subjects with PD following a single oral dose of carbidopa–levodopa 25/250 mg [52]. Other studies have arrived at similar conclusions regarding the negative correlation of levodopa AUC and body weight, with increased prevalence of dyskinesias in subjects of lower body weight [50, 52, 56, 57].

Levodopa AUC and age were positively correlated in both healthy subjects and patients with PD (Online Resource Fig. 4). These results are consistent with reports in the literature with other formulations of levodopa and a decarboxylase inhibitor. Contin and colleagues [58] noted that following administration of levodopa 100 mg with benserazide 25 mg, levodopa AUC was significantly greater in PD patients older than 65 years of age than those under 65 years of age (547 vs. 428 μmol/l). Similarly, Robertson et al. compared the pharmacokinetics of oral levodopa (125 mg) with carbidopa in elderly (69–76 years

of age) and young (21–22 years of age) healthy volunteers [59], and noted a higher AUC for levodopa in elderly versus young subjects (4530 vs. 2926 ng h/mL; $p < 0.01$). The C_{max} values were comparable in the two groups (1922 ng/mL in the elderly subjects compared with 1712 ng/mL in the young subjects). These differences, while statistically significant, were considered modest and not likely to impact dosing.

In the presence of AADC inhibitors, the majority of a levodopa dose is cleared by non-renal elimination mechanisms, and renal excretion of intact levodopa accounts for only approximately 10% of clearance [19]. Renal impairment is considered unlikely to have a clinically significant effect on levodopa pharmacokinetics following the administration of ER carbidopa–levodopa since renal excretion of levodopa accounts for <10% of the overall clearance of levodopa. Thus, while impaired renal function may contribute to some increased exposure of levodopa, the contribution is likely to be minor and not considered clinically significant. carbidopa–levodopa has been used in the treatment of secondary restless legs syndrome in subjects receiving hemodialysis and this has not highlighted any significant safety concerns [60–62]. In clinical practice, the dose of levodopa generally does not have to be adjusted in patients with renal failure [63]. Given the minor contribution of estimated creatinine clearance to the variability in levodopa exposures, renal impairment is unlikely to have a clinically significant effect on ER carbidopa–levodopa pharmacokinetics.

The pharmacodynamics of ER carbidopa–levodopa was characterized in patients with PD who were naïve to levodopa [31] and patients with advanced PD [20, 25]. A disease progression pharmacodynamic model was developed using UPDRS Part II plus III in patients with early PD who were naïve to levodopa [31]. The pharmacodynamic model indicated that the linear progression disease rate was 11.6 UPDRS units/year. The maximum reduction in the UPDRS Part II plus III score of IPX066 at steady state was 76.7% of baseline values, and the estimated ED_{50} for levodopa from IPX066 was 450 mg/day. Pharmacodynamic parameters estimated for ER carbidopa–levodopa capsules were consistent with published reports [64, 65]. In patients with advanced PD, the motor effects (finger tapping, UPDRS Part III, and investigator-rated assessment of motor state) following single and multiple dosing of ER carbidopa–levodopa capsules was described using an effect compartment with a sigmoid E_{max} pharmacodynamic model [25]. The estimated pharmacodynamic parameters (Online Resource Table 2) for UPDRS Part III (E_{max} 63% of baseline; EC_{50} 812 ng/mL; k_{e0} 1.80 h^{-1}; γ 2.5) are comparable with those reported by Trocóniz et al. [66] (E_{max} 49% of baseline; EC_{50} 951 ng/mL; k_{e0} 2.01 h^{-1}; γ 6.2). Similarly, the pharmacodynamic parameters

estimated for the tapping rate are comparable with published reports [55, 67].

The new ER carbidopa–levodopa capsule product is approved in the USA and the EU for the treatment of PD based on studies demonstrating the safety and efficacy in both early and advanced stages of the disease. Data from a 9-month safety and efficacy study in early and advanced PD patients indicates a favorable tolerability and efficacy profile for ER carbidopa–levodopa capsules [68].

7 Conclusions

In summary, the pharmacokinetic and pharmacodynamic studies discussed in this review support the use of ER carbidopa–levodopa capsules as an efficacious and well-tolerated treatment for patients with PD, with possible benefits over other levodopa formulations.

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