Safety measures: Safety was assessed by blood pressure, heart rate, body temperature, ECG, laboratory safety measurements and evaluation of adverse events.

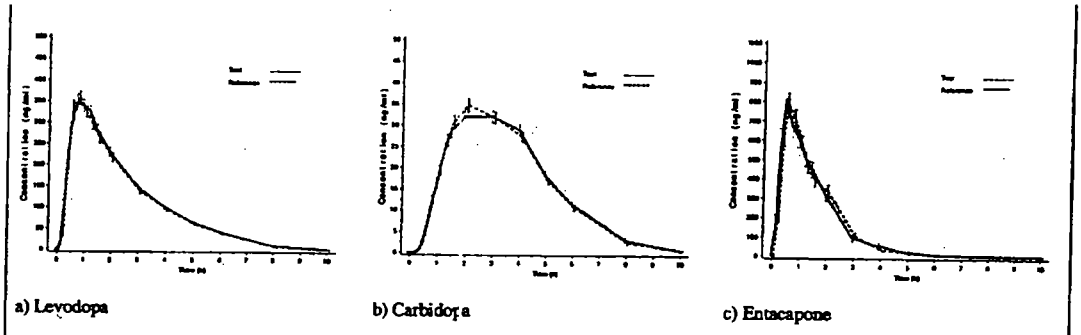
Data analysis: PK & Safety

- The PK parameters AUC0-10. AUC0-inf, Cmax, tmax and tl/2 were calculated for levodopa, carbidopa & entacapone.
- The PK variables, AUC0-10, AUC0-inf and Cmax, were log-transformed and then evaluated using analysis of variance (ANOVA) model appropriate for the underlying cross-over design.
- The evaluation of BE was based on the PK parameters, AUC0-10, AUC0-inf and Cmax of levodopa, carbidopa and entacapone. The 90% confidence intervals (CI) for the ratio between the means of treatments were calculated. If the observed 90% CI for the ratio between the means of treatments falls within a pre-determined acceptance range, treatments are BE. The acceptance range for bioequivalence was 0.80-1.25 (0.70-1.43 if CV is more than 30%).
- For the comparison of tmax the approximate nonparametric confidence intervals for the differences in medians between formulations were calculated in addition to Wilcoxon signed rank test.
- Safety was evaluated with descriptive statistics for vital signs and their mean changes during the study days and at the pre- and post-study visits. For laboratory safety variables descriptive statistics at pre- and post-study visits were evaluated.

Bioassays: Bioassay is discussed in the appendix "Bioanalytical assays section.

Levodopa/carbidopa	[redacted] method
Entacapone	[redacted]

Results:



a) Levodopa b) Carbidopa c) Entacapone

Figure 1. The mean concentrations (±SEM) in plasma for a) levodopa, b) carbidopa and c) entacapone after replicate administration of combination levodopa/carbidopa/entacapone 50/12.5/200 mg (test) and a half tablet of Sinemet® 100/25 mg with Comtess® 200 mg (reference).

Table R6. The mean pharmacokinetic parameters of levodopa, carbidopa and entacapone with 90% confidence interval of the ratio and coefficient of variation after replicate administration of levodopa/carbidopa/entacapone 50/12.5/200 mg tablet (test) and a half tablet of Sinemet® 100/25 mg with Comtess® 200 mg tablet (reference)

		Test		Reference		Geom. means ratio	Log 90% CI
		Mean±SD (n) *	CV	Mean±SD (n)	CV		
AUC_{0-10}	Levodopa	998 ± 310 (83)	17.1	970 ± 287 (84)	20.0	1.03	0.98 – 1.08
(ngxh/ml)	Carbidopa	150 ± 64 (83)	26.3	150 ± 56 (84)	19.4	0.98	0.92 – 1.05
	Entacapone	1249 ± 522 (84)	17.2	1255 ± 424 (84)	15.8	0.96	0.92 – 1.00
$AUC_{0-\infty}$	Levodopa	1044 ± 314 (83)	15.6	1017 ± 288 (84)	17.9	1.03	0.99 – 1.07
(ngxh/ml)	Carbidopa	169 ± 69 (68)	23.0	168 ± 59 (73)	17.1	0.99	0.93 – 1.05
	Entacapone	1279 ±491 (53)	13.7	1276 ± 392 (49)	9.5	1.01	0.96 – 1.06
C_{max}	Levodopa	473 ± 154 (83)	25.3	489 ± 153 (84)	24.8	0.96	0.90 – 1.03
(ng/ml)	Carbidopa	39 ± 16 (83)	28.0	39 ± 14 (84)	25.8	0.98	0.91 – 1.06
	Entacapone	1199 ± 884 (84)	46.1	1152 ± 558 (84)	43.5	0.94	0.84 – 1.06

CV = coefficient of variation (%)

* n = number of observations, number of subjects is 43 for all parameters except for $AUC_{0-\infty}$ of carbidopa 41 and entacapone 33

Summary of results:

- 44 subjects, of which 23 were male and 21 female. The subjects were 58±7.2 (mean±SD) years of age (range 45-75 years), 24 subjects were under 60 years, 17 subjects were over 60 years. Of 17 subjects, 7 were over 65.
- The mean levodopa, carbidopa and entacapone concentrations in plasma are presented in Figure above.

PK results:

- BE exists between the test and the reference treatments (Table above). Specifically, the 90 % CI for the ratio between the means in Cmax, AUC0-10 and AUC0-inf, of the test and the reference treatments were within goal post (0.80-1.25) for all three moieties.

- Comparable values of tmax & t1/2 were observed between the test and the reference.

Tmax (hr) mean (range)		
	test	reference
Levodopa	1.1 (0.5-3.0)	0.9 (0.2-3.0)
Carbidopa	2.5 (1.3-4.0)	2.4 (1.0-5.0)
Entacapone	1.2 (0.2-5.0)	0.9 (0.8-4.0)
t1/2 (hr) mean (range)		
Levodopa	1.7 (1.3-3.1)	1.7 (1.1-2.3)
Carbidopa	1.6 (0.7-3.0)	1.6 (0.9-2.8)
Entacapone	0.8 (0.3-3.1)	0.7 (0.3-2.4)

Bioassays

Levodopa & carbidopa

Summary on the study performance

Parameter	Result	
	Levodopa	Carbidopa
Calibrated Range [ng/ml]		
Defined LOQ [ng/ml]		
Precision (CV %) at the LOQ		
Accuracy (bias %) at the LOQ		
Precision (CV %) at the lowest QC		
Accuracy (bias %) at the lowest QC		

Entacapone

Range ng/ml	
LLOQ ng/ml	
Quality control	
Accuracy (Bias%)	
Precision (RSD%)	

Comments:

Study design: We consider the design acceptable. It is considered acceptable to use replicate, single dose design and average bioequivalence approach to address the issue of bioequivalence of compounds that exhibit high variability .

BE:

- We consider the test product bioequivalent to the reference products. The 90% CI of test-to-reference ratio for 3 active components fell within the recommended 80-125 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf).
- The elimination half-lives and tmax were comparable for test and reference products.
- Intra-individual variability: The coefficient of variation for the Cmax of entacapone both for test & reference products and in study (#95) was more than 30% (Test: 46.1%; reference: 43.5%) (table below).

Table 3. Intrasubject variability (CV, %) for $AUC_{0-\infty}$ and C_{max} of levodopa, carbidopa and entacapone in the bioequivalence studies.

	LCE 100				LCE 50		LCE 150	
Study #	-93		-85		-95		-96	
	$AUC_{0-\infty}$							
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Levodopa	10.2	10.1	14.2	13.5	15.6	17.9	13.1	14.1
Carbidopa	25.7	25.0	32.3	27.7	23.0	17.1	27.5	18.7
Entacapone	15.9	13.2	17.8	23.5	13.7	9.5	19.5	17.4
	C_{max}							
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Levodopa	18.5	16.6	21.4	23.5	25.3	24.8	18.7	22.8
Carbidopa	25.2	20.6	33.0	27.7	28.0	25.8	28.9	20.0
Entacapone	55.7	37.9	52.4	47.5	46.1	43.5	57.8	52.2

Test = test product, LCE 100, LCE 50 or LCE 150
Reference = reference products, Sinemet® 25/100 mg in the respecting dose with test product + Comtan® 200 mg

- The proposed extended limit of CI_{90} to define bioequivalence is not acceptable. However, no CI values fell outside of the goal post.
- This reviewer has confirmed the validity of the statistical analysis (90% CI) using a SAS program (V8) (table below). Dr. Rabindra Patnaik(OGD, HFD-651) was consulted for the model* used for replicate study design. Dr. Le Chnexiong (Statistician, HFD-710) was consulted for the SAS program in general. [*Note: SAS program statements for average BE analysis of replicated crossover studies from "Average, population, and individual approaches to establish bioequivalence" Guidance published in August 1999.
- Additional, Dr Patnaik performed an individual BE for entacapone, no subject by formulation interactions were found.

Table. Comparison of BE analysis for pivotal study of TC® (Levodopa/ carbidopa/entacapone): Sponsor's versus agency's [presented as geometric mean ratio (range of log 90%CI)

PK parameters	Active ingredient	source of analysis	#2939095 (50/12.5/200mg) (replicate ,40-80yrs n=44, males & females)
Cmax	levodopa	Sponsor	0.96 (0.90-1.03)
		Reviewer	0.96 (0.90-1.03)
	carbidopa	sponsor	0.98 (0.91-1.06)
		Reviewer	0.99 (0.91-1.07)
	entacapone	sponsor	0.94 (0.84-1.06)
		Reviewer	0.95 (0.83-1.09)
AUC0-inf	levodopa	Sponsor	1.03 (0.99-1.07)
		Reviewer	1.03 (0.98-1.08)
	carbidopa	sponsor	0.99 (0.93-1.05)
		Reviewer	0.99 (0.93-1.06)
	entacapone	sponsor	1.01 (0.96-1.06)
		Reviewer	0.99 (0.93-1.05)

- % CV for Cmax and AUC 0-inf were comparable for test products and reference product.

6.2.5 Study code: 2939096 (Volume: 52-58)

Study title: Bioequivalence study comparing levodopa/carbidopa/entacapone 150/37.5/200 mg combination tablet with Comtess 200 mg tablet administered with 1½ Sinemet 25-100 mg tablet after a single oral dose in healthy volunteers

Clinical site: [redacted]

Analytical site: The concentrations in plasma for levodopa & carbidopa were determined by [redacted] The concentrations in plasma for entacapone was determined by Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.

Objectives:

- To investigate the bioequivalence of a new levodopa/carbidopa/entacapone 100/25/200mg combination tablet with the commercially available formulations of levodopa/carbidopa (1½ tablet of Sinemet 25-100 mg tablet, Merck & Co, USA) and entacapone (Comtess 200 mg tablet, Orion Pharma, Finland).
- In addition, the intra-subject variability of each active compound, i.e., levodopa, carbidopa and entacapone was evaluated both for the test and the reference treatments.

Methodology:

- a single-dose, randomized, 2-sequence, replicate, crossover study with four study periods separated by at least a 3 weeks (21 days) washout period. Each subject had 6 visits and the total duration of the study was approx. 14 weeks.
- 44 subjects, Caucasian, male or female, 45-80 years of age, weight 50-100 kg, Body Mass Index (BMI) 19-28 kg/m2
- The subjects were randomly allocated to two groups (sequences 1 and 2):

Sequence	Period 1	2	3	4
1	T	R	T	R
2	R	T	R	T

T = test treatment, levodopa/carbidopa/entacapone 150/37.5/200 mg combination tablet
R = reference treatment, 1½ Sinemet 100/25 mg tablet with Comtess 200 mg tablet

- The treatments were administered with 200 ml of water after an overnight fast.
- Test treatment, dose and mode of administration: Single dose of levodopa/carbidopa/entacapone 150/37.5/200 mg, Orion Pharma, Finland, (Batch. no. CA003; Batchsize: [redacted] administered orally.
- Reference treatment, dose and mode of administration: 1 ½ tablet of Sinemet 25-100 mg tablet, Merck & Co, USA (Batch. no.HL 14820 & HL 14820 Halved) with Comtess 200 mg tablet, Orion Pharma, Finland (Batch. no. ZL012) administered orally.

PK measures:

- Blood samples were drawn before dosing (0 min) and at 10, 20, 30,45, 60,75 and 90 minutes, and 2, 3, 4, 5, 6, 8, 10 and 12 hours thereafter.

Safety measures: Safety was assessed by blood pressure, heart rate, body temperature, ECG, laboratory safety measurements and evaluation of adverse events.

Data analysis: PK & Safety

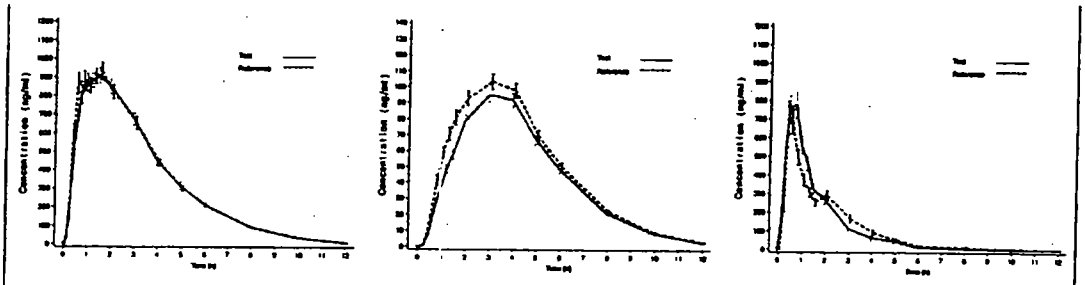
- The PK parameters AUC0-12. AUCo-inf, Cmax, tmax and tl/2 were calculated for levodopa, carbidopa & entacapone.
- The PK variables, AUC0-12, AUC0-inf and Cmax, were log-transformed and then evaluated using analysis of variance (ANOVA) model appropriate for the underlying cross-over design.
- The evaluation of BE was based on the PK parameters, AUC0-12, AUC0-inf and Cmax of levodopa, carbidopa and entacapone. The 90% confidence intervals (CI) for the ratio between the means of treatments were calculated. If the observed 90% CI for the ratio between the means of treatments falls within a pre-determined acceptance range, treatments are BE. The acceptance range for bioequivalence was 0.80-1.25 (0.70-1.43 if CV is more than 30%).
- For the comparison of tmax the approximate nonparametric confidence intervals for the differences in medians between formulations were calculated in addition to Wilcoxon signed rank test.

- Safety was evaluated with descriptive statistics for vital signs and their mean changes during the study days and at the pre- and post-study visits. For laboratory safety variables descriptive statistics at pre- and post-study visits were evaluated.

Bioassays: Bioassay is discussed in the appendix "Bioanalytical assay" section.

Levodopa/carbidopa	[redacted]
Entacapone	

Results:



a) Levodopa b) Carbidopa c) Entacapone

Figure 1. The mean concentrations (±SEM) in plasma for a) levodopa, b) carbidopa and c) entacapone after replicate administration of combination levodopa/ carbidopa/ entacapone 150/37.5/200 mg (test) and one and a half tablet of Sinemet® 100/25 mg with Comtess® 200 mg (reference).

Table R6. Mean pharmacokinetic parameters of levodopa, carbidopa and entacapone with 90% confidence interval of the ratio and coefficient of variation after replicate administration of levodopa/carbidopa/entacapone 150/37.5/200 mg tablet (test) and one and a half tablet of Sinemet® 100/25 mg with Comtess® 200 mg tablet (reference)

		Test		Reference		Geom. means ratio	Log 90% CI
		Mean±SD (n)*	CV	Mean±SD (n)	CV		
AUC_{0-12} (ngxh/ml)	Levodopa	3717 ± 1101 (81)	13.1	3824 ± 1116 (83)	14.1	0.97	0.94 – 1.01
	Carbidopa	488 ± 180 (81)	27.5	551 ± 192 (83)	18.7	0.88	0.82 – 0.93
	Entacapone	1233 ± 373 (81)	19.5	1216 ± 440 (83)	17.4	1.03	0.98 – 1.08
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	3774 ± 1118 (81)	13.2	3880 ± 1128 (83)	14.0	0.97	0.94 – 1.01
	Carbidopa	499 ± 183 (80)	27.3	566 ± 196 (83)	18.5	0.88	0.82 – 0.93
	Entacapone	1281 ±412 (56)	20.5	1270 ± 462 (50)	15.5	1.01	0.95 – 1.07
C_{max} (ng/ml)	Levodopa	1272 ± 329 (81)	18.7	1384 ± 445 (83)	22.8	0.94	0.89 – 0.99
	Carbidopa	107 ± 42 (81)	28.9	121 ± 45 (83)	20.0	0.88	0.82 – 0.94
	Entacapone	1211 ± 738 (81)	57.8	1052 ± 792 (83)	52.2	1.18	1.03 – 1.35

CV = coefficient of variation (%)

*n = number of observations, number of subjects is 43 for all parameters except for $AUC_{0-\infty}$ of entacapone 35

Summary of results:

- 43 subjects, of which 24 were male and 19 female. The subjects were 57.7±7.2 (mean±SD) years of age, 26 subjects were under 60 years, 17 subjects were over 60 years (range 45-74 years).

- The mean levodopa, carbidopa and entacapone concentrations in plasma are presented in Figure above.

PK results:

- BE exists between the test and the reference treatments except for entacapone, which was outside the conventional bioequivalence criteria (Table above). Specifically, while the 90 % CI for the ratio between the means in Cmax, AUC0-12 and AUC0-inf, of the test and the reference treatments were within goal post (0.80-1.25) for all levodopa & carbidopa. the values for entacapone (1.03-1.35) fell outside of the conventional bioequivalence criteria [sponsor's note: falls well within the wider bioequivalence criteria (0.70-1.43) since the coefficient of variation (CV) of Cmax of entacapone was 57.8% for the test and 52.2 % for the reference treatment, see comments below].
- Comparable values of tmax & t1/2 were observed between the test and the reference.

Tmax (hr) mean (range)		
	test	reference
Levodopa	1.5 (0.5-53.0)	1.2 (0.3-4.0)
Carbidopa	3.4 (1.3-6.0)	2.9(0.8-6.0)
Entacapone	1.0 (0.2-5.0)	1.3 (0.2-8.0)
t1/2 (hr) mean (range)		
Levodopa	1.7 (1.2-2.5)	1.7 (1.3-2.2)
Carbidopa	1.7 (1.0-3.2)	1.7 (1.1-2.5)
Entacapone	1.0 (0.4-4.5)	1.0 (0.4-5.9)

Bioassays: (Pre-study bioassay validations is discussed in bioanalytical assay section)

Levodopa/carbidopa Entacapone

Summary on the study performance

Parameter	Result	
	Levodopa	Carbidopa
Calibrated Range [ng/ml]		
Defined LLOQ [ng/ml]		
Precision (CV %) at the LLOQ		
Accuracy (bias %) at the LLOQ		
Precision (CV %) at the lowest QC's		
Accuracy (bias %) at the lowest QC's		

Range (ng/ml)	
LLOQ (ng/ml)	
Quality control	
Accuracy (Bias%)	
Precision (RSD%)	

Comments:

Study design: We consider the design acceptable. It is considered acceptable to use replicate, single dose design and average bioequivalence approach to address the issue of bioequivalence of compounds that exhibit high variability .

BE:

- The proposed extended limit of CI_{90} to define bioequivalence is not acceptable. We consider the test product not bioequivalent to the reference products. However, the sponsor has satisfactorily provided argument that the values of 90% CI that fell outside of recommended values should not be of concern. See separate discussion in this regard in appendix.

  Note: The sponsor proposed that extended limits (90% CI of 70-143%) should be considered for the highly variable compounds and the variation of entacapone Cmax does not result in any safety or tolerability concerns along with some citation of published references. In the pre-NDA meeting, the sponsor was told that the proposed extended limit of CI_{90} to define bioequivalence is not acceptable and was requested to address following 2 issues in the NDA submission: (1) the variability seen in the studies, and (2) the clinical relevance from a safety point of view at the highest recommended daily dose

regarding the two values that fell outside of the recommended values (one in study 93 & one in study 96).

- The elimination half-lives and tmax were comparable for test and reference products.
- Intra-individual variability: The coefficient of variation for the Cmax of entacapone both for test & reference products in study (96) was more than 30% (Test: 57.8%; reference: 52.2%) (table below).

Table 3. Intrasubject variability (CV, %) for $AUC_{0-\infty}$ and C_{max} of levodopa, carbidopa and entacapone in the bioequivalence studies.

	LCE 100				LCE 50		LCE 150	
Study #	-93		-85		-95		-96	
	$AUC_{0-\infty}$							
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Levodopa	10.2	10.1	14.2	13.5	15.6	17.9	13.1	14.1
Carbidopa	25.7	25.0	32.3	27.7	23.0	17.1	27.5	18.7
Entacapone	15.9	13.2	17.8	20.5	13.7	9.5	19.5	17.4
	C_{max}							
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Levodopa	18.5	16.6	21.4	20.5	25.3	24.8	18.7	22.8
Carbidopa	25.2	20.6	33.0	27.7	28.0	25.8	28.9	20.0
Entacapone	55.7	37.9	52.4	47.5	46.1	43.5	57.8	52.2

Test = test product, LCE 100, LCE 50 or LCE 150
Reference = reference products, Sinemet® 25/100 mg in the respecting dose with test product + Comtan® 200 mg

- This reviewer has confirmed the validity of the statistical analysis (90% CI) using a SAS program (V8) (table below). Dr. Rabindra Patnaik(OGD, HFD-651) was consulted for the model* used for replicate study design. Dr. Le Chnexiong (Statistician, HFD-710) was consulted for the SAS program in general. [*Note: SAS program statements for average BE analysis of replicated crossover studies from "Average, population, and individual approaches to establish bioequivalence" Guidance published in August 1999.

Table. Comparison of BE analysis for pivotal study of TC® (Levodopa/ carbidopa/entacapone): Sponsor's versus agency's [presented as geometric mean ratio (range of log 90%CI), bold indicates outside of the recommended range]

PK parameters	Active ingredient	source of analysis	#2939096 (150/37.5/200 mg) (replicate ,40-80yrs n=44, males & females)
Cmax	levodopa	Sponsor	0.94(0.89-0.99)
		Reviewer	0.94 (0.89-1.00)
	carbidopa	sponsor	0.88 (0.82-0.94)
		Reviewer	0.88 (0.82-1.07)
	entacapone	sponsor	1.18 (**1.03-1.35**)
		Reviewer	1.19 (**1.04-1.37**)
AUC0-inf	levodopa	Sponsor	0.97 (0.94-1.01)
		Reviewer	0.94 (0.94-1.00)
	carbidopa	sponsor	0.88 (0.82-0.93)
		Reviewer	0.88 (0.82-1.07)
	entacapone	sponsor	1.01 (0.95-1.07)
		Reviewer	1.02 (0.96-1.08)

Amendment from Division of Scientific Investigations (DSI, HFD-38) consult Dated January 13, 2003

- DSI recommends that study 2939096 is not acceptable for agency review due to non-compliance with the BE regulation for retention of reserve samples[21 CFR 320.38]. The authenticity of the drugs used in this study cannot be assured since the clinical site failed to select & retain the reserve samples.

Specifically, BE regulation requires the reserve samples should be retained at the clinical site (i.e. [redacted] or at an independent third party. Instead, the study drugs were prepackaged as unit dose by sponsor (Orion) and shipped to the clinic. The clinic [redacted] returned a set of 10 unused unit doses to Orion after study completion. Orion cannot be considered as an independent third party.

- The OCPB has taken DSI recommendation into consideration, however, concluded that study # 96 should be incorporated into the review for the reasons described below: (a) All the transfers of drug products were properly documented (from the Sponsor to the Clinical site as well as from the Clinical site to the Sponsor). Dr. Sriram Subramaniam from DSI has provided information to confirm this. (b) All the drug products for three pivotal BE studies (#93, #95, #96) were provided by the same provider, the authenticity of the drug products was assured in study #93. (c) The bioanalytical methods for 3 moieties were validated and reproducible in analytical site. (d) In study #96, both clinical and analytical sites have satisfactorily addressed the other issues cited on the Form 483. There are no other issues in study 96 that raise a concern related to study conduct. The sponsor should be warned that in the future such noncompliance to BE regulation will result in the BE studies being non-acceptable.
- Two other issues cited to the clinical site were resolved satisfactorily: (1) The conduct of nicotine/cotinine test for study subjects could not be verified since the clinic failed to locate the record. This reviewer has briefly searched Pub-med and found no documented evidence that nicotine affects the PK of levodopa, carbidopa or entacapone. Thus, this deficiency is unlikely to affect the outcome of the study. (2) Source data were changed without justification. In 2 subjects, the observed times for the 20minutes blood collection were changed by 10 minutes 1-3 months later without documentation. However, this practice was not prevalent.
- Five other issues cited to the analytical site were resolved satisfactorily: (1)Failure to assure accuracy of standards [redacted] Due to a [redacted] concentrations of study samples were calculated using the calibration curve from a previous run. In response, Site deleted the questionable data from 2 subjects and recalculated the statistics and concluded study outcomes were unaffected. (2) Failure to [redacted] Carbidopa subject concentration in study #96 were overestimated by [redacted] since the concentrations for the carbidopa stock solutions were not corrected for [redacted] Reviewer note: since this applied to both the test & reference products, the ratio of the test to reference product (BE criteria) is unlikely to be affected. However, this may affect the cross-study comparison of the carbidopa plasma levels from 3 different strengths. The carbidopa levels from LCE150 may be 3.8% lower than what were reported. (3) The effect of entacapone on the [redacted] was not validated. In response, Site provided the validation in this regard. (4) Inconsistency in selection of PK outliers. The selection criteria was established prior to the analysis. However, this finding does not affect the study, as the reanalyzed values confirmed the original values. (5) Documentation of study lab notebooks was not complete. The Site intends to revise their SOP to assure documentation in future studies.
- DSI also requested a statistical reanalysis to include group effect (group & group*sequence interaction) in the ANOVA model. The reanalysis did not affect the outcome of study 2939096. (Exhibit 8)

EXHIBIT 8 (8)

Estimates of the ratios of the geometric means from the reported results and from the new analyses including group effect and group*seq interaction effect in the model

Study 2939096

		Reported results			Group effect included		
		Estimate	Lower	Upper	Estimate	Lower	Upper
Levodopa	AUC	0.974	0.940	1.009	0.974	0.940	1.009
	$AUC_{0-\infty}$	0.974	0.941	1.009	0.974	0.941	1.009
	C_{max}	0.940	0.890	0.993	0.939	0.889	0.993
Carbidopa	AUC	0.876	0.824	0.931	0.876	0.824	0.932
	$AUC_{0-\infty}$	0.876	0.824	0.931	0.876	0.825	0.931
	C_{max}	0.877	0.822	0.935	0.877	0.822	0.935
Entacapone	AUC	1.026	0.978	1.076	1.026	0.978	1.076
	$AUC_{0-\infty}$	1.006	0.947	1.069	1.005	0.945	1.068
	C_{max}	1.183	1.034	1.354	1.185	1.035	1.355

6.2.6 Analysis of age & gender effect

Source:

(a) Sponsor's analysis: Age >60years versus <60 (45-60) years & males versus females: The sponsor analyzed the effects of age & gender on the PK parameters of levodopa, carbidopa and entacapone from the three bioequivalence studies (# -93, -95, -96) of the combination products. Single dose of LCE (levodopa/carbidopa/entacapone 100/25/200mg (#93), 50/12.5/200mg (#95), 150/37.5/200mg (#96)). Age >60years versus <60years. [Note: age range studied 45-75 years]

(b) Reviewer's analysis: Age 20-38 years versus 45-72 years old: This reviewer also compared results from study #85(males age ranged 20-38 years old) with study #93 (males & females 45-72 years old) since 2 studies are similar except the age range & gender studied.

Literature references:

(c) 71-86 years old versus 22-34 years old: Evans et al Eur L Clin Pharmacol, 17, 215-221 (1980) Systemic availability of orally administered L-dopa in the elderly Parkinsonian patient [current submission: volume 164, p269]

(d) 73 years (69-76) years versus mean age of 22 years old: Robertson et al Br J Clin Pharmac 1989 28, 61-69 The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa [current submission: volume 166 P345].

(e) Zappia et al (2002), Clin Neuropharmacol 2002, Mar-Apr; 25(2): 79-82. Body weight influences PK of levodopa in Parkinson's disease. [(Pub-med search by this reviewer].

(f) Kompoliti et al Neurology 2001; 56 suppl 3:A376 Gender differences in levodopa PK (volume 165, p065)

(g) Evans et al 1981 Neurology 1981; 31:1288-1294. Gastric emptying rate and the systemic availability of levodopa in the elderly Parkinsonian patient. [current submission]

(h) Rainero I et al 1988 Ital J Neurol Sci 255-259. Peripheral PK parameters of levodopa/carbidopa and the on-off phenomenon in Parkinsonian patients [current submission].

(i) Contin M et al 1991, Effect of age on the PK of oral levodopa in patients with Parkinson's disease. Eur J Clin Pharmacol 41:463-466[current submission].

Overall Summary:

Age-effect:

- Levodopa alone: There is a significant age-related alteration to the disposition of orally administered L-dopa alone in the elderly PD patients. When given without carbidopa and entacapone, the absorption of levodopa is greater (relative bioavailability: 41% versus 63%, $p<0.01$) and the elimination is slower (23.4 versus 14.2 ml/min/kg, $p<0.01$) in elderly subjects (68-75 years) than in younger subjects which results in a 50% increase in AUC following a single IV dose of 50mg or oral dose of 250mg levodopa.
- Robertson et al: Following significant changes in elderly (68-75 years) had been observed: the bioavailability is significantly higher (41% versus 63%, $p<0.01$), clearance is significantly slower (23.4 versus 14.2 ml. min/kg, $p<0.01$), the Cmax is significantly higher (1077 versus 1842 ng/ml, $p<0.05$), the AUC is significantly higher (1056 versus 2512 ng.h/ml).
- Levodopa + carbidopa: In the presence of carbidopa, the absorption of levodopa is similar (83%) between the elderly and the young. The clearance of levodopa (following iv 50mg) is slower (23.4 versus 14.2 ml. min/kg, $p<0.01$)
- Entacapone alone: Entacapone PK is independent of age. No differences were noted in the rate of adverse events attributable to entacapone by age or gender. (entacapone label).

Each reference are discussed below:

(a) **Sponsor's analysis: Age >60 years versus <60 (45- 60) years & males versus females**:

The sponsor analyzed the effects of age & gender on the PK parameters of levodopa, carbidopa and entacapone from the three bioequivalence studies (# -93, -95, -96) of the combination products. Single dose of LCE (levodopa/carbidopa/entacapone 100/25/200mg (#93), 50/12.5/200mg (#95), 150/37.5/200mg (#96)). Age >60years versus <60years.

Method

- In addition, the PK parameters of entacapone were analyzed by combining the data from all the three studies as the dose of entacapone was the same in the studies.
- The subjects were divided into two groups on the basis of age, below and above 60 years, and on the basis of gender. The analyses were performed with and without bodyweight as covariate in the statistical analysis model.
- The BE was tested in subgroup analysis and results showed that the test and reference products were similar within the subgroups

Table 3. Demographic characteristics (mean, range) of healthy volunteers in the bioequivalence studies of the triple combination products.

	LCE 100		LCE 50	LCE 150
Study #	-93	-85	-95	-96
N	44	44	44	44
Gender (m/f)	17/27	44/0	23/21	24/20
Age (yrs)	59 (45 – 72)	24 (20 – 38)	58 (45 – 75)	58 (45 – 74)
N (< 55 yrs)	14	44	17	16
N (55 – 59 yrs)	7	-	10	11
N (60 – 65 yrs)	10	-	10	12
N (> 65 yrs)	13	-	7	5
Weight (kg)	70 (53 – 85)	73 (63 – 85)	73 (50 – 99)	77 (52 – 98)
Height (cm)	169 (156 – 183)	181 (171 – 192)	170 (155 – 188)	172 (155 – 190)

N = number of subjects, m/f = male/female

Table 1 Effects of age on AUC of levodopa, carbidopa and entacapone for the triple combination products

Study # Dose	Population # Subjects Age (mean ± SD) Weight (mean ± SD)	Levodopa AUC mean ± SD (n) (ng-h/mL)	Carbidopa AUC mean ± SD (n) (ng-h/mL)	Entacapone AUC mean ± SD (n) (ng-h/mL)
2939093	< 60 years 12 males, 9 females	2550 ± 579 (40)	628 ± 242 (40)	1380 ± 391 (40)
Levodopa 100 mg Carbidopa 25 mg Entacapone 200 mg	Age 51.7 ± 4.8 Weight 71.1 ± 8.5			
	≥ 60 years 5 males, 18 females	3097 ± 696 (45) *	637 ± 181 (45) *	1493 ± 361 (45) *
	Age 65.8 ± 3.6 Weight 68.7 ± 8.3			
2939095	< 60 years 12 males, 14 females	935 ± 265 (51)	145 ± 54 (51)	1121 ± 525 (51)
Levodopa 50 mg Carbidopa 12.5 mg Entacapone 200 mg	Age 53.4 ± 4.0 Weight 72.7 ± 10.9			
	≥ 60 years 10 males, 7 females	1097 ± 353 (32) *	158 ± 78 (32)	1445 ± 460 (33) *
	Age 65.4 ± 4.7 Weight 73.0 ± 10.9			*
2939096	< 60 years 15 males, 11 females	3591 ± 1054 (50)	492 ± 174 (50)	1210 ± 356 (50)
Levodopa 150 mg Carbidopa 37.5 mg Entacapone 200 mg	Age 53.5 ± 4.9 Weight 77.4 ± 12.6			
	≥ 60 years 9 males, 8 females	3921 ± 1161 (31)	481 ± 193 (31)	1271 ± 402 (31)
	Age 64.6 ± 4.2 Weight 75.3 ± 11.7			
2939093 2939095 2939096	< 60 years 39 males, 34 females	-	-	1226 ± 443 (141)
	Age 52.9 ± 4.6 Weight 73.9 ± 11.1			
Entacapone 200 mg	≥ 60 years 24 males, 33 females			1415 ± 412 (109) *
	Age 65.3 ± 4.1 Weight 71.9 ± 10.4			*

n = number of observations
AUC = area under the concentration-time curve calculated by trapezoidal rule
* p < 0.05 from ANOVA * p < 0.05 from ANOVA, weight as covariate

Table 2 Effects of gender on AUC of levodopa, carbidopa and entacapone for the triple combination products

Study # Dose	Population # Subjects Age (mean ± SD) Weight (mean ± SD)	Levodopa AUC mean ± SD (n) (ng-h/mL)	Carbidopa AUC mean ± SD (n) (ng-h/mL)	Entacapone AUC mean ± SD (n) (ng-h/mL)
2939093	17 males Age 56.3 ± 8.3	2226 ± 333 (33)	582 ± 184 (33)	1290 ± 314 (33)
Levodopa 100 mg Carbidopa 25 mg Entacapone 200 mg	Weight 76.1 ± 6.1			
	27 females Age 60.8 ± 7.9 Weight 65.9 ± 7.3	3229 ± 576 (52) *	665 ± 222 (52) *	1534 ± 386 (52)
2939095	22 males Age 58.6 ± 8.0	842 ± 231 (42)	150 ± 72 (42)	1182 ± 477 (43)
Levodopa 50 mg Carbidopa 12.5 mg Entacapone 200 mg	Weight 80.0 ± 7.7			
	21 females Age 57.6 ± 6.6 Weight 65.3 ± 8.0	1157 ± 301 (41) *	150 ± 55 (41)	1318 ± 564 (41)
2939096	24 males Age 57.5 ± 7.8	3199 ± 856 (46)	484 ± 194 (46)	1222 ± 404 (46)
Levodopa 150 mg Carbidopa 37.5 mg Entacapone 200 mg	Weight 82.1 ± 11.7			
	19 females Age 58.4 ± 6.3 Weight 69.6 ± 8.8	4398 ± 1022 (35) *	492 ± 164 (35)	1248 ± 333 (35)
2939093 2939095 2939096	63 males Age 57.6 ± 7.9 Weight 79.7 ± 9.3	-	-	1227 ± 409 (122)
Entacapone 200 mg	67 females Age 59.1 ± 7.1 Weight 66.7 ± 8.0			1387 ± 453 (128)

n = number of observations
AUC = area under the concentration-time curve calculated by trapezoidal rule
* p < 0.05 from ANOVA * p < 0.05 from ANOVA, weight as covariate

Sponsor's summary of results: Levodopa/carbidopa/entacapone combination:

Age:

Levodopa:

- AUC: The AUC of levodopa was higher (ranged from 9- 21%) in elderly (60-75 years) than in the younger subjects (45-60years) but the magnitude of increase was only statistically significant for the LCE 100. After taking bodyweight into account, the AUC was statistically significantly higher for the LCE 100 and LCE 50 but not for the LCE 150.
- Cmax: The Cmax was comparable between elderly (over 60 years) and young (45-60 years) subjects. (data not shown).

Carbidopa:

- For the pharmacokinetic parameters (Cmax & AUC) of carbidopa there is no statistically significant difference between age subgroups (Cmax data not shown).

Entacapone:

- Cmax: The Cmax was comparable between elderly (over 60 years) and young (45-60 years) subjects (data not shown).
- The AUC of entacapone was higher (ranged from 5- 29%) in elderly than in the younger subjects in one study (#95, statistically significant). In the pooled analysis the AUC of entacapone was statistically significantly higher in elderly but the difference was small and therefore not clinically significant (see separate discussion on the Cmax of entacapone).
- Previously, no PK or PD differences between young and elderly healthy subjects was observed following single dose of 200mg entacapone with or without coadministration of levodopa/carbidopa (100mg/50mg). In a parallel-group single dose design study, after a single 200mg dose of entacapone either with or without 100mg/25 mg levodopa/carbidopa administration in 15 healthy young (20-24 years) and 16 healthy elderly (64-76 years) subjects, the data clearly demonstrate that there were no PK or PD differences between the groups. Dr Al-Habet, the CPB reviewer, indicated that a multiple dose study is more appropriate in elderly, the target patient population, who will be taking this drug for long term therapy (NDA 20-796, Comtan. submission date 01/01/1998, study report 2939045).

Safety: The sponsor also compared the adverse events by subgroups (age & gender) from studies 93, 95 and 96.

Sponsor concluded:

- Age: After taking bodyweight into account, the AUC was statistically significantly higher for the LCE 100 and LCE 50 but not for the LCE 150. Thus, aging may increase the bioavailability of levodopa to a small extent. For the pharmacokinetic parameters of carbidopa there is no statistically significant difference between age subgroups. In the pooled analysis the AUC of entacapone was statistically significantly higher in elderly but the difference was small and therefore not clinically significant.
- Gender: The AUC of levodopa differed significantly in males and females. It was statistically significantly higher in females in all the three studies. However, further analysis of the data, with bodyweight as a covariate, suggests that the higher AUC in females can be primarily explained by differences in bodyweight. For carbidopa and entacapone no difference was observed between males and females.
- Safety (gender & age): There was an overall tendency of females to report more often adverse events on both study treatments than males. However, there was no significant difference in the rates of adverse events by sex between the test and reference drugs. Similarly, there was no significant difference in the rates of adverse events by age between the test and reference treatments. The subgroup analysis by weight from studies 93, 95 and 96 suggested a slight trend for higher rates of some adverse events in subjects weighing below 75 kg compared to those over 75 kg, but none of these differences can be regarded as clearly significant or conclusive. Most important, there were no differences in the adverse events by weight between the test and reference treatments.

- In conclusion, : gender-related differences were primarily due to differences in bodyweight and the dose adjustment on the basis of age or gender does not appear to be necessary.

Reviewer's Comments:

- No study subjects were older than 75 years old.
- The comparison was made between 45-60 years old and 60-75 years old healthy subjects.
- The sponsor did not provide the weight-corrected comparisons. The weight was one of the covariates evaluated in the analytical model.
- The effect of body-weight on PK of levodopa: Zappia et al (2002), an article this reviewer retrieved from the Pub-med, had systematically evaluated the effect of body weight on PK of levodopa in Parkinson's disease. The results indicated that AUC & elimination t1/2 of levodopa are inversely correlated with body weight. When compared to male counterpart, female Parkinson's disease patients were significantly lighter and had a significantly greater AUC and a greater percentage of women showed levodopa peak-dose dyskinesia.

(b) **Reviewer's analysis : Age 20-38 years versus 45-72 years old:**

This reviewer also compared results from study #85 (LCE 100/25/200mg, males, age ranged 20-38 years old) with study #93 (LCE 100/25/200mg, males & females 45-72 years old) since 2 studies are similar except the age range & gender studied.

Summarized below (Table) are the results from cross-study comparisons of LCE 100/25/200mg tablet formulation in healthy male & female volunteers aged ranging 45-72 years versus healthy male volunteers age 20-38 years:

- % diff [45-72 yrs (M+F) vs 20-38 yrs (M)]: The mean % increases in PK parameters (AUC & Cmax) for levodopa are approximately 50-60%. The mean % increases of carbidopa is approximately 60% in AUC & 26% in Cmax. The mean % increases of entacapone is approximately 11% in AUC & 24% in Cmax.

Breakdown in subgroups (20-38 yrs, 45-60yrs, 60-72yrs, males & females)

- % diff [45-60 yrs (M+F) vs 20-38 yrs (M)]: The mean % increases in PK parameters (AUC & Cmax) for levodopa are approximately 40%. The mean % increases of carbidopa is approximately 40% in AUC & 16 % in Cmax. The mean % increases of entacapone is negligible in AUC and is approximately 12% in Cmax.
- % diff [60-72 yrs (M+F) vs 20-38 yrs (M)]: The mean % increases for levodopa are approximately 70% in AUC and 50% in Cmax. The mean % increases of carbidopa is approximately 58% in AUC & 22 % in Cmax. The mean % increases of entacapone is negligible in Cmax and is approximately 14% in AUC.
- % diff [60-72 yrs (M+F) vs 45-60 yrs (M+F)]: The mean % increases for levodopa are approximately 21% in AUC and 8% in Cmax. The mean % increases of carbidopa is approximately 10% in AUC & negligible in Cmax. The mean % increases of entacapone is approximately 12% in AUC, and mean decreases in Cmax is 10%.
- % diff (F versus M, 45-72 yrs): The mean % increases for levodopa are approximately 54% in AUC and 35% in Cmax. The mean % increases of carbidopa is approximately 25% in AUC & 17 % in Cmax. The mean % increases of entacapone is negligible in Cmax and is approximately 26% in AUC.

Reviewer's Conclusion:

- In summary, age affects the PK parameters (AUC & Cmax) of levodopa & carbidopa. Age has negligible effect on PK parameters (AUC & Cmax)of entacapone.
- In a cross-study comparisons following the administration of single dose LCE 100 in healthy volunteers, the mean plasma exposure (AUC & Cmax) of levodopa in 45-72 years old male & female subjects is approximately 50-60% higher than those from young male subjects (20-38 years old).

Similar value was observed in AUC of carbidopa while the magnitude of increase was smaller in Cmax (26%).

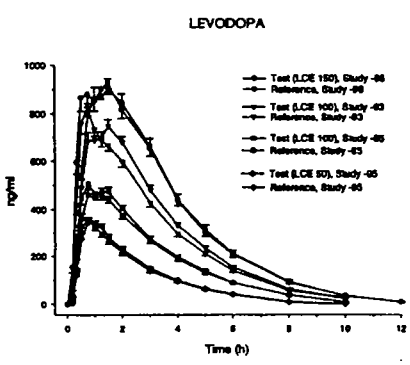
- The gender effect on the PK difference may have contributed to the observed difference between 2 age groups as the difference is minimized when only PK parameters from males were compared. Significant gender differences in PK parameters was observed in subgroup analysis (study #93 or see sponsor's age & gender analyses above).
- In age subgroup analysis (20-38 years, 45-60 year, and 60-72 years), there is clearly a trend in age-effect on PK of levodopa & carbidopa as the age advances the magnitude of % difference increases. (40% increase in <60years old versus 70% increase in >60years old in AUC of levodopa; 35% increase in <60years old versus 50% increase in >60years old in AUC of carbidopa). (see table below for details; Figures below for concentration-time profiles for studies #93 & #85; tables below for summary of PK for studies #93 &#85).

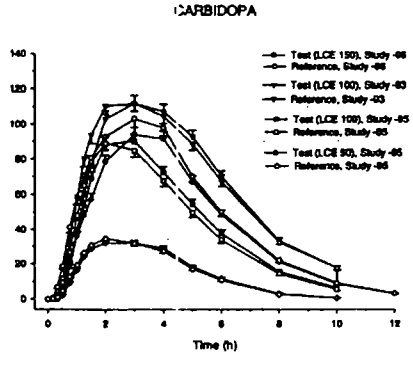
Additional comments:

- There is no information on younger female volunteers.
- No subject was older than 72 years old in study #93, while there were few subjects in study #95 (LCE 50) & #96 (LCE 150) were 72-74 years.

		20-38yrs (M)	45-72 yrs, (M)	45-72 yrs (F)	45-72 yrs (M+F)	45-60 yrs) (M+F)	60-72 yrs) (M+F)	% diff [45-72 yrs (M) vs 20-38yr, (M)]	% diff F vs M (45-72)	% diff [45-72 yrs (M+F) vs 20-38 yrs (M)]]	% diff [(45-60yrs (M+F)) vs 20-38yrs (M)]	% diff [(60-72 yrs (M+F) vs 20-38 yrs (M)]	% diff [60-72yrs (M+F) vs 45-60yrs (M)]
	Study	#85, T(R)	#93, T(R))	#93 T (R)	#93, T(R)	#93, T(R)	#93, T(R)						
Levodopa	AUC (ng.h/ml)	1819 (1810)	2170 (2109)	3333 (3182)	2906 (2808)	2556 (2479)	3090 (2947)	+20 (+16)	+54 (+51)	+60 (+55)	+41 (+37)	+70 (+63)	+21 (+18)
	Cmax (ng/ml)	653 (704)	791 (794)	1055 (1137)	975 (1036)	906 (946)	979 (1025)	+21	+33 (+43%)	+49 (+47)	+38 (+34)	+50 (+46)	+8
Carbidopa	AUC (ng.h/ml)	451 (438)	559 (580)	700 (708)	690 (698)	610 (619)	671 (689.9)	+24	+25 (+22)	+53 (+60)	+35 (+41)	+49 (+58)	+10
	Cmax (ng/ml)	99 (98)	105 (105)	123 (128)	125 (126)	114 (115)	118 (121)	+6	+17	+26 (+28)	+15 (+17)	+20 (+23)	+5
Entacapone	AUC (ng.h/ml)	1305 (1262)	1206 (1276)	1521 (1415)	1450 (1376)	1326 (1330)	1484 (1398)	0	+26 (+10)	+11	0 (+5)	+14 (+10)	+12 (+5)
	Cmax (ng/ml)	1016 (1020)	1080 (1014)	1112 (960)	1259 (1070)	1141 (1037)	1064 (932)	6	0	+24 (+5)	+12 (0)	+5 (-8)	-6(-10)

Entacapone





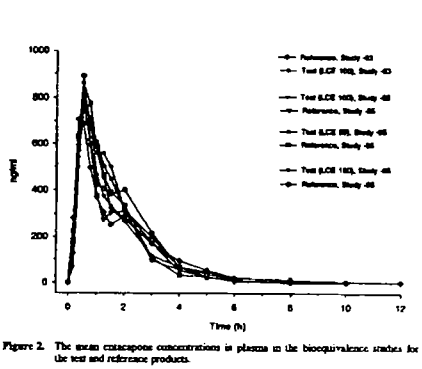


Figure 2. The mean entacapone concentrations in plasma in the bioequivalence studies for the test and reference products.

Table 4. $AUC_{0-\infty}$ and C_{max} for levodopa, carbidopa and entacapone in the bioequivalence studies of the triple combination products.

		Test (mean±SD)	CV	Reference (mean±SD)	CV	Geom. mean ratio	Log 90% CI
LCE 100, Study # -93							
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	2906 ± 715	10.2	2808 ± 725	10.1	1.04	1.01 – 1.07
	Carbidopa	690 ± 227	25.7	698 ± 236	25.0	0.98	0.92 – 1.05
	Entacapone	1450 ± 399	15.9	1376 ± 344	13.2	1.03	0.98 – 1.08
C_{max} (ng/ml)	Levodopa	975 ± 247	18.5	1036 ± 308	16.6	0.96	0.91 – 1.00
	Carbidopa	125 ± 42	25.2	126 ± 42	20.6	0.98	0.92 – 1.04
	Entacapone	1259 ± 712	55.7	1070 ± 460	37.9	1.12	1.00 – 1.26
LCE 100, Study # -85							
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	1819 ± 366	14.2	1810 ± 352	13.5	1.01	0.97 – 1.04
	Carbidopa	451 ± 174	32.3	438 ± 172	27.7	1.02	0.95 – 1.11
	Entacapone	1305 ± 403	17.8	1262 ± 359	20.5	1.02	0.96 – 1.08
C_{max} (ng/ml)	Levodopa	653 ± 165	21.4	704 ± 189	20.5	0.93	0.88 – 0.98
	Carbidopa	99 ± 39	33.0	98 ± 37	27.7	1.00	0.93 – 1.08
	Entacapone	1016 ± 503	52.4	1020 ± 511	47.5	0.99	0.88 – 1.11
LCE 50, Study # -95							
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	1044 ± 314	15.6	1017 ± 288	17.9	1.03	0.99 – 1.07
	Carbidopa	169 ± 69	23.0	168 ± 59	17.1	0.99	0.93 – 1.05
	Entacapone	1279 ±491	13.7	1276 ± 392	9.5	1.01	0.96 – 1.06
C_{max} (ng/ml)	Levodopa	473 ± 154	25.3	489 ± 153	24.8	0.96	0.90 – 1.03
	Carbidopa	39 ± 16	28.0	39 ± 14	25.8	0.98	0.91 – 1.06
	Entacapone	1199 ± 884	46.1	1152 ± 558	43.5	0.94	0.84 – 1.06
LCE 150, Study # -96							
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	3774 ± 1118	13.2	3880 ± 1128	14.0	0.97	0.94 – 1.01
	Carbidopa	499 ± 183	27.3	566 ± 196	18.5	0.88	0.82 – 0.93
	Entacapone	1281 ±412	20.5	1270 ± 462	15.5	1.01	0.95 – 1.07
C_{max} (ng/ml)	Levodopa	1272 ± 329	18.7	1384 ± 445	22.8	0.94	0.89 – 0.99
	Carbidopa	107 ± 42	28.9	121 ± 45	20.0	0.88	0.82 – 0.94
	Entacapone	1211 ± 738	57.8	1052 ± 792	52.2	1.18	1.03 – 1.35

Test = test product, LCE 100, LCE 50 or LCE 150
Reference = reference products, Sinemet® 25/100 mg in the respecting dose with test product + Comtan® 200 mg
Study # -93: number of subjects is 44 except for $AUC_{0-\infty}$ of entacapone 36
Study # -85: number of subjects is 43 except for $AUC_{0-\infty}$ of entacapone 39
Study # -95: number of subjects is 43 except for $AUC_{0-\infty}$ of carbidopa 41 and entacapone 33
Study # -96: number of subjects is 43 except for $AUC_{0-\infty}$ of entacapone 35

Table 1 Effects of age on AUC of levodopa, carbidopa and entacapone for the triple combination products

Study # Dose	Population # Subjects Age (mean ± SD) Weight (mean ± SD)	Levodopa AUC mean ± SD (n) (ng·h/mL)	Carbidopa AUC mean ± SD (n) (ng·h/mL)	Entacapone AUC mean ± SD (n) (ng·h/mL)
2939093 Levodopa 100 mg Carbidopa 25 mg Entacapone 200 mg	< 60 years 12 males, 9 females Age 51.7 ± 4.8 Weight 71.1 ± 8.5	2550 ± 579 (40)	628 ± 242 (40)	1380 ± 391 (40)
	≥ 60 years 5 males, 18 females Age 65.8 ± 3.6 Weight 68.7 ± 8.3	3097 ± 696 (45) *	637 ± 181 (45)	1493 ± 361 (45)
2939095 Levodopa 50 mg Carbidopa 12.5 mg Entacapone 200 mg	< 60 years 12 males, 14 females Age 53.4 ± 4.0 Weight 72.7 ± 10.9	935 ± 265 (51)	145 ± 54 (51)	1121 ± 525 (51)
	≥ 60 years 10 males, 7 females Age 65.4 ± 4.7 Weight 73.0 ± 10.9	1097 ± 353 (32) *	158 ± 78 (32)	1445 ± 460 (33) *
2939096 Levodopa 150 mg Carbidopa 37.5 mg Entacapone 200 mg	< 60 years 15 males, 11 females Age 53.5 ± 4.9 Weight 77.4 ± 12.6	3591 ± 1054 (50)	492 ± 174 (50)	1210 ± 356 (50)
	≥ 60 years 9 males, 8 females Age 64.6 ± 4.2 Weight 75.3 ± 11.7	3921 ± 1161 (31)	481 ± 193 (31)	1271 ± 402 (31)
2939093 2939095 2939096 Entacapone 200 mg	< 60 years 39 males, 34 females Age 52.9 ± 4.6 Weight 73.9 ± 11.1	-	-	1226 ± 443 (141)
	≥ 60 years 24 males, 33 females Age 65.3 ± 4.1 Weight 71.9 ± 10.4			1415 ± 412 (109) *

n = number of observations
AUC = area under the concentration-time curve calculated by trapezoidal rule
* $p < 0.05$ from ANOVA ° $p < 0.05$ from ANOVA, weight as covariate

(c) **71-86 years old versus 22-34 years old: Evans et al Eur L Clin Pharmacol, 17, 215-221 (1980) Systemic availability of orally administered L-dopa in the elderly Parkinsonian patient [current submission: volume 164, p269]**

- Dose studied: levodopa alone, single oral dose 300mg, fasted state, food was withheld for 3 hours post dose
- 5 PD patients age range 71-86 years old, 3F/2M versus 7 healthy subjects, age range 22-34 years
- In a panel of 5 very elderly PD patients (71, 74, 77, 78, 86), there was a significantly ($p<0.02$) larger AUC in the elderly PD patients (mean 234.69 ug min/ml; SD=84.70) compared to the young healthy volunteers (mean 82.33ug min/ml; SD=31.00). A significant ($p<0.02$) correlation existed between the AUC and age ($r=0.7970$, $n=11$) among the subjects studied. Other PK parameters such as t1/2, Cmax, were comparable between 2 groups. Mean tmax was 84 min in elderly PD patients and 35 mins in young subjects, however, the difference was not significant.
- Bioassay: [redacted]. LOQ: [redacted] Linear over the range of [redacted]

Comment:

- An approximate 3-fold increase in the mean AUC was observed in the elderly PD patients as compared to the young, healthy subjects.
- Considerable intersubject variability: ~40%

- Sample number is small: healthy subjects (n=7) & PD patients (n=5).
- Age groups studied are at the extremes of age scale: 22-34 years versus 71-86 years.
- Comparison was made between patients and healthy subjects.
- Concomitant medications: digoxin (n=3), diuretics n=3), KCl (n=2), benzhexol (n=1) and nicotinic acid (n=1).

(d) 73 (69-76) years versus mean age of 22 years old: Robertson et al Br J Clin Pharmac 1989 28, 61-69 The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa [current submission: volume 166 P345]

Dose

- levodopa alone, single oral dose of 250mg or iv dose of 50mg , 2F+7M healthy elderly subjects with mean age 71yrs (68-75) versus 8 young healthy subjects (mean age 22years)
- levodopa (125mg, po) or (50mg iv) +carbidopa [(100mg(1h before) & 50mg (6 hours after) the levodopa dose], 4F+4M healthy subjects with mean age 73years (69-76) versus 8 young healthy subjects (mean age 22 years).

Results:

Table 2 Pharmacokinetic parameters following oral and intravenous administration of levodopa alone

Study A (levodopa alone)	*Young*	*Elderly*	P
Intravenous (50 mg)			
AUC (ng ml^{-1} h)	541 ± 140	806 ± 94	< 0.01
CL (ml min^{-1} kg^{-1})	23.4 ± 4.1	14.2 ± 2.8	< 0.01
V_{ss} (l kg^{-1})	1.65 ± 0.39	1.01 ± 0.29	< 0.002
V_{ss} (l kg^{-1} lbm)	1.89 ± 0.47	1.29 ± 0.34	< 0.05
$t_{1/2}$ (h)	1.3 ± 0.3	1.3 ± 0.2	NS
MRT (h)	1.2 ± 0.3	1.2 ± 0.2	NS
Oral (250 mg)			
C_{max} (ng ml^{-1})	1077 ± 577	1842 ± 901	< 0.05
t_{max} (h)	0.8 ± 0.6	0.9 ± 0.8	NS
AUC (ng ml^{-1} h)	1056 ± 282	2512 ± 588	< 0.002
$t_{1/2}$ (h)	1.5 ± 0.4	1.4 ± 0.3	NS
MRT (h)	1.8 ± 0.4	2.3 ± 0.7	NS
MAT (h)	0.6 ± 0.5	0.9 ± 0.7	NS
Bioavailability (*F*)	0.41 ± 0.16	0.63 ± 0.12	< 0.01

For abbreviations in this and subsequent tables, see under Methods.

Table 3 Pharmacokinetic parameters following oral and intravenous administration of levodopa combined with carbidopa

Study B (levodopa + carbidopa	*Young*	*Elderly*	P
Intravenous (50 mg)			
AUC (ng ml^{-1} h)	1377 ± 219	2121 ± 230	< 0.01
CL (ml min^{-1} kg^{-1})	9.3 ± 1.0	5.8 ± 0.9	< 0.01
V_{ss} (l kg^{-1})	0.93 ± 0.19	0.62 ± 0.15	< 0.05
V_{ss} (l kg^{-1} lbm)	1.2 ± 0.3	0.9 ± 0.2	NS
$t_{1/2}$ (h)	1.5 ± 0.2	2.0 ± 0.5	NS
MRT (h)	1.7 ± 0.3	2.0 ± 0.4	NS
Oral (125 mg)			
C_{max} (ng ml^{-1})	1712 ± 769	1922 ± 563	NS
t_{max} (h)	1.4 ± 0.7	1.4 ± 0.7	NS
AUC (ng ml^{-1} h)	2926 ± 542	4530 ± 1034	< 0.01
$t_{1/2}$ (h)	1.6 ± 0.3	2.1 ± 0.4	NS
MRT (h)	3.1 ± 1.1	3.0 ± 0.4	NS
MAT (h)	1.4 ± 1.1	1.1 ± 0.6	NS
Bioavailability (*F*)	0.86 ± 0.19	0.85 ± 0.14	NS

Summary of results:

- The plasma clearance of levodopa following intravenous administration of 50 mg was 14.2 ±2.8 (s.d.) ml /min/kg in the elderly compared with 23.4 ±4.1 ml/min/kg in the young ($P < 0.01$) which resulted in a 49% greater area under the plasma concentration-time curve (AUC) in the older subjects ($P < 0.01$). The volume of distribution (Vss) was lower in the elderly (1.01 ±0.29 L/kg) than in the young (1.65 ±0.39 l/kg) ($P < 0.002$).
- Following oral administration of 250 mg of levodopa the AUC was 2512 ± 588 ng h/ml in the elderly compared with 1056 ±282 ng h/ml in the young ($P < 0.002$). Cmax was also significantly greater in the elderly ($P < 0.05$). The bioavailability of levodopa was significantly greater in the elderly (0.63 ±0.12 compared with 0.41 ±0.16. $p < 0.01$).
- In the presence of carbidopa, the plasma clearance of intravenous levodopa (50 mg) was reduced in both age groups but remained lower in the elderly (5.8± 0.9 ml/min/kg compared with 9.3± 1.0 ml/min/kg; $p < 0.01$). This resulted in a 54% greater AUC in the older subjects ($P < 0.01$). The Vss was also reduced in both age groups and the age related difference remained (0.62 ±0.15 L/kg in the elderly compared with 0.93 ±0.19 L/kg in the young; $p < 0.05$).
- Following oral administration of 125 mg of levodopa in the presence of carbidopa, the AUC was significantly greater in the elderly (4530 ±1034 ng h/ml compared with 2926 ±542 ng h/ml, $p < 0.01$). This was due solely to the lower systemic clearance in the elderly because carbidopa abolished

the age difference in the bioavailability of levodopa (0.85 ±0.14 in the elderly compared with 0.86 ±0.19 in the young).

- The results indicate that decarboxylation is the age dependent component of the first pass metabolism of levodopa.
- The lower plasma clearance and Vss in elderly subjects given carbidopa suggest that other aspects of the disposition are affected by age.

Reviewer's Comments:

- Bioassay: [redacted] LOQ: [redacted] Linear over the range. Coefficient of variation was [redacted] at [redacted] & [redacted] and [redacted] at [redacted]
- An approximate 1.5-fold increase in the mean AUC was observed in the elderly healthy subjects as compared to the young, healthy subjects.
- Considerable intersubject variability: ~50%
- Sample number is small: young (n=8) versus elderly (n=8) healthy subjects
- Ratio of levodopa to carbidopa was different than the marketed Levodopa/carbidopa products (4:1 or 10:1 versus 1:1 at 2 different time points 1 hour before and 6 hours after the levodopa dose).

(e) Zappia et al (2002), Clin Neuropharmacol 2002, Mar-Apr; 25(2): 79-82. Body weight influences PK of levodopa in Parkinson's disease. [(Pub-med search by this reviewer].

- 160 sporadic Parkinson's disease; oral acute levodopa 250mg

Upon adjustment for body weight:

- Plasma levodopa AUC and body weight were significantly and inversely correlated as well as the elimination of the t1/2 of levodopa and body weight.
- When compared with male counterpart, female Parkinson's patients were usually significantly lighter and reported to have a significantly greater AUC, and a greater percentage of women showed levodopa peak-dose dyskinesia observed during the course of the disease.

(f) Kompoliti et al Neurology 2001; 56 suppl 3:A376 Gender differences in levodopa PK [volume 165, p065]

- Post-menopausal women and 12 men with PD, on stable maintenance dose of levodopa, received a single dose of 100/25mg levodopa/carbidopa.
- Bioavailability of levodopa is significantly higher in women than men. After correction for body weight, compared to men, mean AUC in women is 82% higher (23.27±7.29 ng/ml versus 42.33 ±6.98 ng/ml, p<0.0001) and mean Cmax is 58% higher(880±33% versus 1388±42%, p=0.0019) than men.

(g) Evans et al 1981 Neurology 1981; 31:1288-1294. Gastric emptying rate and the systemic availability of levodopa in the elderly Parkinsonian patient.

(f) 6 women with PD (age 72-83 years, with 39-76 kg), the majority of the whom were receiving therapy with Sinemet. Drug therapy was discontinued at least 12 hours before the study. Five age-matched non-PD subjects (4 F +1M, age 73-86 years, weight 44-76kg) who had not previously been challenged with either levodopa or carbidopa, six young volunteers (2F+4M, age 22-31 years, weight 53-70kg). 500mg levodopa as solution in orange juice was given, food was withheld for at least 3 hours.

(g) The bioavailability is enhanced in both elderly groups.

(h) A 250 % increases in plasma levodopa AUC & Cmax were reported in 6 woman Parkinson's disease patients (72-83 years old) when compared to young healthy volunteers (22-31 years old, male and females).

(i) There is no difference in levodopa PK (tmax, AUC, t1/2, gastric emptying time) between healthy aged subjects and PD patients except for Cmax [1.90+0.39 (1.53-2.51) ng/ml versus 3.14+1.30 (2.20-5.33) ng/ml, p<0.025].

(j) The PK in non-PD elderly subjects are significantly different than young healthy subjects: The magnitude of changes are as follows: +116% in Cmax, +193% in AUC.

Table. Gastric emptying rate and pharmacokinetic parameters* pertaining to the elderly parkinsonian patients (n = 8), elderly nonParkinsonian patients (n = 5), and young healthy volunteers (n = 6) administered a single oral 500-mg dose of levodopa as a solution. Mean values (± SD) of the parameter together with the range are given for each subject group.

Group	Elderly parkinsonian patients		Young healthy volunteers		Elderly nonparkinsonian patients
T_{lag}† (min)	109.0 66.9-454.3	$p < 0.025$‡	49.4 32.1-132.3	$p < 0.005$	146.2 99.6-195.6
t_{max} (min)	41.0 ± 34.4 20-93	$p > 0.1$	35.5 ± 41.6 11-120	$p > 0.1$	58.2 ± 86.0 10-210
C_{max} (μg/ml)	3.14 ± 1.30 2.20-5.33	$p < 0.005$	0.58 ± 0.29 0.49-1.30	$p < 0.005$	1.50 ± 0.39 1.53-2.51
$T_{1/2}$ † (min)	82.4 66.5-113.7	$p > 0.1$	87.3 43.4-146.3	$p > 0.1$	77.9 56.0-154.4
C_{min} (μg/ml)	0.20 ± 0.12 0.11-0.43	$p < 0.005$	0.05 ± 0.04 0.02-0.12	$p < 0.005$	0.25 ± 0.22 0.12-0.62
AUC‖ (μg/min/ml)	398.74 ± 131.24 328.57-685.27	$p < 0.005$	116.42 ± 49.21 61.24-185.18	$p < 0.005$	341.92 ± 123.43 216.22-519.11
			$p > 0.1$		

*For abbreviated parameter definitions see text.
†Harmonic mean.[19]
‡Statistical analysis was carried out using Mann-Whitney U test.

(h) **Rainero I et al 1988 Ital J Neurol Sci 255-259. Peripheral PK parameters of levodopa/carbidopa and the on-off phenomenon in Parkinsonian patients.**

- There is a statistically significant (r=0.42, p<0.05) correlation between the AUC and age in all subjects examined (controls and parkinsonians)
- The PK parameters (AUC, Cmax, tmax) of the levodopa/carbidopa (250/25mg) are similar in 11 healthy volunteers (5F+6M mean age 58.3 (range 42-68 years old)) and 16 PD patients, with and without the on-off phenomenon. PD patients: 9M +7F, mean age 63.1 (range 49-77 years old). The duration of symptoms ranged from 1 month to 20 years.

TABLE 1. *Pharmacokinetic parameters of absorption of levodopa/carbidopa in normals and in parkinsonian patients*

	N	Age (yrs)	$AUC_{(0-\infty)}$ (H × μ/mg/ml)	C_{max} (μg/ml)	T_{max} (min)
Controls	11	58.3 ±9.8	3.06 ±0.4	1.07 ±0.4	166 ±52.6
Parkinsonians	16	63.1 ±10.1	3.38 ±1.1	1.35 ±0.4	135 ±60.9

(i) **Contin M et al 1991, Effect of age on the PK of oral levodopa in patients with Parkinson's disease. Eur J CLin Pharmacol 41:463-466**

- PK of levodopa/benserazide (100/25mg) was investigated in 40 PD patients(34-78 years) who were on chronic therapy: Patients were fasted overnight, last dose of levodopa was given 12 hours prior to the study dose, low protein breakfast was allowed 2 hours after the dose. Concurrent medications include bromocriptine, amantadine, quinidine, L-thyroxine, nicardipine, nifedipine and digoxin. Concurrent medications were withheld on the study day.
- The age of patients was positively correlated with the AUC of levodopa (r=0.39) and plasma elimination t1/2 (r=-0.489). When compared to younger group (34-65 years), the AUC of levodopa was significantly greater in older group (65-78 years) (428±102 versus 547±100

umol. min/L after correction for levodopa test dose), coupled with reduced apparent clearance (8.1 versus 10.7 ml/min/kg) and longer elimination t1/2 (54.6 versus 67.6 min).

6.2.7 Summary of sponsor's justifications for the 2 values of 90% CI that fell outside of goal post and its clinical relevancy from a safety viewpoint at the highest recommended daily dose

Note: The sponsor developed a fixed dose combination tablet containing three previously marketed active agents, levodopa/carbidopa and entacapone in three different strengths for the treatment of Parkinson's disease. Each strength consists of a 4 to 1 ratio of levodopa to carbidopa and a fixed dose of 200mg entacapone. The sponsor conducted three separate pivotal BE studies with each different strength of to-be-marketed combination tablet against marketed Sinemet (levodopa/carbidopa, 100/25mg tablet) and Comtess(entacapone 200mg). In addition, the sponsor submitted a BE study comparing reference tablet Sinemet US versus Finland product since both tablets were used in the pivotal BE studies. Entacapone is marketed as Comtan or Comtess in the US or Finland, respectively.

Overall summary of BE results: Two 90% CI values for entacapone were 1.00-1.26 for the Cmax of 100/25/200 and 1.03-1.35 for the Cmax of 150/37.5/200mg tablets.

Table 1 : OCPB's summary of geometric mean ratio of Cmax & AUC from 5 BE studies of TC® (Levodopa/ carbidopa/entacapone) : [results presented as mean (range), bold indicates outside of the recommended range] (excerpted from OCPB review of the pre-NDA meeting package)

	Study # (strength) (study design)	#0097008 (100/25mg) (US VS Finnish Sinemet) (non-replicate 18-45 yrs n=40, males & females)	#29390 85 (100/25/200mg) (replicate 18-38 yrs, n=44, males)	#2939095 (Pivotal) (50/12.5/200mg) (replicate, 45-75yrs, n=44, males & females)	#2939093 (pivotal) (100/25/200mg) (replicate, 45-72yrs n=44, males & females)	#2939096 (pivotal) (150/37.5/200 mg) (replicate,45-74 yrs n=44, males & females)
Cmax	levodopa	1.02 (0.94-1.11)	0.93(0.88-0.98)	0.96 (0.90-1.03)	0.96 (0.91-1.00)	0.94(0.89-0.99)
	carbidopa	0.98 (0.88-1.11)	1.00 (0.93-1.08)	0.98 (0.91-1.06)	0.98 (0.92-1.04)	0.88 (0.82-0.94)
	entacapone		0.99 (0.88-1.11)	0.94 (0.84-1.06)	1.12 **(1.00-1.26)**	1.18 **(1.03-1.35)**
AUC0-inf	levodopa	0.99 (0.95-1.03)	1.01 (0.97-1.04)	1.03 (0.99-1.07)	1.04 (1.01-1.07)	0.97 (0.94-1.01)
	carbidopa	0.99 (0.89-1.11)	1.02 (0.95-1.11)	0.99 (0.93-1.05)	0.98 (0.92-1.05)	0.88 (0.82-0.93)
	entacapone		1.02 (0.96-1.08)	1.01 (0.96-1.06)	1.02 (0.98-1.07)	1.01 (0.95-1.07)

Sponsor proposed:

- The sponsor proposed that extended limits (CI 90% of 70-143%) should be considered for the highly variable compounds and the variation of entacapone Cmax does not result in any safety or tolerability concerns and provided some citation of published references. Since these extended limits were not justified, in the pre-NDA meeting, the sponsor was requested to address following 2 issues in the NDA submission: (1) the variability seen in the studies, and (2) the clinical relevance from a safety point of view at the highest recommended daily dose regarding the two values that fell outside of the recommended BE goal post. Note: The recommended dose of Comtan (entacapone) is one 200 mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily (200 mg × 8 = 1600 mg per day). Clinical experience with daily doses above 1600 mg is limited.

Summarized below are the justifications (justifications from this reviewer will be indicated)

- Study #93 (LCE 100 is BE in younger (study #85) and the value of 100-126 (in study #93) only marginally exceeds the goal post.
- Intra-individual variability The coefficient of variation for the Cmax of entacapone both for test & reference products in all studies was more than 30% (Test: 47.5-57.8%; reference: 37.9-52.2%) (table below).

Table 3. Intrasubject variability (CV, %) for $AUC_{0-\infty}$ and C_{max} of levodopa, carbidopa and entacapone in the bioequivalence studies.

	LCE 100				LCE 50		LCE 150	
Study #	-93		-85		-95		-96	
	$AUC_{0-\infty}$							
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Levodopa	10.2	10.1	14.2	13.5	15.6	17.9	13.1	14.1
Carbidopa	25.7	25.0	32.3	27.7	23.0	17.1	27.5	18.7
Entacapone	15.9	13.2	17.8	20.5	13.7	9.5	19.5	17.4
	C_{max}							
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Levodopa	18.5	16.6	21.4	20.5	25.3	24.8	18.7	22.8
Carbidopa	25.2	20.6	33.0	27.7	28.0	25.8	28.9	20.0
Entacapone	55.7	37.9	52.4	47.5	46.1	43.5	57.8	52.2

Test = test product, LCE 100, LCE 50 or LCE 150
Reference = reference products, Sinemet® 25/100 mg in the respecting dose with test product + Comtan® 200 mg

- In study on LCE 150, low entacapone peak concentrations were observed for the reference product during the 2nd period (Fig below). The sponsor indicated that there was no obvious reason for this but it appeared by chance during this particular period for the reference product.

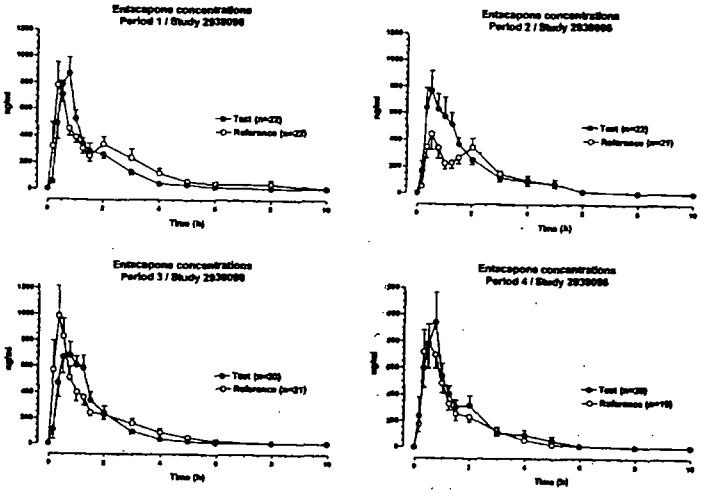


Figure 3. The entacapone concentrations (mean±SEM) for each period after the test (LCE 150) and reference (Sinemet® + Comtan®) products.

- The mean Cmax values for entacapone were not higher for the LCE 150 tablet than for the LCE 50 & LCE100 tablets (Table below). The ratio of the test and reference products was 1.18 for LCE150 and 0.99 & 1.12 for LCE100, and 0.94 for LCE50. The highest determined entacapone concentrations were [redacted] ng/ml for LCE 50 of the test product and [redacted] ng/ml for LCE 150 of the reference product .

Table 4. Entacapone C_{max} (mean ±SD, range) in the bioequivalence studies.

	LCE 100				LCE 50		LCE 150	
Study #	-93		-85		-95		-96	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Mean ±SD	1259±712	1070±460	1016±503	1020±511	1199±884	1152±558	1211±738	1052±792
Range	[redacted]							

Test = test product, LCE 100, LCE 50 or LCE 150
Reference = reference products, Sinemet® 25/100 mg in the respecting dose with test product + Comtan® 200 mg

- The elimination half-life of levodopa, active moiety of antiparkinsonian activity, was similar between the test and the reference products(table below).

Table 6. $T_{1/2}$ values (hours; mean, range) for levodopa, carbidopa and entacapone in four bioequivalence studies

Study #	Substance	Dose (mg)	Test product	Test	Reference
-85	Levodopa	100	LCE 100	1.7 (1.2-2.2)	1.7 (1.3-2.2)
-93	Levodopa	100	LCE 100	1.7 (1.3-2.1)	1.7 (1.3-2.0)
-95	Levodopa	50	LCE 50	1.7 (1.3-3.1)	1.7 (1.1-2.3)
-96	Levodopa	150	LCE 150	1.7 (1.2-2.5)	1.7 (1.3-2.2)
-85	Carbidopa	25	LCE 100	1.7 (1.3-2.7)	1.7 (1.2-3.4)
-93	Carbidopa	25	LCE 100	2.0 (1.4-4.0)	2.1 (1.5-4.9)
-95	Carbidopa	12.5	LCE 50	1.6 (0.7-3.0)	1.6 (0.9-2.8)
-96	Carbidopa	37.5	LCE 150	1.7 (1.0-3.2)	1.7 (1.1-2.5)
-85	Entacapone	200	LCE 100	0.7 (0.3-2.2)	0.7 (0.3-2.5)
-93	Entacapone	200	LCE 100	0.8 (0.3-3.8)	0.8 (0.4-3.8)
-95	Entacapone	200	LCE 50	0.8 (0.3-3.1)	0.7 (0.3-2.4)
-96	Entacapone	200	LCE 150	1.0 (0.4-4.5)	1.0 (0.4-5.9)

Reference: Study Report # -85, -93, -95, -96

- Overall, the mean tmax of levodopa was reached slightly later with the combination product than the reference product. There were some differences in the tmax values of carbidopa and entacapone. However, for LCE 150 the values of tmax for levodopa, carbidopa and entacapone are considered not different between the test and reference products (Table below).

Table 5. The t_{max} for levodopa, carbidopa and entacapone in the bioequivalence studies of the triple combination products

Substance	Test (median, range)	Reference (median, range)	Median difference	Log 95% CI
LCE 100, Study # -93				
Levodopa	1.3 (0.5 – 3.0)	0.8 (0.3 – 3.0)	0.324	0.19 – 0.50
Carbidopa	3.0 (1.5 – 5.0)	3.0 (1.3 – 5.0)	0.50	0.25 – 0.75
Entacapone	0.8 (0.2 – 4.0)	0.5 (0.2 – 3.0)	0.168	0 – 0.40
LCE 100, Study # -85				
Levodopa	1.3 (0.3 – 5.0)	1.0 (0.3 – 3.0)	0.188	0.063 – 0.31
Carbidopa	3.0 (1.3 – 5.0)	2.0 (1.3 – 5.0)	0.375	0.13 – 0.50
Entacapone	0.5 (0.3 – 5.0)	0.5 (0.2 – 4.0)	0.043	-0.25 – 0.29
LCE 50, Study # -95				
Levodopa	1.0 (0.5 – 3.0)	0.8 (0.2 – 3.0)	0.125	0.043 – 0.31
Carbidopa	2.0 (1.3 – 4.0)	2.0 (1.0 – 5.0)	0.25	0 – 0.50
Entacapone	1.0 (0.2 – 5.0)	0.8 (0.2 – 4.0)	0.25	0.11 – 0.42
LCE 150, Study # -96				
Levodopa	1.3 (0.3 – 5.0)	1.0 (0.3 – 4.0)	0.188	-0.13 – 0.48
Carbidopa	3.0 (1.3 – 6.0)	3.0 (0.8 – 6.0)	0.438	0 – 0.75
Entacapone	0.8 (0.2 – 5.0)	0.5 (0.2 – 8.0)	-0.02	-0.56 – 0.29

Test = test product, LCE 100, LCE 50 or LCE 150
Reference = reference products, Sinemet® 25/100 mg in the respecting dose with test product + Comtan® 200 mg
Study # -93: number of subjects is 44
Studies # -85, -95 and -96: number of subjects is 43

- The sponsor indicated that the LCE tablets were well tolerated. Specifically,

(a) Altogether, only a few subjects discontinued in these studies. In three cases the discontinuation occurred as the result of an adverse event (fatigue, upper respiratory tract infection, bone disorder).

(b) No serious adverse events were reported in these bioequivalence studies. The most commonly reported adverse events were nausea, headache, upper respiratory tract infections and fatigue. The most typical adverse events assessed to have a positive causal relationship to the study treatment (ADR) were nausea, headache, and dizziness for some subjects in the study of the combination product LCE 100, headache in the study of LCE50 and for LCE 150, nausea, headache and vomiting.

(c) There were no significant differences in the AE profiles between the test and the reference products of any strength except that nausea was observed more frequently with the LCE 150 tablet than with the reference treatment. The sponsor suggested that as there were no differences in the levodopa concentrations between the test and reference products in the study of LCE 150 this difference in entacapone was probably observed by chance. Specifically, in Study 96, nausea, a typical

dopaminergic side effect, was reported more often after the test product (13 subjects) than after the reference product (6 subjects). The highest levodopa dose (150 mg) was used in this study and therefore a higher rate of nausea was expected in this study than in other studies. The individual plasma concentrations of levodopa, carbidopa and entacapone of all of the subjects reporting nausea in this study were assessed. However, no relation to any of the plasma concentrations (either at the time of the event or during the day) was seen when compared with the concentrations in the other periods or with those in the subjects not reporting nausea. Thus the difference in the frequency of nausea, which is typically related to levodopa, is most probably explained by chance. There were no significant differences in the rates of other symptoms suggesting comparable tolerability between the test (LCE) and reference products. It is also worth noting that many reported adverse events, such as headache, respiratory tract infections, fatigue and dizziness are rather unspecific symptoms and commonly seen in "healthy volunteer studies without any obvious causal relationships with the study treatments.

[Reviewer's Note: Nausea was among one of the most commonly observed adverse events associated with the used of entacapone and was not seen at an equivalent frequency among the placebo-treated patients (see entacapone label). Nausea is also one of the common AEs from levodopa. Therefore, the combination of higher Cmax of entacapone (as opposed to reference product) and the highest dose of levodopa/carbidopa (as opposed to LCE50 & LCE100) in LCE150 tablets may contribute to more frequent nausea.]

Comparison of most common adverse events by severity and causality indicated no significant difference between the test and reference treatments (Tables below). Most of the events were considered to be unrelated to the treatments, except nausea (it was considered to be related in 88% cases after the LCE administration and in 87% cases after the reference administration) as a dopaminergic effect.

(d) Both vital signs and ECG conduction times varied within normal limits for each treatment and did not indicate any difference between the test and the reference products over several measurements during the study days. No clinically significant changes were observed from baseline to the time point of maximum plasma concentrations of both levodopa and entacapone.

Table 4. The most common adverse events (>2% frequency) reported in studies 85, 93, 95 and 96.

Adverse event	Test (LCE) (n=176)		Reference (n=176)	
	n	%	N	%
Headache	41	23.3	34	19.3
Nausea	25	14.2	15	8.5
Upper respiratory tract infection	13	7.4	9	5.1
Fatigue	9	5.1	5	2.8
Vomiting	7	4.0	5	2.8
Dizziness	8	4.5	7	4.0
Diarrhoea	6	3.4	4	2.3
Rhinitis	5	2.8	4	2.3
Influenza-like symptoms	5	2.8	1	0.6
Back pain	4	2.3	2	1.1
Pharyngitis	3	1.7	4	2.3

n = number of subjects
Reference: ISS Table 9.2, ISS Post-text Table 2.

Table 5. Severity and causality of adverse events by studies.

Study No	Treatment	Severity			Causality	
		Mild n (%)	Moderate n (%)	Severe n (%)	Not related n (%)	Related n (%)
85	Test (LCE 100)	59 (95.0)	3 (0.5)	0 (0.0)	48 (77.4)	14 (22.6)
	Reference	42 (100)	0 (0.0)	0 (0.0)	37 (88.1)	5 (11.9)
93	Test (LCE 100)	46 (76.7)	14 (23.3)	0 (0.0)	43 (71.1)	17 (28.3)
	Reference	51 (83.6)	10 (16.4)	0 (0.0)	40 (65.6)	21 (34.4)
95	Test (LCE 50)	4 (36.4)	7 (63.6)	0 (0.0)	5 (45.5)	5 (45.5)
	Reference	6 (75.0)	2 (25.0)	0 (0.0)	4 (50.0)	4 (50.0)
96	Test (LCE 150)	8 (33.3)	15 (62.5)	1 (4.2)	3 (12.5)	21 (87.5)
	Reference	7 (50.0)	7 (50.0)	0 (0.0)	5 (35.7)	9 (64.3)

Reference: ISS Table 9.5, ISS Post-text Table 3.

- Furthermore, from literature data, there was no dose-relationship with tolerability when entacapone was given without levodopa in single doses from 25 to 800 mg [13], or when entacapone in doses from 50 to 400 mg was given together with single dose levodopa/carbidopa (100/25mg) [14].

Similarly, there were no dose-related differences in the occurrence of adverse events or in any other safety variables when entacapone was administered repeatedly at 100, 200, and 400 mg doses up to 6 times daily doses of levodopa/carbidopa (100/25mg) in PD patients [15]. Thus, the available data indicate that the variation in the entacapone Cmax seen in two of the bioequivalence studies does not result in any safety or tolerability concern. [Reviewer's note: Mean age of PD patients was 48±8 years (range 48-77 years).]

13. Keranen T, Gordin A, Karlsson M, Korpela K, Pentikainen PJ, IRita H, et al. Inhibition of soluble catechol-O-methyltransferase and single-dose pharmacokinetics after oral and intravenous administration of entacapone. Bur J Clin Pharmacol 1994;46:151-7.
14. Keranen T, Gordin A, Harjola VP, Karlsson M, Korpela K, Pentikainen PJ, et al. The effect of catechol-O-methyl transferase inhibition by entacapone on the pharmacokinetics and metabolism of levodopa in healthy volunteers. Clin Neuropharmacol 1993;16(2):145-56.
15. Heikkinen H, Nun JG, LeWin PA, Koller WC, Gordin A. The effects of different repeated doses of entacapone on the pharmacokinetics of L-Dopa and on the clinical response to L- Dopa in Parkinson's disease. Clin Neuropharmacol 2001;24(3):150-7.

Amendment: (Information available in clinical section volume 64, 166)
Note: Additional supporting data in this regard were submitted under clinical sections.

- The highest levels of entacapone seen in the BE studies are within the range reported earlier in volunteers and in PD patients. Entacapone has wide range of safety margin and lack of dose-tolerability correlation. Specifically, submitted under NDA20-796 Comtan: No clear dose-relation regarding entacapone administered in healthy volunteers as a single dose up to 800mg or as repeated doses of 800mg tid for 7 days. No tolerability problems have been seen in PD patients receiving higher than currently recommended dose of entacapone administered in combination with levodopa/DDC inhibitor, e.g., as single dose up to 800mg or 400mg given 4-6 times daily for 2 weeks. In previous study in PD patients, there is no dose relation seen between the frequency and type of adverse events and entacapone dose (100mg, 200mg, 400mg) or in the vital signs or ECG. Previously, the highest measured entacapone levels in PD patients after a 200mg dose was [redacted] ng/ml and the highest ever-measured entacapone level in PD patients was [redacted] ng/ml after 800mg of entacapone. The highest individual plasma levels of entacapone in 3 BE studies was [redacted] ng/ml (LCE 50, test product), and [redacted] ng/ml after the reference product (LCE 150) were within the previously reported ranges. No AEs were associated with these high levels either in the current LCE BE studies or in previously studies in PD patients.
- Available pre-clinical data indicate that entacapone should not penetrate through to the brain in any significant extent at concentration levels below 5-6 ug/ml. At the level of 15ug/ml, the inhibition of COMT enzymes is only mild to modest and the first measurable metabolic effects in animals are seen at very high doses, corresponding approximately to levels over 90ug/ml or more of entacapone. These levels are above the average peak levels of entacapone seen after the recommended 200mg dose in man. Moreover, this finding in animal models are in agreement with the human PET data in PD patients. Ceravolo et al reported recently that another COMT inhibitor tocapone, which has potential to penetrate into the brain, produced PET findings indicating COMT inhibition, while no such finding have been reported with entacapone.

6.3 Formulations

The LCE 50, 100, & 150 tablet formulations used in the BE studies (#85, 93, 95, 96) were all final-to-be-marketed formulations. The tablet batches (LCE 50 batch CA002, LCE 150 batch CA003) used in the these studies were produced at production scale. LCE100 tablet (studies #85 &#93) was produced in batches [redacted] of the production scale. Formulation & batch data are attached (tables below).

Three strengths are not compositionally proportional. Entacapone dose is fixed at 200mg for all strengths. Levodopa & carbidopa, on the other hand, are proportionally increased at a fixed ratio of 4 to 1: 50/12.5mg, 100/25mg; 150/37.5mg.

Table 3.2. The compositions of formulations used in the bioequivalence studies # 2939085, 2939093, 2939095 and 2039096

Unit formula, mg/tablet	Formulation 50 1 F	Formulation 100 5 F	Formulation 150 1 F
Entacapone	200.0	200.0	200.0
Levodopa	50.0	100.0	150.0
Carbidopa monohydrate			
starch			
Mannitol			
Croscarmellose sodium			
Povidone K 30			
Magnesium stearate			
Core weight (mg)			
Hypromellose			
Sucrose			
Titanium dioxide			
Yellow iron oxide			
Red iron oxide			
Magnesium stearate			
Polysorbate 80			
Glycerol 85%			
Tablet weight (mg)	*457*	*587*	*715*

Table 3.1. Combination tablet formulations used in the pilot absorption and bioequivalence studies

Study #	Formulation code Batch #	Dosage Form and Strength	Batch size	Formulation or significant manufacturing change (if any) and reason for change	Effect of Change
2939075[1)]	100 8 C MTY66-Y23-03	LCE 100		NA	NA
	100 17 B MTY66-Y22-03	LCE 100		NA	
2939078[1)]	100 4 E MTY66-Z33-03	LCE 100		NA	NA
	100 1 F MTY66-Z32-03	LCE 100		NA	
2939085	100 5 F BC002-2	LCE 100		NA	NA
2939093	100 5 F BC002-2	LCE 100		NA	NA
2939095	50 1 F CA002	LCE 50		NA	NA
2939096	150 1 F CA003	LCE 150		NA	NA

6.4

[1)] Pilot absorption study to support formulation development (compositions in Table 3.3.)

7 Page(s) Withheld

specific case, the sponsor has provided satisfactory justifications for the selection of methods for each moiety and strengths.

- Overall, we find the proposed dissolution methods for each moiety acceptable. However, based on the dissolution profiles from biobatches, the specifications should be tightened. This reviewer has briefly surveyed the dissolution profiles from the stability batches and biobatches at release and found them similar. The Review Chemist Dr. Martha Heimann has been consulted for the stability data.
- Comments to the sponsor:

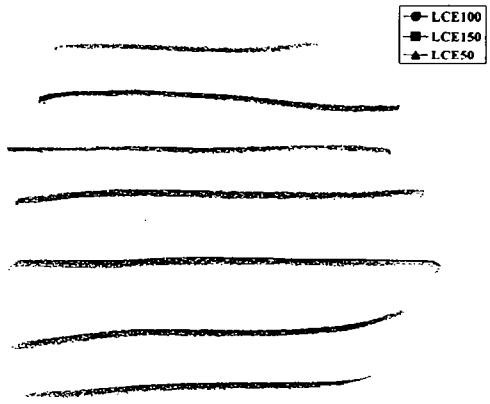
(a) Overall, we find the proposed dissolution methods for each moiety acceptable. However, based on the dissolution profiles from biobatches, the specifications should be tightened.

Agency's recommendation

Moiety		**Specification**	**Specification**		**Method**
		LCE 50	LCE 100	LCE 150	
Levodopa	Sponsor proposed	Q= [redacted] at 45 min	Q= [redacted] at 45 min	Q= [redacted] at 45 min	Apparatus 1 /basket 50rpm 750ml, 0.1 MHCl 37°C
	Agency recommends	**Acceptable**	**Acceptable**	**Q= [redacted] at 45 min**	**Acceptable**
Carbidopa	Sponsor proposed	Q= [redacted] at 45 min	Q= [redacted] at 45 min	Q= [redacted] at 45 min	Apparatus 1 /basket 50rpm 750ml, 0.1 MHCl 37°C
	Agency recommends	**Acceptable**	**Acceptable**	**Q= [redacted] at 45 min**	**Acceptable**
Entacapone	Sponsor proposed	Q= [redacted] at 45 min	Q= [redacted] at 45 min	Q= [redacted] at 45 min	[redacted] 37°C
	Agency recommends	**Q= [redacted] at 45 min**	**Q= [redacted] at 45 min**	**Q= [redacted] at 45 min**	**Acceptable**

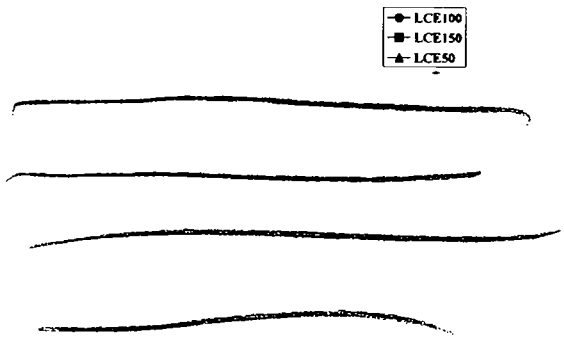
		LCE 50	LCE 100	LCE 150
Levodopa	Sponsor proposed	Q= [redacted] at 45 min	Q= [redacted] at 45 min	Q= [redacted] at 45 min
	Agency recommends	**Acceptable**	**Acceptable**	**Q= [redacted] at 45 min**

Levodopa: Dissolution profile



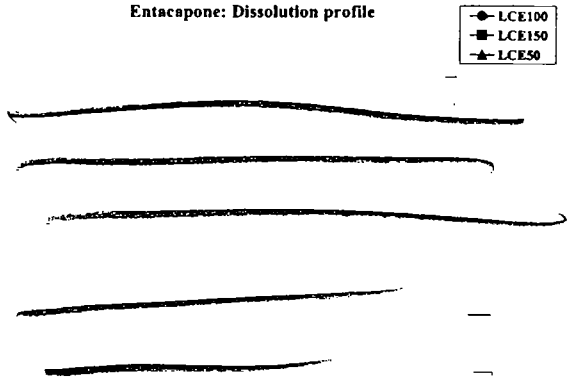
		LCE 50	LCE 100	LCE 150
Carbidopa	Sponsor proposed	Q= [redacted] at 45 min	Q= [redacted], at 45 min	Q= [redacted], at 45 min
	Agency recommends	**Acceptable**	**Acceptable**	**Q= [redacted] at 45 min**

Carbidopa: Dissolution profile



		LCE 50	LCE 100	LCE 150
Entacapone	Sponsor proposed	Q= [redacted] at 45 min	Q= [redacted] at 45 min	Q= [redacted] at 45 min
	Agency recommends	**Q= [redacted] at 45 min**	**Q= [redacted], at 45 min**	**Q= [redacted] at 45 min**

Entacapone: Dissolution profile



Summary of dissolution profiles from the biobatches:

LCE Strengths (mg)	Lot #	BE studies		Levodopa (Q= — at 45min)			Carbidopa (Q= — at 45')			entacapone (Q= — at 45')		
			collection time (min)	mean % dissolved	range	SD (%)	mean % dissolved	range	SD (%)	mean % dissolved	range	SD (%)
50/12.5/200 CA002 #95			10	15	—	3.3	13	—	3.4	18	—	1.8
			20	51	—	4.8	52	—	4.1	67	—	2.3
			30	**83**	—	**3.6**	**82**	—	**3.3**	**86**	—	**1**
			45	**99**	—	**1**	**96**	—	**2.8**	**93**	—	**1.1**
			60	100	—	1	97	—	2.9	96	—	1.1
100/25/200 BC002-2 #85 #93			10	9	—	1.8	9	—	1.9	16	—	2.3
			20	41	—	3.6	40	—	4.2	65	—	3.5
			30	**73**	—	**4.2**	**73**	—	**4.1**	**85**	—	**2.9**
			45	**99**	—	**1.2**	**99**	—	**2.7**	**93**	—	**2.4**
			60	100	—	1.3	100	—	3.1	96	—	2.1
				Levodopa (Q= — at 45min)			Carbidopa (Q= — at 45')			entacapone (Q= — at 45')		
			collection time (min)	mean % dissolved	range	SD (%)	mean % dissolved	range	SD (%)	mean % dissolved	range	SD (%)
150/37.5/200 CA003 #96			10	8	—	1.1	7	—	1.2	9	—	2.1
			20	31	—	2.7	31	—	2.8	45	—	5.1
			30	**57**	—	**3.8**	**57**	—	**3.3**	**81**	—	**3.8**
			45	**87**	—	**2**	**86**	—	**2.7**	**97**	—	**1.1**
			60	95	—	2.8	94	—	3	100	—	1.1

6.5 Bioanalytical assays

5 BE studies submitted including 3 pivotal BE studies (#93, #95, and #96) were conducted and analyzed in different places/countries. — methods along with different methods of sample preparation — were used for determination of plasma levels of levodopa and carbidopa. No cross-validation information is provided. However, since independent BE studies were performed for each strength, cross-validation is not absolutely necessary. — nethod was used for determination of plasma levels of entacapone in all 4 BE studies where entacapone was administered either as Stalevo or separately as Comtan tablet.

Overall, the method validation for 3 moieties was found to be acceptable in terms of reproducibility, specificity, sensitivity, linearity, precision and accuracy. The limit of quantification for levodopa is — (study #93), — (study #85) or — (study #08); carbidopa is — (#08) or — (#85, #93, #95, and #96); entacapone is — We note that the mean recoveries for levodopa and carbidopa were relative low using — method. Mean recoveries for all three analytes were — method, #study 95 & 96) or — nethod, #93 & #85) for levodopa, — nethod, #study 95 & 96) or — nethod, #93 & #85) for carbidopa, and — for entacapone.

Briefly, the different sample extraction methods described below have been used in the various sites for the 5 BE studies:

- — method for entacapone at Orion Pharma, Espoo, Finland (Studies # -85, -93, -95, -96)

- [redacted] nethod for levodopa and carbidopa at Orion Pharma, Espoo, Finland (Studies #-85, -93)
- [redacted] method for levodopa and carbidopa at [redacted] (Studies # -95, -96)
- [redacted] method for levodopa and carbidopa at [redacted] Study # 0097008).

This reviewer has summarized the clinical & analytical sites, bioassays for 5 BE studies of Stalevo® (Levodopa/carbidopa/entacapone)

Study # (strength) (study design)	#0097008 (100/25mg) (US VS Finnish Sinemet) (non-replicate 18-45 yrs n=40, males & females)	#29390 85 (100/25/200mg) (replicate 18-45 yrs, n=44, males)	#2939095 (Pivotal) (50/12.5/200mg) (replicate ,40-80yrs, n=44, males & females)	#2939093 (pivotal) (100/25/200mg) (replicate ,40-80yrs n=44, males & females)	#2939096 (pivotal) (150/37.5/200 mg) (replicate ,40-80yrs n=44, males & females)
Test product/ strengths	US Sinemet (Levodopa/carbidopa 100/25mg)	Levodopa/carbidopa/ entacapone 100/25/200mg	Levodopa/carbidopa/e ntacapone 50/12.5/200mg	Levodopa/carbidopa/ entacapone 100/25/200mg	Levodopa/carbidopa/e ntacapone 150/37.5/200 mg
Reference product	Finland Sinemet Levodopa/carbidopa 100/25mg)	Finnish Sinemet/ (Levodopa/carbidopa , 100/25mg)/ Comtess (200mg)	Finnish Sinemet (½ Levodopa/carbidopa, 100/25mg /Comtess (200mg)	US Sinemet Levodopa/carbidopa, 100/25mg)/ Comtess (200mg)	Finnish Sinemet (1½ Levodopa/carbidopa, 100/25mg) /Comtess (200mg)
Clinical site	[redacted]	Pharmacokinetic Research Unit of the Department of Pharmacokinetics, Orion Corporation Orion Pharma, Harmaaparrankuja 1 FIN-02200 Espoo, Finland.	[redacted]	Pharmacokinetic Research Unit of the Department of Pharmcokinetics, Orion Corporation Orion Pharma, Harmaaparrankuja 1, FIN-02200 Espoo, Finland.	[redacted]
Investigator	[redacted]				
Bio-analytical site: Levodopa/ carbidopa	[redacted]	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.	[redacted]	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland	[redacted]
Method: Levodopa/ carbidopa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-study validation report	[redacted] KX010	[redacted])11137	[redacted] 3/01-05	[redacted] 011137	[redacted] 3/01-05
Pre-study validation (Sensitivity of method /range)	Levodopa | carbidopa: [redacted]	Levodopa | carbidopa: [redacted]	Levodopa | carbidopa: [redacted]	Levodopa | carbidopa: [redacted]	Levodopa | carbidopa: [redacted]

3 Page(s) Withheld

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**21,485**	**Brand Name**	**Stalevo**
Relevant IND/NDA	**NDA 20,796 (entacapone), IND 60,554 (Levodopa/Carbidopa/ Entacapone**	**Generic Name**	**Levodopa/Carbidopa/ Entacapone**
		Drug Class	**Parkinsonism drug**
OCPB Division (I, II, III)	**I**	**Indication(s)**	**Treatment of patients with idiopathic Parkinson disease with the signs & symptoms of end-of –dose wearing-off**
Medical Division	**HFD-120**	**Dosage Form/strengths**	**Tablets** **(Levodopa/Carbidopa/Entacapone:** **50/12.5/200 mg;** **100/25/200mg;** **150/37.5/200mg)**
OCPB Reviewer	**Wen-Hwei Chou, Pharm.D., Ph.D.**	**Dosing Regimen**	[redacted] **Stalevo tablet. Maximum daily dose of Stalevo is eight tablets per day.**
OCPB Team Leader	**Ramana, Uppoor. Ph.D.**	**Route of Administration**	**po**
		Sponsor	**Orion Pharma, Inc.**
Date of Submission	**06/24/02**	**Priority Classification**	**S**
Estimated Due Date of OCPB Review	**01/31/03**		
PDUFA Due Date	**04/24/03**		

Background

The sponsor developed a fixed dose combination tablet containing three previously marketed active agents, levodopa/carbidopa and entacapone in three different strengths for the treatment of Parkinson's disease. Each strength consists of a 4 to 1 ratio of Levodopa to carbidopa and a fixed dose of 200mg entacapone. Levodopa is an antiparkinsonian drug and mediates the final clinical effect of this fixed combination while carbidopa or entacapone have no clinical efficacy per se. Carbidopa and entacapone both reduce the peripheral metabolism of levodopa and therefore, enhance the availability of levodopa for the brain and affect the clinical effects of levodopa.

This submission is entirely based on the pharmacokinetic/ BE studies. No clinical trial in target population was conducted. The sponsor submitted a total of 7 PK/BE studies along with literature-based special population and metabolism/drug-drug interaction information. The sponsor conducted three separate pivotal BE studies with each different strength of to-be-marketed combination tablet against marketed Sinemet (levodopa/carbidopa, 100/25mg tablet) and Comtan (entacapone 200mg). In addition, the sponsor submitted a BE study comparing reference tablet Sinemet US versus Finland product since both tablets were used in the pivotal BE studies. Entacapone is marketed as Comtan or Comtess in the US or Finland, respectively.

Division Due Date	**02/24/03**		**Number of studies reviewed**	**Critical Comments If any**
Clin. Pharm. and Biopharm. Information				

	"X" if included at filing	Number of studies submitted		
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			[redacted] for levodopa/carbidopa/entacapone 5 BE studies including 3 pivotal BE studies were conducted and analyzed in different places/countries. (see appendix) No cross-validation information is provided. However, independent BE studies were performed for each strength.
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	x			**Literature references**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	x			literature reference

pediatrics:				
geriatrics:	x			**literature references**
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**x**	**7**		Comtan/Comtess (entacapone 200mg tablet) and Sinemet tablet (levodopa/carbidopa 100/25 mg) were used as reference products . Summary of results from 5 BE studies is attached in appendix. Two CI values for entacapone were 1.00-1.26 for the Cmax of 100/25/200 and 1.03-1.35 for the Cmax of 150/37.5/200mg tablets. The sponsor proposed that extended limits (CI90% of 70-143%) should be considered for the highly variable compounds and the variation of entacapone Cmax does not result in any safety or tolerability concerns along with some citation of published references. In the pre-NDA meeting, the sponsor was requested to address following 2 issues in the NDA submission: (1) the variability seen in the studies, and (2) the clinical relevance from a safety point of view at the highest recommended daily dose regarding the two values that fell outside of the recommended values.

traditional design; single / multi dose:	x	3 (sd)	1	Comparing reference product Sinemet (US vs Finnish product, 100/25mg, n=1, #0097008), Pilot absorption studies (n=2, #2939075, #2939078, formulation development). Only #0097008 will be fully reviewed since all 4 BE studies including 3 pivotal BE (#-93, #-95, #-96) below are conducted using to-be-marketed formulation.
replicate design; single / multi dose:	x	4 (sd)	4	#085, young male 100/25/200mg (final formulation to be marketed, [redacted] scale, Finnish Sinemet/Comtess as reference products), #095 (pivotal), male/female,50/12.5/200mg (final formulation to be marketed, [redacted] scale, Finnish Sinemet/Comtess as reference products), #093 (pivotal), male/female, 100/25/200mg (final formulation to be marketed. [redacted] scale, US Sinemet/Comtess as reference products) #096 (pivotal), male/female, 150/37.5/200mg (final formulation to be marketed [redacted] scale, Finnish Sinemet/Comtess as reference products)
Food-drug interaction studies:				No study was requested (since this medication is taken up to 8 times per day) as discussed at pre-NDA meeting. Food-effect will rely only on literature, if available.
Dissolution:	x	3	3	The sponsor was requested in the pre-NDA meeting to justify and submit to section 6 the proposed different dissolution methods and specifications for 3 active ingredients. According to the sponsor, the details of the selection and justification are submitted in the CMC section 4 A III 8 "Validation of dissolution method for levodopa and carbidopa' and Validation of dissolution method for entacapone".
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				

Literature References	x	~24	~24	For Clinical Pharmacology/special populations/DDI/dosage and administration
Total Number of Studies		~34	32	
Filability and QBR comments	**"X" if yes**	Comments		
Application filable ?	**X**	• According to the sponsor, the requested justification of proposed different dissolution methods and specifications for 3 strengths is described in more detailed in CMC section 4 A III 8 "Validation of the dissolution method for levodopa and carbidopa". • DS I audit will be requested for both clinical and analytical sites for 2 pivotal BE studies (#-93 & #-96). Results from the audit will provide some information on the validation of different bioanalytical methods across s different study sites, and BE of US versus Finnish Sinemet reference tablet. • The sponsor has complied with Agency's pre-NDA meeting requests regarding the paper form and electronic submissions of individual data of each measure including demographics, PK parameters and safety measurements in the HPK section.		
Comments sent to firm ?		In order to facilitate the review, • Submit additional copy of the selection and justification of proposed different dissolution methods and specifications for 3 active ingredients. The sponsor indicated that they were submitted under CMC section 4 A III 8 the "Validation of the dissolution method for levodopa and carbidopa" and "Validation of the dissolution method for entacapone". • Submit additional copy of volume 64, 163-167 where the references for label in the sections of Clinical Pharmacology, drug interactions, and Dosage/Administration are located. • Provide in electronic format the annotated "MicroSoft Word" version of proposed label with side-by side comparisons with the approved Sinemet and Entacapone labels.		
QBR questions (key issues to be considered)	• Are 3 different strengths of Stalevo bioequivalent to the reference products? If not, does the sponsor adequately justify its clinical relevancy from a safety viewpoint at the highest recommended daily dose? (summary of results from 5 BE studies is attached in appendix) • Are bioanalytical methods to determine plasma concentrations of levodopa/carbidopa/entacapone adequately validated pre- and within-studies? • Are the proposed dissolution methods and specifications proper to discriminate sub-optimal batches? • Does the proposed dosage and administration adequately address the issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms as requested in the pre-NDA meeting? • Does the proposed labeling language adequately reflect current knowledge of Levodopa/carbidopa/entacapone from the Clinical Pharmacology and Biopharmaceutics perspective as requested in the pre-NDA meeting? If not, what are the areas that need to be updated?			
Other comments or information not included above				
Primary reviewer Signature and Date	**Wen-Hwei Chou Pharm.D., Ph.D.**			
Secondary reviewer Signature and Date	**Ramana Uppoor, Ph.D.**			

CC: NDA 21-485, HFD-850(Lee), HFD-120(CSO), HFD-860(Mehta, Marroum, Uppoor, Chou), CDR (B. Murphy)

Appendix

*DSI audit will be requested for: Study #2939093 & #2939096

This reviewer has summarized the clinical and analytical sites for 5 BE studies of Stalevo® (Levodopa/carbidopa/entacapone)

Study # (strength) (study design)	#0097008 (100/25mg) (US VS Finnish Sinemet) (non-replicate 18-45 yrs n=40, males & females)	#29390 85 (100/25/200mg) (replicate 18-38 yrs, n=44, males)	#2939095 (Pivotal) (50/12.5/200mg) (replicate, 45-75yrs, n=44, males & females)	#2939093 (pivotal) (100/25/200mg) (replicate, 45-72yrs n=44, males & females)	#2939096 (pivotal) (150/37.5/200 mg) (replicate,45-74 yrs n=44, males & females)
Test product/ strengths	US Sinemet (Levodopa/carbidopa 100/25mg)	Levodopa/carbidopa /entacapone 100/25/200mg	Levodopa/carbidopa /entacapone 50/12.5/200mg	Levodopa/carbidopa /entacapone 100/25/200mg	Levodopa/carbidopa /entacapone 150/37.5/200 mg
Reference product	Finland Sinemet Levodopa/carbidopa 100/25mg)	Finnish Sinemet/ (Levodopa/carbidopa, 100/25mg)/ Comtess (200mg)	Finnish Sinemet (½ Levodopa/carbidopa, 100/25mg /Comtess (200mg)	US Sinemet Levodopa/carbidopa, 100/25mg)/ Comtess (200mg)	Finnish Sinemet (1½ Levodopa/carbidopa, 100/25mg) /Comtess (200mg)
Clinical site	[redacted]	Pharmacokinetic Research Unit of the Department of Pharmacokinetics, Orion Corporation Orion Pharma, Harmaaparrankuja 1, FIN-02200 Espoo, Finland.	[redacted]	Pharmacokinetic Research Unit of the Department of Pharmcokinetics, Orion Corporation Orion Pharma, Harmaaparrankuja 1, FIN-02200 Espoo, Finland.	[redacted]
Investigator	[redacted]				
Bio-analytical site: **Levodopa/ carbidopa:**	[redacted]	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.	[redacted]	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland	[redacted]
Method: **Levodopa/ carbidopa:**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bio-analytical site: **Entacapone**	na	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.
Method: **Entacapone**	**na**	[redacted]			

Analytical methods:

Levodopa/carbidopa/entacapone: [redacted]

Levodopa/carbidopa: 3 different methods were used in different sites

[redacted] at Orion Pharma, Finland (studies #-85, #-93)

[redacted]

Entacapone: [redacted] at Orion Pharma, Finland, in all studies.

Table 1 : OCPB's summary of geometric mean ratio of Cmax & AUC from 5 BE studies of TC® (Levodopa/ carbidopa/entacapone) : [results presented as mean (range), bold indicates outside of the recommended range] (excerpted from OCPB review of the pre-NDA meeting package)

	Study # (strength) (study design)	#0097008 (100/25mg) (US VS Finnish Sinemet) (non-replicate 18-45 yrs n=40, males & females)	#29390 85 (100/25/200mg) (replicate 18-45 yrs n=44, males)	#2939095 (50/12.5/200mg) (replicate ,40-80yrs n=44, males & females)	#2939093 (100/25/200mg) (replicate ,40-80yrs n=44, males & females)	#2939096 (150/37.5/200 mg) (replicate ,40-80yrs n=44, males & females)
Cmax	levodopa	1.02 (0.94-1.11)	0.93(0.88-0.98)	0.96 (0.90-1.03)	0.96 (0.91-1.00)	0.94(0.89-0.99)
	carbidopa	0.98 (0.88-1.11)	1.00 (0.93-1.08)	0.98 (0.91-1.06)	0.98 (0.92-1.04)	0.88 (0.82-0.94)
	entacapone		0.99 (0.88-1.11)	0.94 (0.84-1.06)	1.12 **(1.00-1.26)**	1.18 **(1.03-1.35)**
AUC0-inf	levodopa	0.99 (0.95-1.03)	1.01 (0.97-1.04)	1.03 (0.99-1.07)	1.04 (1.01-1.07)	0.97 (0.94-1.01)
	carbidopa	0.99 (0.89-1.11)	1.02 (0.95-1.11)	0.99 (0.93-1.05)	0.98 (0.92-1.05)	0.88 (0.82-0.93)
	entacapone		1.02 (0.96-1.08)	1.01 (0.96-1.06)	1.02 (0.98-1.07)	1.01 (0.95-1.07)

6.7 Sponsor proposed label

Starting next page is the proposed label for LCE tablets submitted on 11/14/2002.

Note: The sponsor submitted a revised label for LCE (03/13/2003, E-doc). This reviewer has surveyed the label and found 2 changes: (1) Trade name change from [redacted] to Stalevo. (2) A paragraph regarding biliary obstruction under "Precautions" section was added. This reviewer has made these 2 changes accordingly.

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8/13/02 06:21:55 PM
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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21,485	Submission Dates: 05/02/2003
Brand Name	Stalevo tablet
Generic Name	Levodopa/Carbidopa/Entacapone (LCE)
Primary Reviewer	Wen-Hwei Chou, Pharm.D., Ph.D.
Team Leaders	Ramana Uppoor, Ph.D.
OCPB Division	HFD-860
OND Division	HFD-120, Neuropharmacological drug products
Sponsor	Orion Pharma, Inc.
Submission Type; Code	Response to approvable letter dated 04/25/2003
Formulation; Strength	Film-coated Tablets (Levodopa/Carbidopa/Entacapone) LCE 50: 50/12.5/200 mg LCE 100: 100/25/200mg LCE 150: 150/37.5/200mg
Indication	Treatment of patients with idiopathic Parkinson's disease with the signs & symptoms of end-of –dose wearing-off
Proposed dose	A direct switch of patients taking levodopa/carbidopa 100/25mg (4:1) standard release tablet with or without entacapone to corresponding doses of LCE tablet. Max 8 tablets/day. No more than 1 Stalevo tablet per each dosing

This review evaluates the sponsor's response to the approvable letter dated April 25, 2003. The Agency requested the sponsor to revise the proposed labeling especially in the Pharmacokinetics (PK) section. The sponsor stated that they had basically accepted all the revisions & recommendations made by the Agency in the Approvable letter. They have revised certain portions of PK section as suggested by the Agency, and in addition, they have made only some minor corrections and modifications to the labeling text.

Recommendation

Overall, the Office of Clinical Pharmacology and Biopharmaceutics finds the revised label of Pharmacokinetics section acceptable with minor changes (see page 2 for details).

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT initialed by Ramana Uppoor, Ph.D. _____

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

c.c.: NDA 21-485, HFD-120 (Feeney, Bastings, Wheelous), HFD-860 (Mehta, Sahajwalla, Uppoor, Chou)

Agency Proposed minor labeling changes (05/08/2003)

Note: Changes are indicated as follows: (a) Red/underlined text indicates addition; (b) Strikethrough indicates deletion. [] indicates explanation which should not be incorporated in the final label.

Pharmacokinetics

The pharmacokinetics of Stalevo tablets have been studied in healthy subjects (age 45-75 years old). Overall, following administration of corresponding doses of levodopa, carbidopa and entacapone as STALEVO or as carbidopa/levodopa product plus Comtan® (entacapone) tablets, the mean plasma concentrations of levodopa, carbidopa, and entacapone are comparable.

Absorption/Distribution:

Both levodopa and entacapone are rapidly absorbed and eliminated, and their distribution volume is moderately small. Carbidopa is absorbed and eliminated slightly more slowly compared with levodopa and entacapone. There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone, particularly concerning its C_{max}.

The food-effect on the STALEVO tablet has not been evaluated.

Levodopa

The pharmacokinetic properties of levodopa following the administration of single dose STALEVO™ (carbidopa, levodopa and entacapone) tablets are summarized in Table 1.

Table 1. Pharmacokinetic characteristics of levodopa with different tablet strengths of STALEVO (mean ±SD)

Tablet strength	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)
12.5 - 50 - 200 mg	1040 ± 314	470 ± 154	1.1 ± 0.5
25 - 100 - 200 mg	2910 ± 715	975 ± 247	1.4 ± 0.6
37.5 - 150 - 200 mg	3770 ± 1120	1270 ± 329	1.5 ± 0.9

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa (see PRECAUTIONS).

Levodopa is bound to plasma protein only to a minor extent (about 10-30%).

Carbidopa

Following administration of STALEVO as a single dose to healthy male and female subjects, the peak concentration of carbidopa was reached within 2.5 to 3.4 hours on average. The mean C_{max} ranged from about 40 to 125 ng/ml and the mean AUC from 170 to 700 ng•h/ml, with different STALEVO strengths providing 12.5 mg, 25 mg, or 37.5 mg of carbidopa.

Carbidopa is approximately 36 % bound to plasma protein.

Entacapone

Following administration of STALEVO as a single dose to healthy male and female subjects, the peak concentration of entacapone in plasma was reached within 1.0 to 1.2 hours on average. The mean C_{max} of entacapone was about 1200 ng/mL and the AUC 1250 to 1450 ng•h/mL after administration of different STALEVO strengths all providing 200 mg of entacapone.

[The text is deleted since this is for Comtan, not Stalevo]. The plasma protein binding of entacapone is 98% over the concentration range of 0.4 - 50 µg/mL. Entacapone binds mainly to serum albumin.

Metabolism and Elimination:

Levodopa
The elimination half-life of levodopa, the active moiety of antiparkinsonian activity, was 1.7 hours (range 1.1-3.2 hours).

Levodopa is extensively metabolized to various metabolites. Two major pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT).

Carbidopa
The elimination half-life of carbidopa was on average 1.6 to 2 hours (range 0.7-4.0 hours).

Carbidopa is metabolized to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone
The elimination half-life of entacapone was on average 0.8 to 1 hours (0 - 4.5 hours).

Entacapone is almost completely metabolized prior to excretion with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is isomerization to the cis-isomer, the only active metabolite. Entacapone and the cis-isomer are eliminated in the urine as glucuronide conjugates. The glucuronides account for 95 % of all urinary metabolites (70% as parent- & 25% as cis-isomer- glucuronides). The glucuronide conjugate of the cis-isomer is

inactive. After oral administration of a 14C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces.

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs when they are administered repeatedly.

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