

Clinical Review Section

**9. Integrated Review of Safety**

I describe in this section the safety results from the bioequivalence studies. These studies were short-term pharmacokinetic safety, which are useful mostly to support the safety of the new combination in reference to approved products administered jointly (as in clinical practice). The safety data are therefore limited in scope, and do not encompass the usual extent of studies expected in a typical NDA. Instead, the sponsor, as agreed with the Agency, refers to approved NDAs of the individual products.

**9.1 Description of Patient Exposure**

A total of 176 healthy volunteers participated in bioequivalence studies. Demographics of these subjects are summarized in Table 14.

**Table 14: Patient exposure in bioequivalence studies (from Table 3, page 311, Vol. 1.1)**

Study #	LCE 100		LCE 50	LCE 150
	-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

The number of doses of test and reference drugs administered to subjects is listed in Table 15.

**Table 15: Exposure in bioequivalence studies (from Table 2, page 310, Vol. 1.1)**

Studies	Dose strengths (L/C/E mg)	Test (LCE)		Reference	
		1 dose	2 doses	1 dose	2 doses
2939085	100/25/200	44	42	43	41
2939093	100/25/200	44	43	44	43
2939095	50/12.5/200	44	41	43	41
2939096	150/37.5/200	44	40	43	40
<b>Total</b>		<b>176</b>	<b>166</b>	<b>173</b>	<b>165</b>

L/C/E = levodopa / carbidopa/ entacapone

Reference: Post-text Table 1

**9.2 Methods and Specific Findings of Safety Review****9.2.1 Entacapone safety profile**

In the entacapone NDA 20-796, the most frequently reported adverse events attributed to entacapone as an adjunct to levodopa were dyskinesia, nausea, urine discoloration, diarrhea and abdominal pain. There have been rare reports of liver function test abnormalities, but no causal relationship has been established with entacapone. In NDA 20-796, entacapone did not have any significant effect on heart rate, blood pressure or ECG.

I consulted the primary safety review of Dr. Michael Sevka, and of the safety Team Leader Greg Burkhart. The safety reviewers noted the absence of evidence suggesting that entacapone could cause hepatocellular injury, which is important considering the hepatotoxicity of tolcapone, a compound of the same class. The safety reviewers noted that there is little experience above 1600 mg per day (maximum recommended dosage). The overall dropout rate was greater on entacapone than placebo (17.6% versus 13.0%), with the difference increasing when focusing on dropouts attributed to AE (14.3% versus 8.5%). Dose-related abdominal pain and non dose-dependent diarrhea caused discontinuation of entacapone respectively in 2% and in 1.5 % patients. Nausea, dyskinesia and hallucinations were also cause for adverse dropout. Dr. Sevka noted that when the data of the three double blind trials are combined, the most common AEs with an incidence greater than 5% and greater than placebo are dyskinesia (28.8%), nausea (14.5%), abnormal urine (13.1%), diarrhea (10.1%), dizziness (9.9%), abdominal pain (9.1%), pain (6.4%), fatigue (6.2%), and constipation (5.9%). The safety reviewers noted that the events most strongly associated with entacapone appear to be greater than placebo only in patients who were less than 65 kg at baseline. They noted that the analysis of blood pressure was for the most part inconclusive regarding entacapone capacity to cause orthostasis, and blood pressure measurements were probably not timed to the dose. The safety reviewers had no major concerns in terms of death, and serious adverse events. There was no increase in clinically significant laboratory abnormalities, vital signs and ECG abnormalities.

Since the approval of the entacapone NDA (1999), nine periodic reports were submitted to the Agency, covering the period up to January 2002. No labeling changes have been required. About 2000 PD patients received entacapone in the entacapone NDA, and more than 100,000 patients have been prescribed entacapone post-marketing.

**9.2.2 LCE combination safety assessment**

I reviewed Study 85, 93, 95 and 96 in greater detail in the section on "Individual Study Reviews (Safety)". I summarize here the key observations in these studies.

Study 85 had a different schedule of safety assessments than Study 93, 95 and 96. Patients in Study 85 had vital signs and ECG recorded only at the pre- and post-study visits, whereas patients in the three other bioequivalence studies (Study 93, 95 and 96) had additional

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assessments at the day of study drug administration. The timing of assessments in Study 93, 95 and 96 on the day of study drug administration is listed in Table 16.

**Table 16: Timing of assessments in bioequivalence studies (from Table 7.2, page 211, Vol. 1.64)**

Time (time, hours)	Day 1		Day 2 (Study drug administration day)										
	21	22	7 -1	8 0	9 +1	10 +2	11 +3	12 +4	13 +5	14 +6	16 +8	17 +9	18/20 <sup>1</sup> +10/12
Drug intake				•									
ECG			•		•	•						•	
BP&HR (supine and standing)			•		•	•			•		•		•
Temperature			•		•	•			•		•		•
Inquiry of AEs/Symptoms	•		•										•

1) In study 93 and 95 last assessments at 10 hour, and in study 96 at 12 hour

As the studies were all single dose studies in healthy volunteers, the number of adverse dropouts (ADO) was not unexpectedly very low in individual studies. Three subjects (1.7%) out of 176 participants had ADOs, and only one ADO (Study 85, subject 26) was considered to be possibly drug related.

The narratives of the ADOs are listed below.

**Subject 26 – Study 85:**

This 23-year old, 63 kg male had taken one single dose of combination tablet (100/25/200 mg) before discontinuation due to fatigue, nausea, vomiting, and faintness. Symptoms started about 30 min after study drug administration and continued during 2.5 hours. The AEs were assessed to have a positive causality to study drug. At the post-study visit the subject was stated healthy. I concur that LCE is probably responsible for the symptoms, given the close temporal relationship.

**Subject 1- Study 93:**

This 45-year old, 56 kg female had history of mild hypotension and tension headache. She had taken three single doses of combination tablet of LCE 100 before discontinuation due to upper respiratory tract infection. Symptoms had started during the wash out period after the third study day and continued during 2 weeks. At the post-study visit the subject was stated healthy. In the opinion of the investigator the AE was not related to study drug. I concur that the AE was probably not related to the LCE combination.

**Subject 5 -Study 95:**

This 61-year old, 67 kg Caucasian female had taken three single doses of LCE (50/12,5/200 mg) before discontinuation. Symptoms (pain and edema in the left leg) started 18 days after the second study day. The subject discontinued the study at the third study period due to periostitis which was treated with antibiotics. In the opinion of the investigator the AE was unlikely related to study drug. I concur that the relationship to the study drug is unlikely.

**Deaths**

There was no death in bioequivalence studies.

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**Serious Adverse Events**

No serious adverse events occurred in bioequivalence studies.

**Adverse events**

The overall frequency of AEs for LCE and the reference drug across combined studies is listed in Table 17.

**Table 17: Adverse events in studies 85, 93, 95 and 96 (from Table 9.1, page 212, Vol. 1.64)**

Treatment	Number of subjects	Total number of subjects with AEs	Total number of AEs	Number of subjects discontinuing due to an AE
Test (LCE)	176	80	189	1
Reference	176	66	154	2

The overall frequency of the most common adverse events (headache, nausea, upper respiratory tract infections and fatigue) was comparable between LCE and the reference products (Table 18), except for nausea, where the incidence was almost 6% higher when receiving LCE. This was particularly true for Study 96, where nausea was reported in 13 subjects after LCE (29.5%) versus 6 subjects after the reference product (13.6%). The highest levodopa dose (150 mg) was used in this study (see section 13.1.4 for detailed analysis).

**Table 18: Most common adverse events (>2% frequency) reported in studies 83, 93, 95 and 96 (from table 4, page 312, Vol. 1.64)**

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

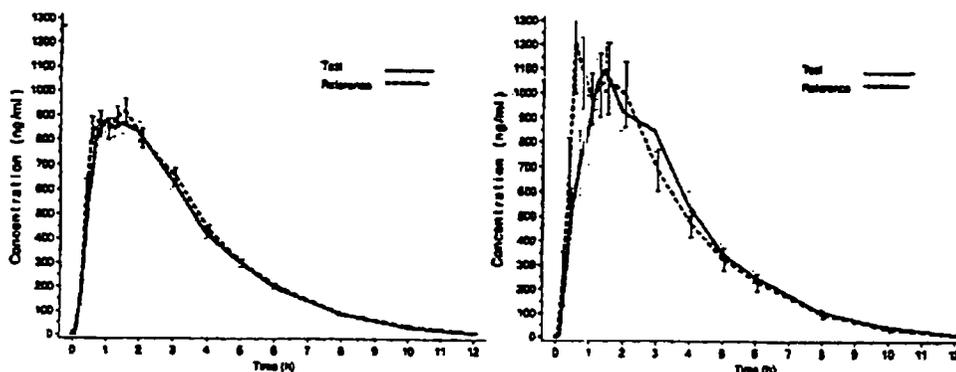
n = number of subjects

Reference: ISS Table 9.2, ISS Post-text Table 2.

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The sponsor compared the levodopa average concentration for subjects not reporting nausea and reporting nausea during the treatment periods, and found no difference between LCE and the reference drugs. In that study, average levodopa AUC and C<sub>max</sub> were numerically higher with the reference drug than for LCE, so that the AE can not be imputed to a difference of levodopa levels. Also, the incidence of nausea was higher with the reference product in Study 93 (LCE 100), and was absent in Study 95 (LCE 50).

Figure 10: Comparison of levodopa average concentration for subjects not reporting nausea (left) and reporting nausea (right) during the treatment periods (from Table 9.1, page 214, Vol. 1.64)



Nausea = Yes, Number of periods 15 (Test) and 7 (Reference). Nausea= No, Number of periods 69 (Test) and 76 (Reference).

Comparison of most common adverse events by severity and causality indicated no significant difference between the test and reference treatments (Table 19). Most of the events were considered to be unrelated to the treatments, except for nausea (considered to be related in 88% after the LCE administration and in 87% after the reference administration).

Table 19: Severity and causality of adverse events by studies (from ISS table 9.5, page 216, Vol. I.64)

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.

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**Adverse events by subgroups**

There was an overall tendency of females to report more often adverse events on both treatments than males, but there were no significant differences between the test and reference drugs. There was no significant difference in the rate of adverse events by age between the test and reference treatments.

The subgroup analysis by weight from studies 93, 95 and 96 suggested a trend for higher rates of some adverse events in subjects weighing below 75 kg compared to those over 75 kg, but there were no difference in the adverse events by weight between the test and reference treatments.

**Adverse events by study**

I review adverse events by study in detail in section 13.1. Overall, the incidence of side effects was similar between the test and reference drug across studies, with a few exceptions. The sponsor did not perform any statistical analysis between study treatments because of the low number of subjects and AEs.

In Study 96, as discussed above, nausea was more frequent when receiving LCE 150 (29.5%) than when receiving the reference drug (13.6%). The sponsor suggests that this occurred by chance, but is noteworthy that this is also the study where entacapone  $C_{max}$  did not meet the bioequivalence criteria. I discuss this issue in section 13.1.4.

In study 85, subjects had more headache (36.4%) with LCE 100 than with the reference drug (27.3%). Dizziness was also more frequent with LCE 100 (13.6%) than with the reference drug (4.5%). The same was true for nausea, with a 13.65% occurrence with LCE 100, and a 2.3% occurrence with the reference drug.

In study 93, nausea was more frequent with the reference drug (18.2%) than with LCE 100 (13.6%). Upper respiratory tract infection was more frequent with LCE 100 (15.9%) than with the reference drug. Dizziness was more frequent with the reference drug (11.4%) than with the test drug (4.5%).

In study 95, very few AEs were reported, with the exception of headache, which had a similar incidence for the test and for the reference drug.

Overall, there was no clear trend for a difference in incidence of AEs between LCE and the reference drug, with the possible exception of nausea, more frequent for the LCE combination in two studies (85 and 96). In a third study (93), nausea was more frequent for the reference drug, and nausea was absent in the fourth study (95), so that this observation remains inconclusive. I also noted that the only severe AE across all four bioequivalence studies was nausea in a patient receiving LCE 150 in study 96.

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Table 20: AEs by study (from Table 9.3, page 215, Vol. 1.64)

Adverse events	Study 85 At Orion (LCE 100)		Study 93 At Orion (LCE 100)		95 At CRO/German (LCE 50)		96 At CRO / German (LCE 150)	
	Test	Reference	Test	Reference	Test	Reference	Test	Reference
Headache	16 (36.4)	12 (27.3)	13 (29.5)	12 (27.3)	6 (13.6)	5 (11.4)	6 (13.6)	5 (11.4)
Nausea	6 (13.6)	1 (2.3)	6 (13.6)	8 (18.2)	0 (0.0)	0 (0.0)	13 (29.5)	6 (13.6)
Upper resp. tr. inf.	6 (13.6)	6 (13.6)	7 (15.9)	3 (6.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	4 (9.1)	2 (4.5)	4 (9.1)	3 (6.8)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Vomiting	1 (2.3)	0 (0.0)	4 (9.1)	5 (11.4)	0 (0.0)	0 (0.0)	2 (4.5)	0 (0.0)
Dizziness	6 (13.6)	2 (4.5)	2 (4.5)	5 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	3 (6.8)	2 (4.5)	3 (6.8)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	5 (11.4)	4 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza-symptoms	0 (0.0)	0 (0.0)	2 (4.5)	0 (0.0)	3 (6.8)	1 (2.3)	0 (0.0)	0 (0.0)
Back pain	2 (4.5)	1 (2.3)	2 (4.5)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	2 (2.5)	2 (4.5)	1 (2.3)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reference: Post-text Table 2

**Laboratory findings**

As all clinical studies were conducted in healthy volunteers who received a maximum of four single doses, no particular laboratory findings were expected to be seen. There were no clinically significant abnormalities associated with the study treatments and no differences between the LCE combination and the reference treatment.

One subject in study 95 had elevated urea and creatinine values, considered related to dehydration. In study 96, elevated values for glucose were noted in some subjects, but patients were not fasting. None was considered associated with study drug or clinically relevant. Since laboratory testing was done only pre- and post-study, remote from study drug administration, this has no real clinical significance since values were similar at both time points, respectively  $5.9 \pm 1.6$  mmol/L at pre-study, and at  $6.3 \pm 2.3$  mmol/L at post-study. Glucose values were elevated in eleven subjects at the pre-study visit, and in 18 subjects at the post-study visit.

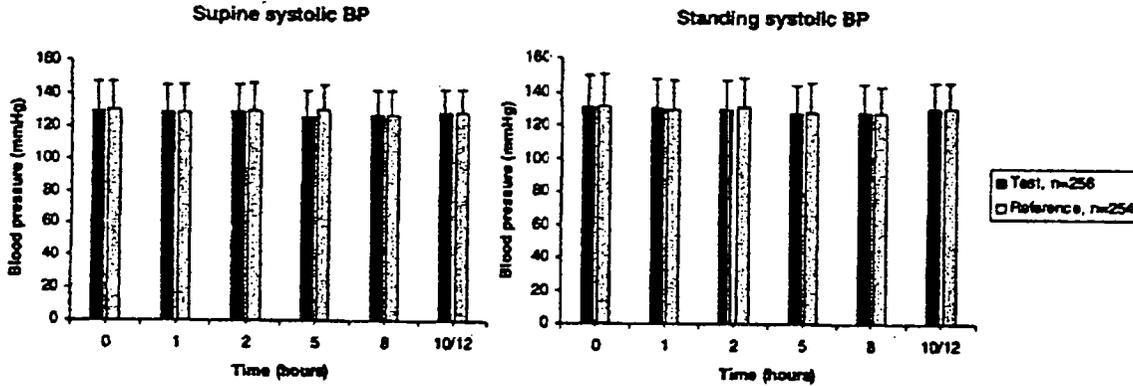
**Vital signs**

Blood pressure values and heart rates were followed on study days in studies 93, 95 and 96 before drug administrations and regularly thereafter for 12 hours.

There were no withdrawals or serious adverse event reports due to vital sign abnormalities in any study. There were no significant changes in the systolic or diastolic blood pressure values or heart rates by time or between the test and reference treatments (Figure 11).

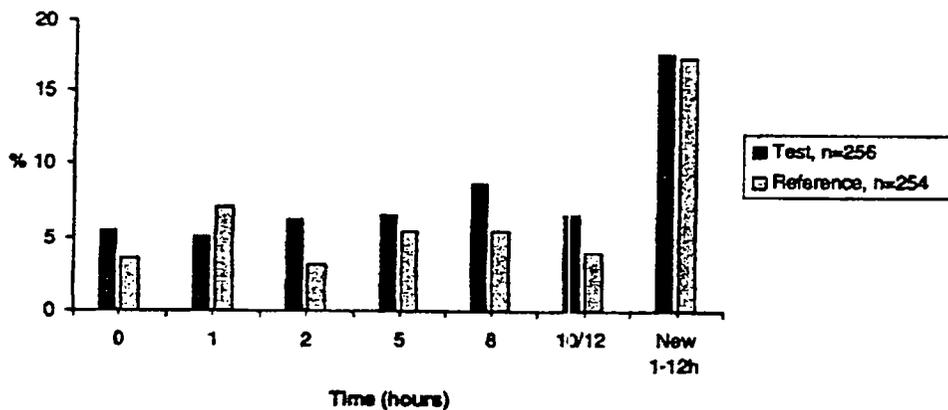
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Figure 11: Mean (+SD) systolic blood pressure in supine and standing positions by time between the test and reference treatments (from figure 11.1, page 224, Vol. 1.64))



The overall frequency of potentially significant orthostatism (defined as reduction in systolic blood pressure >15 mmHg between the supine and standing positions) was comparable between the groups (Figure 12) and the incidence of any 'newly occurring reduction' (i.e. not seen at baseline) was the same (17%) in the test and reference groups. No dose-time correlations were found. In summary, no significant changes were seen after the test and reference treatments in the vital signs and no difference was found between the test and reference treatments.

Figure 12: Proportion of periods with potential significant orthostatism (> 15 mmHg systolic blood pressure drop between supine and standing position) after study drug administrations (n= number of observation periods) (from figure 11.3, page 226, Vol. 1.64))



ECGs

ECGs were recorded in Study 93, 95 and 96 on study days at baseline, and at 1 hour, 2 hours and 9 hours after drug administration. There were no dropouts or serious adverse events due to ECG

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abnormalities in any of the studies. The mean conduction times for the PQ, QRS and QTc intervals across all three studies are summarized in Figure 13. There were no changes in average ECG conduction times by time or between the test and reference treatments.

Figure 13: ECGs parameters (mean +/- SD) at baseline and at 1, 2 and 9 hours (from table 12.1 page 227, Vol. 1.64)

ECG-interval	Treatment*	Baseline	1 h	2 h	9 h
PQ (ms)	Test (LCE)	177.3 ± 23.6	179.2 ± 23.5	178.6 ± 22.6	176.3 ± 22.0
	Reference	173.8 ± 24.8	178.7 ± 23.5	178.0 ± 23.1	176.7 ± 23.2
QRS (ms)	Test (LCE)	84.6 ± 17.8	84.4 ± 17.6	84.6 ± 16.8	84.0 ± 17.4
	Reference	88.1 ± 17.6	84.3 ± 17.4	83.9 ± 16.8	83.7 ± 17.3
QTc (ms)	Test (LCE)	405.9 ± 22.0	404.2 ± 24.3	405.2 ± 24.4	399.5 ± 21.6
	Reference*	406.5 ± 22.3	404.2 ± 23.8	405.7 ± 23.4	399.8 ± 20.5

\* Test n= 255, Reference n=254, n = number of observation periods

Reference: ISS Table 12.1, ISS Post-text Tables 9.1.1-9.1.3

The proportion of recorded interval values indicating any potentially clinically significant prolongations of the PQ (>200 ins), QRS (>120 ins) or QTc (>440 ms) intervals was small on both treatments and no dose-time correlations were found.

Table 21: Proportion of PQ, QRS and QTc intervals with potentially prolonged duration (from table 12.2, page 229, Vol. 1.64).

ECG variable	Treatment	Abnormality	0 h	1 h	2 h	9 h	New 1-9 h
PQ duration (> 200 ms)	Test	Baseline and at 1-2-9 h	5.1 %	4.7 %	4.7 %	4.3 %	-
		Newly occurring	-	3.5 %	1.2 %	0.4 %	5.1 %
PQ duration (> 200 ms)	Reference	Baseline and at 1-2-9 h	5.9 %	3.9 %	4.3 %	3.9 %	-
		Newly occurring	-	1.6 %	0.8 %	0.8 %	3.1 %
QRS duration (>120 ms)	Test	Baseline and at 1-2-9 h	2.0 %	1.6 %	1.6 %	2.0 %	-
		Newly occurring	-	0 %	0 %	0 %	0 %
QRS duration (>120 ms)	Reference	Baseline and at 1-2-9 h	1.6 %	1.6 %	1.6 %	1.6 %	-
		Newly occurring	-	0 %	0 %	0 %	0 %
QTc duration (> 440 ms)	Test	Baseline and at 1-2-9 h	7.5 %	4.3 %	5.5 %	2.4 %	-
		Newly occurring	-	3.9 %	3.2 %	0 %	7.1 %
QTc duration (> 440 ms)	Reference	Baseline and at 1-2-9 h	6.7 %	3.5 %	4.3 %	1.2 %	-
		Newly occurring	-	2.4 %	2.8 %	0.8 %	5.9 %

\* Test n= 255, Reference n=254, n = number of observations

Reference: Post-text Table 9.2.1-9.2.3

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I looked at the QTc distribution in Study 96 (Table 22). Maximal values were borderline high in most arms of the study (i.e. in the 450-470ms range), except for one arm with the reference drug where maximum QTc values were in the 490ms, including prior to study drug administration.

**Table 22: QTc's distribution in Study 96 (from table 11.3.14.2)**  
 Table 11.3.14.2 Descriptive statistics for QTc-interval (ms) during study periods

		Time after drug ingestion			
		0 h	1 h	2 h	9 h
Formulation	Period				
Test	1st MEAN	413	414.2	413.7	407.3
	SD	21.3	23.4	28.9	19.4
	SEM	4.5	5	6.2	4.1
	MIN	384.1	366.8	365.4	368.7
	MAX	473.6	476.3	476.3	455
	N	22	22	22	22
Test	2nd MEAN	414.8	415.9	412.4	406.4
	SD	24.1	23.6	24.9	22.3
	SEM	5.1	5	5.3	4.8
	MIN	380.4	379.1	375.5	371.8
	MAX	475.9	472.3	470.5	480
	N	22	22	22	22
Test	3rd MEAN	408.4	407	411.6	405.9
	SD	18.3	23.8	30.1	23.6
	SEM	4.2	5.5	6.9	5.4
	MIN	381.4	374.6	357.3	361.4
	MAX	445.4	445.4	486.8	469.5
	N	19	19	19	19
Test	4th MEAN	411.2	413.7	417.5	404.4
	SD	23.7	17.6	21.5	21
	SEM	5.3	3.9	4.8	4.7
	MIN	371.3	386.4	385	373.6
	MAX	454.6	449.1	455.9	464.1
	N	20	20	20	20
Reference	1st MEAN	411.4	410.4	412.6	403.9
	SD	23	26.1	23.7	17.6
	SEM	4.9	5.6	5.1	3.8
	MIN	373.6	365	376.9	365
	MAX	462.7	475.9	487.7	435.9
	N	22	22	22	22
Reference	2nd MEAN	408.5	411	413.1	401.7
	SD	25	22.1	23.5	17.4
	SEM	5.5	4.8	5.1	3.8
	MIN	360.4	377.7	375	366.8
	MAX	472.3	472.3	457.7	437.7
	N	21	21	21	21
Reference	3rd MEAN	415.7	416.1	418.5	410.1
	SD	18	19.6	21.7	19.7
	SEM	3.9	4.3	4.7	4.3
	MIN	372.7	385.9	381.8	380
	MAX	457.3	468.2	462.7	458.6
	N	21	21	21	21
Reference	4th MEAN	410.6	413.7	413.8	405.5
	SD	25.6	30.5	27.5	25
	SEM	5.9	7	6.3	5.7
	MIN	384.1	377.3	377.7	371.8
	MAX	495	499.1	496.3	476.3
	N	19	19	19	19

Note: QTc calculated according to formula  $QTc = QT(ms) + 1000 * 0.102111 * (1-RR(s))$ , where 0.102111 is the b coefficient from the linear regression of  $QT(ms) = a + b * RR(ms)$  at pre-study visit.

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**Entacapone C<sub>max</sub> variability**

In regard to the safety implications of the variability of entacapone C<sub>max</sub>, the sponsor argues that entacapone has a wide therapeutic window (see section 5.1.1). The sponsor observes that in NDA 20-796 (entacapone), no clear dose-relation regarding adverse events was established when entacapone was administered in high doses in healthy subjects, e.g. as a single dose up to 800 mg or as repeated doses of 800 mg t.i.d. for 7 days. The sponsor reports no tolerability problems in PD patients receiving higher than the currently recommended dose of entacapone administered in combination with levodopa/DDC inhibitor, e.g. as single dose up to 800 mg or 400 mg given 4 to 6 times daily for 2 weeks. In a previous study with PD patients (Study 28, not part of this NDA), there was no dose relation between the frequency and type of adverse events and entacapone dose (100 mg, 200 mg, 400 mg) or in the vital signs or ECG (Table 23).

**Table 23: Number of adverse events by severity and causality during two-week treatment periods with placebo and 100 mg, 200 mg and 400 mg of entacapone in patients with PD. (from Study 28 report)**

Dose of entacapone (mg)	Severity			Causality				Total
	Mild	Mod- erate	Severe	None	Unlikely	Possible	Probable	
0 (placebo)	29	22	8	13	5	24	17	59
100	19	29	6	7	5	27	15	54
200	30	17	8	7	1	27	20	55
400	17	19	12	7	4	17	20	48

Reference: Study 28 report, (ref # 10)

The same was true for orthostatic hypotension (Table 24).

**Table 24: Occurrence of orthostatic hypotension (the difference between supine and standing systolic HP ≥ 30 mmHg,) with placebo and 100 mg, 200mg and 400 mg doses of entacapone (Study 28 report)**

Dose of entacapone (mg)	Hours after the test dose of levodopa				
	1.0 (n)	2.0 (n)	3.0 (n)	4.0 (n)	6.0 (n)
0 (placebo)	5	4	2	4	0
100	3	5	0	4	2
200	0	2	3	2	1
400	3	5	4	2	0

n= the number of patients with an episode of orthostatic hypotension at a given time point, all patients (n=25) were included in the analysis

Reference: Study 293928 report, (ref. # 10, 11)

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The sponsor also argues that, in bioequivalence studies, the highest individual plasma concentration of entacapone was  $\sim$  ng/ml after the test product and  $\sim$  ng/ml after the reference product. The sponsor observed that these peak levels are comparable with those observed in PD patients (the highest entacapone level in a PD patient after a dose of 200 mg was  $\sim$  ng/ml). COMMENT: This is modestly compelling, since pharmacokinetics may be different in PD patients, and even higher entacapone peak concentrations could theoretically occur in PD patients.

The highest ever-measured entacapone concentration in a PD patient was  $\sim$  ng/ml after 800 mg of entacapone (Study 17, patient 7). Dr. Sevka, in his safety review of the entacapone NDA, cites a level of  $\sim$  ng/ml after a 800 mg dose. I am not sure if this relates to the same patient. In the entacapone NDA, there was also a clinical trial (28) where the highest daily entacapone dose was administered – 2400 mg per day for 14 days (400mg six times per day), to 15 of 25 randomized patients. The other ten patients took 1600 mg or 2000 mg per day (four or five times 400 mg). The trial had a complete crossover design without washout, hence has limited value. Four arms were used: placebo, 100mg, 200 mg and 400 mg, for two weeks. No adverse events were associated with these levels. Serial vital signs were obtained for at least four hours during each testing session (at the end of 2 weeks of treatment). No statistically significant differences were noted between treatment groups for supine and standing systolic and diastolic blood pressure, or heart rate. Similar incidence of orthostatic hypotension was observed at all dose levels. Despite its limited design, this study gives some reassurance about the safety of higher dosages of entacapone. This supports the sponsor argument about the wide safety margin of entacapone and the lack of dose-tolerability correlation, and suggests that the variability in the entacapone peak concentration is unlikely to be associated with any safety concerns.

### Brain effects of entacapone

At the pre-NDA meeting, the Agency raised the question of whether entacapone is able to cross the blood-brain barrier and enter the brain, which could be associated with safety concerns. This was considered a potential issue because of the entacapone  $C_{max}$  values exceeding the conventional bioequivalence limits in Study 96. The following observations must be interpreted in reference to a  $C_{max}$  around 1  $\mu$ g/ml after oral administration of 200 mg entacapone in the human.

In two studies sponsored by Orion in  $\sim$  entacapone distribution was studied in rats after both intravenous and oral administration of radiolabeled entacapone. After a 3 mg/kg IV dose<sup>3</sup> or after repeated oral dosing with 10 mg/kg for 7 days<sup>4</sup>, brain radioactivity peaked respectively at 0.02% and <0.01% of the injected dose.

The sponsor states that “the COMT enzyme in the rat striatum was only slightly and transiently inhibited after a 1 mg/kg dose given iv and 10 mg/kg given orally (average  $C_{max}$  5.6  $\mu$ g/ml and 6.4  $\mu$ g/ml, respectively). I reviewed that study report. I concur that the inhibition was transient, mostly present in the first hour after administration. However, inhibition was more than slight in

<sup>3</sup> Study F90032870213

<sup>4</sup> Study BP964312100001

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my opinion, reaching respectively 25% and 45% inhibition of central COMT after a 1 mg/kg dose given iv and 10 mg/kg given orally. The degree of inhibition seen at 10mg/kg seems to contradict the radiolabeled entacapone distribution study, since a 45% COMT inhibition suggests that entacapone reached the striatum at higher concentration than suggested (<0.01%). Inhibition was still 15% three hours after administration of the 1mg/kg iv dose. Peak  $C_{max}$  ( $\approx$   $\mu$ g/ml) after the 1mg iv dose was about 5-6 times higher than the peak  $C_{max}$  after administration of 200 mg entacapone orally in the human. In that study, ED 50 after an oral dose was estimated at 24.2mg/kg. Inhibition was also marked in the striatum after 30mg/kg entacapone (reaching 76% at 1-hour, and still at 59% at 3 hours after administration). There was no clear NOEL, so that the study remains inconclusive, but suggests that a significant inhibition of striatal COMT can occur when a certain threshold of entacapone exposure is reached<sup>5</sup>.

Two studies (not sponsored by Orion) have also investigated striatal COMT inhibition and the effects of entacapone on striatal extracellular levels of homovanillic acid (HVA) in rats using microdialysis techniques. HVA is a metabolite of dopamine, expected to decrease if COMT inhibition occur. In one study, the sponsor reports that only doses  $\geq$  30 mg/kg with intraperitoneal administration had measurable effects on HVA levels in the striatum<sup>6</sup>. However, I reviewed that study, and I could only find one single dose studied: the ip 10 mg/kg dose. As reported by the sponsor, that dose had no significant effect on HVA. I could not find any reference to doses higher than 10mg/kg in the referred article. However, I identified in another article a reference to a 1992 Kaakola and Wurtman study where a 30mg/kg dose was tested, and where reportedly only the 30mg/kg dose decreased basal striatal HVA<sup>7</sup>.

In another study of striatal HVA levels in rats<sup>8</sup>, COMT inhibition was 100% after oral administration of 30 mg/kg, and 80% after 10 mg/kg. A 10% and 20% striatal COMT-inhibition was seen at dose of 2.5 mg/kg, and 5 mg/kg of entacapone, respectively. The sponsor estimated that these correspond approximately to 7.5  $\mu$ g/ml and 15  $\mu$ g/ml entacapone  $C_{max}$ , respectively (but actual PK data were not recorded in that study). These figures seem too high to me, since measured mean  $C_{max}$  was 6.4  $\mu$ g/ml after repeated administration of 10mg/kg in rats in a study cited above. These authors found that only the highest dose of 30 mg/kg of entacapone (which corresponds approximately to a 90  $\mu$ g/ml entacapone  $C_{max}$ ) had measurable metabolic effects on HVA level. The proposed explanation is that even with 80% COMT inhibition, the residual 20% activity is enough to methylate L-dopa and dopamine to the same extent as control animals.

The sponsor conclusion is that preclinical data suggest that entacapone should not penetrate through to the brain in any significant extent at blood concentration levels below 5-6  $\mu$ g/ml. The interpretation of significant must be discussed: 45% striatal COMT inhibition has been seen in

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<sup>5</sup> Study F90032670213

<sup>6</sup> S. Kaakkola and R Wurtman. Effects of catechol-o-methyltransferase inhibitors and L-3,4 dihydroxyphenylalanine with or without carbidopa on extracellular dopamine in the rat striatum. *J Neurochem* 1993; 60:137-144.

<sup>7</sup> S. Kaakkola and R Wurtman. Effect of COMT inhibitors on striatal dopamine metabolism: a microdialysis study. *Brain Res* 1992; 597:241-249.

<sup>8</sup> T Brannan, A Prikbojan, M Yahr. Peripheral and central inhibitors of catechol-o-methyl transferase effects on liver and brain COMT activity and L-Dopa metabolism. *J Neural Transmission*. 1997; 104:77-97.

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the rat at that exposure level. No elevation of HVA is seen with an inhibition as high as 80%, suggesting that even 20% residual COMT activity is sufficient for a normal metabolism. In that sense, the penetration can be interpreted as non-significant. On the other hand, there is a marked COMT inhibition at that dose level, and it is unclear how these levels translate to the human striatum. The safety margin is relatively slim. Other limitations are that toxicokinetics were not obtained in most of these studies, and entacapone blood concentrations are speculative.

Finally, the sponsor cited two PET studies in PD patients suggest that entacapone does not induce any significant brain COMT inhibition. The first study by Ruottinen et al. showed that increased FDOPA uptake with entacapone, but provide no information on central COMT inhibition<sup>9</sup>. In the second study, by the same author, I found no data or discussion regarding the central effect of entacapone.<sup>10</sup>

Overall, the sponsor's argument against a central COMT inhibition in the human after administration of entacapone is less than compelling, but seems to indicate that even if inhibition occurs, it presumably has no metabolic or clinical consequence, given the residual COMT activity expected if a 200 mg dose is administered.

### 9.2.3 Drug interactions

Interaction studies have shown that entacapone does not interact with the MAO-B inhibitor selegiline, the MAO-A inhibitor meclizemide or the neuronal uptake inhibitor imipramine. On the basis of interaction studies in healthy volunteers, entacapone may potentiate the chronotropic and arrhythmogenic effects of intravenously administered isoproterenol and epinephrine. Many parkinsonian patients in phase II and III studies used dopamine agonists, amantadine or anticholinergic, and other concomitant medications typically administered to the elderly, in combination with entacapone and levodopa/DDC inhibitor, without any apparent interactions. There is no evidence that concomitant use of entacapone in combination with other antiparkinsonian drugs would give rise to clinically significant or hazardous interactions.

The sponsor has recently reviewed the interaction with antidepressants. During the post-marketing phase only incidental reports of suspected interactions have been received during with the use of entacapone together with antidepressants. Of currently available antidepressants only the SSRI paroxetine has been identified to go through O-methylation in its metabolism (carrying a theoretical risk for interaction when O-methylation inhibited by entacapone) and due to limited experience caution is advised when using such a combination.

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<sup>9</sup> Ruottinen EM, Rhine JO, Oikonen VI, Bergman IR, Haaparanta MT, Solin OH, Ruotsalainen UH, Rhine UK. Striatal 6-[18P] fluorodopa accumulation after combined inhibition of peripheral catechol-O-methyltransferase and monoamine oxidase type B: differing response in relation to presynaptic dopaminergic dysfunction. *Synapse* 1997 Dec;27(4):336-46; Ruottinen EM, Niiniviita M, Bergman I, Oikonen V, Solin O, Eskola O, Eronen E, Sonninen F, Rhine UK. Detection of response to COMT inhibition in FDOPA PET in advanced Parkinson's disease requires prolonged imaging. *Synapse* 2001 Apr; 40(1): 19-26

<sup>10</sup> H Ruottinen et al. Striatal 6-F18 fluorodopa accumulation after combined inhibition of peripheral catechol-O-methyltransferase and MAO type B: differing response in relation to presynaptic dopaminergic inhibition.

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**9.3 Summary of Critical Safety Findings and Limitations of Data**

Levodopa combined with carbidopa has been available on the market for over 30 years and large numbers of PD patients have been already treated with this combination. The safety profile of this combination is well established.

The safety of entacapone has been studied by the sponsor and by Novartis in about 3,500 PD patients treated with entacapone, and over ~~---~~ PD patients have been exposed to entacapone up to the end of 2001 (post-marketing).

The tolerability of the LCE 50, LCE 100 and LCE 150 (test) tablets was similar to that seen with the corresponding doses of Sinemet and Comtan (reference) in the four bioequivalence studies. Since entacapone C<sub>max</sub> was not bioequivalent between LCE 150 and the reference products, safety data were important to qualify the safety of the new combination. There were no significant changes in the vital signs or ECGs associated with the test or reference administrations. Particularly, there was no evidence for an increased orthostatism with the LCE combination. The laboratory analyses did not indicate any concern, as expected in these short-term bioequivalence studies. There was a higher incidence of nausea in two bioequivalence studies with the LCE combination, but the opposite was true in the third study, and no nausea at all was seen in the last study. There was no clear association of nausea with the plasma level of any of the drugs, and it is possible that this represents a random variation.

Overall the safety data produced with the fixed combination ICE products indicates no new safety concerns.

**10. Dosing, Regimen, and Administration Issues**

Administration issues are some of the most important of this NDA. The sponsor believes that the LCE combination tablet will offer several advantages for PD patients, mostly a smaller size than current Comtan tablets, and a smaller number of tablets than levodopa/carbidopa tablets and entacapone taken separately. Four different levodopa/carbidopa tablet strengths are currently available in the US, namely 100/10 mg, 100/25 mg, 250/25 mg and sustained-release tablets of 100/25 mg and 200/50 mg. The LCE combination is proposed in three different strengths: 50/12.5 mg, 100/25 mg or 150/37.5 mg of levodopa/carbidopa with 200 mg of entacapone.

The maximum daily recommended dose for entacapone is 1600 mg. This limits the total recommended daily number of LCE combination tablets to eight, regardless of the strength, since all three strengths contain the same amount of entacapone (200 mg). Thus the maximum daily levodopa dose with LCE will be 1200 mg (8 tablets of LCE 150), which is the first disadvantage of the LCE combination. Another disadvantage is that the flexibility in dosing is reduced. In the following sections, I will review and discuss various situations and issues related to initiating the LCE combination or switching the existing levodopa therapy to the LCE combination in these situations.

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**10.1 LCE combination coverage of patients usual levodopa requirement (individual doses and total daily doses)**

The first issue is how comprehensively the LCE combination products will cover individual patient levodopa dose requirements.

**10.1.1 Individual doses**

The sponsor reviewed the data for each individual levodopa dose used by fluctuating PD patients in two phase III studies of the entacapone NDA (“Seesaw” Study 2939044 and “Nomecomt” Study 2939033). The assessment (including approximately 38000 single doses) showed that about 50% of the levodopa dose strengths used were 100 mg and another 30% were 50 mg or 150 mg. Therefore the three combination tablet strengths proposed should cover about 80% of the levodopa dose requirements of fluctuating PD patients. The evaluation of these studies also showed that the majority of patients (approximately 80%) used levodopa/carbidopa products with a ratio 4:1. This ratio is also used in the proposed fixed dose combination product.

**10.1.2 Total daily dose**

An associated issue is how comprehensively will the fixed combination products cover the total daily levodopa dose requirements. The analysis of the entacapone Phase III studies (“Seesaw” and “Nomecomt”) indicated that approximately 70% of patients used ≤ 800 mg levodopa/day (Table 25).

**Table 25: Distribution of daily levodopa doses in Nomecomt (Study 33) and Seesaw (Study 44) studies (from table 2, page 163, Vol. 1.64)**

Levodopa dose (mg)	NOMECOMT		SEESAW		NOMECOMT & SEESAW	
	%	Cumulative	%	Cumulative	%	Cumulative
≤399	9.1	9.1	10.4	10.4	9.8	9.8
400-599	29.9	39.0	29.5	39.9	29.7	39.5
600-799	31.2	70.1	24.6	64.5	27.6	67.1
800-999	11.7	81.8	13.1	77.6	12.5	79.5
≥1000	18.2	100.0	22.4	100.0	20.5	100.0

The Seesaw and Nomecomt studies were initiated in 1993-94. The sponsor states that later studies have shown that total daily levodopa dosages are decreasing. This is shown in Table 26, where the data from two more recent entacapone studies (“Celomen” Study 63 and “UK-Irish” Study 65) and from recently published studies in fluctuating PD patients are displayed. These more recent data suggest that the daily levodopa dose is lower in patients using a combination of levodopa and a dopamine agonist.

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**Table 26: Daily levodopa dose and a mean single dose in recent studies in advanced PD patients. Data are at baseline for total group. In addition, levodopa dose at the end of study with a dopamine agonist or a COMT inhibitor is given in parentheses (from Table 3, page 164, Vol. 1.64)**

Study [reference]	Study drug	n (n for active drug)	Mean daily levodopa dose; mg	Mean daily dosing frequency	Mean single dose; mg
Celomen [5]	Entacapone	301 (197)	571 (530)	5.5	106
UK-Irish [6]	Entacapone	300 (203)	612 (584)	4.2	146
Olanow et al. 1994 [7]	Pergolide	378 (189)	911 (656)	na	na
Baas et al. 1997 [8]	Tolcapone	177 (119)	668 (555)	na	na
Kurth et al. 1997 [9]	Tolcapone	161 (119)	848 (807)	6.3	135
Lieberman et al. 1997 [10]	Pramipexole	351 (179)	831 (634)	na	na
Myllylä et al. 1997 [11]	Tolcapone	154 (96)	733 (678)	6.1	120
Rajput et al. 1997 [12]	Tolcapone	202 (136)	866 (640)	5.4	160
Adler et al. 1998 [13]	Tolcapone	215 (143)	840 (618)	5.7	145
Lieberman et al. 1998 [14]	Ropinirole	149 (95)	789 (517)	na	na
The Tolcapone Study Group [15]	Tolcapone Bromocriptine	146	765	na	na
Pinter et al. 1999 [16]	Pramipexole	78 (34)	569 (511)	na	na
Hutton et al. 2001 [17]	N-0923	67 (55)	782 (607)	na	na

n, number of patients; na, not available

**COMMENT:** the dose reduction of levodopa over the years is modest at best, since for example in the last study cited, the Hutton Study, the average levodopa dose was 782 mg without agonist or COMT inhibitor, and 607 mg with an agonist or an inhibitor. This dosage range appears very similar (even higher) than that of earlier trials. Also, the sponsor did not provide a distribution of doses in these studies, as in the Nomecont and Seesaw studies, such as a direct comparison is different. In addition, the population studied may have been different as well. Overall, that type of comparison is very difficult.

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**10.2 Initiation of LCE combination in patients on levodopa/carbidopa, and entacapone, administered separately****10.2.1 Patients receiving individual doses corresponding to LCE tablet dosages, with a total daily dose under 1200 mg**

The sponsor believes that there should be no difficulties in initiating treatment with the LCE combination products in patients currently using entacapone and levodopa/carbidopa when a corresponding-dose triple combination product is available. The sponsor proposes that these patients can be switched directly to the corresponding-dose triple combination product.

**COMMENT:** this is the easier situation, and I concur that direct switching should not be an issue in this case.

**10.2.2 Patients receiving individual doses not corresponding to LCE tablet dosages, with a daily dose under 1200 mg**

The sponsor proposes that for patients not currently receiving a dose covered by the three LCE strengths some levodopa dosage modifications may be needed. However, as far as possible the daily levodopa dose should remain the same on switching to the LCE formulation. For patients who use an individual levodopa dose of 200 mg or more with entacapone, there is no corresponding dose option in the LCE products.

**COMMENT:** the sponsor here is suggesting that patients have their schedule of administration adjusted, or their individual doses modified to allow administration of LCE tablets. I do not support that recommendation. If patients receive levodopa doses not covered, the LCE combination is not suited, except if there is a valid reason to decrease the levodopa dosage. It is often difficult to fine tune levodopa dose schedule in advanced PD patients, and the benefit offered by the LCE combination does not outweigh, in my opinion, the risk of breaking the balance of levodopa schedule of administration.

**10.2.3 Patients receiving total levodopa daily doses above 1200 mg**

Since the maximum daily recommended dose for entacapone is 1600 mg, the total recommended daily number of LCE combination tablets is limited to eight, which in turn limits the maximum daily levodopa dose to 1200 mg (8 tablets of LCE 150). The sponsor suggests that in these patients it is possible to use either triple combination tablets and conventional levodopa/carbidopa tablets.

**COMMENT:** combining LCE tablets and separate products is a source of confusion, and would probably lead to administration errors. The LCE combination should be discouraged in this setting. The case for the 50-200 mg sustained-release tablet may be different, since smaller doses of levodopa with entacapone in the LCE combination may provide a similar effect, but this situation should be evaluated in clinical studies to support that type of switching.

**10.2.4 Patients on Sinemet CR (sustained-release)**

The sponsor proposes that it may be possible to switch fluctuating PD patients currently using sustained-release levodopa/carbidopa and entacapone to the triple combination products. The sponsor notes that the bioavailability of levodopa from sustained-release products is about 70-75% relative to the standard levodopa/carbidopa products. The sponsor estimates that the levodopa AUC produced by Sinemet CR 50-200 + entacapone 200 mg should be approximately comparable to that produced by the 150/37.5/200 mg triple combination tablet. Another point to consider is that the levodopa absorption profiles for the sustained-release and combination products are different. Levodopa is absorbed rapidly from LCE combination tablets ( $T_{max}$  1-1.5 h) whereas absorption is delayed for Sinemet CR products ( $T_{max}$  2-3 h).

**COMMENT:** In my opinion, given the PK differences between Sinemet and Sinemet CR, switching from Sinemet CR to the triple combination is not recommended. There are many changes involved in this situation, i.e. different pharmacokinetics of levodopa (sustained-release to immediate release), and COMT inhibition. This is clearly a situation where a maximum of flexibility is needed, and separate drug products should be used instead of a fixed preparation. Alternatively, the sponsor may design a study to investigate that situation.

**10.2.5 Patients taken levodopa/carbidopa tablets with a ratio different from 4:1 (i.e. 10:1)**

Levodopa products with two different levodopa/carbidopa ratios, 4:1 and 10:1 are currently available in the United States. In the LCE combination tablets, the ratio chosen is 4:1. The sponsor suggests that the minimum daily carbidopa dose should be 70-75 mg to ensure effective peripheral dopa decarboxylase inhibition, and that the amount of carbidopa in products with the 10:1 ratio, (especially in the 100/10 mg product), may not be sufficient for effective peripheral DDC inhibition.

There is evidence in clinical studies to indicate that the levodopa: carbidopa ratio of 4:1 is used more frequently. For instance in the Seesaw study (part of the entacapone NDA), 21 % patients used Sinemet with the 10:1 ratio, and 8% used a mix of the 10:1 and the 4:1 ratio. The sponsor conducted Study 83 (see section 5.2.1) to support that patients currently using levodopa/carbidopa products with a ratio 10:1 can be switched to the LCE product. In Study 83, entacapone increased levodopa AUC similarly irrespective of the levodopa/carbidopa ratio. Consequently, the sponsor suggests that there should be no problems initiating the triple combination preparation in PD patients who use entacapone with levodopa/carbidopa in a ratio 10:1.

**COMMENT:** In Study 83, the sponsor provided good evidence that entacapone increases levodopa AUC similarly irrespective of the levodopa/carbidopa ratio. However, as exemplified by the direct comparison of levodopa/carbidopa 100/10 and 100/25 (without entacapone) in that study, the higher dose of carbidopa in products with the 1:4 ratio may lead to higher exposure to levodopa – independently of the entacapone effect -, i.e. levodopa AUC was 1209 with the 100/10 product and 1434 with the 100/25 product. This means that switching from individual levodopa/carbidopa products with the 10:1 ratio to the LCE combination would induce a higher exposure to levodopa, regardless of the effect of entacapone.

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**10.2.5 LCE combination initiation in patients on levodopa treatment but who have not been previously treated with Comtan.**

The sponsor argues that in principle, initiation of treatment with the triple combination product is no different than initiation of treatment with Comtan (entacapone). However, due to the fixed combination of levodopa-carbidopa-entacapone strengths in LCE tablets, the most important issue is the possible need for a change in the daily levodopa dose after initiating treatment with entacapone. As entacapone may intensify the dopaminergic adverse effects of levodopa, such as dyskinesia, nausea, or orthostatic hypotension, the present Comtan labeling recommends to reduce the daily levodopa dose especially in those patients whose daily levodopa dose is >800 mg or if patients have moderate or severe dyskinesias before beginning entacapone. Based on the available data at the time of Comtan approval, a dose reduction was required in 58% patients.

The sponsor has further analyzed the databases from clinical studies relevant for this issue and believes that PD patients without previous dyskinesias can be treated successfully by direct initiation of treatment with LCE. The sponsor analyzed data from the four placebo-controlled studies (6 month double-blind) part of the entacapone NDA. The main emphasis of the analysis was to identify baseline indicators for levodopa dose reduction when entacapone was initiated in PD patients with end of dose wearing off (EODWO). Of these studies the Nomecomt (Study 33) and the Seesaw (Study 44) studies included only fluctuating PD patients (n=171 and n=205, respectively). In the Celomen (Study 63) and UK-Irish (Study 65) studies, 84% (n=260, total n=301) and 57% (n=172, total n=300) of patients, respectively, were fluctuating based on the diary data obtained at study entry. Entacapone or placebo was added to the levodopa/DDC inhibitor treatment for 6 months. Other antiparkinsonian drug treatments were allowed and their dosages were kept stable. In these studies, daily levodopa dose was decreased by 40 to 100 mg with entacapone, compared to placebo.

The sponsor's analysis included baseline levodopa dose, dyskinesia status (based on the UPDRS part IV question 32), and duration of levodopa therapy and OFF status (UDPDRS part IV question 39). Of these variables, the presence of dyskinesia and the total daily levodopa at baseline were predictive of the need for levodopa dose reduction after the initiation of entacapone treatment. In 96% of patients who do not experience dyskinesias and whose levodopa dose is <600 mg/day, entacapone was initiated without change of daily levodopa dose. The higher the daily levodopa dose and the more dyskinesias the patient has at baseline the more frequently there was a need to reduce the daily levodopa dose when entacapone was started. Dyskinesias seemed more predictive for levodopa dose reduction than the daily levodopa dose (Table 27).

**Table 27: Proportion of patients decreasing levodopa dose after entacapone initiation as grouped by baseline levodopa dose and presence of dyskinesia (data from entacapone studies 33, 44, 63, 65, from ISS table 14.1).**

	Levodopa < 600 mg/day (N=180)	Levodopa 600-800 mg/day (N=153)	Levodopa > 800 mg/day (N=105)
No dyskinesia (N=159)	4 %	21 %	28 %
Dyskinesia present (N=279)	31 %	43 %	66 %

Reference: ISS Table 14.1, ISS Post-text Table 10

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The sponsor compared entacapone between patients with and without dyskinesias (Table 28). The benefits to motor fluctuations and clinical disability were comparable between the groups.

**Table 28: Effects of entacapone on time, off time, ADL and motor scores in fluctuating patients grouped by their baseline dyskinesia status (Studies 33, 44, 63 and 65) (from table 6, page 141, Vol. 1.64).**

Variable	Patient group	n	Baseline	At month 6	Change
ON time (h)	No dyskinesia	164	9.8 (2.5)	10.9 (2.9)	1.1 (2.8)
	Dyskinesia presence	283	9.7 (2.5)	11.2 (2.7)	1.4 (2.6)
OFF time (h)	No dyskinesia	164	6.1 (2.6)	5.1 (3.1)	-1.1 (2.6)
	Dyskinesia presence	283	6.6 (2.7)	5.1 (2.8)	-1.4 (2.4)
UPDRS 2 (ADL)	No dyskinesia	169	11.6 (5.9)	10.3 (5.6)	-1.2 (3.4)
	Dyskinesia presence	296	12.5 (5.8)	11.4 (6.2)	-0.7 (3.7)
UPDRS 3 (motor)	No dyskinesia	169	24.5 (12.1)	20.4 (11.6)	-4.4 (8.7)
	Dyskinesia presence	294	23.8 (12.6)	21.2 (12.6)	-2.7 (8.5)

UPDRS, Unified Parkinson's Disease Rating Scale

The overall rate of patients with or without pre-existing dyskinesia completing these studies was comparable (80.1% versus 82.8%). Adverse events were reported less frequently by patients without pre-existing dyskinesia compared to those with pre-existing dyskinesia (Table 29). In patients without pre-existing dyskinesia, the rate of dyskinesia as an adverse event was not different between the entacapone and placebo groups (9.2% vs. 12.0%, respectively). The sponsor believes that this indicates that the tolerability of Comtan when added to levodopa in PD patients without dyskinesia is good (and better than in patients already experiencing dyskinesia, as would be expected due to the difference between the disease stage of these patients). The sponsor does not expect that direct the initiation of LCE with corresponding dose strengths for patients without pre-existing dyskinesia to have any significant reduction in the tolerability compared to Comtan added separately. COMMENT: This mostly applies, in my opinion, to patients with a total daily dose of levodopa prior to the conversion not exceeding 600 mg. It clearly does not apply to patients with a total daily dose exceeding 800 mg (see Table 27), where about 28% of patients are expected to need a levodopa dose reduction.

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Table 29: Most common adverse events (>5%) reported by the presence of dyskinesia at baseline in PD patients with EODWO (studies 33, 44, 63 and 65) (from table 14.4, ISS, page 238, Vol. 1.64)

Adverse Event	Entacapone N=447		Placebo N=333	
	Dyskinesia + N=283 %	Dyskinesia - N=174 %	Dyskinesia + N=225 %	Dyskinesia - N=108 %
Dyskinesia	35.2	9.2	4.4	12.0
PD aggravated	19.6	9.8	18.7	17.6
Nausea	15.0	13.8	6.2	5.6
Hyperkinesia	14.3	5.7	6.2	2.8
Urine abnormal	14.0	11.5	0	0
Diarrhoea	10.3	11.5	4.4	5.6
Hypokinesia	8.3	11.5	8.4	6.5
Dizziness	10.6	9.2	5.8	8.3
Constipation	8.0	10.3	4.0	2.8
Tremor	3.3	9.2	4.4	12.0
Abdominal pain	6.3	8.6	3.6	6.5
Insomnia	7.6	2.9	7.1	7.4
Fatigue	3.3	6.9	3.6	2.8
Back pain	4.3	6.3	2.2	3.7
Pain	5.0	6.3	3.6	5.6
Fall	6.0	4.0	6.2	4.6
Hallucination	4.3	5.7	4.9	4.6

Reference: ISS Table 14.4, ISS Post-text Table 12

10.2.6 Overdosage

There have been no reported cases of either accidental or intentional overdose with the combination of levodopa, carbidopa and entacapone. There have been no postmarketing reports worldwide of either accidental or intentional overdose with entacapone. COMT inhibition by entacapone is dose-dependent. A massive entacapone overdose may theoretically produce 100% inhibition of the COMT enzyme, thereby preventing the O-methylation of endogenous and exogenous catecholamines. The highest single dose of entacapone in clinical studies was 800 mg, resulting in a maximum plasma concentration of  $\sim$   $\mu$ g/ml, and the highest daily dose was 2400 mg, administered in one study as 400 mg six times daily with levodopa/carbidopa for 14 days in 15 Parkinson's disease patients and in another study as 800 mg t.i.d for 7 days in 8 healthy volunteers. At this daily dose, the peak plasma concentrations of entacapone averaged 2.0  $\mu$ g/ml (compared to 1.2  $\mu$ g/ml with 200 mg entacapone). Abdominal pain and loose stools were the most commonly observed adverse events during these studies. Clinical experience with daily doses above 1600 mg is limited

Reports of levodopa-carbidopa or levodopa-benserazide overdose reported in the published literature are also very limited. The sponsor identified four reports of levodopa overdose in the literature. In 1975 Hoehn and Rutledge reported a case of a 61-year-old parkinsonian patient, who ingested approximately 100 g of levodopa in a period of 12 hours. The patient developed initial hypertension rapidly followed by hypotension of a few hours duration, prolonged symptomatic postural hypotension, sinus tachycardia, mental confusion, insomnia, and anorexia.

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These symptoms gradually subsided over the course of 1 week<sup>11</sup>.

In 1991 Sporer described the case of a 57-year-old woman, who developed choreiform movements after ingestion of 15 to 17 tablets of carbidopa-levodopa 10/100 tablets (carbidopa 150 mg and levodopa 1500 mg) along with ibuprofen, carisoprodol, hydrocodone and acetaminophen. The choreiform symptoms persisted despite treatment with naloxone, morphine and diazepam. Due to elevated levels of serum creatine phosphokinase followed by myoglobinuria she required treatment with non-depolarising muscle relaxants and ventilatory support for a period of 60 hours, after which her chorea resolved<sup>12</sup>.

The third report is a case of a voluntary levodopa intoxication in an 84-year-old male described by Barcat et al<sup>13</sup>. The patient had no medical history other than Parkinson's disease and severe depression. Although he administered 60 tablets of Madopar 125 mg (levodopa/benserazide) in a suicide attempt, his hemodynamic condition remained stable throughout the event. Rapid atrial fibrillation observed on day 1 was converted to sinus rhythm by amiodarone. On the 3rd day increased serum urea nitrogen and creatinine were observed and the patient became oliguric. The patient's renal insufficiency was treated with intravenous fluid and furosemide and gradually improved during the following month.

Stuerenburg and Schoser illustrated in 1999 the case of a 76-year-old man with chronic lung disease (treated with a home oxygen appliance) and Parkinson's syndrome, who took simultaneously 30 tablets of carbidopa/levodopa (50/200 mg)<sup>14</sup>. The patient became anxious and depressed half an hour after taking the tablets, followed by agitation, hallucinations and restlessness during the next hour, arterial hypertension and sinus tachycardia were also observed. According to the report, all of the neuropsychiatric signs of levodopa intoxication were resolved one day later. The peak serum concentration of levodopa was > 66000 ng/ml, which is about 30 times higher than that to be expected after taking one tablet of 50/200 mg of carbidopa/levodopa, this decreased in 15 hours to almost normal levels.

**COMMENT:** I also conducted a Medline search (MeSH browser) for "levodopa" and toxicity. I found all four reports cited by the sponsor, plus and additional one, for which no abstract was available<sup>15</sup>.

Based on these reports, major overdosages of levodopa is most likely to be associated with the central symptoms of dopaminergic overstimulation (as in the case reported by Sporer), while more modest overdosages are more likely to be associated with hemodynamic changes (e.g. hypotension, tachycardia) and with psychiatric symptoms (as in the case reported by Hoehn and

<sup>11</sup> Hoehn MM, Rutledge CO. Acute overdose with levodopa. Clinical and biochemical consequences. *Neurology*. 1975 Aug;25(8):792-4

<sup>12</sup> Sporer KA. Carbidopa-levodopa overdose. *Am J Emerg Med*. 1991 Jan;9(1):47-8

<sup>13</sup> Barcat D, Constans J, Delpeu K, Banwarth B, Conri C. Acute renal failure after massive voluntary intoxication with levodopa (MODOPAR)]. *Therapie*. 1998 Nov-Dec;53(6):598-600.

<sup>14</sup> Stuerenburg HJ, Schoser BG. Acute overdosage and intoxication with carbidopa/levodopa can be detected in the subacute stage by measurement of 3-o-methyldopa. *J Neurol Neurosurg Psychiatry*. 1999 Jul;67(1):122-3.

<sup>15</sup> Giovine A, Renis M, Bertolino A. In vivo studies of catechol-O-methyl transferase activity following intoxication with ethanol, L-dopa and dopamine-derived alkaloids. *Pharmacol Res Commun*. 1977 Feb;9(2):203-14

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Rutledge).

**11. Use in Special Populations**

**11.1 Evaluation of Evidence for Gender, Age, Race, or Ethnicity Effects on Safety or Efficacy**

There is no difference in pharmacokinetics of entacapone between young adults and elderly people (entacapone NDA). I verified that statement in the clinical review of Dr. Richard Tresley, who reviewed the original entacapone NDA. Both male and female elderly subjects were included in three main bioequivalence studies since PD occurs in both sexes and patients are generally over 40 years of age. Sex or age does not have influence on the efficacy and safety of entacapone (based on the entacapone NDA).

There may be differences in levodopa pharmacokinetics between young and elderly subjects and also between sexes. First, some studies indicate that levodopa clearance is reduced in elderly subjects and consequently levodopa AUC is higher in elderly than young subjects. Second, the bioavailability of levodopa may be greater in women than in men. However, there is no difference in levodopa pharmacokinetics between healthy aged subjects and PD patients. No published data are available on the effect of age and sex on the pharmacokinetics of carbidopa.

The sponsor compared AEs incidence by sex in the three bioequivalence studies which included patients of both sexes (Study 93, 95 and 96). There was an overall tendency for females on both study treatments to report more adverse events than males. However, there were no significant differences in the rates of adverse events occurring by sex between the test and reference groups (Table 30).

**Table 30 AEs by sex in study 93, 95 and 96 (from Table 9.7, page 218, Vol. 1.64)**

Adverse event	Females N = 68		Males N = 64	
	Test N (%)	Reference N (%)	Test N (%)	Reference (N%)
Headache	16 (23.5)	19 (27.9)	9 (14.1)	3 (4.7)
Nausea	12 (17.6)	12 (17.6)	7 (10.9)	2 (3.1)
Upper resp tract infection	4 (5.9)	2 (2.9)	3 (4.7)	0 (0.0)
Fatigue	4 (5.9)	3 (4.4)	0 (0.0)	0 (0.0)
Vomiting	4 (5.9)	5 (7.4)	2 (3.1)	0 (0.0)
Dizziness	2 (2.9)	4 (5.9)	0 (0.0)	0 (0.0)
Diarrhoea	3 (4.4)	2 (2.9)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza-like symptoms	2 (2.9)	0 (0.0)	3 (4.7)	0 (0.0)
Back pain	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	1 (1.5)	2 (2.9)	0 (0.0)	0 (0.0)

Reference: Post-text Table 4

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The sponsor also compared AEs by age from Study 93, 95 and 96 (Study 85 only included young males). There was no significant difference between age groups. In subjects under age 60, nausea appeared more frequent with LCE (13.3%) than with the test drug (6.7%).

### 11.2 Evaluation of Pediatric Program

The sponsor requested a waiver for pediatric studies, given the age distribution of Parkinson's disease, which occurs almost exclusively in the adult population. I recommend that a waiver be granted.

### 11.3 Comments on Data Available or Needed in Other Populations

#### 11.3.1 Pregnancy

Pregnancy Category C. In embryofetal development studies, increased incidences of fetal variations were evident in litters from rats treated with the highest dose (maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximum recommended daily dose (MRDD) of 1600 mg), in the absence of overt signs of maternal toxicity. Increased frequencies of abortions and late/total resorptions and decreased fetal weights were observed in the litters of rabbits treated with maternotoxic doses (plasma AUCs 0.4 times those in humans receiving the MRDD). There was no evidence of teratogenicity in these studies. However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in the litters of dams treated with doses leading to exposure corresponding to seven times the human exposure at MRDD, in the absence of maternotoxicity. Administration to female rats of doses leading to exposure 28 times higher than exposure in humans at MRDD, during the latter part of gestation and throughout lactation, produced no evidence of developmental impairment in the offspring. The LCE combination combines entacapone with carbidopa-levodopa. Carbidopa-levodopa caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa-levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa-levodopa to 20 times/10 times the maximum recommended human dose of carbidopa-levodopa. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. Use of the LCE combination in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child. There is no experience from clinical studies regarding the use of the LCE combination in pregnant women. In animal studies, carbidopa and entacapone were excreted into maternal rat milk. It is not known whether entacapone or carbidopa-levodopa is excreted in human milk.

#### 11.3.2 Liver insufficiency

The pharmacokinetics of entacapone have been studied in patients with liver cirrhosis (entacapone NDA). Entacapone AUC and C<sub>max</sub> were almost doubled in patients with mild to moderate liver impairment. The effect of hepatic impairment on the pharmacokinetics of levodopa and carbidopa has been poorly investigated, and the sponsor and I could not find any

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publication on the topic in the literature. The current Comtan label recommends that patients with hepatic impairment be treated with caution when levodopa/carbidopa/entacapone is given.

### 11.3.3 Renal insufficiency

The pharmacokinetics of entacapone in patients with moderate to severe renal insufficiency has been studied in the entacapone NDA. The impaired renal function did not change clinically significantly the pharmacokinetic of entacapone. The sponsor could find no published data on the effect of renal impairment on the pharmacokinetic of levodopa and carbidopa. The Sinemet label recommends administering Sinemet cautiously to patients with severe renal disease.

**COMMENT:** I did a Medline search with the keywords "levodopa" and "renal and "failure". I could not identify any relevant article, out of 41 "hits". With the keyword "levodopa" AND "liver" and "failure", I found no information relevant to the pharmacokinetics of levodopa in case of renal failure (68 hits). Instead, I found several articles citing a use of levodopa as a symptomatic treatment in patients with liver failure.

## 12. Conclusions and Recommendations

### 12.1 Conclusions

The sponsor developed a fixed dose combination tablet containing three previously marketed active agents, levodopa, carbidopa and entacapone. The proposed doses are 50/12.5/200mg, 100/25/200mg, and 150/37.5/200mg of levodopa/carbidopa/entacapone (LCE), respectively. Each strength consists of a 4 to 1 ratio of levodopa to carbidopa and a fixed dose of 200mg entacapone. The proposed indication is the treatment of patients with idiopathic Parkinson's disease (PD) who experience the signs and symptoms of end-of-dose "wearing off" (same as current entacapone indication).

The application is based on bioequivalence studies between the fixed dose combination and the individual products. The safety and efficacy evaluation relies mostly of the clinical experience with the individual products, both as evaluated in their respective NDAs and in the post-marketing experience. This experience is relevant, since entacapone is already used exclusively in association with levodopa/carbidopa, and the risk/benefit of the fixed dose combination tablet is essentially the risk/dose benefit of entacapone itself, with a few differences however.

In terms of benefit, the fixed dose combination allows patients to simplify their therapy by taking a smaller number of tablets, i.e. one instead of two at each dosing time. Fixed dose combination tablets are also smaller, and possibly easier to swallow.

In terms of safety, the main difference with individual products is that by definition the fixed dose removes part of the flexibility in administering these drugs, which may be problematic in some of these patients with advanced Parkinson's disease. This poses some issues at the time of treatment initiation, when the dose of levodopa may need to be adjusted (reduced) in some patients, and also limits the population which may use the fixed dose combination, since the total

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daily levodopa dosage is limited by the recommended maximum number of tablets administered daily – eight – because entacapone daily dose may not exceed 1600 mg. An additional safety issue is the confusion induced by the availability of a new form of levodopa tablet, and possible administration errors, especially if patients are prescribed levodopa in different formulation (i.e. both Sinemet and the fixed dose combination).

In bioequivalence studies, the fixed dose combination tablet was not fully bioequivalent to the individual products, because entacapone  $C_{max}$  exceeded the upper limit of the confidence interval (CI) in two studies (mostly in one study with the 150/37.5/200mg preparation – 12% above upper CI limit, and to lesser degree in one study with the 100/25/200mg, where entacapone  $C_{max}$  exceeded the upper CI limit by 0.5%). This bioinequivalence was expected by the sponsor and discussed prior to the studies by the sponsor, given the known variability in entacapone pharmacokinetics. The Agency agreed to consider safety data in case the fixed dose combination was not fully bioequivalent – which occurred. One of the main concerns was about the possibility of levodopa toxicity, with adverse events associated, such as orthostatic hypotension, or nausea.

Safety data were overall reassuring, with no difference in vital signs and no increased incidence of orthostatic hypotension. There was some evidence in two studies that nausea may be more frequent with the fixed dose combination, but this was not supported by the two other studies, so that the evidence remains unconvincing. From a clinical perspective, I don't view the  $C_{max}$  bioinequivalence of entacapone as an issue holding approval, for several reasons. First, the fixed dose combination was bioequivalent for levodopa and carbidopa. Since the clinical effect of entacapone is not direct, but the result of the effect of entacapone on levodopa pharmacokinetics, the bioinequivalence of entacapone ( $C_{max}$ ) is less of an issue. Second, the fixed dose combination was bioequivalent for entacapone AUC in all studies, and AUC may be more clinically relevant than  $C_{max}$  for this drug, given its indirect effect through levodopa metabolism. Third, entacapone pharmacokinetics variability was known before this study, and it was expected that entacapone would not be bioequivalent in some studies, given the prior knowledge of this drug. Fourth, entacapone has a large therapeutic index.

In my opinion, most the issues reside in the dosing and initiation of the drug. I don't see any significant issue in switching patients already taking the individual drug products to the corresponding dose of the fixed dose combination, or initiating the fixed dose combination in patient who don't experience dyskinesia and who receive a daily levodopa dose up to 600 mg daily. In all other situations, I consider that patients should be titrated with the individual drug products prior to switching to the LCE combination, because dose adjustment are likely to be necessary, and the fixed dose combination does not provide the flexibility needed in that situation.

## 12.2 Recommendations

On a clinical perspective, I recommend approval of the fixed dose combination tablet, but with changes from the sponsor's proposal in the dosage and administration of the fixed dose combination.

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I agree to allow direct initiation of the fixed dose combination in patients already receiving a corresponding dose of individual products, or in patients with no dyskinesia and who receive a total daily dose of levodopa up to 600mg.

For the following situations, I recommend re-titration with the individual drug products prior to switching to the fixed dose combination:

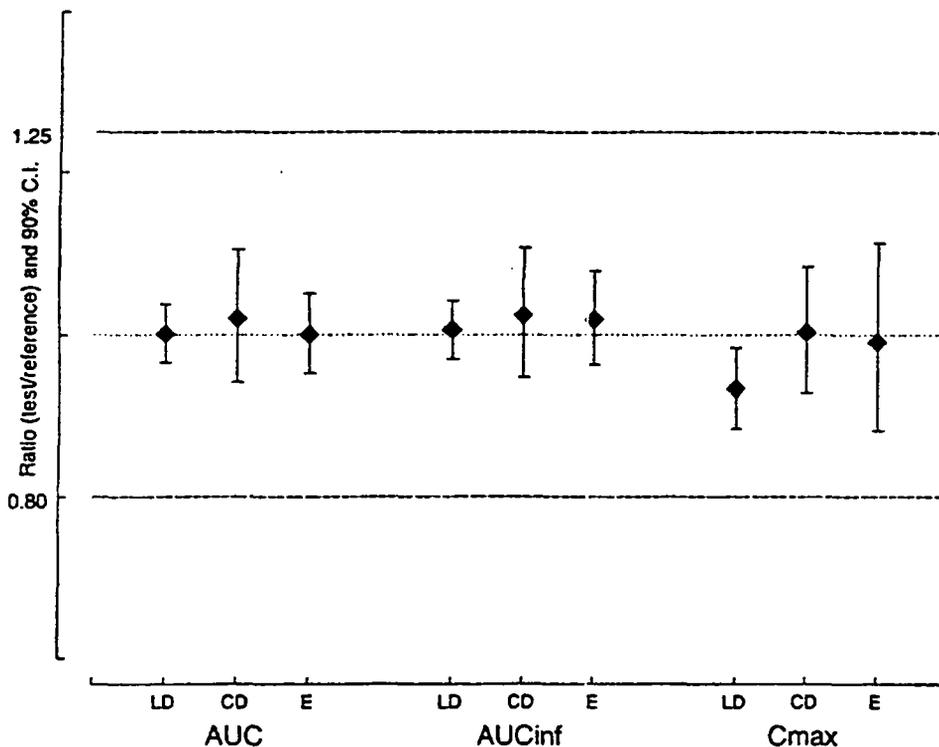
- Patients on Sinemet CR (sustained-release)
- Patients taken levodopa/carbidopa tablets with a ratio different from 4:1 (i.e. 10:1)
- Patients receiving a total daily levodopa dose above 600 mg
- Patients experiencing dyskinesia.

**13. Appendix****13.1 Individual Study Reviews (Safety)****13.1.1 Study 85**

Study 85 report is presented in volumes 65-68. Study 85 compared the LCE 100/25/200 combination with Sinemet 100/25 and entacapone 200 mg. The study design is reviewed in section 5.1.1. This was a single-dose, randomized, replicate, crossover study with four study periods separated by at least two weeks. 41 subjects out of 44 randomized (young healthy Caucasian male volunteers) completed all four study treatment periods. Mean age was 24y ±4.3; range 20-38y. This study had a limited assessment of safety. On pre- and post-study visits, laboratory tests, and a 12-lead ECG was recorded in the supine position, and diastolic/systolic blood pressure and heart rate were measured in the sitting position and after at least 2 minutes of rest. Given the absence of ECG or vital sign evaluation close to the study drug administration time, very limited information was expected from these measurements. Pharmacokinetic (PK) results are summarized in Figure 14. PK Results are also discussed in section 5.1.1.

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Figure 14: Confidence interval for the ratio between the means of treatments for levodopa(LD), carbidopa (CD) and entacapone (E) in Study 85.



Three subjects discontinued the study prematurely. One subject discontinued due to an adverse event of fatigue, (moderate intensity), nausea, vomiting, and faintness starting 30 minutes after taking the LCE tablet, and continuing for 2.5 hours (first treatment period). The AE was considered related to the study drug. One subject withdrew his consent to the study after the second treatment period and one subject discontinued-due-to-personal reasons after the third treatment period. No serious adverse events were reported in this study.

The adverse events (AEs) reported were all mild or moderate. Altogether, 25 (57%) subjects reported 68 AEs on the test treatment and 24 (55%) subjects reported 49 AEs on the reference treatment (respectively 16 and 6 AEs were treatment-related). Headache, nausea and dizziness were the most typical AEs. I noticed a higher incidence of headache, nausea, and dizziness with the test drug. The drugs were bioequivalent in this study, so that these observations are probably observed by chance (Table 31). Also, when only treatment related AEs are considered, these differences disappear (Table 32). There was no death or serious adverse event in this study.

As expected, ECG, vital signs and laboratory tests did not identify any particular safety signal. ECG was normal for all subjects at the pre- and post- study visit. There were no clinically significant changes in individual laboratory assessments at the pre- and post-study visit.

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Individual changes in blood pressure and heart rate were small and unlikely to have any significance.

**Table 31: Adverse events in study 85 (from table R7, page 46, Vol 65).**

**Table R7 Number of subjects reporting adverse events (subject count) after the test and the reference treatment**

Adverse event	Test treatment (N=44)		Reference treatment (N=44)	
	N	%	N	%
headache	16	36.4	12	27.3
upper respiratory tract infection	6	13.6	6	13.6
rhinitis	5	11.4	4	9.1
dizziness	6	13.6	2	4.5
nausea	6	13.6	1	2.3
fatigue	4	9.1	2	4.5
diarrhea	3	6.8	2	4.5
pharyngitis	2	4.5	2	4.5
back pain	2	4.5	1	2.3
allergic reaction	1	2.3	1	2.3
pain			2	4.5
hypoesthesia			1	2.3
vomiting	1	2.3		
stomatitis	1	2.3		
abdominal pain	1	2.3		
flatulence	1	2.3		
coughing			1	2.3
asthenia	1	2.3		
leg pain	1	2.3		
pain			2	4.5
skeletal pain			1	2.3
sweating increased			1	2.3
allergy	1	2.3		
arrhythmia	1	2.3		
myalgia			1	2.3
tendon disorders	1	2.3		
injection site pain	1	2.3		
dermatitis fungal			1	2.3
skin disorder			1	2.3
fall	1	2.3		

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**Table 32: Treatment-related adverse events in Study 85**

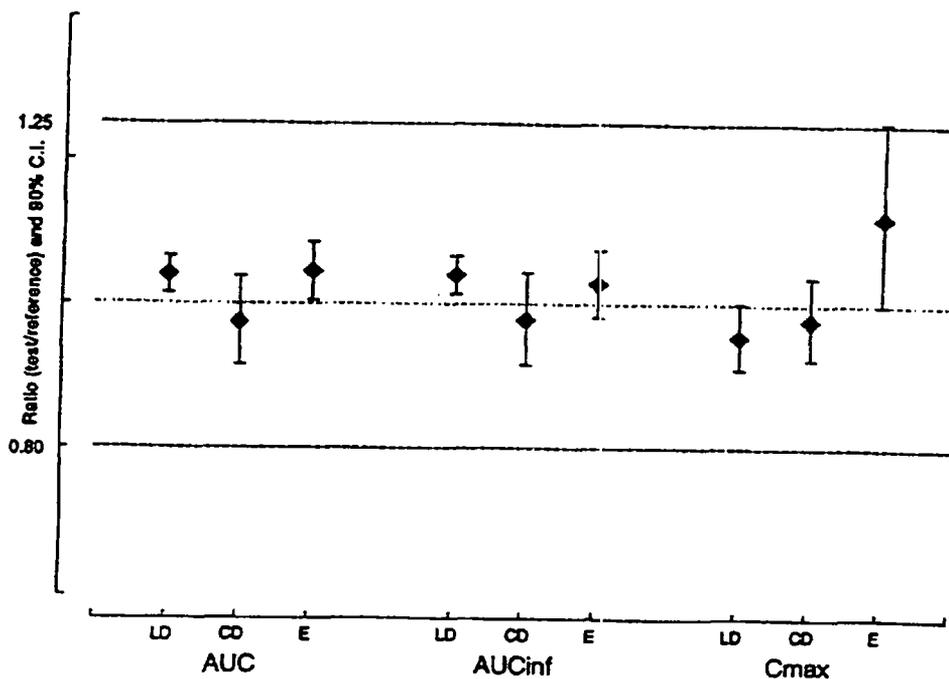
**Table R8** Number of subjects reported ADRs (subject count) after the test and reference formulations.

Adverse reaction	drug	Test treatment		Reference treatment	
		No	%	No	%
headache		4	9.1	3	6.8
dizziness		3	6.8	1	2.3
nausea		3	6.8		
diarrhea		1	2.3	2	4.5
fatigue		2	4.5		
vomiting		1	2.3		
flatulence		1	2.3		

**13.1.2 Study 93**

Study 93 was a bioequivalence study comparing the levodopa/carbidopa/entacapone 100/25/200 mg combination tablet with Comtess 200 mg tablet administered with Sinemet 25-100 mg tablet after a single oral dose in healthy volunteers. The study design is reviewed in section 5.1.1. This was a single-dose, randomized, 2-sequence, replicate, crossover study with four study periods separated by at least a 3 weeks washout period. Safety was assessed at each study visit by vital signs (blood pressure, heart rate and body temperature, before dosing and 1, 2, 5, 8, and 10 hours thereafter, ECG before dosing and 1, 2, and 9 hours thereafter) and at pre- and post-study visit. The safety laboratory parameters were determined at pre- and post-study visits. Pharmacokinetic results are summarized in Figure 15. Entacapone was not fully bioequivalent ( $C_{max}$ ), but the CI excess was minimal (0.01), and not clinically significant (see 5.1.1 for discussion).

**Figure 15: Confidence interval for the ratio between the means of treatments for levodopa (LD), carbidopa (CD) and entacapone (E) in Study 93.**



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A total of 42 out of 44 subjects completed all four study treatment periods. All subjects were Caucasians (27F-17M). Mean age was  $59 \pm 8.3$  y. Age range was 45-72 y.

Two subjects discontinued the study prematurely; one subject discontinued due to an adverse event (upper respiratory tract infection eight days after the third treatment period) and one subject withdrew his consent to the study after the third treatment period. No serious adverse events were reported in this study. The adverse events (AEs) reported were all of mild or moderate severity. 27 (61%) subjects reported 79 AEs on the test treatment and 24 (55%) subjects reported 80 on the reference treatment (respectively 28 and 25 events were considered treatment-related).

**Table 33: Number of subjects reporting adverse events in study 85 (from table R7, page 47, Vol. 69).**

Table R7. Number of subjects reporting adverse events (subject count) after test or reference formulation

Adverse event	Test formulation (N=44)		Reference formulation (N=44)	
	N	%	N	%
headache	13	29.5	12	27.3
nausea	6	13.6	8	18.2
upper respiratory tract infection	7	15.9	3	6.8
vomiting	4	9.1	5	11.4
fatigue	4	9.1	3	6.8
dizziness	2	4.5	5	11.4
diarrhea	3	6.8	2	4.5
insomnia	2	4.5	2	4.5
back pain	2	4.5	1	2.3
traumatic hematoma	2	4.5	1	2.3
pharyngitis	1	2.3	2	4.5
herpes simplex	1	2.3	2	4.5
influenza-like symptoms	2	4.5	0	0
myalgia	2	4.5	0	0
hypotension postural	1	2.3	1	2.3
hypokinesia	1	2.3	0	0
constipation	1	2.3	0	0
Tooth-ache	1	2.3	0	0
coughing	1	2.3	0	0
dyspnea	1	2.3	0	0
arthritis	1	2.3	0	0
ischial neuralgia	1	2.3	0	0
muscle weakness	1	2.3	0	0
gait abnormality	0	0	1	2.3
paresthesia	0	0	1	2.3
Adverse event	Test formulation (N=44)		Reference formulation (N=44)	
	N	%	N	%

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sensory disturbance	0	0	1	2.3
vertigo	0	0	1	2.3
abdominal pain	0	0	1	2.3
gastroenteritis	0	0	1	2.3
mouth dry	0	0	1	2.3
hypotension	0	0	1	2.3
arthralgia	0	0	1	2.3
tendon disorder	0	0	1	2.3
pruritus	0	0	1	2.3
urinary tract infection	0	0	1	2.3
conjunctivitis	0	0	1	2.3
altered temperature sensation	0	0	1	2.3

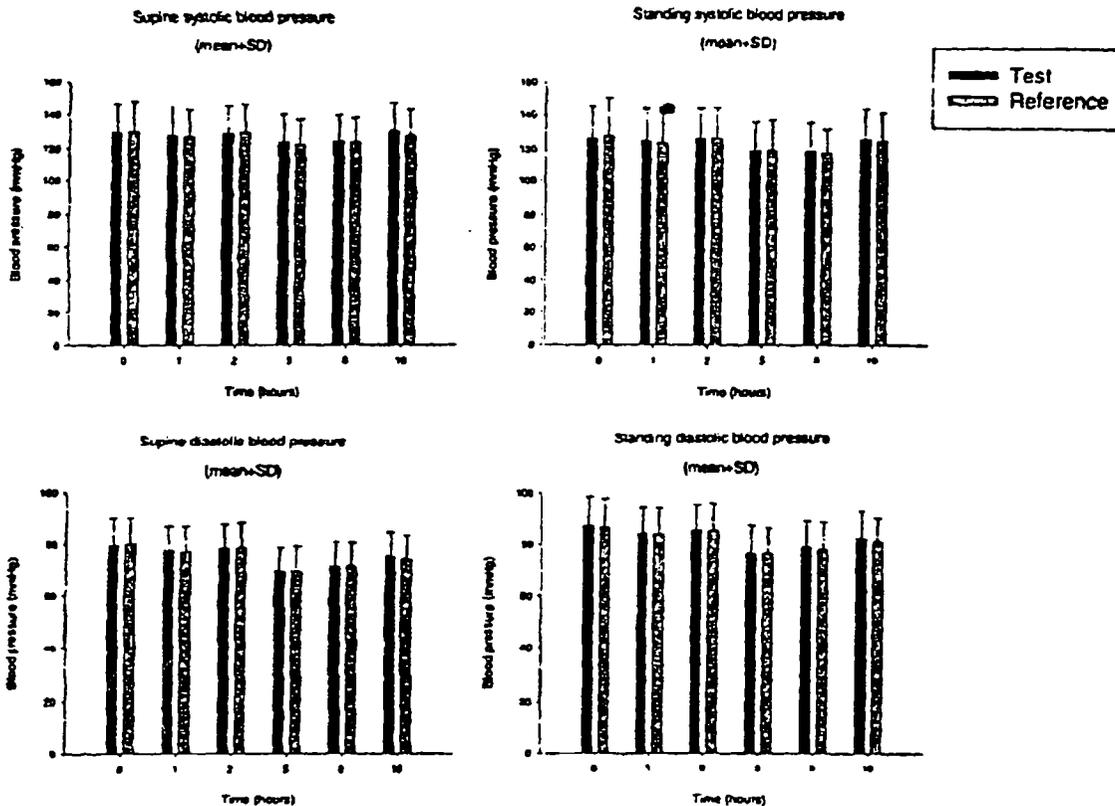
In this study, there was no clinically significant difference between the test and the reference drug for the incidence of adverse events. Nausea and dizziness were slightly more frequent with the reference drug than with the test drug. Again, this finding is probably explained by chance. No clinically significant differences were observed in mean and individual vital signs or ECG conduction times, or laboratory values between the pre- and post-study visits, with the exception on one subject (#18) who had a BUN value elevated at 9 mmol/L at the post-study visit. This was normalized later, and attributed to a concomitant treatment, not specified. I reviewed concomitant medications for this patient. These were aspirin, gramicidin, cromoglicic acid, levocabastine, and chloramphenicol. It is unclear which of these drugs the sponsor judged to be responsible for the elevated BUN.

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In addition to vital signs at the pre- and post-study visit, patients in Study 93 had vital signs taken on the day of study drug administration, to identify if orthostatic hypotension occurred.

Figure 16: Mean systolic and diastolic blood pressure during study days (from Fig R7, page 52, Vol. 69.)



There was no tendency to orthostatic hypotension around  $T_{max}$  and there was no clinically significant difference between the study drugs. The sponsor looked at the number of subjects with greater than 15 mmHg difference in supine-standing systolic BP, which is a more clinically meaningful assessment than mean figures. There was no meaningful difference between the treatment groups around  $T_{max}$  (1-2h), and observations at the last timepoints are probably unrelated to the study drugs (Table 34).

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Table R11. Number of subjects (%) with over 15 mmHg orthostatic reduction between supine and standing systolic blood pressures after the test and the reference treatment administrations.

Treatment	0 h	1 h	2 h	5 h	8 h	10 h
Test (n=87)*	13 (14.9%)	10 (11.5%)	10 (11.5%)	14 (16.1%)	20 (23.0%)	16 (18.4%)
Reference (n=87)*	7 (8.0%)	13 (14.9%)	6 (6.9%)	10 (11.5%)	12 (13.8%)	9 (10.3%)

\* n = number of observations

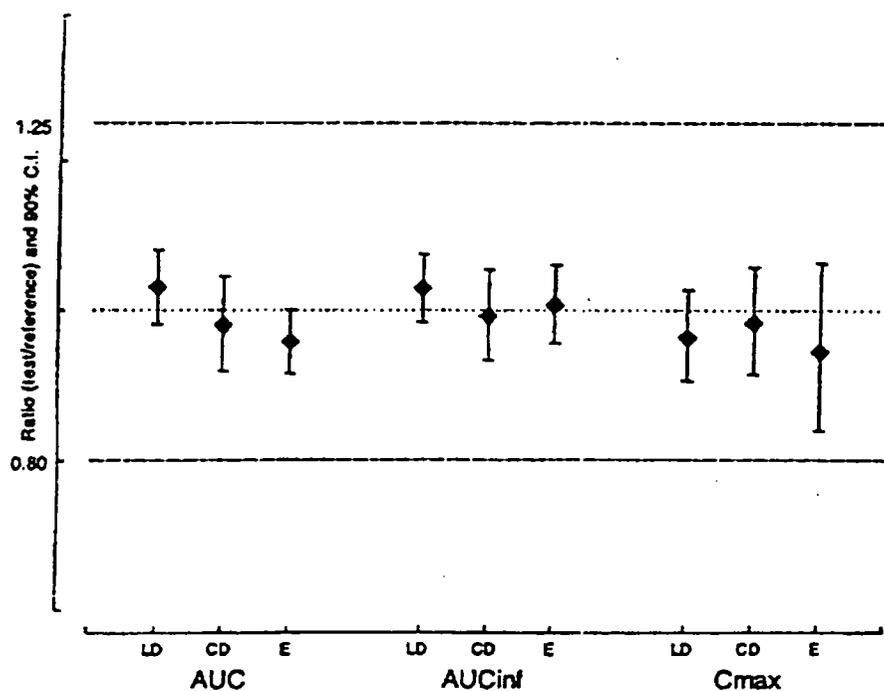
Table 34: Subjects with over 15 mmHg orthostatic hypotension in Study 93

When considering blood pressure decrease >20mmHg in SBP with >25 beat/min increase in heart rate (considered by the sponsor as the threshold for orthostatic hypotension), two patients met that criteria after taking the test drug, versus six patients after the reference drug.

13.1.3 Study 95

Study 95 was a bioequivalence study comparing the LCE 50/12.5/200 mg with the commercially available formulations of Sinemet 100/25 mg (a half tablet contained 50/12.5 mg levodopa/carbidopa and Comtess (entacapone 200 mg). The study design is reviewed in section 5.1.1 This was a single-dose, randomized, replicate, cross-over bioequivalence study with four study periods separated by a washout period of at least 3 weeks. Pharmacokinetic results are summarized in Figure 17 and reviewed in section 5.1.1. The LCE combination was bioequivalent to individual products (reference).

Figure 17: Confidence interval for the ratio between the means of treatments for levodopa (LD), carbidopa (CD) and entacapone (E) in Study 95.



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Safety was assessed at each study visit by vital signs (blood pressure, heart rate and body temperature, before dosing and 1, 2, 5, 8, and 10 hours thereafter), ECG (before dosing and 1, 2, and 9 hours thereafter) and at pre- and post-study visit. The safety laboratory parameters were determined at pre- and post-study visits.

40 subjects out of 44 randomized completed all four study periods. The mean age of subjects (all Caucasian) was 58.0±7.2 years (23M/21F). Age range was 45-75 years. Four subjects discontinued their participation in the study: one subject withdrew after the first period (reason: lost to follow-up), one subject after the second period (reason: withdrawal of consent), and two subjects after the third period (reasons: AE bone disorder and personal reason). The bone disorder AE was reported as periostitis, starting 18 days after the reference drug administration. I concur with the sponsor that causality of the reference drug is unlikely.

No serious adverse events were reported in this study. The adverse events (AEs) reported were all mild or moderate in severity. 9 (20.5%) subjects reported 12 AEs on the test formulation and 7 (15.9%) subjects reported 9 AEs on the reference formulation (respectively 7 AEs on the test formulation and 5 AEs on the reference formulation were treatment-related). There was no clinically significant difference between the test and reference drugs (Table 35).

**Table 35: Number of subjects reporting adverse events in Study 95**

Adverse event	Test formulation (N=44)		Reference formulation (N=44)	
	N	%	N	%
Headache	6	13.6	5	11.4
Influenza-like symptoms	3	6.8	1	2.3
Extrasystoles	1	2.3	0	0
AV-block (first degree)	0	0	1	2.3
ECG abnormal	0	0	1	2.3
Bone disorder	1	2.3	0	0

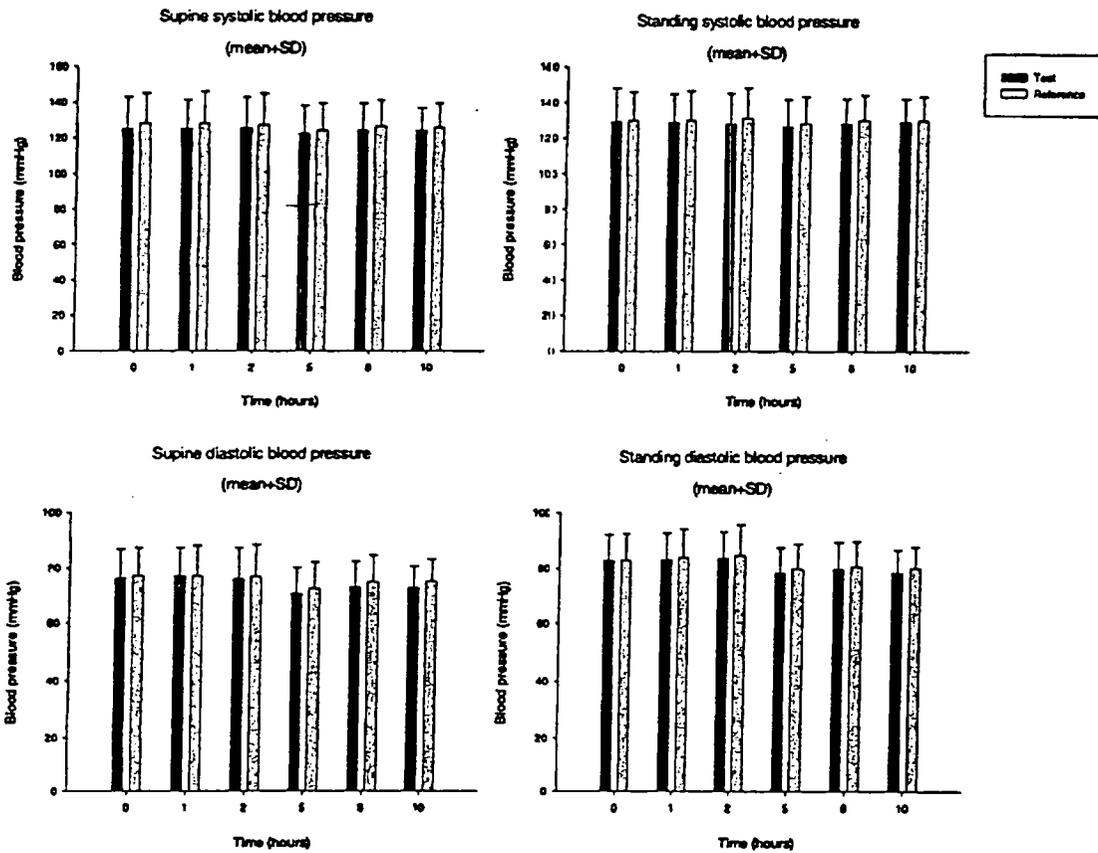
As expected, there was no clinically significant change in hematology or clinical chemistry values between the pre- and post-study visits, both in terms of averages and individual changes, with one exception. Subject 13 had a creatinine value of 149 µmol/L and urea at 11.3 mmol/L at the post-study visit. This was considered as an AE of moderate severity by the investigator. Four weeks later, the creatinine level was 114 µmol/L (within normal limits), and urea at 6.8 mmol/L (within normal limits). The sponsor considered that the values outside of the reference range were due to fluid deficiency. This is a possible explanation, but there are some arguments against it. In addition to these laboratory abnormalities, the patient also had low Hb (114g/L), which is not expected in case of dehydration, and elevation of thrombocytes (517E9/L) and leukocytes (11.5E9/L), suggesting some kind of inflammatory syndrome and/or infection. Of course, since this was noted at the post-study visit, it is also not possible to relate it directly to the test or to the reference drug, and there is a time lag between the last study drug administration and the time of blood draw.

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In addition to vital signs at the pre- and post-study visit, patients in Study 95 had vital signs taken on the day of study drug administration, to identify if orthostatic hypotension occurred.

Figure 18 shows that the test and reference drugs were not clinically different in term of systolic and diastolic blood pressure, and that there were no orthostatic changes in blood pressure.

Figure 18: Mean systolic and diastolic blood pressures during the study days (from Figure R5, page 53, Study 95 report).



When considering blood pressure decrease >20mmHg in SBP with >25 beat/min increase in heart rate (considered by the sponsor as the threshold for orthostatic hypotension), two patients met that criteria after taking the test drug, versus six patients after the reference drug. The sponsor also looked at the number of subjects with greater than 15 mmHg difference in supine-standing systolic BP. There was no meaningful difference between the treatment groups (Table 36).

**Table 36: Subjects with over 15 mmHg orthostatic hypotension in Study 95**

Treatment	0 h	1 h	2 h	5 h	8 h	10 h
Test (n=84)*	1 (1.2%)	2 (2.4%)	5 (5.9%)	2 (2.4%)	2 (2.4%)	1 (1.2%)
Reference (n=83)*	2 (2.4%)	2 (2.4%)	1 (1.2%)	4 (4.8%)	2 (2.4%)	-

\* n = number of observations

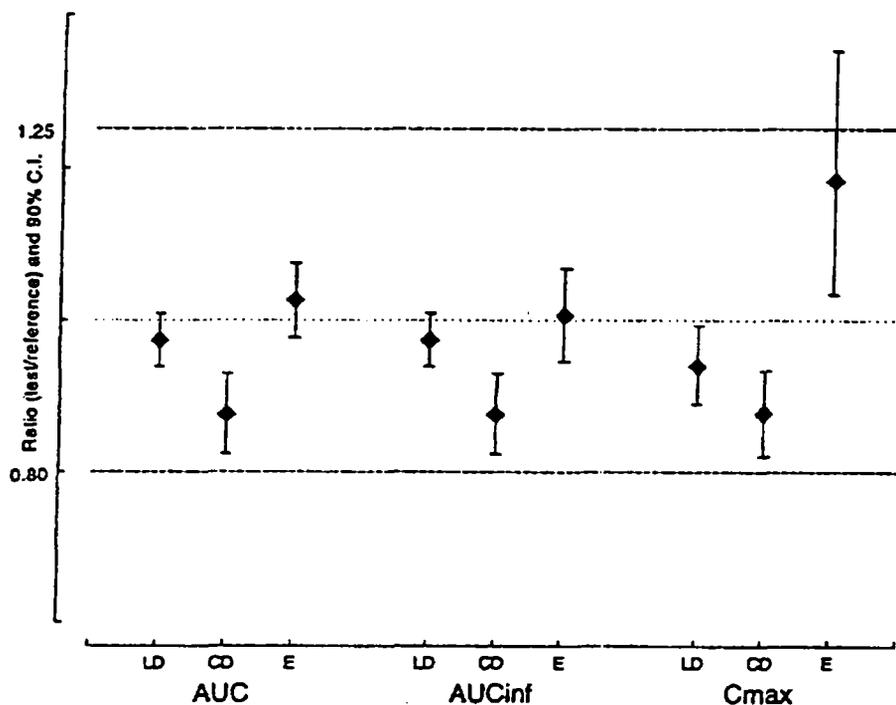
There was no clinically significant change in EGG conduction times between the pre- and post-study visit and between the study and the test drug. ECGs were also obtained on study days at 1, 2 and 9 hours after drug administration. No clinically significant differences between the test and study drug were observed.

**13.1.4 Study 96**

Study 96 was a bioequivalence study comparing levodopa/carbidopa/entacapone 150/37.5/200 mg combination tablet with Comtan 200mg tablet administered with one and a half Sinemet® 100/25mg tablet after a single oral dose in healthy volunteers. The study design is reviewed in section 5.1.1. This was a single-dose, randomized, replicate, cross-over bioequivalence study with four study periods separated by a washout period of at least 3 weeks. Safety was assessed at each study visit by vital signs (blood pressure, heart rate and body temperature, before dosing and 1, 2, 5, 8, and 10 hours thereafter, ECG before dosing and 1, 2, and 9 hours thereafter) and at pre- and post-study visit. The safety laboratory parameters were determined at pre- and post-study visits. Symptoms and adverse events were recorded throughout the study, beginning from the moment the informed consent was signed until the post-study visit.

39 subjects out of 44 randomized completed all four study periods. All subjects were healthy Caucasians (24M/20F). Mean age was 57.7±7.2 years. Age ranged 45-74 years. Pharmacokinetic results are summarized in section 5.1.1. In this study, entacapone C<sub>max</sub> did not meet standard bioequivalence criteria (**Figure 19**).

Figure 19: Confidence interval for the ratio between the means of treatments for levodopa (LD), carbidopa (CD) and entacapone (E) in Study 96.



Five subjects discontinued their participation in the study: one subject withdrew after the first period, two after the second period (reason for all three: withdrawal of consent), and two subjects after the third period (reasons: withdrawal of consent and personal reason). No serious adverse events were reported in this study.

There was an imbalance in AE reports in this study: 19 (43.2%) subjects reported 30 AEs on the test treatment and 11 (25.0%) subjects reported 16 AEs on the reference treatment (respectively 25 events on the test treatment and 10 events on the reference treatment had positive causality to the study treatment). Nausea and headache were the most frequent AEs for both treatments. There was a trend for a significant difference ( $p=0.07$ , ChiSq) in the distribution of nausea, with the LCE combination being worse (Table 37). The reason behind the higher incidence of nausea with the test drug is somewhat puzzling. A possibility is that it occurred in those patients who had higher entacapone  $C_{max}$  and exceeded the bioequivalence range. However, entacapone peak concentrations – even though not bioequivalent – were not higher than seen in some other studies of this NDA (see Entacapone  $C_{max}$  variability for discussion). Also, levodopa is typically more associated than entacapone to the incidence of nausea, but levodopa was bioequivalent between the test and the study drug for both  $C_{max}$  and AUC (Figure 19).

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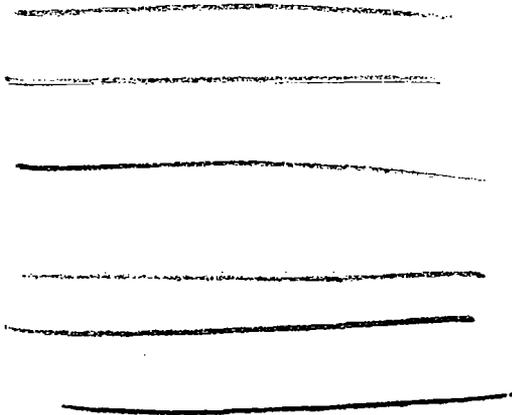
**Table 37: Number of subjects reporting adverse events in Study 96**

Adverse event	Test formulation (N=44)		Reference formulation (N=44)	
	N	%	N	%
Nausea	13	29.5	6	13.6
Headache	6	13.6	5	11.4
Vomiting	2	4.5	0	0
Extrasystoles	0	0	2	4.5
ECG abnormal	1	2.3	1	2.3
Fatigue	1	2.3	0	0
Otitis media	1	2.3	0	0

To better investigate the causality for this nausea, I looked at entacapone  $C_{max}$  in patients who had a nausea AE versus those who did not in the "ae.xpt" dataset. I identified 22 records of nausea, in a total of 14 subjects. Five subjects experienced nausea in a least one period on both the test and reference treatment. Six subjects experienced nausea only on one (out of two) period on the test drug, and two on both periods on the test drug (LCE combination). One subject experience nausea only on one (out of two) period on the reference drug.

In the group receiving the test drug (LCE combination), entacapone  $C_{max}$  was not significantly different between patients with and without nausea (Figure 20).

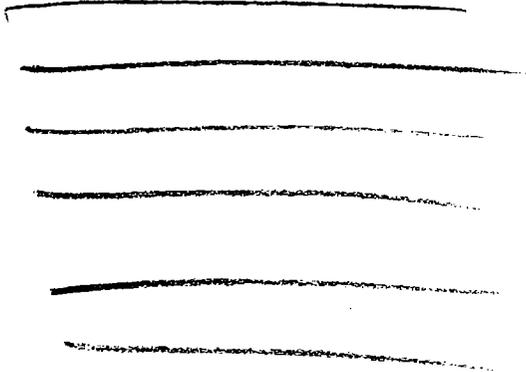
**Figure 20: Entacapone  $C_{MAX}$  by NAUSEA (1=Yes; 2=No) for subjects on test drug (LCE combination)**



I also compared entacapone  $C_{max}$  between patients on the test drug or reference drug who had nausea. Entacapone  $C_{max}$  was not significantly different between the test or reference drug (Figure 21).

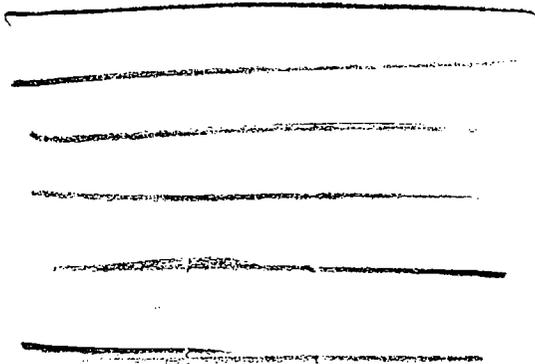
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Figure 21: Entacapone C<sub>MAX</sub> by treatment group (test versus reference) for patients with nausea.



For the entire population, I compared entacapone C<sub>max</sub> (regardless of the treatment group) between patients who experienced nausea and those who did not. Entacapone concentrations were not significantly different between these groups (Figure 22).

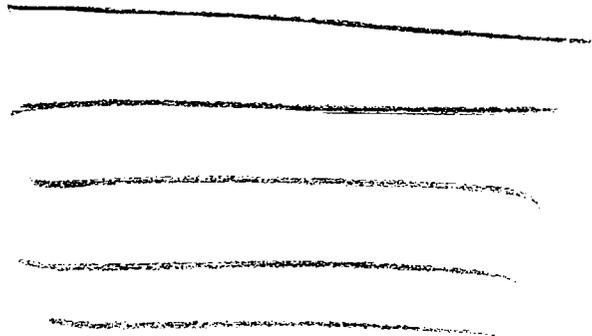
Figure 22: Entacapone C<sub>MAX</sub> by nausea for all subjects (test and reference combined; 1 = nausea, 2 = no nausea).



Since I could not relate nausea to entacapone C<sub>max</sub>, I also looked at the relationship between levodopa C<sub>max</sub> and the incidence of nausea. In a one-way analysis of levodopa C<sub>max</sub> by nausea (Figure 23), I identified a trend for higher levodopa C<sub>max</sub> in patients with nausea (p=0.067).

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**Figure 23: Oneway Analysis of levodopa C<sub>MAX</sub> by nausea (1=nausea; 2=no nausea) for all subjects (test and study group combined).**

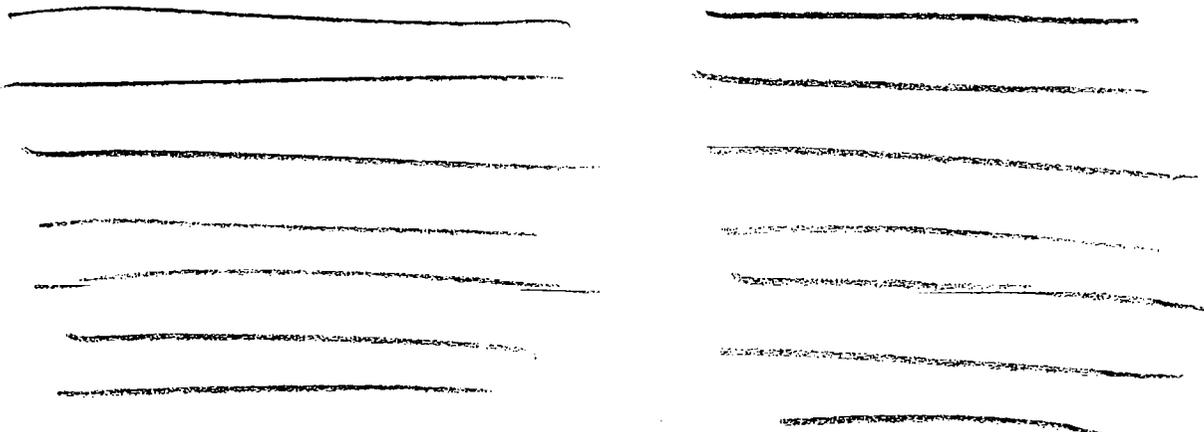


The trend was present both for the test (A) and the reference group (B) (Figure 24).

**Figure 24: Levodopa C<sub>MAX</sub> by nausea for the test and the reference group (1=nausea; 2=no nausea)**

**A: TEST**

**R: REFERENCE**



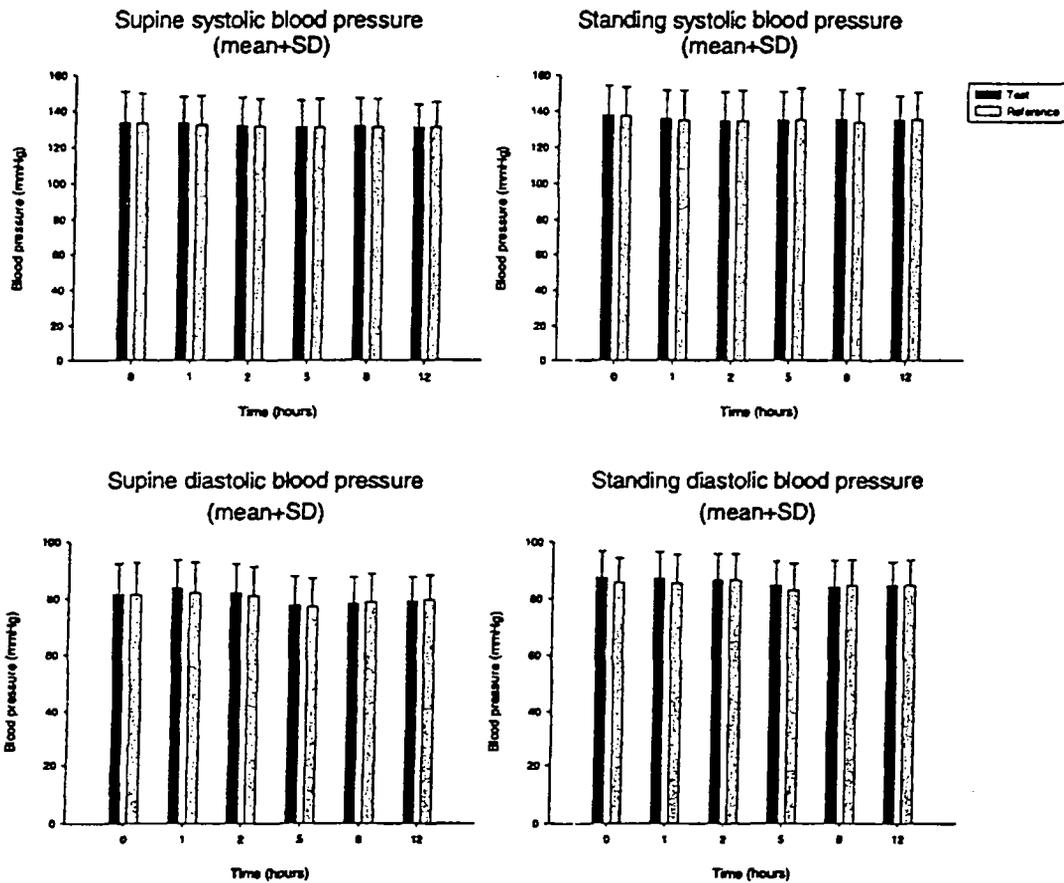
There was not clinically significant deviation in mean and individual laboratory values between the pre-study and post-study visits. There were elevated glucose values in ten subjects pre-study and fifteen subjects post-study. However, sampling was not made in a fasting state, and abnormalities were not attributed to the study treatment.

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Vital signs varied within normal limits for each treatment at the pre- and post-study visits. In addition to vital signs at the pre- and post-study visit, patients in Study 96 had vital signs taken on the day of study drug administration, to identify if orthostatic hypotension occurred.

Figure 25 shows that the test and reference drugs were not clinically different in term of systolic and diastolic blood pressure, and that there were no orthostatic changes in blood pressure.

Figure 25: Mean systolic and diastolic blood pressures during the study days (from Figure R5, page 54, Study 96 report).



The sponsor also looked at the number of subjects with greater than 15 mmHg difference in supine-standing systolic BP. Three patients met that criteria with the test drug, versus five with the reference drug (Table 38). This is reassuring in terms of safety of the LCE combination, since one of the major concerns if strict bioequivalence was not respected was precisely an excess of occurrence of orthostatic hypotension.

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**Table 38: Subjects with over 15 mmHg orthostatic hypotension in Study 96 (from table R11, Study 96 report).**

**Table R11. Number of subjects (%) with over 15 mmHg ortostatic reduction between supine and standing systolic blood pressures aftet test and reference treatment administrations.**

Treatment	0 h	1 h	2 h	5 h	8 h	12 h
Test (n=84)*	-	1 (1.2%)	1 (1.2%)	1 (1.2%)	-	-
Reference (n=83)*	-	3 (3.6%)	1 (1.2%)	-	-	1 (1.2%)

\* n = number of observations

ECG conduction times varied had no clinically significant change between the pre- and post-study visits for each treatment. ECGs were also obtained on study days at 1, 2 and 9 hours after drug administration. No clinically significant differences between the test and study drug were observed. There were two subjects (36 and 38) with QTc-interval in the range 480-500 ms during six ECG recordings. The maximum increase in QT-interval form baseline was 11%. These changes were not considered to be related to study treatments. These changes were not considered to be related to the study treatments. Long QRS-interval were noted in 5 subjects (subject nos. 1, 3, 22, 27 and 38, 120 ms or more at least one measurement). Four of them had incomplete or complete right bundle branch block (RBBB) from the beginning of the study. Four subjects (3, 8, 36 and 37) had PQ-interval more than 200 ms (at least one measurement); 3 of them had first degree AV-block. Six subjects had non-specific ST changes during at least one measurement. One subject had biphasic P-wave. However, these changes were considered to be clinically non-significant and unrelated to the study treatments by the investigator.

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