CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-485

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	21-485
Sponsor:	Orion
Drug:	Stalevo
Proposed Indication:	Parkinson's disease
Material Submitted:	Response to approvable letter
Correspondence Date:	5/2/03
Date Received / Agency:	5/2/03
Date Review Completed	5/5/03
Reviewer:	Eric P. Bastings, MD

INTRODUCTION

Orion is submitting an amendment to NDA 21-485 in response to an approvable letter issued April 25, 2003. The only outstanding issues in the approvable letter concerned labeling. The sponsor is proposing a revised version of the patient insert. The sponsor has revised certain portions of the Pharmacokinetics section, as suggested by the division, and made some minor corrections and modifications to the labeling text.

PROPOSED LABELING CHANGES

Description

No changes.

Clinical pharmacology

Mechanism of action: No changes.

Pharmacokinetics: This section has several changes. The division requested that the sponsors limit the discussion in this section only to the findings with the combination product, and add relevant data only from the current (Stalevo) NDA in the "pharmacokinetics" text sections. In the case of carbidopa, the division suggested that the deviation from linearity can be described along with a complementary statement describing any contradictory observations from the literature. This sections is now as follows (labeling changes proposed by the sponsor in pink):

Pharmacokinetics

[redacted]

Overall, following administration of corresponding doses of levodopa, carbidopa and entacapone as STALEVO or as [redacted] carbidopa/levodopa product plus Comtan® (entacapone) tablets, the mean plasma concentrations of levodopa, carbidopa, and entacapone are comparable.

[redacted]

Absorption/Distribution:
Both levodopa and entacapone are rapidly absorbed and eliminated, and their distribution volume is moderately small. Carbidopa is absorbed and eliminated slightly more slowly compared with levodopa and entacapone. There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone, particularly concerning its C_{max}. The food-effect on the STALEVO tablet has not been evaluated.

Levodopa

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

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

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

[redacted]

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

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

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

Carbidopa is approximately 36 % bound to plasma protein.

Entacapone
Following administration of STALEVO as a single dose to healthy male and female subjects, the peak concentration of entacapone in plasma was reached within 1.0 to 1.2 hours on average. The mean C_{max} of entacapone was about 1200 ng/mL and the AUC 1250 to 1450 [redacted]

— mL after administration of different STALEVO strengths all providing 200 mg of entacapone.

. The plasma protein binding of entacapone is 98% over the concentration range of 0.4 - 50 µg/mL. Entacapone binds mainly to serum albumin.

Clinical studies
The only update is a change of table numbers reflecting the deletion of a table as recommended by the division. This is acceptable.

Indications
No changes.

Contraindication
No changes.

Warnings
No changes.

Precautions
No changes.

Adverse reactions
Table numbers updated to reflect deletion of a table. This is acceptable.

Drug abuse and dependence
No changes.

Overdosage
No changes.

Dosage and administration
The sponsor did one single change as follows: "Individual tablets should not be fractionated and only one tablet should be administered at each dosing interval.

Generally speaking, STALEVO should be used as a substitute for patients already stabilized on equivalent doses of carbidopa-levodopa and entacapone. However, some patients who have been stabilized on a given dose of carbidopa/levodopa may be treated with STALEVO if a decision has been made to add entacapone (see below)."

Reviewer's comment: This change is not acceptable because it changes the meaning of the whole paragraph.

How supplied
No changes.

OCPB Revised Pharmacokinetics section

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewed the clinical pharmacology section of the revised labeling and found the section acceptable with minor changes. OCPB proposed changes are shown in blue here below, with proposed deletions in blue strikethrough.

Pharmacokinetics

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

Absorption/Distribution:

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

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

Levodopa

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

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

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

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

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

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

Carbidopa is approximately 36 % bound to plasma protein.

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

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

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

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

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

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

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

Entacapone is almost completely metabolized prior to excretion with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is

isomerization to the cis-isomer, the only active metabolite. Entacapone and the cis-isomer are eliminated in the urine as glucuronide conjugates. The glucuronides account for 95 % of all urinary metabolites (70% as parent- & 25% as cis-isomer- glucuronides). The glucuronide conjugate of the cis-isomer is inactive. After oral administration of a 14C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces. Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs when they are administered repeatedly.

Reviewer's comment: I agree with OCPB recommendations.

CONCLUSIONS

1. The proposed changes are acceptable on a clinical standpoint, with the exception of the wording change in the "dosage and administration" section, which should remain as sent in the approvable letter.
2. OCPB reviewed the clinical pharmacology section. I concur with the proposed OCPB changes.
3. The sponsor did not describe in labeling the deviation from linearity for carbidopa pharmacokinetics. I do not view this as critical or holding approval.

RECOMMENDATION

On a clinical standpoint, I recommend approval, with the minor labeling changes proposed by OCPB, and with the "dosage and administration section" kept unchanged from the label sent to the sponsor with the approvable letter.

APPROVED LABEL

STALEVO™ LABELING

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30 Draft Labeling Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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5/15/03 09:44:52 AM
MEDICAL OFFICER

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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Generic Name:	**Levodopa/Carbidopa/Entacapone**
Sponsor:	**Orion Pharma**
Indication:	**Parkinson's disease**
NDA:	**21-485**
Original Receipt Date:	**6/26/02**
Clinical Reviewers:	**Eric Bastings, MD**
Review Author:	**Eric Bastings, MD**
Review Completed:	**2/12/03**

Table of Contents

Clinical Review for NDA 21-485

Executive Summary

1. Recommendations

1.1 Recommendation on Approvability

The sponsor developed a fixed dose combination tablet containing three previously marketed active agents, levodopa, carbidopa and entacapone. Three strengths are proposed: 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 the current entacapone indication).

The application is based on bioequivalence studies between the fixed dose combination and the individual marketed products (Sinement and Comtan/Comtess). 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 patients with advanced Parkinson's disease. An additional safety issue is the confusion induced by the availability of a new form of levodopa tablet, and possible administration errors.

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. The sponsor expected this bioinequivalence, and the Agency agreed to consider safety data in case the fixed dose combination was not fully bioequivalent – which occurred.

Safety data were overall reassuring. From a clinical perspective, I don't view the bioinequivalence of entacapone C_{max} 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 its effect on levodopa pharmacokinetics, the bioinequivalence of entacapone is less of an issue. Second, the bioinequivalence of entacapone only concerned C_{max}, and entacapone was bioequivalent for the AUC in all studies. Third,

entacapone pharmacokinetic variability was known before the studies of this NDA, and safety was similar with the LCE combination and with the individual drug products. Fourth, entacapone had a large therapeutic index, which makes pharmacokinetic variability less of a problem.

The main issues reside in the dosing and initiation of the combination product (see section 2.4). From a clinical perspective, I recommend approval of the fixed dose combination tablet, but with changes from the sponsor's proposal for the dosage and administration of the fixed dose combination.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

I have no specific post-marketing recommendation, other than the usual reporting requirements.

2. Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

The sponsor developed a fixed dose combination tablet containing three previously marketed active agents, levodopa, carbidopa and entacapone ("LCE combination"), in three different strengths. The proposed indication for the LCE combination 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 the current entacapone indication). The LCE combination would be indicated for the adult population.

The sponsor believes that a reduction of the number of tablets to be swallowed would be beneficial, as many patients with advanced PD have swallowing problems (with an additional possible benefit of a smaller size of LCE tablets than single entacapone tablets). The sponsor does not expect that the LCE combination changes the level of efficacy or safety compared to the separate products, but suggests that compliance may be improved.

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.

This submission is entirely based on pharmacokinetic studies, carried out in healthy volunteers, mostly elderly, along with literature-based special population and metabolism/drug-drug interaction information. The sponsor conducted four bioequivalence studies in a total of 176 healthy subjects, evaluating each strength of the combination against marketed Sinemet (levodopa/carbidopa, 100/25mg tablet) and Comtan (entacapone 200mg). In addition, the sponsor submitted a bioequivalence study comparing the reference tablet Sinemet marketed in the United States versus the Sinemet marketed in Finland, since both tablets were used in separate bioequivalence studies. The sponsor also studied the effect of entacapone on different levodopa/carbidopa doses. To support the safety and efficacy of the LCE combination, the sponsor referred largely to the approved entacapone NDA (20-796). No clinical trial was conducted in Parkinson's disease patients.

2.2 Efficacy

This NDA does not contain any new efficacy data. Instead, the sponsor is referring to the entacapone, and levodopa/carbidopa NDAs. The efficacy of levodopa/carbidopa and entacapone is already established in PD patients with end of dose wearing off (EODWO). NDA 20-796 showed that entacapone combined with each dose of levodopa significantly increases the ON-time and decreases parkinsonian disability. The entacapone clinical effects are thought to result from pharmacokinetic effects on levodopa, namely, a bioavailability increase and more sustained plasma levels.

The sponsor suggests that the combination of levodopa/carbidopa/entacapone in one single tablet will provide the same efficacy as seen when the preparations are given in separate tablets, but will also result in a simplification of treatment in clinical practice (entacapone is always taken simultaneously with levodopa/carbidopa). Since bioequivalence studies part of this NDA showed that levodopa, carbidopa and entacapone C_{max} and AUC always exceed the inferior limit for bioequivalence to the existing products given separately, I concur that the efficacy of the LCE combination should be the same as that of the existing products given separately.

There are however some issues with dosing of the LCE combination, which I discuss below.

2.3 Safety

The sponsor largely refers to the entacapone NDA (20-796) to support the safety of the LCE combination. In addition, data were obtained in bioequivalence studies, in support of the safety of the LCE combination, especially relevant since the LCE 150 (and LCE 100 to a lesser extent) was not fully bioequivalent to the individual products given separately. Entacapone safety was evaluated in NDA 20-796.

In the new bioequivalence studies reviewed here, the LCE combination did not lead to a higher incidence of orthostatic hypotension than individual products. There was a higher incidence of nausea with the LCE 150/37.5/200mg tablet (LCE 150) than with the individual products. I could not relate the incidence of nausea to a higher entacapone C_{max} in these patients (see 13.1.4). Also, the higher incidence of nausea was not associated to other dopaminergic toxicity symptoms, so that I can not rule out that it occurred purely by chance. Overall, no new safety concern emerged with the LCE combination.

There is no evidence of long-term safety problems with entacapone, including in post-marketing safety reports. No clinically significant drug interactions attributed to the combination of levodopa/carbidopa/entacapone have been reported in the literature in PD patients.

2.4 Dosing

The LCE combination is intended to replace the administration of separate drug products. A such, the initiation of LCE in patients already receiving entacapone and levodopa/carbidopa and changing to the corresponding dose of the LCE tablet, is clearly the easiest situation, since patients are already titrated. That switch poses no safety or efficacy concern.

The initiation of LCE for patients not previously receiving entacapone is a very different situation, since it may require re-titration of the dose of levodopa/carbidopa (whose efficacy may be enhanced by entacapone, with possible levodopa toxicity induced). The sponsor suggests that initiation of LCE in that situation is possible and manageable if patients are not already experiencing dyskinesia. The sponsor re-analyzed the data from the entacapone NDA, and determined that levodopa doses above 800 mg at baseline and dyskinesia at baseline are the main predicting factors for a levodopa dose reduction after adding-on entacapone. Based on this finding, the sponsor suggests that no significant safety risks are expected when initiating LCE in patients not previously receiving entacapone, if the daily dose of levodopa was under 800 mg at baseline and if patients were not experiencing dyskinesias at baseline. The sponsor acknowledges that the daily dose may need to be reduced in patients that may experience dyskinesias. I agree that switching to the LCE combination for patients receiving less than 600 mg levodopa total daily dose at baseline and experiencing no dyskinesias at baseline should not pose any significant safety concern, and that the daily dosage of LCE may need to be reduced only in a minority of patients (4% based on the sponsor's analysis). I view the situation of patients receiving 600-800 mg levodopa at baseline as different, since over 20% are expected to require dose adjustment. In this setting, I recommend to first titrate the patients with the individual products, before switching to the LCE combination.

In patients on relatively high levodopa doses (> 800 mg/day) and/or already experiencing significant dyskinesia, and as agreed by the sponsor, dose adjustment with levodopa/carbidopa and entacapone separately is necessary before changing to LCE, in order to avoid a significant worsening of dyskinesias and dopaminergic toxicity.

The sponsor suggests that switching patient on Sinemet CR (slow release) to the LCE combination is possible. In this situation as well, I recommend dose adjustment with levodopa/carbidopa and entacapone separately before changing to LCE, given the multiple pharmacokinetic changes induced by the switching, including a different absorption profile. This is clearly a situation where a maximum of flexibility is needed.

Finally, since the maximum daily dose of levodopa is 1200 with the LCE combination (based on a maximum recommended dose of 1600 mg of entacapone, limiting the number of daily tablets of LCE to eight), patients receiving more than 1200 mg levodopa daily are not candidate to be switched to the LCE combination (maybe with the exception of patients not receiving entacapone at baseline, where a reduction of the daily requirements in levodopa may occur).

2.5 Special Populations

2.5.1 Sex/Age

Again, most of the information on special populations originates from the entacapone NDA and from the literature. There is no difference in pharmacokinetics of entacapone between young adults and elderly people (entacapone NDA). Both male and female elderly subjects were included in three main bioequivalence studies of this NDA, since Parkinson's Disease occurs in

both sexes and in patients generally over 40. 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 adverse events (AEs) incidence by sex in the three LCE bioequivalence studies which included patients of both sexes. There was an overall tendency for females to report more adverse events than males. However, there was no clinically significant difference in the rate of adverse events occurring by sex between the test (LCE) and reference (individual products) groups.

The sponsor also compared AEs by age in the three LCE bioequivalence studies which included patients of age 45-75 (the other bioequivalence 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%).

2.5.2 Pregnancy: Pregnancy Category C.

Entacapone: in embryo-fetal development studies, increased incidences of fetal variations were evident in litters from rats treated with the highest dose, 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. 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 was observed, in the absence of maternotoxicity. Administration to female during the latter part of gestation and throughout lactation produced no evidence of developmental impairment in the offspring.
Carbidopa-levodopa: carbidopa-levodopa caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa-levodopa tested. Levodopa crosses the human placental barrier. Carbidopa concentrations in fetal tissue appeared to be minimal.
Entacapone/carbidopa/levodopa: 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.

2.5.3 Pediatric population:

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.

2.5.4 Liver impairment

The pharmacokinetics of entacapone have been studied in patients with liver cirrhosis (entacapone NDA). Entacapone AUC and C_{max} 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, since no publication on the topic could be found in the literature. The current Comtan label recommends that patients with hepatic impairment be treated with caution when levodopa/carbidopa/entacapone is given.

2.5.5 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 and I 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.

Clinical Review

3. Introduction and Background

The sponsor developed a fixed dose combination tablet containing three previously marketed active agents, levodopa, carbidopa and entacapone, in three different strengths for the treatment of Parkinson's disease (PD).

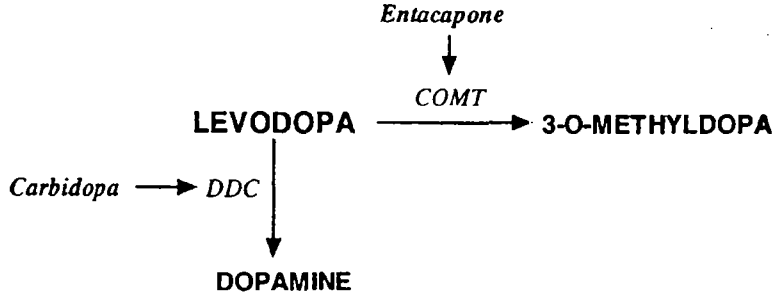
This submission is entirely based on pharmacokinetic studies, carried out in healthy volunteers, mostly elderly, along with literature-based special population and metabolism/drug-drug interaction information. The sponsor conducted four bioequivalence studies, evaluating each strength of the combination against marketed Sinemet (levodopa/carbidopa, 100/25mg tablet) and Comtan (entacapone 200mg). In addition, the sponsor submitted a bioequivalence study comparing Sinemet marketed in the United States versus Sinemet marketed in Finland, since both tablets were used in the bioequivalence (BE) studies. The sponsor also studied the effect of entacapone on different levodopa/carbidopa doses. To support safety and efficacy of the new fixed dose combination, the sponsor also refers to the approved entacapone NDA (20-796). No clinical trial was conducted in the target population (Parkinson's disease).

3.1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The sponsor developed a fixed dose combination tablet containing three previously marketed active agents for the treatment of Parkinson's disease: levodopa, carbidopa and entacapone (I refer to the "LCE combination" or "LCE" in this review document. The sponsor proposed the trade name "Atrelar" for the combination, but the final trade name is apparently not yet decided. The trade name [redacted] has been rejected by the Agency. The sponsor has submitted an alternate trade name, "Stalevo", under review by DMETS.

Levodopa (drug responsible for the final clinical effect of the combination) is metabolized mainly via two pathways: decarboxylation by aromatic L-amino acid decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT) (Figure 1). Due to extensive peripheral metabolism, less than 1% of a oral levodopa dose reaches the brain. Carbidopa and entacapone both reduce the peripheral metabolism of levodopa and increase levodopa bioavailability. Levodopa and carbidopa are already marketed in combination, and entacapone is always administered simultaneously with levodopa/carbidopa. The sponsor developed a fixed combination product in an effort to simplify therapy.

Figure 1: Levodopa metabolism



The proposed indication for the LCE combination is the treatment of patients with idiopathic PD who experience the signs and symptoms of end-of-dose "wearing off" (same as current entacapone indication).

The sponsor believes that it would be beneficial if the number of tablets to be swallowed is reduced, as many patients with advanced PD have swallowing problems, with an additional benefit of a smaller size for combination tablets than for single entacapone tablets. The sponsor does not expect that the LCE combination will change the level of efficacy or safety compared to separate products, but suggests that compliance may be improved.

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 sponsor states that these levodopa doses cover the majority of the single doses used by PD patients in the two phase III studies of entacapone NDA 20-796. The sponsor suggests that the majority of patients (approximately 80%) used levodopa/carbidopa products with a ratio 4:1 in the entacapone phase III studies of NDA 20-796. This issue will be discussed in section 10. Dose regimen would be individually adapted to each patient, as for the separate products.

The LCE combination would be indicated for the adult population.

3.2 State of Armamentarium for Indication(s)

Current therapies for Parkinson's disease are symptomatic. Levodopa (precursor of dopamine) remains the most effective drug for the treatment of PD. Levodopa has complex clinical pharmacokinetics, because of erratic absorption, short half-life, and peripheral O-methylation. Controlled-release levodopa preparations (e.g. Sinemet CR) were developed for the treatment of PD patients with motor fluctuations.

Levodopa is usually administered in combination with a dopa-decarboxylase enzyme (DDC) inhibitor, e.g. carbidopa. The use of this combination improves the bioavailability of levodopa because less of the administered levodopa is metabolized in peripheral tissues. A fixed combination of levodopa and carbidopa has been in clinical use for more than 25 years. The proportions of levodopa:carbidopa have been either 10:1 or 4:1. The causative relationship between levodopa and the long-term motor complications of therapy, along with the possibility that levodopa may be toxic to dopaminergic neurons in vivo, has led to a move away from its use in early Parkinson's disease.

Entacapone blocks the catechol-O-methyltransferase enzyme, which metabolizes levodopa to 3-O-methyldopa. It is used in combination with levodopa and carbidopa in patients with end-of-dose fluctuations. Entacapone does not have any therapeutic effect when administered alone. Entacapone and levodopa have similar pharmacokinetic properties and thus entacapone is used concomitantly with each levodopa dose. The established dose is 200 mg with each individual levodopa doses up to 8 times daily (maximal daily dose 1600 mg). Entacapone therapeutic

response to each levodopa dose is attributable to the prolongation of the elimination of plasma levodopa, leading to more sustained levels. Two COMT inhibitors are currently available, Tasmar and Comtan. However, Tasmar has be associated to liver toxicity.

There are also several synthetic dopaminergic agonists available, used either a single agents, or in association with dopa/carbidopa. The dopamine agonists include ergot derivatives (bromocriptine, pergolide, lisuride and cabergoline), non-ergoline derivatives (pramipexole, ropinirole and piribedil) and apomorphine. They are used in monotherapy and as an adjunct to levodopa in early and advanced PD.

Centrally-acting antimuscarinic drugs, amantadine, and monoamine oxidase-B (MAO-B) inhibitors are also used. Amantadine and the anticholinergics have limited efficacy and limiting side effects. The MAO-B inhibitor selegiline may have the dual effect of reducing dopamine catabolism and limiting the formation of neurotoxic free radicals, but the neuroprotective effect is controversial.

Finally, surgical options have become available in recent years: ablation procedures (pallidotomy) have been mostly replaced by deep brain stimulation. The surgical option is mostly used in more advanced cases.

No single best treatment exists for an individual patient with PD. Particularly in the advanced stage of the disease, treatment is individually adapted.

3.3 Important Milestones in Product Development

Separate drug products of levodopa/carbidopa have been on the market for several years. FDA approved levodopa in 1970 and the first levodopa/carbidopa combination product (Sinemet) in 1975. Entacapone (Comtan) was granted a marketing authorization by European Union in September 1998 and by FDA in October 1999. The clinical efficacy and safety of entacapone given with levodopa/carbidopa was established in NDA 20-796.

The Orion-sponsored IND for the combination product (IND 60-554) was submitted on 06/26/00. Dr. Len Kapcala is the medical reviewer who was assigned to this IND. A Pre-IND meeting was held in March 2000. In this meeting, the rationale and the development program for the triple combination product was discussed with the Agency. FDA agreed that Orion Pharma may develop a combination product of levodopa/carbidopa/entacapone in three different tablet strengths (50/12.5/200 mg, 100/25/200 mg, and 150/37.5/200 mg). To avoid confusion amongst patients and physicians, the Agency encouraged the Sponsor to advise how the combination should be used. The Sponsor replied that the triple combination is intended to be used as a stand-alone therapy and expects that the most severe patients will continue to be treated with levodopa/carbidopa with Comtan and not with the triple combination. The Agency stated that the possible problems to be considered with fixed dose products include an increase in the incidence of confusion among drug products, and that these combinations will not be appropriate in all patients.

The Sponsor proposed to develop the LCE combination for the same indication as Comtan, and to base approval on bioequivalence studies with the individual approved products. Regarding the reference treatments in bioequivalence studies, FDA agreed that Comtan 200 mg given with a standard release levodopa/carbidopa (Sinemet) would be appropriate. The Sinemet 100/25 mg tablets were to be used as a half tablet, one tablet, or one and a half tablet, according to the triple combination tablet strength tested for bioequivalence. If every ingredient of the component were proportionally equal, then only one bioequivalence study would be necessary. Since the ratios of the three combination products are different, three different studies were required.

If the reference product Sinemet was not purchased in the United States market but in Finnish market, the bioequivalence between the United States and the Finnish Sinemet was to be established.

Since entacapone is known to be a highly variable drug (NDA 20-796), the sponsor asked the Agency to consider extended confidence interval limits (70-143%) for entacapone C_{max} in bioequivalence studies. The Agency considered that all the three components would have to meet the conventional (80-125%) confidence interval limits. The Sponsor argued that the highly variable nature of entacapone C_{max} was shown in an earlier study in NDA 20-796 (Study 2939060). The Sponsor intended to power the bioequivalence studies for the triple combination to meet the conventional confidence interval limits, but noted that it may be impossible to make entacapone C_{max} fall within these conventional limits. The Agency informed the sponsor that would the conventional bioequivalence limits not be completely met, the sponsor could discuss and justify why they feel that this has no implications in terms of efficacy and safety, and that the Agency would evaluate whether the product is approvable without being bioequivalent.

The Agency recommended the recording of vital signs and ECG repeatedly after study drug administration in the bioequivalence studies. These data could be used to support safety if the bioequivalence criteria were not completely met. The Agency recommended that the sponsor include both genders in the studies. The Agency also recommended that bioequivalence studies include older subjects since Parkinson's patients are generally over 40 years of age.

The Agency noted that a small percent of entacapone can get into the CNS and may alter therapeutic equivalence, based on literature articles suggesting that, depending on the dose, the extent of central COMT inhibition with entacapone may vary and might be of therapeutic significance. FDA asked Orion to address this issue and particularly to address whether the extent of central penetration and activity of entacapone may alter the therapeutic effect.

The Agency agreed that the NDA for the triple combination product may be based on bioequivalence studies and that there is no need to include any additional safety or efficacy studies in PD. The Sponsor was allowed to cross-refer to the entacapone NDA 20-796 for efficacy and safety.

The Agency requested that the combination mouse micronucleus test be repeated. The Agency also requested to see the results of segment II teratology studies.

A teleconference was held in October 2000, in order to complete the discussion on the bioequivalence studies protocols. The major topic was the subject population. The Agency suggested Orion to perform these studies in line with a new bioequivalence guideline released by FDA in October 2000 ("Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. General Considerations"). In agreement with this recommendation, Orion performed the major bioequivalence studies (Studies 93, 95, and 96) in male and female subjects. Orion states that as many subjects over age 60 as possible were enrolled.

Orion was required to collect orthostatic vital sign data to characterize potential orthostatic effects. The Agency recommended that heart and blood pressure be measured while supine and after standing (at least after 2 minutes) to characterize the maximal potential change, and that temperature and ventilatory rate be collected along with the heart rate/blood pressure. Since T_{max} occurs at one to two hours post dose, the Agency asked that orthostatic vital signs be taken near T_{max} at both one and two hours post dosing. The Agency stated that ECGs would be desirable at both one and two hours after dosing. These data could be used as supporting safety information. The Agency sated that C_{max} should be included as a standard for determining bioequivalence, and that the usual bioequivalence standards are $AUC_{0-infinity}$ and C_{max}.

A Pre-NDA meeting was held in December 2001. FDA considered acceptable to use replicate, single dose design and average bioequivalence approach to address the issue of bioequivalence of compounds that exhibit high variability. If the triple combination tablet did not meet the conventional bioequivalence criteria but exceeded the upper limit, the Agency recommended Orion to justify why this is of no concern from a safety point of view considering also the repeated administration of the product. The Agency restated that extended limit of confidence interval to define bioequivalence are not acceptable. The sponsor was asked to address the variability seen in the studies, and the clinical relevance from a safety point of view at the highest recommended daily dose regarding the values that fell outside of the recommended values.

The sponsor was asked to include a drug-drug interaction (DDI) section that addresses DDI among 3 different active ingredients. The sponsor was asked to follow the labeling format of entacapone, to update labeling language for levodopa and carbidopa by performing a literature search and exploring available databases to incorporate all the relevant information into labeling. The Agency noted that the following was lacking in the proposed label information on the combination product from the bioequivalence studies versus individual entities:

The Agency noted that the sponsor claims that the combination product without providing any supporting evidence. The Agency asked that the sponsor provide supportive information from the entacapone NDA and from the literature regarding food effects on levodopa and carbidopa. FDA advised Orion to address labeling issues regarding switching paradigms to the triple combination product in PD patients on different tablet strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations.

3.4 Other Relevant Information

Entacapone has been in clinical use since 1999 in the United States and since 1998 in Europe, and it is marketed in 60 countries worldwide. The sponsor states that more than 100,000 patients had been exposed to entacapone by the end of year 2001.

3.5 Important Issues with Pharmacologically Related Agents

Tolcapone, an earlier COMT inhibitor, has been associated to a risk of potentially fatal, acute fulminant liver failure, which is the object of a black box warning. As of October 1998, three cases of fatal fulminant hepatic failure have been reported from approximately 60,000 patients providing about 40,000 patient years of worldwide use. This incidence may be 10- to 100-fold higher than the background incidence in the general population. Hepatoxicity has not been reported with entacapone.

4. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

I refer to the separate review documents of the FDA chemistry reviewer, Pharmacology/Toxicology reviewer, and Biopharmaceutics reviewer for detailed review. In the following subsections, I summarized the information as presented by Orion, with my personal comments as applicable.

4.1 Chemistry

Each LCE tablet contains a combination of the three drug substances: levodopa, carbidopa and entacapone. The dose strengths of levodopa and carbidopa in 4:1 ratio are 50/12.5 mg, 100/25 mg and 150/37.5 mg combined with 200 mg of entacapone in each tablet. The abbreviations LCE 50, LCE 100 and LCE 150 are used in the documentation for the different strengths of the drug products: LCE 50 for 50/12.5/200 mg, LCE 100 for 100/25/200 mg, LCE 150 for 150/37.5/200 mg.

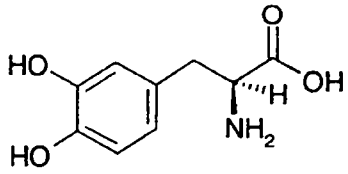
In the LCE-tablet, the amount of entacapone is 200 mg regardless of the amount of levodopa and carbidopa. The amount of entacapone is the same as in the presently marketed entacapone tablets. Thus the maximum daily dosage on entacapone is 8 x 200 mg = 1600 mg, i.e. approximately 30 mg/kg for a person weighing 50 kg. If the highest strength of LCE-preparation (150/37.5/200 mg) is taken eight times per day, the maximal daily dose of levodopa/carbidopa would be 1200/300 mg, which represents 24 mg/kg of levodopa and 6 mg/kg of carbidopa per day for a person weighing 50 kg.

The drug products are film-coated tablets, provided in HDPE containers in pack sizes of [redacted] 100 and 250 tablets. Maximum storage time up to date has been [redacted]. A shelf-life of [redacted] is proposed for LCE 50, LCE 100 and LCE 150 tablets at this stage of the continuing stability testing.

4.1.1 Levodopa ((S)-(3 ,4-Dihydroxyphenyl)alanine) (Figure 2)

Chemical name: (--)-L-(alpha)-amino-(beta)-(3,4-dihydroxybenzene) propanoic acid

Figure 2: Levodopa structure



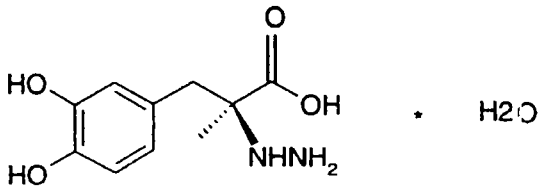
Molecular formula: $C_9H_{11}NO_4$
Relative molecular mass: 197.19

4.1.2 Carbidopa (Benzenepropanoic acid) (Figure 3)

Chemical name: a-hydrazino-3 ,4-dihydroxy-a-methyl-monohydrate
(-)-L-cx-Hydrazino-3 ,4-dihydroxy-x-methylhydrocynnamic acid monohydrate

Molecular formula: C10H14N2O4*H20
Relative molecular mass: 244.2 (as monohydrate); 226.2 (as anhydrous).

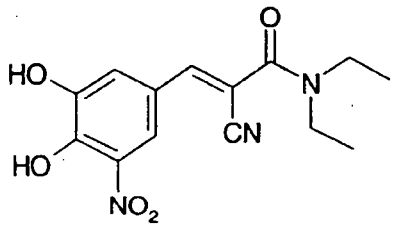
Figure 3: Carbidopa structure



4.1.3 Entacapone (Figure 4)

Chemical name: (E)-2-cyano-3-(3 ,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide.

Figure 4: Entacapone structure



Molecular formula: $C_{14}H_{15}N_3O_5$
Relative molecular mass: 305.

4.2 Nonclinical Pharmacology

The Nonclinical Pharmacology and ADME sections are cross-referenced to Comtan NDA 20-796. Also other parts of Nonclinical Toxicology, except combination toxicity, are also cross-referenced to Comtan NDA 20-796.

The sponsor reported that no signs of interaction in the toxicity between levodopa/carbidopa and entacapone were observed in the subchronic combination toxicity studies in rats and cynomolgus

monkeys. All signs of toxicity observed in the 13-week studies with levodopa/carbidopa/entacapone were related to pharmacological effects of levodopa.

No carcinogenicity studies have been conducted with levodopa/carbidopa/entacapone combination. As a phase IV commitment to Comtan NDA, a two-year mouse carcinogenicity with entacapone is ongoing because of a high incidence of premature mortality observed in mice receiving the highest dose level of entacapone in the original study. The Agency has confirmed that there is no need to perform carcinogenicity with the combination.

In embryo-fetal development studies combining high doses of entacapone to low multiple of pharmacological doses of levodopa/carbidopa did not induce signs of maternal or fetal toxicity in rats or rabbits.

In combination embryo-fetal development studies, there was no indication of maternal or fetal toxicity in rats administered up to 600 mg/kg/day entacapone with 40/10 mg/kg/day of levodopa/carbidopa or in rabbits, administered up to 150 mg/kg/day of entacapone with 40/10 mg/kg/day of levodopa/carbidopa. Based on these results, the sponsor concluded that combining high doses of entacapone to low multiple of pharmacological doses of levodopa/carbidopa does not affect the fetal development in rats or induce teratogenic effects in rabbits reported previously when high doses of levodopa/carbidopa was administered alone. Since levodopa alone and combined with carbidopa have been reported to induce visceral and skeletal malformations in rabbits, and since levodopa crosses the human placental barrier, enters the fetus, and is metabolized, the sponsor considers that Pregnancy Category C is applicable to LCE product.

Entacapone was studied in combination with levodopa and carbidopa in bacterial mutagenicity test and twice in mouse micronucleus test. As advised by the Agency, the micronucleus test was repeated using (six times) higher dose level for levodopa/carbidopa than that used in the first test. No signs of genotoxicity were observed in any of the studies performed with entacapone in combination with levodopa/carbidopa. The sponsor concluded that entacapone in combination with levodopa and carbidopa is not mutagenic in bacterial mutagenicity test and does not induce chromosomal or other DNA damage in vivo at the dose levels applied.

The drug substance carbidopa contains [redacted] impurities which required qualification [redacted] The limit suggested for [redacted] in the specifications is [redacted] The corresponding limits suggested for [redacted] are [redacted] and [redacted] respectively. In the studies performed for qualification purposes, the sponsor believes that reasonable exposure factors were achieved for the impurities and the results did not indicate any special hazard to man. Therefore, based on the data from the 28-day toxicity study and the genotoxicity studies performed, the sponsor concluded that the [redacted] impurities [redacted] at the suggested specification limits of [redacted] respectively, have been qualified.

The drug product contains [redacted] degradation products that required qualification: [redacted] .. The proposed specification limit for the [redacted] is [redacted] The [redacted] is the [redacted] .. Therefore, the sponsor considers that the [redacted] does not require further qualification. The proposed specification limit for [redacted] is [redacted] This degradation product is a [redacted] The results from the 28-day toxicity study and the mouse micronucleus assay did not indicate any special hazard to man. The exposures achieved on mg/kg/day-basis were at least 28 times higher in animals than the maximal exposure in man. Therefore, the sponsor considers that the [redacted] at the suggested specification limits of [redacted] respectively, have also been qualified.

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5. Human Pharmacokinetics and Pharmacodynamics

I refer the reader to the separate review document from biopharmaceutics. I review here the design and pharmacokinetic results of the bioequivalence studies. I reviewed the safety data of the bioequivalence studies in section 9.2.2. The basic clinical pharmacokinetics (PKs) of entacapone and its effects on the PKs of levodopa and carbidopa have already been studied in the Comtan NDA 20-796. Entacapone is rapidly absorbed, with a C_{max} of approximately 1 hour. Entacapone plasma elimination half-life is 0.4 to 0.7 hour in the β phase and 2.4 hours in the γ phase. It has 35% absolute bioavailability after oral administration, secondary to first-pass clearance. Entacapone is 98% protein bound. It is not distributed widely in tissues and is almost completely metabolized before excretion (0.1%-0.2% of dose unchanged in urine). The drug inhibits erythrocyte-soluble COMT activity in a dose-dependent fashion (48% after a 400-mg dose, 82% after an 800-mg dose). The inhibitory effect of entacapone is reversible, with recovery of soluble COMT activity within 4 to 8 hours. The development program for the new triple combination product is based on bioequivalence human studies with existing individual drug products as reference (Table 1).

Table 1: LCE combination development program

Study #	Ref.	Type and design of study	N	Population	Dose (mg)
-93	[1]	Phase I bioequivalence study: open, single-dose, replicated, randomized, cross-over study (test vs. ref. vs. test vs. ref.). Washout 14 days.	44	healthy elderly male and female	**Test:** LCE 100/25/200 (LCE100) **Reference:** Sinemet® 25-100mg , Merck, *US + Comtess® 200 mg*
-85	[2]	Phase I bioequivalence study: open, single-dose, replicated, randomized, cross-over study (test vs. ref. vs. test vs. ref.). Washout 21 days.	44	healthy young male	**Test:** LCE 100/25/200 (LCE 100) **Reference:** Sinemet® 25/100 mg, MSD, Finland + Comtess® 200 mg
-95	[3]	Phase I bioequivalence study: open, single-dose, replicated, randomized, cross-over study (test vs. ref. vs. test vs. ref.). Washout 21 days.	44	healthy elderly male and female	**Test:** LCE 50/12.5/200 (LCE 50) **Reference:** Sinemet® 25/100 mg ½ tabl., MSD, Finland + Comtess® 200 mg
-96	[4]	Phase I bioequivalence study: open, single-dose, replicated, randomized, cross-over study (test vs. ref. vs. test vs. ref.). Washout 21 days.	44	healthy elderly male and female	**Test:** LCE 150/37.5/200 (LCE 150) **Reference:** Sinemet® 25/100 mg 1½ tabl., MSD, Finland + Comtess® 200 mg
0097008	[5]	Phase I bioequivalence study: open, single-dose, randomized, cross-over study (test vs. ref.). Washout 7 days.	40	healthy young male and female	**Test:** Sinemet® 25-100 mg, Merck, US **Reference:** Sinemet® 25/100 mg, MSD, Finland

LCE = levodopa/carbidopa/entacapone triple combination tablet

The LCE 100 tablet was tested in two different studies (Study 93 and Study 85) in two different populations (elderly versus young). The other strengths, LCE 50 and LCE 150, were tested in bioequivalence Studies 95 and 96, respectively. In addition, Study 0097008 was conducted to establish bioequivalence between Sinemet 25/100 mg purchased in the United States (Merck & Co) and Sinemet 25/100 mg purchased in Finland (MSD).

The reference product was Sinemet 100/25 mg standard release tablet in doses of 12.5/50 mg (a half tablet), 25/100 mg (one tablet) and 37.5/150 mg (one and a half tablet) administered with entacapone 200 mg. Sinemet purchased in Finland was used in three studies (Study 85, Study 95, and Study 96) and Sinemet purchased in the United States in one study (Study 93).

The first bioequivalence study of the combination product LCE 100 (Study 85) was conducted in healthy young male volunteers. Following the new FDA guidance on bioequivalence studies, all three combination products were investigated in healthy male and female volunteers with an age range representative of the Parkinson's disease patient population (Studies 93, 95, and 96).

Because the sponsor was aware of the variability of entacapone, levodopa and carbidopa pharmacokinetics, he used replicate administration of both test and reference products to investigate the intrasubject variability. In accordance with FDA recommendations (see Important Milestones in Product Development), the sponsor implemented repeated safety measurements to support the safety of the triple combination product at peak concentrations in case the bioequivalence criteria were not completely met in the forthcoming studies (which occurred).

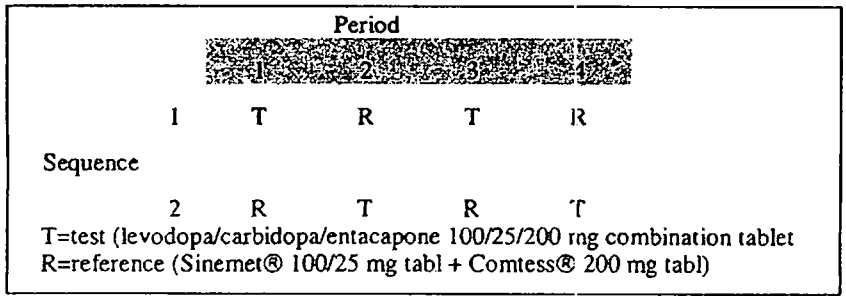
5.1 Pharmacokinetics

5.1.1 LCE Bioequivalence studies

Study design

Studies 93, 95, and 96, conducted in healthy elderly volunteers, had an open, randomized, cross-over and replicate design with two sequences of drug administration (sequence 1 = Test/ Reference/Test/Reference and sequence 2 = Reference/Test/Reference/Test), to which subjects were randomly allocated. A single dose of the test and the reference products were administered twice with 200 ml of water after an overnight fast. The washout period between administrations was at least 21 days (**Figure 5**).

Figure 5: Study design



Blood samples were collected before dosing (0 min), 10, 20, 30, 45, 60, 75, 90 minutes, and 2, 3, 4, 5, 6, 8 and 10 hours after drug administration. For the highest dose of levodopa (150 mg) an additional sample was collected at 12 hours after dosing. Safety was followed during each study by measurement of vital signs (blood pressure, heart rate and body temperature) before dosing and at 1, 2, 5, 8 hours after dosing and once more after the last blood sample collected at the 10 or 12 hours. An ECG was recorded before dosing and 1, 2, and 9 hours after dosing. In addition, laboratory assessments, EGG and vital sign measurements were performed at the pre- and post-study examinations.

Study 85, in young male volunteers, was the first of the two bioequivalence studies on the combination product LCE 100. Study 85 had same design as the other three studies, with the differences that it was conducted in young male volunteers (n=44), and there was no repeated measurement of vital signs and ECG on the days of administration of the study drug. Laboratory safety assessments, EGG and measurements of blood pressure and heart rate were performed at the pre- and post-study examination only.

Data analysis

Standard non-compartmental pharmacokinetic analysis methods were used. The primary parameters for the evaluation of bioequivalence for levodopa, carbidopa and entacapone were $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}. In addition, T_{max} and $T_{1/2}$ were determined. $AUC_{0\text{-}inf}$, $AUC_{0\text{-}ast}$ and C_{max} were log-transformed and then evaluated using an analysis of variance (ANOVA) model appropriate for the underlying crossover design. The 90% confidence intervals for the ratio of the geometric means were calculated. The standard acceptance range for bioequivalence was 0.80-1.25. The intrasubject variability of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}ast}$ and C_{max} was evaluated and the coefficient of variation was calculated. For the comparison of T_{max} the approximate nonparametric confidence intervals for the differences in medians between products were calculated in addition to the Wilcoxon signed rank test.

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

Bioequivalence studies results

PK results (C_{max}) of four bioequivalence studies comparing LCE 100 (Study 85 and Study 93), LCE 50 (Study 95) and LCE 150 (Study 96) with Sinemet and entacapone in corresponding doses (reference products), are shown in Figure 6 (for entacapone), Figure 7 (for carbidopa), and Figure 8 (for levodopa).

Figure 6: Entacapone bioequivalence studies results (from fig 2, page 248, Vol. 1.1)

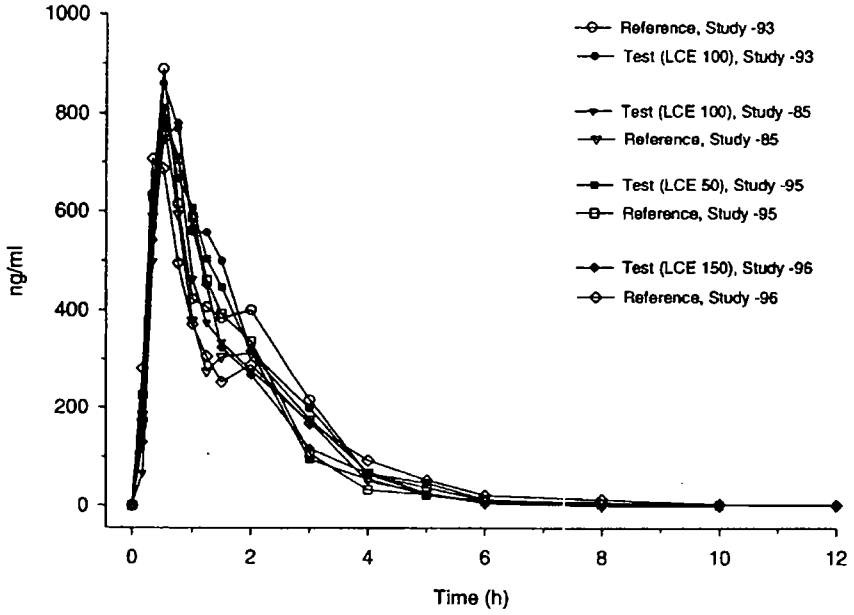


Figure 7: Carbidopa bioequivalence studies results (from fig 2, page 73, Vol. 1.64)

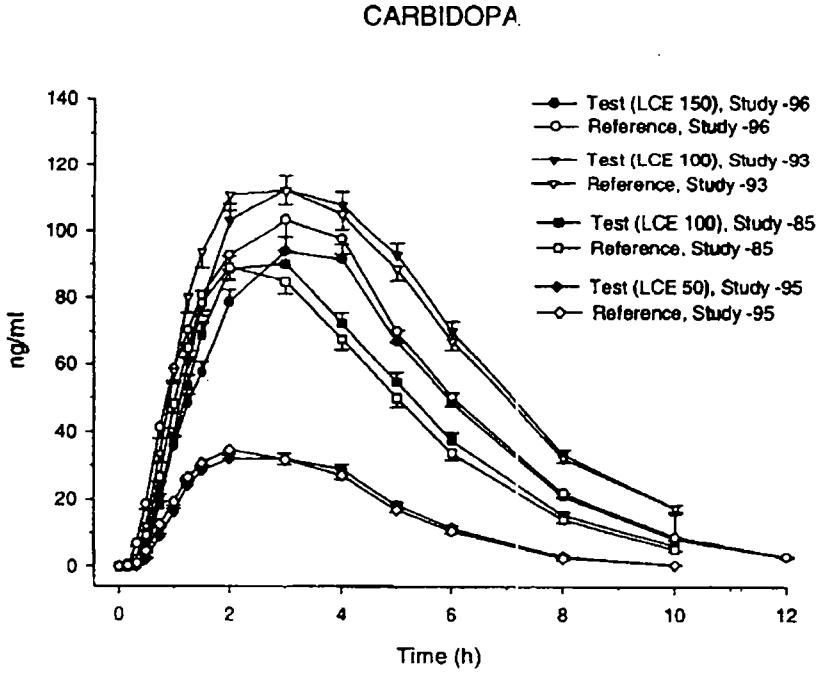
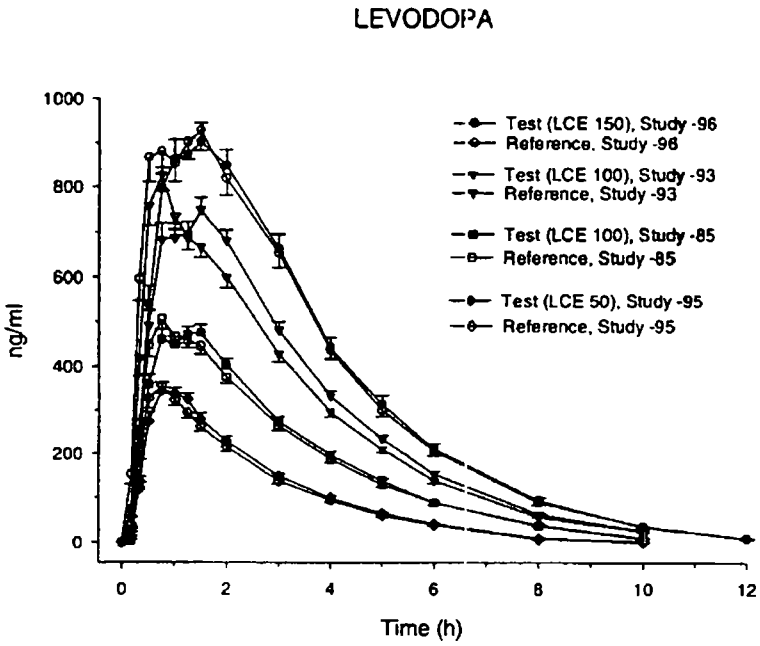


Figure 8: Levodopa bioequivalence studies results (from fig 2, page 73, Vol. 1.64)



PK results (C_{max}, AUC) are also summarized in Table 2.

Table 2: AUC and Cmax results in LCE combination bioequivalence studies (from Table 3, page 71, Vol. 1.64)

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

Test = test product, LCE 100, LCE 50 or LCE 150

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

Study # -93: number of subjects is 44 except for $AUC_{0-\infty}$ of entacapone 36

Study # -85: number of subjects is 43 except for $AUC_{0-\infty}$ of entacapone 39

Study # -95: number of subjects is 43 except for $AUC_{0-\infty}$ of carbidopa 41 and entacapone 33

Study # -96: number of subjects is 43 except for $AUC_{0-\infty}$ of entacapone 35

In all studies the 90% confidence intervals for $AUC_{0-\infty}$ were within the standard bioequivalence criteria (0.80-1.25) regarding levodopa, carbidopa and entacapone. The 90% confidence intervals for levodopa and carbidopa C_{max} were also within the 0.80-1.25 range.

For entacapone C_{max}, the 90% confidence intervals were between 0.84-1.35. In two studies (LCE 50 and LCE 100 in Study 83), confidence intervals were within the acceptable range of 0.80-1.25. In the third study (LCE 100 in Study 93), the upper limit of the confidence interval was

marginally higher than 1.25, at 1.255. In the fourth study (LCE 150), the upper confidence interval was 1.35.
COMMENT: the marginally elevated value of 1.255 is not particularly worrisome for entacapone, especially regarding bioequivalence established with the same dose in Study 85, and regarding bioequivalence for AUC in all studies. The value of 1.35 for LCE 150 C_{max} is more significant and justifies safety data to support approval (I review safety data in section 9). Again, this value must be counter-balanced by the fact that for LCE 150, entacapone AUC met bioequivalence criteria with the reference products, and that entacapone has limited toxicity and a large therapeutic index. In a Orion sponsored-study, entacapone decreased the COMT activity from predose leve by 25%, 33% and 32% respectively for a 100, 200, and 400 mg dose. Correspondingly, the 3-OMD concentrations decreased by 39%, 54%, and 66% with 100-, 200-, and 400-mg doses, respectively. The elimination half-life of L-Dopa was prolonged by 23%, 26%, and 48%, and the area under the curve of L-Dopa increased by 17%, 27%, and 37% with the increasing doses[1].

Also, the sponsor also argues that the high variability in entacapone C_{max} is already known and that entacapone belongs to a highly variable drug class. In the bioequivalence studies, intrasubject variability (measured by CV) ranged from 37.9% to 57.8% for both the test and reference products. Entacapone plasma levels were not exceptionally high in those studies where the upper confidence limit was exceeded compared to other studies (Figure 9). The sponsor suggests that the high upper confidence interval limit in Study 96 was mainly due to rather low plasma levels of entacapone following reference treatment in one period (Table 3).

[1] Heikkinen H, Nutt JG, LeWitt PA, Koller WC, Gordin A. The effects of different repeated doses of entacapone on the pharmacokinetics of L-Dopa and on the clinical response to L-Dopa in Parkinson's disease.Clin Neuropharmacol 2001 May-Jun;24(3):150-7.

Figure 9: Mean entacapone concentrations in bioequivalence studies (from fig 3, page 73, Vol. 1.64)

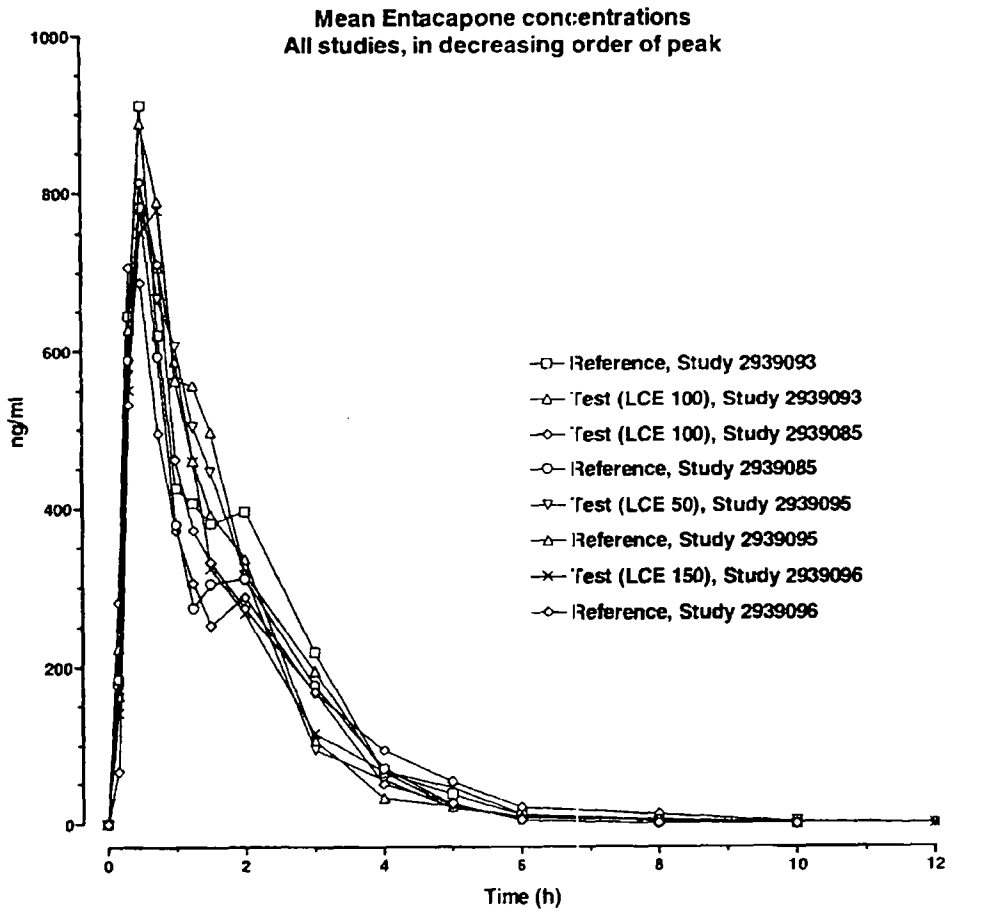


Table 3: C_{max} values of entacapone in Study 93 and 96 (from Table 5, page 75, Vol. 1.64)

Study #	Period	Test product	Test		Reference	
			mean	range	mean	range
-93	1. (n=21-22)	LCE 100	1016	[illegible]	1065	[illegible]
	2. (n=20-22)	LCE 100	1438	[illegible]	928	[illegible]
	3. (n=21-22)	LCE 100	1267	[illegible]	1245	[illegible]
	4. (n=21)	LCE 100	1307	[illegible]	1026	[illegible]
-96	1. (n=22)	LCE 150	1118	[illegible]	1065	[illegible]
	2. (n=21)	LCE 150	1307	[illegible]	763	[illegible]
	3. (n=20-21)	LCE 150	1110	[illegible]	1264	[illegible]
	4. (n=19)	LCE 150	1383	[illegible]	1123	[illegible]

Reference: Study reports # -93 and -96
n = 81-85 (n, number of observations)

COMMENT: I agree with the Sponsor observation for rather low C_{max} for reference entacapone in Study 96. Also, entacapone mean entacapone C_{max} for the reference product in Study 95 (1152) was close to C_{max} for the test product entacapone in Study 96 (1211) – in a similar subject population.

Median levodopa T_{max} was slightly longer with the test products than with the reference products (Table 4). Carbidopa and entacapone T_{max} were similar for the test and reference products.

Table 4: T_{max} in bioequivalence studies (from Table 6, page 77, Vol. 1.64)

Study #	Substance	Dose (mg)	Test product	Test	Reference
-85	Levodopa	100	LCE 100	1.3 (0.3-5.0)	1.0 (0.3-3.0)
-93	Levodopa	100	LCE 100	1.3 (0.5-3.0)	0.8 (0.3-3.0)
-95	Levodopa	50	LCE 50	1.0 (0.5-3.0)	0.8 (0.2-3.0)
-96	Levodopa	150	LCE 150	1.3 (0.3-5.0)	1.0 (0.3-4.0)
-85	Carbidopa	25	LCE 100	3.0 (1.3-5.0)	2.0 (1.3-5.0)
-93	Carbidopa	25	LCE 100	3.0 (1.5-5.0)	3.0 (1.3-5.0)
-95	Carbidopa	12.5	LCE 50	2.0 (1.3-4.0)	2.0 (1.0-5.0)
-96	Carbidopa	37.5	LCE 150	3.0 (1.3-6.0)	3.0 (0.8-6.0)
-85	Entacapone	200	LCE 100	0.5 (0.3-5.0)	0.5 (0.2-4.0)
-93	Entacapone	200	LCE 100	0.8 (0.2-4.0)	0.5 (0.2-3.0)
-95	Entacapone	200	LCE 50	1.0 (0.2-5.0)	0.8 (0.2-4.0)
-96	Entacapone	200	LCE 150	0.8 (0.2-5.0)	0.5 (0.2-8.0)

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

Apparent elimination half lives for levodopa, carbidopa and entacapone were comparable between the test and reference products for all three components (**Table 5**)

Table 5: T ½ in the bioequivalence studies (from Table 8, page 78, Vol. 1.64)

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

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

COMMENT: Another observation is the non-linearity of levodopa AUC (Table 6, Table 7). On the other hand, levodopa C_{max} was relatively dose-proportional. The effect was similar for both the test and the reference drug, and is not unique to the LCE combination. Levodopa – even administered alone - has complex pharmacokinetics.

Table 6: Comparison of levodopa PKs with rising doses of levodopa (reference)

	50mg	100 mg	150mg
AUC	1017	2808	3880
C_{MAX}	489	1036	1384

Table 7: Comparison of levodopa PKs with rising doses of levodopa (test)

	50mg	100 mg	150mg
AUC	1044	2906	3774
C_{MAX}	473	975	1272

In Study 83 (see 5.2.1), the sponsor obtained data with Sinemet co-administered with placebo, which are directly relevant to this issue. The same non-linearity of levodopa AUC was observed in Study 83, which confirms that this is not related to entacapone or the LCE combination, but to levodopa itself (Table 8). Lower levodopa AUC values in Table 8 than in Table 6 and Table 7 is explained by the co-administration of entacapone for observations in Table 6 and Table 7.

Table 8: Levodopa (Sinemet) AUC

	50mg	100 mg	150mg
AUC	590	1434	2399

5.1.2 Bioequivalence study comparing Sinemet purchased from US vs. Finnish market (Study 0097008)

The bioequivalence study for the comparison of Sinemet 25-100 mg purchased in the United Sates and Sinemet 25/100 mg purchased in Finland was performed with an open, randomized, 2-sequence, cross-over design in 40 healthy young male and female volunteers. A single dose of the test and the reference formulation was separated by a washout period of 7 days. Safety data in this study are not directly relevant to the LCE combination. The results of this study are presented in Table 9. The Sinemet products were bioequivalent.

Table 9: Sinemet bioequivalence study results (from Table 2, page 245, Vol. 1.1)

	Substance	Test (mean±SD) [1]	Reference (mean±SD) [1]	Geom. means ratio[2]	Log 90% CI
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	1730± 487	1722 ± 472	0.99	0.95 – 1.03
	Carbidopa	323 ± 130	318 ± 131	0.99	0.89 – 1.11
C_{max} (ng/ml)	Levodopa	1029 ± 349	996 ± 296	1.02	0.94 – 1.11
	Carbidopa	71.1 ± 30.1	72.3 ± 33.1	0.99	0.88 – 1.11
t_{max} (h)	Levodopa	0.5 (0.25 – 1.67)	0.5 (0.25 – 2.50)	0.125	0.00 – 0.25
	Carbidopa	2.5 (1.0 – 4.0)	2.5 (0.5 – 4.0)	0.167	-0.167 – 0.50

Number of subjects is 39 for all parameters except for $AUC_{0-\infty}$ of levodopa 38 and $AUC_{0-\infty}$ of carbidopa 37.

[1] For t_{max} median, range

[2] For t_{max} median difference

5.2 Pharmacodynamics

5.2.1 Study of the effect of entacapone with different levodopa/carbidopa doses (Study 83)

To confirm that entacapone will provide comparable levodopa levels irrespective of the levodopa/carbidopa ratio (levodopa products with different levodopa/carbidopa ratios, namely 4:1 and 10:1 are available in United States), the sponsor conducted Study 83, a double-blind,

single-dose, placebo-controlled study, in 47 healthy subjects. In a Medline search I conducted about entacapone, I identified that the sponsor recently published the results of this study in a peer reviewed journal[2]. The ratio of 4:1 is currently mainly used in the United States and was chosen for the combination tablets. In the entacapone phase III study performed in US (Study 44), about 20% of patients used the product with 10:1 ratio.

Entacapone 200 mg or placebo was given with levodopa/carbidopa in doses 50/12.5, 100/10, 100/25, 200/50 and 250/25 mg. Each subject received two different levodopa/carbidopa doses, each dose once with entacapone and once with placebo (four-way cross-over).

Entacapone increased levodopa plasma levels and decreased 3-OMD levels approximately similarly irrespective of levodopa/carbidopa ratio (Table 10). Entacapone did not affect carbidopa pharmacokinetics. The sponsor suggests that there should be no problems to initiate the triple combination preparation in PD patients who at present use entacapone with levodopa/carbidopa in a ratio 10:1. However, even if entacapone effect is similar regardless of the carbidopa ratio, levodopa AUC appears higher with the 1:4 than with the 1:10 produt (i.e. 1434 ng/ml versus 1209 ng/ml respectively for the 100/25 and 100/10 products), so that conversion to the LCE combination for patients on levodopa/carbidopa 1:10 products may lead to higher levodopa exposure.

Table 10: Effect of entacapone on levodopa AUC (from Table 10, page 80, Vol. 1.64)

Group	Number of subjects	Levodopa/ carbidopa dose (mg)	Placebo (Mean ± SD)	Entacapone (Mean ± SD)	p-value	Mean change (%) (90% CI)
I	16	50/12.5	590 ± 119	758 ± 196	<0.001	+27 (18, 37)
	15	150/37.5	2399 ± 416	3115 ± 798	<0.001	+27 (18, 38)
II	16	100/10	1209 ± 272	1554 ± 324	<0.001	+29 (19, 39)
	16	100/25	1434 ± 347	1901 ± 418	<0.001	+33 (23, 44)
III	14	200/50	3196 ± 433	4448 ± 724	<0.001	+38 (29, 47)
	14	250/25	3677 ± 615	5011 ± 938	<0.001	+35 (26, 44)

[2] Heikkinen H, Varhe A, Laine T, Puttonen J, Kela M, Kaakkola S, Reinikainen K. Entacapone improves the availability of l-dopa in plasma by decreasing its peripheral metabolism independent of l-dopa/carbidopa dose. Br J Clin Pharmacol 2002 Oct;54(4):363-71.

6. Description of Clinical Data and Sources

6.1 Overall Data

For my review, I used volumes 1.1, and 1.64-1.89 of the NDA. I also conducted Medline searches on some specific items, as described in my review.

6.2 Table Listing the Clinical Trials (Table 11)

Table 11: Clinical trials in NDA 21-485

Study	Type and design	N	Population	Dose
93	Phase 1 bioequivalence study. Open-label, single-dose, replicated, randomized cross-over study (test vs. ref vs. test vs. ref).	44	Healthy elderly male and female	Test: LCE 100 Reference: Sinemet 25-100 (US) + Comtess 200 mg
85	Phase 1 bioequivalence study. Open-label, single-dose, replicated, randomized cross-over study (test vs. ref vs. test vs. ref).	44	Healthy young male	Test: LCE 100 Reference: Sinemet 25-100 (FI) + Comtess 200 mg
95	Phase 1 bioequivalence study. Open-label, single-dose, replicated, randomized, cross-over study (test vs. ref vs. test vs. ref).	44	Healthy elderly male and female	Test: LCE 50 Reference: Sinemet 25-100 ½ tablet (Fi) + Comtess 200 mg
96	Phase 1 bioequivalence study. Open-label, single-dose, replicated, randomized, cross-over study (test vs. ref vs. test vs. ref).	44	Healthy elderly male and female	Test: LCE 150 Reference: Sinemet 25-100 1½ tablet (Fi) + Comtess 200 mg
0097-008	Phase 1 bioequivalence study. Open-label, single-dose, randomized, cross-over study (test vs. ref).	40	Healthy young male and female	Test: Sinemet 25-100 (US) Reference: Sinemet 25-100 (Fi)
83	double-blind, single-dose, placebo-controlled study, four-way cross-over	47	Healthy young male and female	Entacapone 200 mg or placebo; Levodopa/carbidopa in doses 50/12.5, 100/10, 100/25, 200/50 and 250/25 mg.

6.3 Postmarketing Experience

The combination has not been approved in any country. Entacapone has been in clinical use for more than three years in the United States and in Europe, and it is marketed in 60 countries worldwide. More than [redacted] patients had been exposed to entacapone by the end of year 2001. The sponsor has sent several post-marketing safety reports to FDA, with no particular safety signal. I also checked the last entacapone annual report, dated 12/19/02. The sponsor reports that the estimated patient exposure from Sept 01 to Aug 02 is [redacted] patient years, and that the cumulative market exposure equals [redacted] patient years. In the annual report, the sponsor provided the results on long term open-label studies, extension of controlled trials used in the entacapone NDA. No new safety concern emerged from these studies, and no change in labeling was proposed. I also queried the AERS database on Comtan. There were 706 preferred terms reported. I list in all preferred terms reported at least 10 times.

Table 12: Preferred term reported at least 10 times in the AERS database

Preferred term	N
Hallucination	17
Confusion	15
Dyskinesia	15
Tremor	12
Coma	12
Diarrhea	11
Hypotension	10
Pyrexia	10
rhabdomyolysis	10

Hypotension, diarrhea, hallucinations, dyskinesia, rhabdomyolysis, pyrexia, and confusion are all reported in entacapone patient insert under "precautions". Tremor is expected in Parkinson's patients. I reviewed the coma cases (Table 13), since this was an unexpected adverse event. In most cases, multiple factors were possibly responsible for the reported adverse event, and the responsibility of entacopone was unlikely or impossible to determine. Two separate reports were filed for the same case on two occasions (ten separate patients out of 12 reports).

Table 13: Coma cases

Description (in addition to coma)	Outcome	Entacapone responsibility?*
Neuroleptic malignant syndrome (NMS) after D/C dopaminergic agonists	Recovered	Unlikely
NMS/rhabdomyolysis – on entacapone for >10 months	Death	?
UTI/ rhabdomyolysis/hypotension	Recovered	?
Sepsis/fever	Recovered	Unlikely
Coma due to dothiepin (Dosulepin) overdose	Recovered	No
Liver failure/multiple medical problems/	Death	?
Coma following neurosurgical procedure (reported X2)	Recovered	Unlikely
Sudden onset of sleep/hypothyroidism/dehydration	Recovered	?; Responsibility imputed to bromocriptine
Lactic acidosis/muscle "hyperactivity"/confusion	?	Possible
Liver necrosis/hepatotoxicity possible, but liver damage likely related to large bile duct obstruction and ulcerative colitis	Death	?

*As determined by me after reviewing narrative and AERS report.

There was no rare adverse event which had an incidence clearly over expected background rate.

7. Clinical Review Methods

7.1 How the Review was Conducted

Since this NDA is based on a bioequivalence strategy, I did not re-evaluate the efficacy of the individual components (levodopa, carbidopa and entacapone), which are already used in

association in clinical practice. My review focused on the safety results of the bioequivalence studies, with a particular emphasis on differences between the LCE combination and the reference drugs (Sinemet and Comtan), since the new LCE combination is not fully bioequivalent to the existing product given separately. I did not review in detail the pharmacokinetic aspects of the bioequivalence studies, which were the object of a separate review by the clinical pharmacology reviewer.

7.2 Overview of Materials Consulted in Review

This NDA was almost entirely a paper NDA. I used for my review Volumes 1.1, and 1.64-1.89. The sponsor submitted electronically datasets for all bioequivalence studies. I used these datasets in my safety analysis.

7.3 Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI investigation was requested for two sites. Results are pending.

7.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

Trials were conducted in accordance with accepted ethical standards.

7.5 Evaluation of Financial Disclosure

The sponsor certified that he has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 542(a). The sponsor certified that each listed clinical investigator had no proprietary interest in this product or a significant equity in the sponsor. The sponsor certifies that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

8. Integrated Review of Efficacy

There was no efficacy study part of this application. This NDA was based on establishing bioequivalence of the LCE combination with Sinemet and Comtan administered separately as reference products.

The benefits of Comtan have been demonstrated by two pivotal studies and supported by a third study in NDA 20-796. There were significant improvements in the entacapone-treated patients compared with placebo in both ON-time and in the secondary efficacy parameters assessing parkinsonian disability (global evaluations both by the patients and investigators and the Unified Parkinson's Disease Rating Scale (UDPRS) scores). The levodopa dose was significantly reduced on average by about 100 mg in both studies for patients taking entacapone, which has implication in the determination of the appropriate dosage for the LCE combination. The sponsor states that the clinical benefit derived from entacapone treatment occurred irrespective of the levodopa dose reductions.
COMMENT: This last statement is speculative.