CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-485

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21,485	Submission Dates: 06/24/2002 11/14/2002 12/03/2002 03/13/2003 (E-doc, revised label, name change from [redacted] to Stalevo) 03/19/2003 (Response to issue regarding plasma carbidopa levels)
Brand Name	Stalevo tablet
Generic Name	Levodopa/Carbidopa/Entacapone (LCE)
Relevant IND/NDA	NDA 20,796 (Comtan ®, entacapone) IND 60,554 (Levodopa/Carbidopa/Entacapone)
Primary Reviewer	Wen-Hwei Chou, Pharm.D., Ph.D.
Team Leaders	Ramana Uppoor, Ph.D.
OCPB Division	HFD-860
OND Division	HFD-120, Neuropharmacological drug products
Sponsor	Orion Pharma, Inc.
Submission Type; Code	S
Formulation; Strength	Film-coated Tablets (Levodopa/Carbidopa/Entacapone) LCE 50: 50/12.5/200 mg LCE 100: 100/25/200mg LCE 150: 150/37.5/200mg
Indication	Treatment of patients with idiopathic Parkinson's disease with the signs & symptoms of end-of –dose wearing-off
Proposed dose	A direct switch of patients taking levodopa/carbidopa 100/25mg (4:1) standard release tablet with or without entacapone to corresponding doses of LCE tablet. Max 8 tablets/day. No more than 1 Stalevo tablet per each dosing

1 Executive Summary

This review evaluates a new combination tablet containing three previously marketed active agents, levodopa, carbidopa and entacapone in three different strengths for the treatment of Parkinson's disease. Each strength consists of a 4 to 1 ratio of levodopa to carbidopa and a fixed dose of 200mg entacapone in a standard release formulation LCE tablets (levodopa /carbidopa/entacapone: 50/12.5/200mg, 100/25/200mg, 150/37.5/200mg). The fixed dose of 200mg entacapone design is based on the marketed Comtan (entacapone) product. The recommended dose of Comtan(entacapone) is one 200mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily. This submission is entirely based on pharmacokinetic/BE studies. As requested, the sponsor had conducted BE study for each strength since three strengths are not compositionally proportional. Three pivotal BE studies had included elderly subjects (>60 years old, range 45-74 years old). No clinical trial was conducted in target population.

At the pre-NDA meeting, two values of 90% CI were noted to be outside of recommended BE goal post (80-125). The sponsor was told that their proposed extended limits (90% CI of 70-143%) for the highly variable compounds is not acceptable and following comments were conveyed to the sponsor: (a) If bioequivalence testing fails by a small percentage, it may be acceptable to base approval upon clinical efficacy equivalence or safety profile. Justification for using clinical equivalence as criteria for approval should be provided by the Sponsor. (b) It may be possible to show therapeutic equivalence by levodopa level if the test and reference products are bioequivalent regarding levodopa but the bioequivalence criteria are not fully met regarding carbidopa or entacapone. (c) However, a small percent of entacapone can get into the CNS and may alter therapeutic equivalence. Therefore, the Sponsor should address this issue and particularly address whether the extent of central penetration and activity of entacapone may alter the therapeutic effect. The clinical efficacy equivalence & safety profiles regarding these 2 CI values for entacapone are reviewed by clinical division. This review is only focused from Clinical Pharmacology & Biopharmaceutics perspective as to whether the sponsor had adequately justified its clinical relevancy from a safety viewpoint at the highest recommended daily dose.

The sponsor proposed a direct switch of patients taking levodopa/ carbidopa 100/25mg (4:1) standard release tablet with Comtan (entacapone) to corresponding doses of LCE tablet. The maximum recommended daily dose of Stalevo is 8 tablets per day. No more than one Stalevo tablet should be taken at each dosing administration.

OCPB noted in the Pre-NDA meeting package that the sponsor proposed

. Clinical division (Dr. Katz) clearly indicated that LCE may only be allowed to be replacement therapy for 3 individual entities. The sponsor was requested to clearly address in the "dosage and administration" section of label the issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms. Briefly, the sponsor proposed the following: (a) How to transfer patients taking carbidopa-levodopa preparations and Comtan® (entacapone) tablets to STALEVO: Patients who are currently treated with Comtan (entacapone) 200mg tablet with each dose of standard release carbidopa-levodopa, can be directly switched to the corresponding strength of STALEVO containing the same

(b) How to transfer patients not currently treated with Comtan® (entacapone), from carbidopa-levodopa to STALEVO®: Patients with Parkinson's disease who experience the signs and symptoms of end-of-dose "wearing-off" on their current standard release carbidopa-levodopa treatment

[redacted] This section is reviewed by the Clinical division. It should be noted that the sponsor remained silent in the proposed label regarding the use of Stalevo in levodopa naive patients.

In addition, the sponsor proposed that [redacted] All the pivotal BE studies were conducted in fasted state. However, no food-effect study was conducted. At the Pre-NDA meeting, OCPB noted that no food effect study was conducted with this combination tablet. Clinical division indicated that since this medication is to be taken up to 8 times per day dosing based on food effect may not be practical and food effect with entacapone may be enough. As discussed at pre-NDA meeting, we will rely only on literature for food effect, if available. The sponsor was requested to provide supportive information from entacapone NDA and literature regarding food effects on levodopa and carbidopa. Literature suggested that PK of levodopa is less predictable and food delayed the absorption & reduced the peak plasma levodopa level. However, information from the literature may not be relevant to this combination product due to the different formulations evaluated in literature. OCPB recommends label should state that food-effect was not evaluated for this combination tablet.

Overall, from the Clinical Pharmacology and Biopharmaceutics perspective, the sponsor has submitted sufficient information to support the approval of LCE tablets in three strengths (LCE50, LCE100, and LCE150). This is based on the BE of LCE 50 & LCE 100 tablets to the corresponding doses of reference products of Sinemet (levodopa/carbidopa) and Comtess (entacapone) tablets in healthy volunteers age between 45-74 years old. Reference tablet (US and Finland Sinemet products) for levodopa/carbidopa are BE. Comtess or Comtan is the same product manufactured in the same place but marketed in Finland or US respectively. LCE150 failed to demonstrate BE with regard to Cmax of entacapone with a 90% CI of 103-135 which exceeds the recommended BE 80-125 goal post. Slightly higher mean plasma entacapone concentrations were observed following administration of LCE150 than the corresponding dose of reference tablets (~15% higher, 1211$\pm$738 versus 1052$\pm$792ng/ml). Nausea is more frequent in the test drug group than the reference group. Even though the entacapone level was not much higher than the other studies; the concurrent higher levodopa (150mg in LCE 150) and higher entacapone in current study may have contributed to more frequently observed nausea in the group receiving test drug.
It should be noted that as indicated in the entacapone label, nausea was the one of the side effects that is associated with entacapone when compared to without entacapone treatment.

From the Clinical Pharmacology & Biopharmaceutics perspective, the sponsor's justifications related to safety of this higher Cmax of entacapone are reasonable and the increase in plasma entacapone levels is unlikely to result in significant safety or tolerability concerns. Based on the short elimination t1/2 of levodopa and entacapone, it is unlikely that there would be substantial accumulations upon repeated dosing. This reviewer had discussed safety issues related to this increase in entacapone levels in LCE150 test product with the review Medical officer, Dr. Eric Bastings. In addition to sponsor's analysis, Dr. Bastings also performed several comparisons of levodopa or entacapone levels between the subjects experiencing nausea or without nausea. The results indicated that more nausea observed in the LCE150 test product group may be due to chance alone. Across BE studies, there is no consistency regarding test product group experiencing more nausea.

When plasma PK parameters of levodopa, carbidopa and entacapone were compared across 3 strengths of LCE tablets from 3 different BE studies, the plasma Cmax as well as AUC of carbidopa did not show a rank order increase across 3 strengths for test products: LCE50 (carbidopa 12.5mg) <LCE150 (carbidopa 37.5mg) <LCE100 (carbidopa 25mg). Similar observations were seen in the reference tablets. Potential causes of this variation are unclear at this point. Several considerations such as variability from cross-study comparison and lack of dose-linearity for carbidopa are discussed in this review but results are inconclusive. Upon Agency's request, the sponsor had provided similar justification regarding this inconsistency in PK parameters of carbidopa in 3 pivotal BE studies.

Labeling issues regarding special populations (elderly, female, low body weight) that are not unique to the combination product are discussed and warrant further evaluation for all the levodopa, carbidopa, and entacapone products. The sponsor proposed to use labels of marketed products Sinemet (levodopa/carbidopa) and entacapone as template. Only recently approved entacapone label contains information regarding special populations. The sponsor was requested at the pre-NDA meeting to incorporate into the label the information regarding age & gender from the available source (literature & BE studies). From the available sources, following were consistently observed in special populations (elderly, female, low-body weight): (a) significantly higher plasma levodopa exposures (Cmax & AUC). The magnitude of increase in plasma levodopa levels ranged from 50-250%. (b) The clearance is significantly decreased. (c) Relative bioavailability is significantly increased. (d) AUC & t1/2 of Levodopa are correlated with age. (e) AUC & t1/2 of Levodopa are significantly and inversely correlated with body weight. In addition, more peak-dose dyskinesia was observed in female with low body weight. Overall, special caution should be exercised in these subsets of Parkinson's disease patients who are more prone to achieve higher plasma levodopa levels. Higher peak plasma levodopa concentration has been linked to side effects such as dyskinesia, nausea. It should be noted that in current clinical practice, the dosing regimen of levodopa products does not recommend adjustment for body weight and the dosing schedule is unevenly divided during the day. Additionally, considering all the factors (age, gender, body weight) that would elevate plasma levodopa, carbidopa, or entacapone concentrations, the overall magnitude of increase in plasma exposure of levodopa, carbidopa, and entacapone in these subsets of Parkinson's patients warrants further evaluation.

In general, relevant information in this regard should be incorporated into the label such as special populations in the PK, precaution, and dosage & administration sections for all the products of levodopa, carbidopa, and entacapone. Lower dose or less frequent dosing should be considered in the subsets of Parkinson's disease patients including elderly patients, female patients, and patients with low body weight in general. However, OCPB does not recommend incorporating language regarding these special populations in this combination product for the following reasons: (a)This combination tablet is not indicated for initial treatment. (b) Dose titration with levodopa and/or carbidopa products is a routine practice in treating Parkinson's disease. (c) More appropriate initiative should be considered in incorporating information regarding special populations in levodopa and/or carbidopa products that are indicated for initial treatment. (d) There are limitations in drawing conclusions from cross-study comparison due to the variability. OCPB recommends that descriptive pharmacokinetics in age & gender analysis from 3 BE studies of Stalevo should be incorporated in PK section of label.

Division of Scientific Investigation (DSI) inspection was requested for 2 pivotal BE studies. Two studies were conducted in different countries. Bioanalytical methods for levodopa and carbidopa were different and carried out in different laboratories. Form 483 was issued for both studies at both clinical & analytical sites. Overall, the DSI concluded that study #93(LCE100) is acceptable for agency review since the sponsor's response to Form 483 was satisfactory. The conclusion of BE for LCE100 tablet is not affected. Study #96 (LCE150), on the other hand, DSI recommended not acceptable for agency review due to noncompliance with the Bioequivalence (BE) regulation for retention of reserve samples [21 CFR 320.38], thus the authenticity of the drug products used in the study #96 cannot be assured. Specifically, BE regulation requires the reserve samples should be retained at the clinical site (i.e. [redacted] or at an independent third party. Instead, the study drugs were prepackaged as unit dose by sponsor (Orion) and shipped to the clinic. The clinic [redacted] returned a set of 10 unused unit doses to Orion after study completion. Orion cannot be considered as an independent third party. The OCPB has taken DSI recommendation into consideration, however, concluded that study # 96 should be incorporated into the review for the reasons described below: (a) All the transfers of drug products were properly documented (from the Sponsor to the Clinical site as well as from the Clinical site to the Sponsor). Dr. Sriram Subramaniam from DSI has provided information to confirm this. (b) All the drug products for three pivotal BE studies (#93, #95, #96) were provided by the same provider, the authenticity

of the drug products was assured in study #93. (c) The bioanalytical methods for 3 moieties were validated and reproducible in analytical site. (d) In study #96, both clinical and analytical sites have satisfactorily addressed the other issues cited on the Form 483. There are no other issues in study 96 that raise a concern related to study conduct. The sponsor should be warned that in the future such noncompliance to BE regulation will result in the BE studies being non-acceptable.

The proposed *in vitro* dissolution methods are also found to be acceptable. However, OCPB recommends change in the dissolution specifications.

The OCPB also proposes revisions to the proposed labeling text.

1.1 Recommendation

Overall, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the Clinical Pharmacology & Biopharmaceutics sections of NDA 21-485 acceptable for Stalevo (levodopa/carbidopa/entacapone) 50/12.5/200mg & 100/25/200mg tablets. The Stalevo (levodopa/carbidopa/entacapone) 150/37.5/200mg are not BE to reference tablets. Entacapone Cmax was higher when compared to reference product. The medical officer should evaluate whether the higher peak levels of entacapone achieved with LCE 150 are clinically significant.

The OCPB finds the proposed *in vitro* dissolution methods acceptable. However, the dissolution specifications need to be tightened.

The OCPB recommends revisions to the proposed labeling text; the revisions are described in labeling comments section (page33) of the main review.

1.2 Comments to the Sponsor

1. In vitro-dissolution methods & specifications

Overall, we find the proposed dissolution methods for each moiety acceptable. However, based on the dissolution profiles from biobatches, the specifications for all 3 moieties should be tightened.

Agency recommendation

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

2. Label: The Office of Clinical Pharmacology and Biopharmaceutics recommends revisions to the proposed labeling text, the revisions are described in labeling Section (page 33) of the main review.

3. In the future, the sponsor should fully comply with the Bioequivalence Regulation (21 CFR 320.38) in retaining reserve samples. The response to Form 483 from Clinical site ([redacted]) has clearly indicated that the sponsor, Orion Pharma has now changed the procedure for taking the reserve samples and storing of them. The free selection samples will be offered for the investigator performing the BE/BA studies, as well as the storing of the samples will be under investigator's responsibility. Noncompliance in this regard is a major flaw and may result in BE studies being not acceptable.

4. [redacted]

1.3 SIGNATURES

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

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

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

OCPB Briefing Date: 03/28/2003
Briefing Attendees: Malinowski H; Lazor J; Bastings E; Heimann M; Mehta M; Sahajwalla C; Uppoor R; Nallani S; Kenna L; Roshni R; Chou W.
c.c.: NDA 21-485, HFD-120 (Feeney, Bastings, Wheelous T), HFD-860 (Mehta, Sahajwalla, Uppoor, Chou)

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3 SUMMARY OF CPB FINDINGS

This review evaluates a new combination tablet containing three previously marketed active agents, levodopa, carbidopa and entacapone in three different strengths for the treatment of Parkinson's disease. Three strengths are not compositionally proportional. Each strength consists of a 4 to 1 ratio of levodopa to carbidopa and a fixed dose of 200mg entacapone in a standard release formulation LCE tablets (levodopa /carbidopa/entacapone: 50/12.5/200mg, 100/25/200mg, 150/37.5/200mg). The fixed dose of 200mg entacapone design is based on the marketed Comtan (entacapone) product. The recommended dose of Comtan(entacapone) is one 200mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily. This submission is entirely based on pharmacokinetic/BE studies. As requested, the sponsor had conducted BE study for each strength since three strengths are not compositionally proportional. Three pivotal BE studies had included elderly subjects (>60 years old, range 45-74 years old). No clinical trial was conducted in target population.

Dosage & Administration: The sponsor proposed a direct switch of patients taking levodopa/ carbidopa 100/25mg (4:1) standard release tablet with Comtan (entacapone) to corresponding doses of LCE tablet. The maximum recommended daily dose of Stalevo is 8 tablets per day. No more than one Stalevo tablet should be taken at each dosing administration. This is based on the following: (a) the clinical experience with daily doses above 1600mg entacapone is limited. (b) the recommended dose of entacapone-alone tablet is one 200mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily (200mg X 8=1600mg).

The sponsor proposed that

OCPB noted in the Pre-NDA meeting package that the sponsor proposed

Dr.Katz clearly indicated that LCE may only be allowed to be replacement therapy for 3 individual entities. The sponsor was requested to clearly address in the "dosage and administration" section of label the issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms. The sponsor addressed in the clinical section various issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms. This section is reviewed by the Clinical division.

The sponsor submitted a total of 7 PK/BE studies. As requested by Agency, the sponsor performed 3 different studies for 3 different strengths combination products because the ingredients of combination products were not compositionally proportional. Of these 7 studies, 5 were reviewed. Specifically, the sponsor conducted three separate pivotal BE studies with each different strength of to-be-marketed LCE tablet against marketed Sinemet (levodopa/carbidopa, 100/25mg tablet) and Comtess (entacapone 200mg) in healthy volunteers age between 45-74 years old. Additional BE study was conducted in young volunteers (age between 20-38 years old) with LCE 100. One BE study was conducted to compare Sinemet US versus Finland product since both tablets were used in the pivotal BE studies as reference tablets. Entacapone is manufactured in the same place and marketed as Comtan in the US or Comtess in Finland. Two pilot absorption studies conducted for the purpose of formulation development were not reviewed since all 4 BE studies including 3 pivotal BE (#-93, #-95, #-96) were conducted using to-be-marketed formulation. The in vitro dissolution methods and specifications were evaluated. In addition, literature references regarding age- & gender-effect, food, drug interactions & relevant CPB information were reviewed. Source of literature references includes sponsor's submitted and reviewer's Medline search. Lastly, issues regarding Division of Scientific Investigations (DSI) are also discussed.

The sponsor proposed that [redacted] All the pivotal BE studies were conducted in fasted state. No food-effect study was conducted since this medication is taken up to 8 times per day. As discussed at pre-NDA meeting, we will rely only on literature for food effect, if available. The sponsor was requested to provide supportive information from entacapone NDA and literature regarding food effects on levodopa and carbidopa. OCPB noted in pre-NDA meeting package that the sponsor proposed in the labeling [redacted] without providing any supporting evidence. Only current entacapone labeling indicated that food does not affect PK of entacapone. Dr. Katz indicated the following (a) Is food effect study needed if information on food-effect on entacapone is available? Entacapone is indicated as an adjuvant therapy for Sinemet. (b) Given the maximum doses of 8 times per day dosing regimen for levodopa/carbidopa/entacapone product, it would be impractical to avoid meal when administering LCE tablet.

At the pre-NDA meeting, two values of 90% CI were noted to be outside of recommended BE goal post (80-125). The sponsor was told that their proposed extended limits (90% CI of 70-143%) for the highly variable compounds is not acceptable and following comments were conveyed to the sponsor: (a) If bioequivalence testing fails by a small percentage, it may be acceptable to base approval upon clinical efficacy equivalence or safety profile. Justification for using clinical equivalence as criteria for approval should be provided by the Sponsor. (b) It may be possible to show therapeutic equivalence by levodopa level if the test and reference products are bioequivalent regarding levodopa but the bioequivalence criteria are not fully met regarding carbidopa or entacapone. (c) However, a small percent of entacapone can get into the CNS and may alter therapeutic equivalence. Therefore, the Sponsor should address this issue and particularly address whether the extent of central penetration and activity of entacapone may alter the therapeutic effect. The clinical efficacy equivalence & safety profiles regarding these 2 CI values for entacapone are reviewed by clinical division. This review is only focused from Clinical Pharmacology & Biopharmaceutics perspective as to whether the sponsor had adequately justified its clinical relevancy from a safety viewpoint at the highest recommended daily dose.

CPB-relevant issues & findings are summarized below:

- Are 3 strengths of LCE combination tablets compositionally proportional?.....No, three strengths are not compositionally proportional. Entacapone dose is fixed at 200mg for all strengths. Levodopa & carbidopa, on the other hand, are proportionally increased at a fixed ratio of 4 to 1: 50/12.5mg, 100/25mg; 150/37.5mg. In addition, the inactive ingredients are not compositionally proportional. As requested by Agency, the sponsor conducted BE study for each strength.

- Was the final-to be marketed formulation used in all pivotal BE studies?---------- Final-to-be-marketed formulation for each strength (LCE50, LCE100, and LCE150) was tested in the pivotal studies (#93, #95, and #96).

- Is the reference product Sinemet (levodopa/carbidopa 100/25mg) US product BE to the Finland product since both products were used in the different pivotal BE studies as reference tablets? ---------- The reference tablet Sinemet (levodopa/carbidopa 100/25mg) US tablet is BE to the Finland product.

- What are the PK characteristics of levodopa, carbidopa and entacapone following the administration of LCE tablet and how do they compare to the administration of reference tablets?----------
  (a) Overall, the mean plasma concentration-time profiles of levodopa, carbidopa and entacapone are similar following the administration of three strengths of LCE tablets (LCE50, LCE 100, & LCE150) or administration of corresponding dose of reference tablets (levodopa/carbidopa plus entacapone).

(b) Slightly higher mean peak plasma entacapone concentrations were observed following administration of LCE 150 than the reference tablets (+15% higher).

- Plasma PK parameters (Cmax & AUC) for carbidopa across 3 strengths for test products did not exhibit dose-proportional increases as seen in the plasma levodopa concentrations: LCE50 (carbidopa 12.5mg) <LCE150 (carbidopa 37.5mg) <LCE100 (carbidopa 25mg). Similar observations were seen in reference tablets: ½ Sinemet (carbidopa 12.5mg)< 1½ Sinemet (carbidopa 37.5mg,) < 1 Sinemet (carbidopa 25mg). Potential causes of this variation are unclear at this point. Several considerations such as variability from cross-study comparison and lack of dose-linearity for carbidopa are discussed in this review (QBR section) but results are inconclusive. Upon Agency's request, the sponsor had provided similar justification regarding this inconsistency in PK parameters of carbidopa in 3 pivotal BE studies.

- Are 3 different strengths of Stalevo BE to the reference products? If not, does the sponsor adequately justify its clinical relevancy from a safety viewpoint at the highest recommended daily dose?----------
  (a) The test products of LCE50 & LCE 100 are considered BE to the reference products. LCE150, however, is not BE since the value of 90% CI for Cmax of entacapone does not meet the recommended BE 80-125 goal post. The 90% CI value for Cmax of entacapone was 103-135. Nausea is more frequent in the test drug group than the reference group. The mean entacapone levels in study with LCE 150 were not much higher than the other studies with LCE50 or LCE100, however, the combination of higher levodopa (150mg in LCE 150) and higher entacapone in current study may contribute to the more frequently observed nausea. It should be noted that as indicated in the entacapone label, nausea was the one of the side effects that are associated with entacapone when compared to without entacapone treatment. Based on this information the medical officer should evaluate whether these differences are clinical important.
  (a) The sponsor justified the increase in the entacapone Cmax seen in the BE study and its clinical relevancy from a safety viewpoint at the highest recommended daily dose. From CPB perspective, the sponsor's justification related to safety of this higher Cmax seems reasonable and the increase in entacapone Cmax is unlikely to result in significant safety or tolerability concerns. Based on the short elimination t1/2 of levodopa and entacapone, it is unlikely that there would be substantial accumulations upon repeated dosing. This reviewer had discussed with the review medical officer in this regard. Based on the additional analysis Dr. Bastings had performed, this higher nausea in the test product group (LCE150) may be due to chance alone. In addition to sponsor's analysis, Dr. Bastings also performed several comparisons of levodopa or entacapone levels between the subjects experiencing nausea or without nausea. Across BE studies, there is no consistency regarding test product group experiencing more nausea. There is no distinct difference observed in entacapone levels between subjects with or without nausea.

- Do the PK and safety/efficacy of LCE in special populations (elderly, gender, pediatrics, hepatic or renal impairment) differ from those of LCE in healthy subjects? Does gender affect the PK or safety/efficacy of LCE?------ Stalevo has not been studied in special populations. However, age & gender effect were analyzed from literature and current BE studies. There is consistently significant age & gender effects on the PK of levodopa & carbidopa. Age does not affect PK of entacapone. OCPB does not recommend labeling language regarding special populations since this combination tablet is not indicated for initial treatment & dose titration with levodopa and/or carbidopa products is a routine practice in treating Parkinson's disease. More appropriate initiative to incorporate information regarding special populations should be considered in the labels of levodopa and/or carbidopa products. Several limitations from cross-study comparisons are discussed. OCPB recommends that descriptive pharmacokinetics in age & gender analysis from 3 BE studies of Stalevo should be incorporated in PK section of label.

- Is sponsor's proposed dose administration relative to the food intake adequate? ---- The sponsor proposed tha' [redacted] All the pivotal BE studies were conducted in fasted state. No food-effect study was conducted since this medication is taken up to 8 times per day. As discussed at pre-NDA meeting, we will rely only on literature for food effect, if available. The sponsor was requested to provide supportive information from entacapone NDA and literature regarding food effects on levodopa and carbidopa. OCPB noted in pre-NDA meeting package that the sponsor proposed in the labeling [redacted] without providing any supporting evidence. Only current entacapone labeling indicated that food does not affect PK of entacapone. In the internal discussion, Dr. Katz indicated the following (a) Is food effect study needed if information on food-effect on entacapone is available? Entacapone is indicated as an adjuvant therapy for Sinemet. (b) Given the maximum doses of 8 times per day dosing regimen for levodopa/carbidopa/entacapone product, it would impractical to avoid meal when administering LCE tablet. OCPB recommends label should state that food-effect was not evaluated for this combination tablet. In addition, information from the literature may not be relevant to this combination product due to the variability from cross-study comparison such as different formulations were tested.

- Does the proposed dosage and administration section adequately address the issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms as requested in the pre-NDA meeting?---------- The sponsor has followed Agency's recommendation at the pre-NDA meeting and addressed various issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms. This section is reviewed by the Clinical division. This reviewer noted that the sponsor kept silent in the label regarding levodopa naive patients. This reviewer has discussed with review medical officer in this regard.

- Does the proposed labeling language adequately reflect current knowledge of Levodopa/carbidopa/entacapone from the Clinical Pharmacology and Biopharmaceutics perspective as requested in the pre-NDA meeting? ------The sponsor proposed [redacted] Several safety literature and postmarketing experience update for Sinemet & entacapone were discussed. This reviewer also surveyed Medline for any new information. Overall, the information in DDI section is fairly recent.

- Are the proposed dissolution methods and specifications adequate to discriminate sub-optimal batches? Has the sponsor provided justifications for the proposed methods and specifications?---------(a) The sponsor proposed different methods and specifications for the dissolution of three moieties of Stalevo®, and the dissolution profiles appeared different among 3 different strengths for all three moieties. Generally, same specification should be set for all strengths for each of the moieties in the combination tablet unless warranted by data. In this specific case, the sponsor had provided satisfactory justifications for the selection of methods for each moieties and strengths. (b) Overall, the proposed dissolution method for each moiety is acceptable. However, based on the dissolution profiles from biobatches, the specifications should be tightened. Review Chemist Dr. Martha Heimann has been consulted for the stability data.

- Has the Division of Scientific Investigation inspection been requested? Were the results from the Division of Scientific Investigation inspection satisfactory?---------- DSI inspection was requested for 2 pivotal BE studies: #93 (LCE100) & #96 (LCE 150). Form 483 was issued for both studies at both clinical & analytical sites. Overall, the DSI concluded that study #93 is acceptable for agency review since the sponsor's response to Form 483 was satisfactory. Study #96, on the other hand, DSI recommended not acceptable for agency review due to noncompliance with the regulation for

retention of reserve samples [21 CFR 320.38], thus the authenticity of the drug products used in the study #96 cannot be assured. Specifically, BE regulation requires the reserve samples should be retained at the clinical site (i.e. [redacted], or at an independent third party. Instead, the study drugs were prepackaged as unit dose by sponsor (Orion) and shipped to the clinic. The clinic [redacted] returned a set of 10 unused unit doses to Orion after study completion. Orion cannot be considered as an independent third party. The OCPB has taken DSI recommendation into consideration, however, concluded that study # 96 should be incorporated into the review for the reasons described below: (a) All the transfers of drug products were properly documented (from the Sponsor to the Clinical site as well as from the Clinical site to the Sponsor). Dr. Sriram Subramaniam from DSI has provided information to confirm this. (b) All the drug products for three pivotal BE studies (#93, #95, #96) were provided by the same provider, the authenticity of the drug products was assured in study #93. (c) The bioanalytical methods for 3 moieties were validated and reproducible in analytical site. (d) In study #96, both clinical and analytical sites have satisfactorily addressed the other issues cited on the Form 483. There are no other issues in study 96 that raise a concern related to study conduct. The sponsor should be warned that in the future such noncompliance to BE regulation will result in the BE studies being non-acceptable.

- Are bioanalytical methods to determine plasma concentrations of levodopa/carbidopa/entacapone adequately validated pre- and within-studies?----------Overall, the method validation for 3 moieties were found to be acceptable in terms of reproducibility, specificity, sensitivity, linearity, precision and accuracy. 5 BE studies including 3 pivotal BE studies (#93, #95, and #96) were conducted and analyzed in different places/countries. [redacted] methods along with different methods of sample preparation were used for determination of plasma levels of levodopa and carbidopa. No cross-validation information is provided. However, since independent BE studies were performed for each strength, cross-validation is not absolutely necessary.

Overall, from the Clinical Pharmacology and Biopharmaceutics perspective, the sponsor has submitted sufficient information to support the approval of LCE tablets in three strengths (LCE50, LCE100, and LCE150). This is based on the BE of LCE 50 & LCE 100 tablets to the corresponding doses of reference products of Sinemet (levodopa/carbidopa) and Comtess (entacapone) tablets in healthy volunteers age between 45-74 years old. Reference tablet (US and Finland Sinemet products) for levodopa/carbidopa are BE. Comtess or Comtan is the same product manufactured in the same place but marketed in Finland or US respectively. LCE150 failed to demonstrate BE with regard to Cmax of entacapone with a 90% CI of 103-135 which exceeds the recommended BE 80-125 goal post. Slightly higher mean plasma entacapone concentrations were observed following administration of LCE150 than the corresponding dose of reference tablets (~15% higher, 1211±738 versus 1052±792ng/ml). Nausea is more frequent in the test drug group than the reference group. Even though the entacapone level was not much higher than the other studies; the concurrent higher levodopa (150mg in LCE 150) and higher entacapone in current study may have contributed to more frequently observed nausea in the group receiving test drug.

This reviewer had discussed safety issues related to this increase in entacapone levels in LCE150 test product with the review Medical officer, Dr. Eric Bastings. In addition to sponsor's analysis, Dr Bastings also performed several comparisons of levodopa or entacapone levels between the subjects experiencing nausea or without nausea. The results indicated that more nausea observed in the LCE150 test product group could be due to chance alone. Across BE studies, there is no consistency regarding test product group experiencing more nausea. There is no distinct difference observed in entacapone levels between subjects with or without nausea.

From the Clinical Pharmacology & Biopharmaceutics perspective, the sponsor's justifications related to safety of this higher Cmax of entacapone are reasonable and the increase in plasma entacapone levels is unlikely to result in significant safety or tolerability concerns. Based on the short elimination t1/2 of

levodopa and entacapone, it is unlikely that there would be substantial accumulations upon repeated dosing.

Labeling issues regarding special populations (elderly, female, low body weight) that are not unique to the combination product were discussed and warrant further evaluation for all the levodopa, carbidopa, and entacapone products. The sponsor proposed to use labels of marketed products Sinemet (levodopa/carbidopa) and entacapone as template. Only recently approved entacapone label contains information regarding special populations. The sponsor was requested at the pre-NDA meeting to incorporate into the label the information regarding age & gender from the available source (literature & BE studies). From the available sources, following were consistently observed in special populations (elderly, female, low-body weight): (a) significantly higher plasma levodopa exposures (Cmax & AUC). The magnitude of increase in plasma levodopa levels ranged from 50-250%. (b) The clearance is significantly decreased. (c) Relative bioavailability is significantly increased. (d) AUC & t1/2 of Levodopa are correlated with age. (e) AUC & t1/2 of Levodopa are significantly and inversely correlated with body weight. In addition, more peak-dose dyskinesia was observed in female with low body weight. Overall, special caution should be exercised in these subsets of Parkinson's disease patients who are more prone to achieve higher plasma levodopa levels. Higher peak plasma levodopa concentration has been linked to side effects such as dyskinesia, nausea. It should be noted that in current clinical practice, the dosing regimen of levodopa products does not recommend adjustment for body weight and the dosing schedule is unevenly divided during the day. Additionally, considering all the factors (age, gender, body weight) that would elevate plasma levodopa, carbidopa, or entacapone concentrations, the overall magnitude of increase in plasma exposure of levodopa, carbidopa, and entacapone in these subsets of Parkinson's patients warrants further evaluation.

In general, relevant information in this regard should be incorporated into the label such as special population in the PK, precaution, and dosage & administration sections for all the products of levodopa, carbidopa, and entacapone. However, OCPB does not recommend incorporating language regarding special populations in this combination product for the following reasons: (a) This combination tablet is not indicated for initial treatment. (b) Dose titration with levodopa and/or carbidopa products is a routine practice in treating Parkinson's disease. (c) More appropriate initiative to incorporate information regarding special populations should be considered in levodopa and/or carbidopa products. (d) There are limitations in drawing conclusions from cross-study comparison due to the variability. This review has also summarized age-effect from available sources including literature. Limitations from cross-study comparison are discussed. OCPB recommends that descriptive pharmacokinetics in age & gender analysis from 3 BE studies of Stalevo should be incorporated in PK section of label.

The OCPB recommends revisions to the proposed labeling text.

The OCPB finds the proposed dissolution methods for each moiety acceptable; however, based on the dissolution profiles from biobatches, the specifications should be tightened.

4 QUESTION BASED REVIEW

4.1 General Attributes, Clinical pharmacology

What are the general attributes and clinical pharmacology of LCE tablet?

LCE tablet is a fixed dose combination tablet containing three previously marketed active agents, levodopa, carbidopa and entacapone in three different strengths for the treatment of Parkinson's disease. Each strength consists of a 4 to 1 ratio of levodopa to carbidopa and a fixed dose of 200mg entacapone in

a standard release formulation LCE tablet (levodopa /carbidopa/entacapone: 50/12.5/200mg, 100/25/200mg, 150/37.5/200mg).

Levodopa is an antiparkinsonian drug and mediates the final clinical effect of this fixed combination while carbidopa or entacapone have no clinical efficacy per se. Carbidopa and entacapone both reduce the peripheral metabolism of levodopa and therefore, enhance the availability of levodopa for the brain and affect the clinical effects of levodopa.

Mechanism of action:
Current evidence indicates that symptoms of Parkinson's disease (PD) are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of PD apparently because dopamine does not cross the blood-brain barrier(BBB). Levodopa is a metabolic precursor of dopamine; however, does cross the BBB and presumably converts to dopamine in the brain. When levodopa is administered orally it is rapidly decarboxylated to dopamine by dopa decarboxylase (DDC)/aromatic amino acid decarboxylase (AADC) in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the CNS. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues. Levodopa is an aromatic amino acid and is extensively metabolized to various metabolites. Two most important pathways are decarboxylation by dopa decarboxylase (DDC)/aromatic amino acid decarboxylase (AADC) and O-methylation by catechol-O-methyltransferase (COMT).

Carbidopa: Carbidopa inhibits decarboxylation of peripheral levodopa and does not cross BBB and does not affect the metabolism of levodopa within the central nervous system. The incidence of levodopa-induced nausea and vomiting is less with products containing carbidopa and levodopa. Carbidopa reduces the amount of levodopa required to produce a given response by about 75% by increasing plasma levodopa levels. Carbidopa does not increase the tmax of levodopa while modestly prolongs the plasma t1/2 of levodopa. Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70-100mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Experience is limited with total carbidopa daily doses of greater than 200mg.

Entacapone: When decarboxylation of levodopa is prevented by carbidopa, COMT becomes the major metabolizing enzyme for levodopa catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD). Entacapone is a selective and reversible peripherally acting inhibitor of catechol-O-methyltransferase (COMT). Entacapone is always coadministered with levodopa and carbidopa. When entacapone is coadministered with levodopa and carbidopa, plasma levodopa levels are more sustained than when coadministered as levodopa and carbidopa alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa also lead to increased levodopa effects, sometimes requiring a decrease in the dose of levodopa. With a 200mg single dose of entacapone, maximum inhibition of erythrocyte COMT activity is on average 65% with a return to baseline level within 8 hours. When 200mg entacapone is coadministered with levodopa and carbidopa, the AUC of levodopa is increased by approximately 35% and the elimination t1/2 is prolonged from 1.3 hours to 2.4 hours. In general, entacapone does not affect the average peak levodopa plasma concentration and the time of its occurrence (tmax=1 hour). In the clinical trials when either entacapone or placebo was added to levodopa/carbidopa (or levodopa/benserazide), the most commonly observed adverse events associated with the use of entacapone and not seen at an equivalent frequency among the placebo-treated patients were dyskinesia/hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain.

Dosage & administration: The sponsor proposed a direct switch of patients taking levodopa/carbidopa 100/25mg (4:1) standard release tablet with or without entacapone. Since the recommended dose of entacapone alone tablet is one 200mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily (200mg X 8=1600mg) and clinical experience with daily doses above 1600mg entacapone is limited, the maximum recommended daily dose of Stalevo is 8 tablets per day. No more than one Stalevo tablet should be taken at each dosing administration. If needed, carbidopa-levodopa can be added by carbidopa/levodopa only products concomitantly with a Stalevo tablet.

4.1.1 Formulation

Are 3 strengths of LCE combination tablets compositionally proportional?

No, three strengths are not compositionally proportional. Entacapone dose is fixed at 200mg for all strengths. Levodopa & carbidopa, on the other hand, are proportionally increased at a fixed ratio of 4 to 1: 50/12.5mg, 100/25mg; 150/37.5mg. The fixed dose of 200mg entacapone design is based on the marketed Comtan (entacapone) product. The recommended dose of Comtan(entacapone) is one 200mg tablet administered concomitantly with each levodopa/carbidopa dose to a maximum of 8 times daily. The sponsor was requested to perform 3 different BE studies for 3 different strengths combination product because the ingredients of the products (active & inactive) were not compositionally proportional.

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

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

Was the final-to be marketed formulation used in all pivotal BE studies?

Yes, the LCE 50, 100, & 150 tablet formulations used in the BE studies (#85, 93, 95, 96) were all final-to-be-marketed formulations.

4.2 General pharmacokinetics

Note: The sponsor conducted three separate pivotal BE studies with each different strength of to-be-marketed combination tablet against marketed Sinemet (levodopa/carbidopa, 100/25mg tablet) and Comtess (entacapone 200mg). In addition, the sponsor submitted a BE study comparing Sinemet US versus Finland product since both tablets were used in the pivotal BE studies as reference tablet. Entacapone is manufactured in the same place and marketed as Comtan in the US or Comtess in Finland.

LCE 50	Study #95(45-74yrs), #85 (20-38 yrs)
LCE100	Study #93 (45-72 yrs)
LCE 150	Study #96 (45-74 yrs)

4.2.1 Bioequivalence

Is the Sinemet (levodopa/carbidopa 100/25mg) tablet US BE to Sinemet Finland product since both products were used in the pivotal BE studies as reference tablet?

Yes, the reference tablet Sinemet (levodopa/carbidopa 100/25mg) US versus Finland product is BE. Specifically, the 90% CI of test-to-reference ratio for 2 active components fell within the recommended 80-125 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf). (see study review: #08).

Is Comtess, the reference product for entacapone in all 4 BE studies the same as the Comtan, the entacapone marketed in the U.S?

At the pre-NDA meeting dated 12/20/2001, the sponsor was requested to confirm that Comtan and Comtess is one product marketed in the 2 countries. The sponsor confirmed that both products are same products manufactured at the same site but marketed in two different countries.

What are the PK characteristics of levodopa, carbidopa and entacapone following the administration of LCE tablets and how do they compare to the administration of reference tablets (Sinemet +Comtan)?

Overall, the mean plasma concentration-time profiles of levodopa, carbidopa and entacapone are similar following the administration of three strengths of LCE tablets (LCE50, LCE 100, & LCE150) or administration of the corresponding dose of reference tablets (levodopa/carbidopa plus Comtan).

However, slightly higher mean peak plasma entacapone concentrations were observed following administration of LCE 150 than the reference tablets (~15% higher, 1211±738 versus 1052±792 ng/ml). The mean elimination half-life of levodopa, active moiety of antiparkinsonian activity, was similar [1.7 hours (1.1-3.1 hours)] between the test and the reference products. The mean half-lives for carbidopa and entacapone are comparable. Overall, the mean tmax of levodopa was reached slightly later with the combination product than the reference product. There were some differences in the tmax values of carbidopa and entacapone.

When plasma concentrations of levodopa, carbidopa and entacapone were compared across 3 strengths of LCE tablets from 3 different BE studies in healthy volunteers (age between 45-74 years old), it should be noted that the plasma carbidopa concentrations across 3 strengths did not exhibit dose-proportional increases as seen in the plasma levodopa concentrations. Specifically, the mean plasma carbidopa Cmax values was not in the rank order: LCE50 (carbidopa 12.5mg, 39 ng/ml) <LCE150 (carbidopa 37.5mg, 107 ng/ml) <LCE100 (carbidopa 25mg, 125 ng/ml). Similar observations were seen in the test as well as reference tablets: ½ Sinemet (carbidopa 12.5mg, 39 ng/ml)< 1½ Sinemet (carbidopa 37.5mg, 121 ng/ml) < 1 Sinemet (carbidopa 25mg, 126 ng/ml).

Similar trends were observed for mean plasma AUC0-inf values from both test & reference products: LCE50 (carbidopa 12.5mg, 169 ng h/ml) <LCE150 (carbidopa 37.5mg, 499 ng h/ml) <LCE100 (carbidopa 25mg, 690 ng h/ml). Similar observations were seen in the test as well as reference tablets: ½ Sinemet (carbidopa 12.5mg, 168 ng h/ml)< 1½ Sinemet (carbidopa 37.5mg, 566 ng h/ml) < 1 Sinemet (carbidopa 25mg, 698 ng h/ml).

Potential causes of this variation are unclear. Several considerations maybe related to these observations: (a) Cross-study comparison could contribute to the variability. (b) Limited information on the dose-proportionality of carbidopa.

The sponsor was requested (by Dr John Feeney, the medical team leader) to provide additional information related to the 3 pivotal BE studies and the illogical results of carbidopa levels. The sponsor provided similar justifications as summarized below: (a) Limited information on the PK of carbidopa. Cross-study comparisons from the available sources including literature references & company's database indicated that there are significant differences between studies in carbidopa AUC values even when the populations are comparable. The variability in AUC values is high after both 25mg & 50mg doses (table below after the tables & figs of PK of levodopa/carbidopa/entacapone). (b) The distribution of genders between different BE studies was not comparable. More female subjects were enrolled in the study (#93, LCE 100) table below after the tables & figs of PK of levodopa/carbidopa/entacapone). [Reviewer note: There is a gender effect on PK of carbidopa (see QBR: intrinsic factors section)]. When compared to male subjects, females have 25 % higher AUC and 17% higher Cmax]. (c) Three BE studies were conducted in 2 different countries and different bioanalytical procedures. [LCE50 (#95) & LCE 150 (#96) were conducted in Germany; LCE100 (#93) was in Finland. However, the sponsor did not identify any specific factor that could potentially contribute to the inconsistency in carbidopa.

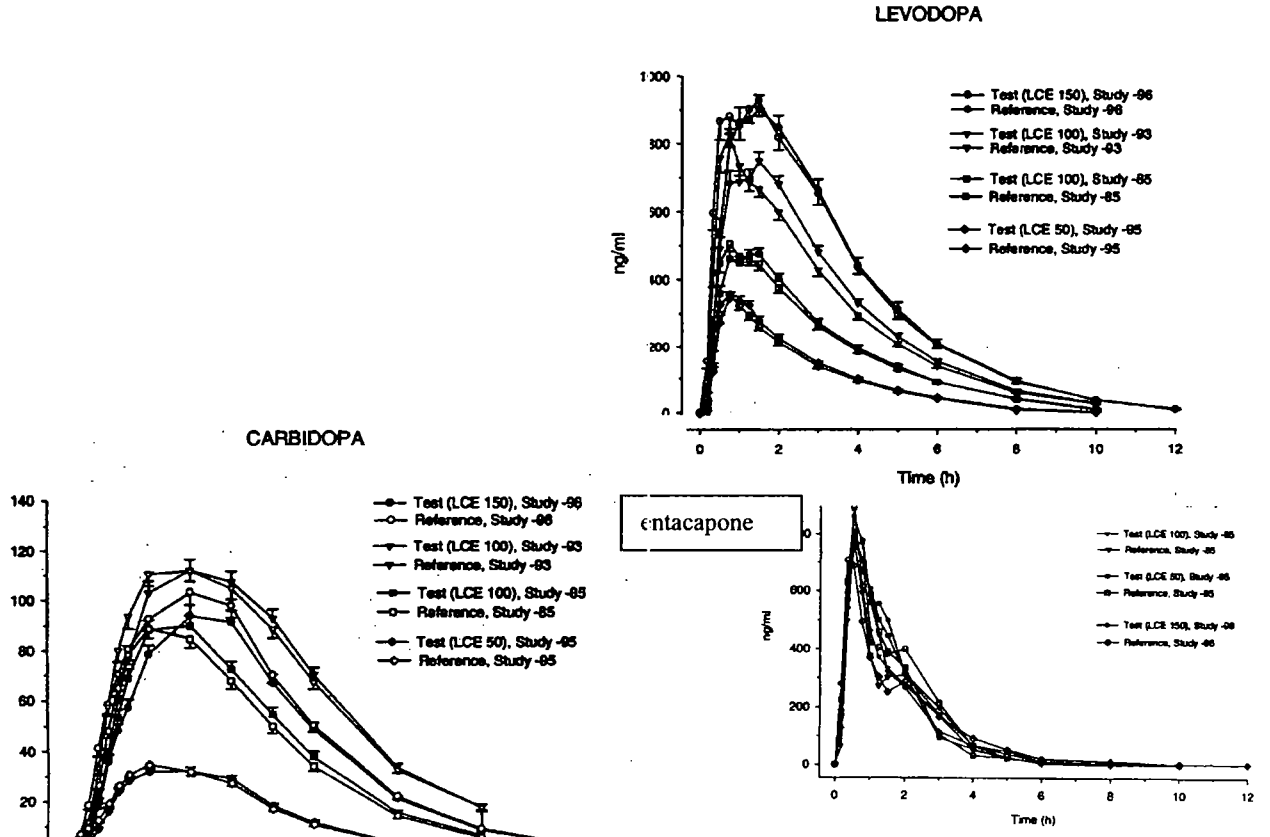


Figure 2. The mean entacapone concentrations in plasma in the bioequivalence studies for the test and reference products.

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

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

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

Sponsor's justification of the inconsistency in carbidopa levels from 3 BE studies

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

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

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

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

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

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

Table 1. Carbidopa C_{max} and AUC values in the LCE bioequivalence Studies 95, 93, and 96

Study	LCE strength	Carbidopa dose (mg)	C_{max} (ng/ml)		AUC (hxng/ml)	
			Test	Reference	Test	Reference
95	LCE 50	12.5	39 ± 16	39 ± 14	150 ± 64*	150 ± 56
93	LCE 100	25	125 ± 42	126 ± 42	633 ± 211*	645 ± 220
96	LCE 150	37.5	107 ± 42	121 ± 45	488 ± 180**	551 ± 192

Test products: LCE 50 = Levodopa/ Carbidopa/Entacapone 50/ 12.5/ 200 mg; LCE 100 = Levodopa/ Carbidopa/Entacapone 100/ 25/ 200 mg; LCE 150 = Levodopa/ Carbidopa/Entacapone 150/ 37.5/ 200 mg
Reference = Comtess + Sinemet 100/25 mg in a corresponding dose
* AUC_{0-10}, ** AUC_{0-12}

Table 2 Carbidopa AUC (±SD) with standard release levodopa/carbidopa in different studies

Carbidopa dose	AUC (hxng/ml)	Subjects	Orion Study No.	Reference
25 mg	749 ± 83	Young, healthy	NA	Kaakkola et al 1985
	165 ± 61	Young, healthy	2939076	Rouru et al 1999
	335 ± 147	Young healthy	2939083	Heikkinen et al 2002
	323 ± 130	Young healthy	0097008	Meyerhoff et al 2001
	431 ± 169	Young healthy	2939085	Lyly et al 2002
	385 (CV% 42)	Young healthy	NA	Carbidopa/Levodopa ANDA # 73-589
	435 ± 91	PD patients	293908	Myllylä et al 1993
50 mg	650 ± 255	Young, healthy	NA	Yeh et al 1989
	386 ± 155	Young, healthy	293922	Ahtila et al 1995
	586 ± 243	Young, healthy	2939085	Heikkinen et al 2002
	810 ± 440	PD patients	293927	Kaakkola et al 1995

NA= Not a study conducted by Orion Corporation for entacapone study program

Table 3. Some demographic characteristics of subjects in Studies 95, 93, and 96

Study	LCE strength	Carbidopa dose (mg)	Weight, (kg) Mean (range)	Dose/kg	Male / Female
95	LCE 50	12.5	70 (50 - 99)	0.17	23 / 21
93	LCE 100	25	70 (53 - 85)	0.35	17 /27
96	LCE 150	37.5	77 (52 - 98)	0.49	24 / 20

LCE 50 = Levodopa/ Carbidopa/Entacapone 50/ 12.5/ 200 mg; LCE 100 = Levodopa/ Carbidopa/Entacapone 100/ 25/ 200 mg; LCE 150 = Levodopa/ Carbidopa/Entacapone 150/ 37.5/ 200 mg

The test products of LCE50 & LCE 100 are considered BE to the reference products. LCE150, however, is not BE since the value of 90% CI for Cmax of entacapone does not meet the recommended BE 80-125 goal post. The 90% CI value for Cmax of entacapone was 103-135. Nausea is more frequent in the test drug group than the reference group. The mean entacapone levels in study with LCE 150 were not much higher than the other studies with LCE50 or LCE100, however, the combination of higher levodopa (150mg in LCE 150) and higher entacapone in current study may contribute to the more frequently observed nausea. It should be noted that as indicated in the entacapone label, nausea was one of the side effects that is associated with entacapone when compared to without entacapone treatment.

The sponsor justified the increase in the entacapone Cmax seen in the BE study and its clinical relevancy from a safety viewpoint at the highest recommended daily dose. From CPB perspective, the sponsor's justification related to safety of this higher Cmax seems reasonable. This reviewer had discussed this increase in entacapone levels in LCE150 test product with the review Medical officer, Dr. Eric Bastings. In addition to sponsor's analysis, Dr. Bastings also performed several comparisons of levodopa or entacapone levels between the subjects experiencing nausea or without nausea. The results indicated that higher nausea observed in the LCE150 test product group may be due to chance alone. Across BE studies, there is no consistency that test product group experienced more nausea. There is no distinct difference observed in entacapone levels between subjects with or without nausea.

Briefly summarized below are the 90% confidence intervals analysis of 3 strength LCE tablets with sponsor's justification of higher entacapone CI value seen in LCE150 from the safety viewpoint (see appendix for more details):
LCE50: The test product of LCE50 is BE to the reference products. Specifically, the 90% CI of test-to-reference ratio for 3 active components fell within the recommended 80-125 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf).

LCE100: The test product of LCE100 is BE to the reference products. Specifically, the sponsor conducted 2 BE studies using LCE 100. One (study #85) was conducted in young healthy male volunteers (age ranged between 20-38 years) and the other (study #93) in healthy male & female volunteers (age ranged between 45-72 years). All but one values of 90% CI of test-to-reference ratio for 3 active components fell within the recommended 80-125 goal-post for average BE assessment for the log transformed PK parameters (Cmax and AUC0-inf). Specifically, one 90% CI value for entacapone was marginally outside of the goal post (100-126). We consider LCE 100 is BE to the reference products for the following reasons: (a) LCE 100 is BE to reference tablets in young healthy volunteers (study #85). (b) The 90% CI is only marginally outside of goal post. (c) The geometric mean ratio is acceptable (1.12). (d)The values of mean Cmax of entacapone were comparable in LCE 50, LCE100 and LCE 150.

LCE 150: The test product of LCE150, however, are not BE to the reference products. Specifically, the 90% CI for Cmax of entacapone was 103-135, which fell outside of the recommended 80-125 goal post.

Sponsor's justifications are briefly summarized below (see appendix for details):

(a) The maximum recommended daily dose of Stalevo is 8 tablets per day (i.e. 1600mg entacapone per day in divided doses). The available literature data indicate that the increase in the entacapone Cmax seen in two of the bioequivalence studies does not result in any safety or tolerability concern. Specifically, there was no dose-relationship with tolerability when entacapone was given without levodopa in single doses from 25 to 800 mg, or when entacapone in doses from 50 to 400 mg was given together with single dose levodopa/carbidopa (100/25mg). Similarly, there were no dose-related differences in the occurrence of adverse events or in any other safety variables when entacapone was administered repeatedly at 100, 200, and 400 mg doses up to 6 times daily doses of levodopa/carbidopa (100/25mg) in PD patients [Reviewer's note: Mean age of PD patients was 48±8

years (range 48-77 years).] Thus, the available data indicate that the increase in the entacapone Cmax seen in two of the bioequivalence studies does not result in any safety or tolerability concern.

(b) The highest individual plasma levels of entacapone in 3 BE studies was [redacted] ng/ml (LCE 50, test product), and [redacted] ng/ml after the reference product (LCE 150) were within the previously reported ranges in PD patients. Previously, the highest measured entacapone levels in PD patients after a 200mg dose was [redacted] ng/ml and the highest ever-measured entacapone level in PD patients was [redacted] ng/ml after 800mg of entacapone. No AEs were associated with these high levels either in the current LCE BE studies or in previous studies in PD patients. From the data submitted under NDA20-796 Comtan: No clear dose-relation regarding entacapone administered in healthy volunteers as a single dose up to 800mg or as repeated doses of 800mg tid for 7 days. No tolerability problems have been seen in PD patients receiving higher than currently recommended dose of entacapone administered in combination with levodopa/DDC inhibitor, e.g., as single dose up to 800mg or 400mg given 4-6 times daily for 2 weeks. In previous study in PD patients, there is no dose relation seen between the frequency and type of adverse events and entacapone dose (100mg, 200mg, 400mg) or in the vital signs or ECG.

(c) Available pre-clinical data indicate that entacapone should not penetrate through to the brain in any significant extent at concentration levels below 5-6 ug/ml. At the level of 15ug/ml, the inhibition of COMT enzymes is only mild to modest and the first measurable metabolic effects in animals are seen at very high doses, corresponding approximately to levels over 90ug/ml or more of entacapone. These levels are above the average peak levels of entacapone seen after the recommended 200mg dose in man. Moreover, these findings in animal models are in agreement with the human PET data in PD patients. Ceravolo et al reported recently that another COMT inhibitor tocapone, which has potential to penetrate into the brain, produced PET findings indicating COMT inhibition, while no such finding has been reported with entacapone.

(d) There were no significant differences in the AE profiles between the test and the reference products of any strength in the BE studies except that nausea was observed more frequently with the LCE 150 tablet than with the reference treatment. However, no relation to any of the plasma concentrations (either at the time of the event or during the day) was seen when compared with the concentrations in the other periods or with those in the subjects not reporting nausea. [Reviewer's note: the combination of higher entacapone Cmax and higher levodopa dose in LCE 150 may both contribute to the more frequent nausea adverse events observed in the group receiving test product (LCE 150) in study #96. Nausea is one of the most common adverse events associated with peak plasma levodopa levels. Nausea is also one of the common adverse events associated with entacapone treatment when compared with levodopa/carbidopa treatment coadministered with or without entacapone].

(e) Overall, levodopa, the active antiparkinsonian agent and carbidopa are BE in all BE studies.

(f) Large intrasubject variability in entacapone measures: The intrasubject variability for the Cmax of entacapone of test & reference products in all studies was more than 30% (Range across 4 replicate design studies: Test: [redacted], reference: [redacted]. There is wide range in the observed peak plasma entacapone levels. The observed peak plasma entacapone concentrations ranged from [redacted] ng/ml following entacapone 200mg dose either in the Stalevo (LCE 150) or administered separately with Levodopa/carbidopa.

(g) In study conducted with LCE 150, low entacapone peak concentrations were observed for the reference product during the 2nd period for no obvious reasons, which may contribute to the overall lower entacapone from reference product.

(h) The mean Cmax values for entacapone were not higher for the LCE 150 tablet than for the LCE 50 & LCE100 tablets.

(i) For LCE 150, the values of tmax for levodopa, carbidopa and entacapone are considered not different between the test and reference products.

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

4.2.2 Intrinsic factors(age, gender, race, hepatic or renal impairment): Additional labeling issues regarding special populations (elderly, female, low body weight) that are not unique to the combination product which warrant further evaluation for all the levodopa, carbidopa, and entacapone products.

Note: Stalevo has not been studied in special populations. The sponsor proposed [redacted] Only recently approved entacapone label contains information regarding special populations. The sponsor was requested at the pre-NDA meeting to incorporate into the label the information regarding age & gender from the available source (literature & BE studies).

Does age and gender affect the PK or PD of levodopa/carbidopa/entacapone? Is dose adjustment based on age or gender recommended? (see appendix for details of age & gender analyses)

Sponsor proposed

Elderly: [redacted]

Gender: [redacted]

Agency's comments:

From the available sources, following were consistently observed in special populations (elderly, female, low-body weight): (a) significantly higher plasma levodopa exposures (Cmax & AUC). The magnitude of increase in plasma levodopa levels ranged from 50-250%. (b) The clearance is significantly decreased. (c) Relative bioavailability are significantly increased. (d) AUC & t1/2 of Levodopa are correlated with age. (e) AUC & t1/2 of Levodopa is significantly and inversely correlated with body weight. In addition, more peak-dose dyskinesia was observed in female with low body weight. Overall, special caution should be exercised in these subsets of Parkinson's disease patients who are more prone to achieve higher plasma levodopa levels. Higher peak plasma levodopa concentration has been linked to side effects such as dyskinesia, nausea. Relevant information in this regard should be incorporated into the label such as special population in the PK, precaution, and dosage & administration sections for all the products of levodopa, carbidopa, and entacapone. It should be noted that in current clinical practice, the dosing regimen of levodopa products does not recommend adjustment for body weight and the dosing schedule is unevenly divided during the day. Additionally, considering all the factors (age, gender, body weight) that would elevate plasma levodopa, carbidopa, or entacapone concentrations, the overall magnitude of increase in plasma exposure of levodopa, carbidopa, and entacapone in these subsets of Parkinson's patients warrants further evaluation.

The labeling issues regarding special populations (elderly, female, low body weight) not unique to the combination product warrant further evaluation for all the levodopa, carbidopa, and entacapone products. In general, relevant information in this regard should be incorporated into the label such as special population in the PK, precaution, and dosage & administration sections for all the products of levodopa, carbidopa, and entacapone. However, OCPB does not recommend incorporating language regarding special populations in this combination product for the following reasons: (a)This combination tablet is not indicated for initial treatment. (b) Dose titration with levodopa and/or carbidopa products is a routine practice in treating Parkinson's disease. (c) More appropriate initiative should be considered in incorporating information regarding special populations in levodopa and/or carbidopa products that indicated for initial treatment. (d) There are limitations in drawing conclusions from cross-study comparison due to the variability. OCPB recommends that descriptive pharmacokinetics in age & gender analysis from 3 BE studies of Stalevo should be incorporated in PK section of label.

Briefly summarized below are the information from available sources (literature & BE studies in current submission). Details can be found in appendix (Page 73)

Elderly:

- From the available sources including literature and BE studies in current submission, the advancing age has significant effect on the PK (AUC & Cmax) of levodopa and/or carbidopa. However, there are several limitations in drawing conclusion on age-effect. Some of the limitations are briefly described below: (a) It should be noted that studies evaluating age effects on levodopa, carbidopa, or entacapone were all conducted following single dose administration, or conducted in healthy volunteers. Therefore, the long-term age-effect from the multiple dose treatment in the target Parkinson's disease patients with different severity of disease state is currently unknown. (b) Different formulations, doses, ratio, relative timing of dose for levodopa/carbidopa were used in different studies. For instance, some studies were conducted with levodopa alone while some were coadministration of levodopa and carbidopa. Except for the BE studies in current submission, there is limited information regarding age-effect with coadministration of levodopa, carbidopa and entacapone. (c) Different populations were compared, for instance, Parkinson's patients versus healthy volunteers. (d) Variability in cross-study comparison. Different bioassays were used; assay sensitivity may affect the results. (e) Different severity of Parkinson's disease patients was studied. The PK and /PD responses to levodopa may vary with different severity of Parkinson's disease state. (f) Limited experience with subjects older than 75 years old. (g) Only one study reported that there is no difference in levodopa PK (tmax, AUC, t1/2, gastric emptying time) between healthy aged

subjects (73-86 years old, 4 F+1M) and Parkinson's elderly patients (n=6, 72-83 years old females) except for Cmax (1.90 ng/ml versus 3.14 ng/ml).

- Also, please see Dr Norman Hershkowitz 's reviews on Sinemet labeling supplements (NDA17,555(056)) regarding geriatric use of levodopa/carbidopa products (IR and CR) and Lodosyn. Dr. Hershkowitz indicated that there is limited information available for levodopa/carbidopa products to conclude no age-effect of levodopa/carbidopa products. Comments regarding intrinsic & extrinsic factors are not unique for LCE product, should apply to all products containing levodopa, carbidopa, levodopa/carbidopa, and/or entacapone

- Summarized below are the age-effects from the available sources which include literature and BE studies from current submission. Details of age subgroup analysis can be found in the appendix. The reported age range in elderly varied from study to study ranging from 60 to 86 years old. The LCE tablets were only studied in healthy subjects age ranging 20 –75 years old

(a) In the elderly (60-86 years old), levodopa bioavailability is enhanced, elimination is decreased resulting in higher plasma exposure (AUC and/or Cmax), and elimination t1/2 is prolonged. The plasma exposure (AUC) of levodopa is found to correlate well with age (between 2 groups: 22-34 years & 71-86 years old; and between 42-77 years old). Similar trend was observed for carbidopa in healthy subjects in 4 BE studies in current submission. There is limited information in the literature regarding the PK of carbidopa. No PK differences were observed between young and elderly healthy subjects (aged between 64-76 years old) following single dose of entacapone with or without coadministration of levodopa/carbidopa (100/50mg). The age-effect on the PK of entacapone has not been evaluated in multiple dose administration, in target Parkinson's disease, or in subjects older than 76 years old.

(b) The magnitude of increase in plasma levodopa concentration is on average 70% in AUC and 50% in Cmax when coadministered as levodopa/carbidopa/entacapone; +50% in AUC when coadministered levodopa with carbidopa only; and two literature reported a +150% in AUC when administered levodopa alone. One report compared postmenopausal women with young healthy volunteers (male & female), a 256% increase was observed in Cmax & AUC of levodopa, however, gender difference may be attributable to this larger magnitude of increase when compared to other studies of similar age.

(c) The magnitude of increases in pharmacokinetic parameters (AUC and Cmax) of levodopa and carbidopa increase with advancing ages. In cross-study age subgroup analysis (20-38 years, 45-60 year, and 60-72 years), there is clearly a trend in age-effect on PK of levodopa & carbidopa as the magnitude of % difference increases as the age advances. (40% increase in <60years old versus 70% increase in >60years old in AUC of levodopa; 35% increase in <60years old versus 50% increase in >60years old in AUC of carbidopa). However, it should be noted that only males were enrolled in the 20-38 years old group (study #85) and there is significant gender effect on the PK of levodopa, i.e. the AUC of levodopa is significantly higher in female between 45-60years old than their counterpart (45-60years old males) in study #93.

(d) Similar but higher magnitude of increase of plasma levodopa exposure in extremely elderly Parkinson's disease patients had been reported in one literature. In a panel of 5 very elderly Parkinson's disease patients (71, 74, 77, 78, 86) receiving single 300mg-levodopa alone treatment in a fasted state, there was a significant ($p<0.02$) increase by 180% reported in AUC in the elderly Parkinson's disease patients (mean 234.69 ug min/ml; SD=84.70) when compared to the young healthy volunteers (mean 82.33ug.min/ml; SD=31.00).

(e) A 250 % increase in plasma levodopa AUC & Cmax was reported in 6 woman Parkinson's disease patients (72-83 years old) receiving a 500mg levodopa in solution when compared to young healthy volunteers (22-31 years old, male and females). However, there is no difference in levodopa PK except 60% increase in Cmax between non-Parkinsonian elderly subjects (76-86 years old) and female Parkinsonian patients. The PK in non-PD elderly subjects are significantly different than young healthy subjects: the magnitude of changes are as follows: +116% in mean plasma Cmax, +193% in mean plasma AUC

Gender:

- The bioavailability of levodopa is constantly significantly higher in women than men resulting in higher AUC & Cmax. The % increase is summarized below:

% increase in female (dose)	AUC	Cmax	Source
Levodopa (levodopa/carbidopa, 100/25mg sd)	82%	58%	Kompoliti et al, PD pts (post-menopausal vs men, corrected for body weight)
Levodopa (LCEs, sd)	54%	35%	BE (#93, 95, 96) (prior to correction of body weight)
carbidopa (LCEs)	25%	17%	
entacapone (LCEs)	26%	~0	

- The sponsor indicated the PK difference observed in the 3 BE studies (age range 45-74 years old)was primarily explained by the body weight. The sponsor indicated the data suggested a slight trend for higher rates of some adverse events in subjects weighing below 75 kg compared to those over 75 kg. However, the sponsor did not provide weight-corrected PK comparison. The % difference in Stalevo was described without the weight-correction. Thus the true difference in these studies in healthy volunteers may be smaller. However, Kompoliti et al reported a 82% increase in AUC and 58% increase in Cmax in Parkinson's disease patients after correcting for body weight. Furthermore, Zappia et al reported in a group of 164 Parkinson's disease patients that plasma levodopa AUC as well as the elimination t1/2 and body weight were significantly and inversely correlated. Women were significantly lighter and had a significantly greater AUC than men. Furthermore, a greater percentage of women showed levodopa peak -dose dyskinesias during the course of disease when compared to men. These data suggested that Parkinson's disease patients with lighter body weight probably received a greater cumulative dosage of levodopa per kilogram of body weight during the long-term treatment, because in clinical practice, levodopa is administered without any adjustment of the dose to body weight. In addition, there was an overall tendency of females to report more often adverse events on both study treatments than males in the BE studies in healthy volunteers aged between 45-74 years old.

Agency recommendation: Label text should include the following information from BE studies:

PK section:

Elderly:

Stalevo tablet has not been studied in Parkinson's disease patients or in healthy volunteers older than 75 years old. In the pharmacokinetics studies conducted in healthy volunteers following single dose of Levodopa/carbidopa/entacapone (as Stalevo or as separate levodopa/carbidopa and Comtan tablets:

Carbidopa

There is no significant difference in the Cmax and AUC of carbidopa between younger (45 – 60 years) and elderly subjects (60 – 75 years).

Levodopa

The AUC of levodopa is higher (on average [redacted]) in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the Cmax of levodopa between younger (45 – 60 years) and elderly subjects (60 – 75 years).

Entacapone
The AUC of entacapone is higher (on average 15%) in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the Cmax of entacapone between younger (45 – 60 years) and elderly subjects (60 – 75 years).

Gender
The bioavailability of levodopa is significantly higher in females when given with or without carbidopa and /or entacapone.

Following [redacted] single dose [redacted] either as Stalevo or as separate levodopa/carbidopa and Comtan tablets in healthy volunteers (age range 45-74 years):
Levodopa
The plasma exposure (AUC & Cmax) of levodopa is significantly higher in females than males (on average, [redacted] for AUC & [redacted] for Cmax). These differences are primarily explained by body weight. Other published literature showed significant gender effect (higher concentrations in females) even after correction for body weight.
Carbidopa:
There is no gender difference in the pharmacokinetics of carbidopa.
Entacapone:
There is no gender difference in the pharmacokinetics of entacapone.

Summary of age-, gender-, and body-weight effect (details can be found in the appendix, page73).
The advancing age has significant effect on the PK of levodopa and/or carbidopa. In the elderly, levodopa bioavailability is enhanced, clearance is decreased resulting in higher plasma exposure (AUC and/or Cmax), and the elimination t1/2 is prolonged. The plasma exposure (AUC) is found to correlate well with advancing age. The LCE tablets were only studied in healthy subjects age ranging 20 –75 years old. Even though advancing age has negligible effect on entacapone, the average % increase Cmax of entacapone in elderly (60-72years) is 24% for LCE150 when compared to young (20-28 years) subjects. There is limited experience from the available sources for levodopa, carbidopa, or entacapone in elderly older than 75 years old.

The bioavailability of levodopa in female is significantly increased resulting in a significant increase in plasma exposure (AUC & Cmax) which is largely explained by the body weight. Since females are normally lighter than males, they receive more mg levodopa per kilogram basis because levodopa dosing regimen is not adjusted for bodyweight. Furthermore, Zappia et al reported in a group of 164 Parkinson's disease patients that plasma levodopa AUC as well as the elimination of the t1/2 of levodopa and body weight were significantly and inversely correlated. Women were significantly lighter and had a significantly greater AUC than men. Moreover, a greater percentage of women showed levodopa-dose dyskinesias when compared with men. These data suggested that lighter Parkinson's disease patients probably received a greater cumulative dosage of levodopa per kilogram of body weight during the long-term treatment, because in clinical practice, levodopa is administered without any adjustment of the dose to body weight.

Taken all together, special caution should be exercised when treating subsets of Parkinson's patients who are more prone to achieve higher plasma levels of levodopa during chronic treatment when administering regular recommended doses. Patients include elderly especially those who are old (>75 years old), female with lower body weight, patients who are have lower body weight or patients who possess a combination

of multiple factors, i.e elderly female patients older than 75 years old with low body weight. Additionally, considering all the factors (age, gender, body weight) that would elevate plasma levodopa, carbidopa, or entacapone concentrations, the overall magnitude of increase in plasma exposure of levodopa, carbidopa, and entacapone in these subsets of Parkinson's patients warrants further evaluation.

Do the PK and safety/efficacy of LCE in special populations (hepatic or renal impairment) differ from those of LCE? Is dose adjustment in special populations (hepatic or renal impairment recommended?

Stalevo has not been evaluated in subjects with hepatic or renal impairment population. The sponsor proposed to use labels from marketed products Sinemet (levodopa/carbidopa) and Comtan (entacapone) as template.

Sponsor proposed:
Renal impairment:

Agency recommendation:
Renal impairment:
Stalevo (Levodopa/carbidopa/entacapone):

[Internal note: levodopa/carbidopa products label indicate caution in dosing severe renal impairment patients: SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.]

Hepatic impairment
Stalevo (levodopa/carbidopa/entacapone):

Did the sponsor investigate the potential race-effect on the PK and safety/efficacy?

No labeling regarding race-effect has been proposed since all the healthy volunteers in the BE studies are Caucasians.

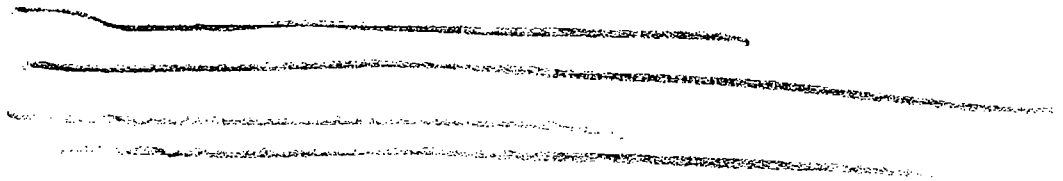
4.2.3 Extrinsic factors: food, DDI

Is sponsor's proposed dose administration relative to the food intake adequate? If not, what would be the Agency's recommendation on Stalevo tablet dosing in relation to meals?

Note: The sponsor proposed that . All the pivotal BE studies were conducted in fasted state. The office of Clinical Pharmacology & Biopharmaceutics noted in pre-NDA meeting package that the sponsor proposed in the labeling that without providing any supporting evidence. Only current entacapone labeling indicated that food does not affect PK of entacapone. In the internal discussion, Dr. Katz indicated the following (a) Is food effect study needed if information on food-effect on

entacapone is available? (Entacapone is indicated as an adjuvant therapy for Sinemet). (b) Given the maximum doses of 8 times per day dosing regimen for levodopa/carbidopa/entacapone product, it would be impractical to avoid meal when administering LCE tablet. As discussed at pre-NDA meeting, we will rely only on literature for food effect, if available. The sponsor was requested to provide supportive information from entacapone NDA and literature regarding food effects on levodopa and carbidopa.

Sponsor proposed:



Agency comments:

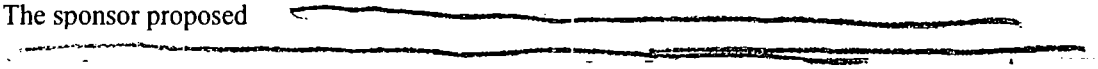
- Literature suggested that PK of levodopa is less predictable and food delayed the absorption & reduced the peak plasma levodopa level. However, information from the literature may not be relevant to this combination product due to the variability from cross-study comparison such as different formulations tested. OCPB recommends label should state that food-effect was not evaluated for this combination tablet.
- Literature information are briefly summarized below: levodopa is absorbed faster when taken without food and meal was reported to reduce peak plasma levodopa concentration and delay absorption in Parkinson's disease patients. The PK of levodopa is less predictable when taken with food. [Note: Some literature reported that plasma levodopa levels exhibit double peaks when taken with food. However, this reviewer has noted in the fasting BE studies, some subjects demonstrated double peaks under fasted condition.] The Cmax was reduced by 29% and tmax was delayed by 34 minutes in Parkinson's disease patients (age range 52-79 years old) taking levodopa/carbidopa in 10: 1 ratio (Nutt et al 1984). However, gastrointestinal symptoms such as abnormal salivation, dysphasia, nausea, constipation, and defecatory dysfunction are common in Parkinson's disease and nausea is one of the common adverse events cause by Levodopa, thus patients usually take levodopa with meals or snack.

- Following text should be incorporated into Label PK section

Food-effect on the combination of levodopa/carbidopa/entacapone tablet has not been evaluated.

Does the proposed labeling text in the DDI reflect current knowledge?

The sponsor proposed



Entacapone was approved fairly recently (12/30/1999). The sponsor had submitted in clinical section the Sinemet interactions search (volume 165, page 169-259; search period 1996-2002) and post-marketing safety experience report for entacapone (A total of 9 periodic reports, latest dated 02/08/2002). A comprehensive search of the published literature relating to Sinemet was undertaken to identify potential interactions, tolerability or safety issues, which may necessitate a change to the current prescribing information. The sponsor indicated that current and relevant Sinemet published safety literature did not reveal an adverse event profile different from that already described in the prescribing information for Sinemet. This reviewer has discussed with Dr. Bastings, the medical reviewer regarding DDI submitted in the clinical section. Following is the excerpt from Dr. Bastings clinical review. The sponsor has recently reviewed the interaction with antidepressants. During the postmarketing phase only incidental reports with suspected interactions have been received during concurrent use of entacapone and

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.

This reviewer also surveyed the Medline for DDI for entacapone, levodopa, and carbidopa. Four more recent (after 2000) literatures have information on levodopa or entacapone interactions. These information are consistent with the information under "Precautions"-"Drug interactions"—"Protein binding" in sponsor proposed label. The proposed label was based on results from in vitro protein binding displacement of entacapone and low protein binding for levodopa and carbidopa. Literature (a) & (b) listed below provided in-vivo confirmation in these regards.

(a) Dingemanse J et al 2002 Br J Clin Pharmacol May 53(5):485-91. In healthy subjects, entacapone displays slight PK interaction with steady-state R-warfarin but, based on the lack of a clinically relevant PD interaction, it appears that it can be used safely in Parkinson's disease patients who are receiving warfarin. The AUC of R-warfarin increased by 18% (90%CI: 111-126) and INR increase by 13%.
(b) Van de Vijver DA et al, 2002, Act Neurol Scan Jan; 105(1):8-12. Influence of benzodiazepines on antiparkinsonian drug treatment in levodopa users. The author concluded that the study did not find any statistically significant increase in antiparkinsonian drug treatment when a benzodiazepine was started in a small population of chronic levodopa users.
(c) Renfrew C et al 2000. Anesthesiology 93:1562: A case report of a 76 years old female with long history of Parkinson's disease taking 200mg entacapone concomitantly with 5 daily doses of levodopa/carbidopa and recent occurrences of closed-angle glaucoma experienced severe hypertension following ephedrine administration.
(d) Kompoliti K et al Neurology 2002 May 14:58(9):1418-22. Gender and pramipexole effects on levodopa PK & PD. The author concluded that pramipexole did not alter levodopa bioavailability.

In summary, the proposed labeling text in the DDI reflects fairly recent knowledge.

4.2.4 Dosage & administration

Does the proposed dosage and administration adequately address the issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms as requested in the pre-NDA meeting?

Note: OCPB noted in the Pre-NDA meeting package that the sponsor proposed [redacted]. Dr. Katz clearly indicated that LCE may only be allowed to be replacement therapy for 3 individual entities. The sponsor was requested to clearly address in the "dosage and administration" section of label the issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms.

Yes, the sponsor has followed Agency's recommendation at the pre-NDA meeting and addressed in the clinical section various issues regarding different strengths, different ratio of carbidopa to levodopa, and different formulations of Sinemet preparations related to switching paradigms. This section is reviewed by the Clinical division.

Briefly, currently the sponsor proposed (a) Direct switch to the corresponding strength of STALEVO® containing the same amount of levodopa for patients taking carbidopa-levodopa preparations and Comtan® (entacapone) tablets. Labeling text indicated that there is [redacted]

[redacted]

For levodopa/carbidopa naive patients, while sponsor addressed this issue in the clinical section, remained silent in the label text. The labeling text [redacted]

4.3 General Biopharmaceutics

4.3.1 Bioassays

Are bioanalytical methods to determine plasma concentrations of levodopa/carbidopa/entacapone adequately validated pre- and within-studies?

Overall, the method validation for 3 moieties were found to be acceptable in terms of reproducibility, specificity, sensitivity, linearity, precision and accuracy. 5 BE studies including 3 pivotal BE studies (#93, #95, and #96) were conducted and analyzed in different places/countries. (see appendix for details). [redacted] methods along with different methods of sample preparation were used for determination of plasma levels of levodopa and carbidopa. No cross-validation information is provided. Since independent BE studies were performed for each strength, cross-validation is not indicated. [redacted] method was used for determination of plasma levels of entacapone in all 4 BE studies where entacapone was administered either as Stalevo or separately as Comtan tablet.

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

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

The limit of quantification of levodopa is [redacted] (study #93). [redacted] (study #85) or [redacted] (study #08); carbidopa is [redacted] (#08) or [redacted] (#85, #93, #95, and #96); entacapone is [redacted] We noted that the mean recoveries for levodopa and carbidopa were relatively low using [redacted] method. Mean recoveries for all three analytes were [redacted] method, #study 95 & 96) or [redacted] method, #93 & #85) for levodopa, [redacted] method, #study 95 & 96) or [redacted] method, #93 & #85) for carbidopa, and [redacted] for entacapone. Details of bioanalytical assays can be found in appendix bioassays section.

4.3.2 In vitro dissolution methods and specifications

Are the proposed dissolution methods and specifications proper to discriminate sub-optimal batches? Has the sponsor provided justifications for the proposed methods and specifications?

Overall, based on the information submitted, we find the proposed two different dissolution methods for three moieties acceptable. Specifically, the sponsor has provided satisfactory justification for the selection of two different dissolution methods for levodopa/carbidopa and entacapone. The sponsor has submitted dissolution profiles for levodopa, carbidopa and entacapone in LCE tablets from different media, apparatus, speed, and [redacted] (for entacapone only). However, based on the dissolution

profiles from biobatches, the specifications for all 3 moieties should be tightened. Detailed review can be found in appendix dissolution method & specifications section (page). (Review Chemist Dr. Martha Heimann has been consulted for the stability data). Generally, same specifications for all strengths and a test specification of Q= [redacted] release are recommended.

The sponsor proposed

The dissolution of LCE 50, LCE 100 and LCE 150 tablets is controlled using two separate dissolution methods for each strength. Note: Dissolution condition: 37°C

Table 6. The dissolution specifications and methods for the LCE 50 and LCE 100 tablets.

Test	Specifications	Method
Dissolution of Levodopa, 45 min Carbidopa, 45 min	min [redacted] USP (Q= [redacted] min [redacted] USP (Q= [redacted]	USP, Apparatus 1 at 50 rpm 750 ml 0.1 M HCl
Dissolution of Entacapone, 45 min	min [redacted] USP (Q= [redacted]	[redacted]

Table 7. The dissolution specifications and methods for the LCE 150 tablet.

Test	Specifications	Method
Dissolution of Levodopa, 45 min Carbidopa, 45 min	min [redacted] USP (Q= [redacted] min [redacted] USP (Q= [redacted]	USP, Apparatus 1 at 50 rpm 750 ml 0.1 M HCl
Dissolution of Entacapone, 45 min	min [redacted] USP (Q= [redacted]	[redacted]

Agency's comment:

- The sponsor proposed different methods and specifications for the dissolution of three moieties of Stalevo®, and the dissolution profiles appeared different among 3 different strengths for all three moieties. Generally, we set same specifications for all strengths for each of the moieties in the combination tablet unless warranted by data. In this specific case, the sponsor has provided satisfactory justifications for the selection of methods for each moieties and strengths.
- Overall, we find the proposed dissolution methods for each moiety acceptable. However, based on the dissolution profiles from biobatches, the specifications for all 3 moieties should be tightened.

Agency Recommendation:

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

*(Review Chemist Dr. Heimann has been consulted for the stability data)

4.3.3 In vitro and in vivo drug release comparisons

Has the sponsor evaluated the relation between in vitro release and the in vivo performance of LCE tablet ?

No, the sponsor did not attempt to develop IVIVC.

4.3.4 DSI inspection

Is the Division of Scientific Investigation (DSI) inspection requested? Were the results from the DSI inspection satisfactory ? (see individual study review for #93 &#96 for details)

DSI inspection was requested for 2 pivotal BE studies: #93 (LCE100) & #96 (LCE 150). Results from the audit will provide some information on the validation of different bioanalytical methods across different study sites. Two studies were conducted at different countries. Bioanalytical methods for levodopa and carbidopa were different and carried out in different laboratories. Form 483 was issued to both studies at both clinical & analytical sites. Overall, the DSI concluded that study #93 is acceptable for agency review since the sponsor's response to Form 483 was satisfactory. Study #96, on the other hand, DSI recommended not acceptable for agency review due to noncompliance with the regulation for retention of reserve samples [21 CFR 320.38], thus the authenticity of the drug products used in the study #96 cannot be assured. Specifically, BE regulation requires the reserve samples should be retained at the clinical site (i.e. [redacted]) or at an independent third party. Instead, the study drugs were prepackaged as unit dose by sponsor (Orion) and shipped to the clinic. The clinic ([redacted]) returned a set of 10 unused unit doses to Orion after study completion. Orion cannot be considered as an independent third party.

The OCPB has taken DSI recommendation into consideration, however, concluded that study # 96 should be incorporated into the review for the reasons described below: (a) All the transfers of drug products were properly documented (from the Sponsor to the Clinical site as well as from the Clinical site to the Sponsor). Dr. Sriram Subramaniam from DSI has provided information to confirm this. (b) All the drug products for three pivotal BE studies (#93, #95, #96) were provided by the same provider, the authenticity of the drug products was assured in study #93. (c) The bioanalytical methods for 3 moieties were validated and reproducible in analytical site. (d) In study #96, both clinical and analytical sites have satisfactorily addressed the other issues cited on the Form 483. The response to Form 483 from Clinical site [redacted] has clearly indicated that the sponsor, Orion Pharma has now changed the procedure for taking the reserve samples and storing of them. The free selection samples will be offered for the investigator performing the BE/BA studies, as well as the storing of the samples will be under investigator's responsibility. There is no other issues in study 96 that raise a concern related to study conduct. The sponsor should be warned that in the future such noncompliance to BE regulation would result in BE studies being unacceptable.

5 Labeling

The sponsor is asked to:

- The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) proposes the following revisions to the sponsor's proposed label based on the information submitted (unless noted, the proposed text is acceptable to OCPB). Sponsor's proposed, Agency's recommended, and currently marketed products (levodopa/carbidopa, entacapone) are summarized in separate columns. Single Strike-through text marks deletions. OCPB's changes of deletion are marked as strikethrough and new proposed texts are underlined. The text within the bracket "[]"explains the proposed changes, or references. Reference # is referred to the reference list under 11/24/2002 E-doc submission (N21-485 Response annoted label.doc). These should not be included in the final label. The reference # can also be found in the attached sponsor proposed label section (Appendix 6.7, page 108).

21 Draft Labeling Page(s) Withheld

6 Appendix

6.1 Table of 5 Bioequivalence studies

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

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

6.2 Individual study review

6.2.1 Study code: 0097008 (Volume: 59-61)

Study title: Bioequivalence study with two levodopa/carbidopa 100/25mg standard released products in healthy volunteers

Clinical site: [redacted]

Analytical site: [redacted]

Objectives:

- To investigate the bioequivalence of Sinemet 25-100 tablet purchased in USA and Sinemet 25/100mg tablet purchased in Finland.

Methodology:

- A single-dose, randomized, 2-sequence, crossover study with 2 study periods separated by at least 7 days washout period.
- 40 subjects, nonsmoker, Caucasian, male or female, 18-45 years of age
- The subjects were randomly allocated to two groups (sequences 1 and 2):

Sequence	Period 1	Period 2
1	T	R
2	R	T

T = test treatment, Sinemet levodopa/carbidopa, 100/25mg (US)
R = reference treatment, Sinemet Levodopa/carbidopa, 100/25 mg tablet (Finland)

- The treatments were administered with 200 ml of water after 10 hours fast.
- Test treatment, dose and mode of administration: Single dose of levodopa/carbidopa 100/25 mg, US, (Merck & Co, USA (Batch. J5802)) administered orally.
- Reference treatment, dose and mode of administration: Sinemet 25-100 mg tablet, MSD, purchased in Finland (Batch. HL14820) administered orally.

PK measures:

- Blood samples were drawn before dosing (0 min) and at 15, 30,45, 60, 80 and 100 minutes, and 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours thereafter.

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

Data analysis: PK & Safety

- The PK parameters AUC0-12. AUCo-inf, Cmax, tmax and tl/2 were calculated for levodopa and carbidopa.
- The PK variables, AUC0-12, AUC0-inf and Cmax, were log-transformed and then evaluated using analysis of variance (ANOVA) model.
- The evaluation of BE was based on the PK parameters, AUC0-12, AUC0-inf and Cmax of levodopa and carbidopa. The 90% confidence intervals (CI) for the ratio between the means of treatments were calculated.
- The observed tmax was evaluated based on the nonparametric test: Koch's stepwise testing procedure together with the derivation of nonparametric CI according to Moses. Test for gender effects were based on the sums over both treatments.
- Safety was evaluated with descriptive statistics for vital signs and their mean changes during the study days and at the pre- and post-study visits. For laboratory safety variables descriptive statistics at pre- and post-study visits were evaluated.

Bioassays: Bioassay is discussed in the appendix bioanalytical assays section (Assay performance on p57).

Levodopa/carbidopa

Results:

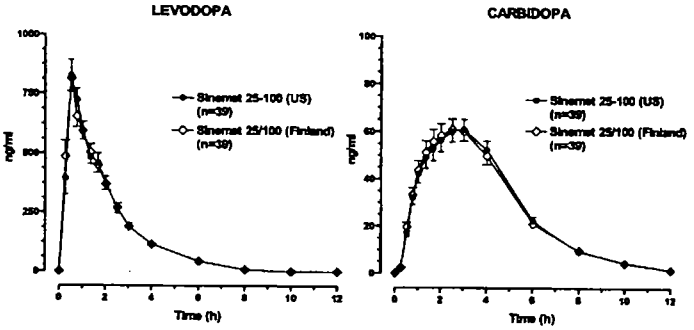


Figure 1. The mean levodopa and carbidopa concentratins (±SEM) in plasma after Sinemet® 25-100 mg purchased from US and Sinemet® 25/100 mg from Finland.

Table 1. Summary of pharmacokinetic parameters and statistics.

		Test (mean±SD) (n) *	Reference (mean±SD) (n)	Geom. means ratio	Log 90% CI	Bioequi-valence acceptance criteria	Bioequi-valent
AUC_{0-tz}	Levodopa	1634 ± 495	1637 ± 470	1.00	0.95 – 1.04	0.80–1.25	Yes
(hxng/ml)	Carbidopa	309 ± 129	307 ± 129	1.01	0.90 – 1.12	0.80–1.25	Yes
$AUC_{0-\infty}$	Levodopa	1730 ± 487	1722 ± 472 *	0.99	0.95 – 1.03	0.80–1.25	Yes
(hxng/ml)	Carbidopa	323 ± 130 *	318 ± 131 *	0.99	0.89 – 1.11	0.80–1.25	Yes
C_{max}	Levodopa	1029 ± 349	996 ± 296	1.02	0.94 – 1.11	0.80–1.25	Yes
(ng/ml)	Carbidopa	71.1 ± 30.1	72.3 ± 33.1	0.99	0.88 – 1.11	0.80–1.25	Yes

AUC0-tz = AUC from zero to last quantifiable sample (ng/ml x h)
$AUC_{0-\infty}$=AUC up to infinity after administration (ng/ml x h)
Cmax =peak concentration (ng/ml)
Geom. means ratio = Geometric means ratio
*) n=38, in all other cases n=39

Summary of results:

- 40 subjects, of which 22 were male and 18 female. Age ranged 22-45 years.
- The mean levodopa and carbidopa concentrations in plasma are presented in Figure above.

PK results:

- BE has been demonstrated between the test and the reference treatments. Specifically, the 90 % CI for the ratio between the means in Cmax, AUC0-12 and AUC0-inf, of the test and the reference treatments were within goal post (0.80-1.25) for carbidopa and levodopa (see table above).
- Comparable values of tmax & t1/2 were observed between the test and the reference.

Tmax (hr) arithmetic mean (SD)		
	test	reference
Levodopa	0.75 (0.42)	0.71 (0.48)
Carbidopa	2.59 (0.94)	2.44 (0.90)
t1/2 (hr) arithmetic mean (SD)		
Levodopa	1.55 (0.25)	1.51 (0.26)
Carbidopa	1.97(0.64)	1.89(0.35)

Comments:

Study design: We consider the design acceptable.

BE:

- We consider the test product bioequivalent to the reference products. The 90% CI of test-to-reference ratio for 2 active components fell within the recommended 80-125 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf).
- The elimination half-lives and tmax were comparable for test and reference products.
- This reviewer has confirmed the validity of the statistical analysis (90% CI) using a SAS program (V8). Dr. Rabindra Patnaik(OGD, HFD-651) was consulted for the model* used for 2x2 crossover study design. Dr. Le Chnexiong (Statistician, HFD-710) was consulted for the SAS program in general. [*Note: SAS program statements for average BE analysis of crossover studies from "Average, population, and individual approaches to establish bioequivalence" Guidance published in August 1999 & In-house BE workshop offered by Dr Patnaik].

Table. Comparison of BE analysis: Sponsor's versus agency's [presented as geometric mean ratio (range of log 90%CI), bold indicates outside of the recommended range]

PK parameters	Active ingredient	source of analysis	0097008 (100/25mg) (US VS Finnish Sinemet) (non-replicate 18-45 yrs, n=40, males & females)
Cmax	levodopa	Sponsor	1.02 (0.94-1.11)
		Reviewer	1.02 (0.94-1.11)
	carbidopa	sponsor	0.98 (0.88-1.11)
		Reviewer	1.01 (0.90-1.1)
AUC0-inf	levodopa	Sponsor	0.99 (0.95-1.03)
		Reviewer	0.97 (0.87-1.05)
	carbidopa	sponsor	0.99 (0.89-1.11)
		Reviewer	1.00 (0.90-1.11)

Bioassays:

Characteristics of the used method are given in the following table:

Calibrated Range	Levodopa Carbidopa	[redacted]
Defined LOQ	Levodopa Carbidopa	[redacted]
Linearity (mean r^2 of the standard curves)	Levodopa Carbidopa	[redacted]
Accuracy [bias %] *(inter-assay)*	Levodopa Carbidopa	between [redacted] between [redacted]
Precision [cv %] (ICH:Intermediate Precision) *(inter-assay)*	Levodopa Carbidopa	between [redacted] between [redacted]

6.2.2 Study code: 2939085 (volume 42-45)

Bioequivalence study comparing 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

Reviewer Note: Study #85 will not be extensively reviewed for the following reasons:

- The test product is BE to the reference product.
- Overall, the study #85 & and #93 is similar except for the subjects' age range and gender. Study #93 enrolled elderly subjects between 45-72 years old males & females. While study #85 enrolled males aged between 20-38 years old (mean 24 years).
- Sinemet products used in #85 & #93 (US versus Finland) are BE. (see Table below & study review of #0097008)
- The bioassays used for levodopa/carbidopa/entacapone are the same as those used in study #93.

Table. Comparison of BE analysis from 3 pivotal studies of TC® (Levodopa/ carbidopa/entacapone): Sponsor's versus agency's [presented as mean (range), bold indicates outside of the recommended range]

PK parameters	Active ingredient	source of analysis	0097008 (100/25mg) (US VS Finnish Sinemet) (non-replicate 18-45 yrs n=40, males & females)	29390 85 (100/25/200mg) (replicate 18-45 yrs n=44, males)	#2939093 (100/25/200mg) (replicate ,40-80yrs n=44, males & females)
Cmax	levodopa	Sponsor	1.02 (0.94-1.11)	0.93(0.88-0.98)	0.96 (0.91-1.00)
		Reviewer	1.02 (0.94-1.11)	ND	0.96 (0.90-1.01)
	carbidopa	sponsor	0.98 (0.88-1.11)	1.00 (0.93-1.08)	0.98 (0.92-1.04)
		Reviewer	1.01 (0.90-1.1)	ND	0.81 (0.92-1.04)
	entacapone	sponsor	ND	0.99 (0.88-1.11)	1.12 (**1.00-1.26**)
		Reviewer	ND	ND	1.12 (**1.00-1.26**)

AUC0-inf	levodopa	Sponsor	0.99 (0.95-1.03)	1.01 (0.97-1.04)	1.04 (1.01-1.07)
		Reviewer	0.97 (0.87-1.05)	ND	1.04 (1.01-1.07)
	carbidopa	sponsor	0.99 (0.89-1.11)	1.02 (0.95-1.11)	0.98 (0.92-1.05)
		Reviewer	1.00 (0.90-1.11)	ND	0.98 (0.92-1.05)
	entacapone	sponsor	ND	1.02 (0.96-1.08)	1.02 (0.98-1.07)
		Reviewer	ND	ND	1.02 (0.98-1.07)

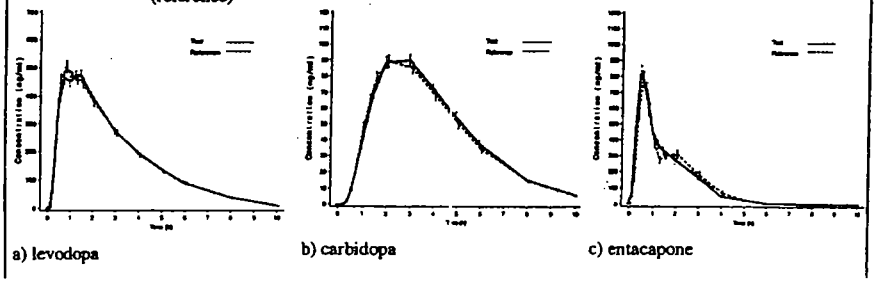
This reviewer has summarized the clinical and analytical sites for 3 BE studies

Study # (strength) (study design)	#0097008 (100/25mg) (US VS Finnish Sinemet) (non-replicate 18-45 yrs n=40, males & females)	#29390 85 (100/25/200mg) (replicate 18-45 yrs, n=44, males)	#2939093 (pivotal) (100/25/200mg) (replicate ,40-80yrs n=44, males & females)
Test product/ strengths	US Sinemet (Levodopa/carbidopa 100/25mg)	Levodopa/carbidopa/entacapone 100/25/200mg	Levodopa/carbidopa/entacapone 100/25/200mg
Reference product	Finland Sinemet Levodopa/carbidopa 100/25mg)	Finnish Sinemet/ (Levodopa/carbidopa, 100/25mg)/ Comtess (200mg)	US Sinemet Levodopa/carbidopa, 100/25mg)/ Comtess (200mg)
Clinical site	[redacted]	Pharmacokinetic Research Unit of the Department of Pharmacokinetics, Orion Corporation Orion Pharma, Harmaaparrankuja 1, FIN-02200 Espoo, Finland.	Pharmacokinetic Research Unit of the Department of Pharmcokinetics, Orion Corporation Orion Pharma, Harmaaparrankuja 1, FIN-02200 Espoo, Finland
Investigator	[redacted]		
Bio-analytical site: **Levodopa/ carbidopa:**	[redacted]	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland
Method: **Levodopa/ carbidopa:**	[redacted]	[redacted]	[redacted]
Bio-analytical site: **Entacapone**	ND	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.	Bioanalytical Laboratory Unit 1 of the Department of Bioanalytics, Orion Corporation Orion Pharma, Orionintie 1, FIN-02101 Espoo, Finland.
Method: **Entacapone**	**ND**	[redacted]	[redacted]

Results:

- The mean levodopa, carbidopa and entacapone concentrations in plasma are presented in Figure below.
- BE has been demonstrated between the test and the reference treatments (Table below). Specifically, the 90 % CI for the ratio between the means in Cmax, AUC0-10 and AUC0-inf, of the test and the reference treatments were within goal post (0.80-1.25) for all three moieties.

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



a) levodopa b) carbidopa c) entacapone

Table R5. The mean pharmacokinetic parameters of levodopa, carbidopa and entacapone with 90% confidence interval of the ratio and coefficient of variation after replicate administration of levodopa/carbidopa/entacapone 100/25/200 mg tablet (test) and Sinemet® 100/25 mg tablet with Comtess® 200 mg tablet (reference)

		Test		Reference		Geom. means ratio	Log 90% CI
		Mean±SD (n)	CV	Mean±SD (n)	CV		
AUC_{0-10} (ngxh/ml)	Levodopa	1757 ± 359 (84)	14.6	1756 ± 344 (85)	13.7	1.00	0.97 – 1.04
	Carbidopa	431 ±169 (84)	33.4	420 ± 166 (85)	28.4	1.02	0.94 – 1.11
	Entacapone	1234 ± 373 (84)	18.9	1228 ± 350 (85)	20.3	1.00	0.95 – 1.05
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	1819 ± 366 (83)	14.2	1810 ± 352 (85)	13.5	1.01	0.97 – 1.04
	Carbidopa	451 ± 174 (84)	32.3	438 ± 172 (85)	27.7	1.02	0.95 – 1.11
	Entacapone	1305 ± 403 (61)	17.8	1262 ± 359 (71)	20.5	1.02	0.96 – 1.08
C_{max} (ng/ml)	Levodopa	653 ± 165 (84)	21.4	704 ± 189 (85)	20.5	0.93	0.88 – 0.98
	Carbidopa	99 ± 39 (84)	33.0	98 ± 37 (85)	27.7	1.00	0.93 – 1.08
	Entacapone	1016 ± 503 (84)	52.4	1020 ± 511 (85)	47.5	0.99	0.88 – 1.11

CV = coefficient of variation (%)
n = number of observations, number of subjects is 43 for all parameters except for entacapone $AUC_{0-\infty}$ the number of subjects is 39

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

Tmax (hr) median (range)		
	test	reference
Levodopa	1.3 (0.3-5.0)	1.0 (0.3-3.0)
Carbidopa	3.0 (1.3-5.0)	2.0 (1.3-5.0)
Entacapone	0.5 (0.3-5.0)	0.5 (0.2-4.0)
t1/2 (hr) mean (SD)		
Levodopa	1.7 ±0.2	1.7 ±0.2
Carbidopa	1.7 ±0.3	1.7 ±0.3
Entacapone	0.7 ±0.4	0.7 ±0.4

- Intra-individual variability: The coefficient of variation for the Cmax of entacapone both for test & reference products and in study (#85) was more than 30% (Test: 52.47%; reference: 47.5%) (table below).

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

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

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

6.2.3 Study code: 2939093 (Volume: 37-41)

Study title: Bioequivalence study comparing 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

Clinical site: Pharmacokinetic Research Unit of the Department of Pharmacokinetics, Orion Corporation Orion Pharma, Harmaaparrankuja 1, FIN-02200 Espoo, Finland.

Analytical site: The concentrations in plasma for levodopa, carbidopa and entacapone were determined by Orion Pharma, Espoo, Finland.

Objectives:

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

Methodology:

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

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

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

- The treatments were administered with 200 ml of water after an overnight fast.
- Test treatment, dose and mode of administration: Single dose of levodopa/carbidopa/entacapone 100/25/200 mg, Orion Pharma, Finland, (Batch. no. BC002-2; Batchsize: [redacted] administered orally.
- Reference treatment, dose and mode of administration: Sinemet 25-100 mg tablet, Merck & Co, USA (Batch. no.J5802) with Comtess 200 mg tablet, Orion Pharma, Finland (Batch. no. ZL012) administered orally.

PK measures:

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

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

Data analysis: PK & Safety

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

Bioassays: Bioassay is discussed in the appendix "Bioanalytical assays". (Assay performance on p 62)

Levodopa/carbidopa	[redacted]
Entacapone	[redacted]

Results:

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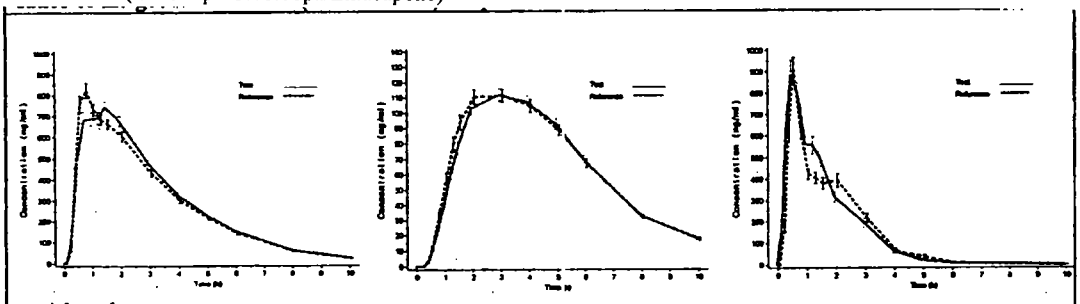

a) levodopa b) carbidopa c) entacapone

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

Table R6. The mean pharmacokinetic parameters of levodopa, carbidopa and entacapone with 90% confidence intervals and coefficient of variation after replicate administration of the test and the reference treatments.

		Test (mean±SD) (n)	CV	Reference (mean±SD) (n)	CV	Geom. mean ratio	Log 90% CI
AUC_{0-10} (ngxh/ml)	Levodopa	2840 ± 697 (85)	9.9	2745 ± 708 (85)	10.0	1.04	1.01 – 1.07
	Carbidopa	633 ± 211 (85)	25.0	645 ± 220 (84)	23.9	0.98	0.92 – 1.04
	Entacapone	1439 ± 377 (85)	15.4	1383 ± 357 (85)	14.7	1.05	1.01 – 1.09
$AUC_{0-\infty}$ (ngxh/ml)	Levodopa	2906 ± 715 (85)	10.2	2808 ± 725 (85)	10.1	1.04	1.01 – 1.07
	Carbidopa	690 ± 227 (84)	25.7	698 ± 236 (83)	25.0	0.98	0.92 – 1.05
	Entacapone	1450 ± 399 (56)	15.9	1376 ± 344 (62)	13.2	1.03	0.98 – 1.08
C_{max} (ng/ml)	Levodopa	975 ± 247 (85)	18.5	1035 ± 308 (85)	16.6	0.96	0.91 – 1.00
	Carbidopa	125 ± 42 (85)	25.2	126 ± 42 (84)	20.6	0.98	0.92 – 1.04
	Entacapone	1259 ± 712 (85)	55.7	1070 ± 460 (85)	37.9	1.12	1.00 – 1.26

CV = coefficient of variation (%)

n = number of observations, number of subjects is 44 for all parameters except for entacapone $AUC_{0-\infty}$ the number of subjects is 36

Summary of results:

- 44 subjects, of which 17 were male and 27 female. The subjects were 59±8.3 (mean±SD) years of age, 14 subjects were under 55 years, 17 subjects were between 55-65 years and 13 subjects were over 65 years (range 45-72 years).
- The mean levodopa, carbidopa and entacapone concentrations in plasma are presented in Figure above.

PK results:

- BE exists between the test and the reference treatments except for entacapone, which was marginally outside the conventional bioequivalence criteria (Table above). Specifically, the 90 % CI for the ratio between the means in Cmax, AUC0-10 and AUC0-inf, of the test and the reference treatments were within goal post (0.80-1.25) for all three moieties, except for Cmax of entacapone which was marginally outside the conventional bioequivalence criteria [sponsor's note: falls well within the wider bioequivalence criteria (0.70-1.43) since the coefficient of variation (CV) of Cmax of entacapone was 55.7% for the test and 37.9 % for the reference treatment, see comments below].
- Comparable values of tmax & t1/2 were observed between the test and the reference.

Tmax (hr) mean (range)		
	test	reference
Levodopa	1.4 (0.5-3.0)	1.0 (0.3-3.0)
Carbidopa	3.2 (1.5-5.0)	2.7 (1.3-5.0)
Entacapone	1.0 (0.2-4.0)	0.8 (0.2-3.0)
t1/2 (hr) mean (range)		
Levodopa	1.7 (1.3-2.1)	1.7 (1.3-2.0)
Carbidopa	2.0 (1.4-4.0)	2.1 (1.5-4.9)
Entacapone	0.8 (0.3-3.8)	0.8 (0.4-3.8)

Bioassays:

Study performance

Levodopa & carbidopa

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

Entacapone

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

Comments:

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

BE:

- We consider the test product bioequivalent to the reference products. The 90% CI of test-to-reference ratio for 3 active components fell within the recommended goalpost of 80-125 for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf).
- The elimination half-lives and tmax were comparable for test and reference products.
- Intra-individual variability: The coefficient of variation for the Cmax of entacapone both for test & reference products and in study (#93) was more than 30% (Test: 55.7%; reference: 37.9%) (table below).

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

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

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

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

- The proposed extended limit of CI_{90} to define bioequivalence is not acceptable. The CI values for entacapone were 1.00-1.26 for the Cmax of 100/25/200. The sponsor proposed that extended limits (CI90% of 70-143%) should be considered for the highly variable drug. However, since BE of

LCE100 strength has been demonstrated in a younger population (study #85) and the 90% CI of geometric mean ratio for Cmax of entacapone is only slightly (126) outside of the goal post (80-125), we consider LCE100 is BE to the reference products.

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

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

PK parameters	Active ingredient	source of analysis	#2939093 (100/25/200mg) (replicate ,40-80yrs n=44, males & females)
Cmax	levodopa	Sponsor	0.96 (0.91-1.00)
		Reviewer	0.96 (0.90-1.01)
	carbidopa	sponsor	0.98 (0.92-1.04)
		Reviewer	0.81 (0.92-1.04)
	entacapone	sponsor	1.12 (**1.00-1.26**)
		Reviewer	1.12 (**1.00-1.26**)
AUC0-inf	levodopa	Sponsor	1.04 (1.01-1.07)
		Reviewer	1.04 (1.01-1.07)
	carbidopa	sponsor	0.98 (0.92-1.05)
		Reviewer	0.98 (0.92-1.05)
	entacapone	sponsor	1.02 (0.98-1.07)
		Reviewer	1.02 (0.98-1.07)

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

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

- Overall, the DSI recommends that study 2939093 is acceptable for agency review after sponsor satisfactorily responded to the Form 483 issued to the clinical & analytical sites.
- DSI also requested a statistical reanalysis to include group effect in the ANOVA model. The reanalysis did not affect the outcome of study 2939093. (Exhibit 8). Specifically, subjects were dosed in 5 groups. The firm was requested to reanalyze and include group, group*sequence interaction as fixed effects.

EXHIBIT 8 (8)

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

Study 2939093

		Reported results			Group effect included		
		Estimate	Lower	Upper	Estimate	Lower	Upper
Levodopa	AUC	1.040	1.014	1.066	1.040	1.014	1.066
	$AUC_{0-\infty}$	1.040	1.014	1.067	1.040	1.014	1.067
	C_{max}	0.955	0.910	1.002	0.955	0.910	1.002
Carbidopa	AUC	0.975	0.916	1.038	0.976	0.917	1.039
	$AUC_{0-\infty}$	0.979	0.917	1.045	0.980	0.918	1.046
	C_{max}	0.979	0.924	1.038	0.981	0.925	1.040
Entacapone	AUC	1.045	1.006	1.086	1.046	1.007	1.086
	$AUC_{0-\infty}$	1.028	0.983	1.076	1.026	0.981	1.073
	C_{max}	1.121	1.001	1.255	1.125	1.005	1.259

- Two other issues were resolved satisfactorily: (a) Inconsistency in selection of subject samples for reanalysis based on poor chromatography (PC) or injection error. In response, the Site deleted the questionable standards and recalculated subject samples. Similar results (<3.5% difference to the original) were obtained and study outcomes were not significantly affected. (b) Lack of procedure to assure accuracy of analytical runs following interruption due to [redacted] system failure. However, this finding does not affect the acceptability since 5 out of 6 QCs that were analyzed prior to the failure were acceptable and concentrations from few subject samples following the interruption fell within the range of the QCs analyzed with these samples.

6.2.4 Study code: 2939095 (Volume: 46-51)

Study title: Bioequivalence study comparing levodopa/carbidopa/entacapone 50/12.5/200 mg combination tablet with Comtess 200 mg tablet administered with ½ Sinemet 25-100 mg tablet after a single oral dose in healthy volunteers

Clinical site: [redacted]

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

Objectives:

- To investigate the bioequivalence of a new levodopa/carbidopa/entacapone 50/12.5/200 mg combination tablet with the commercially available formulations of levodopa/carbidopa (1/2 of Sinemet 25-100 mg tablet, Merck & Co, USA) and entacapone (Comtess 200 mg tablet, Orion Pharma, Finland).
- In addition, the intra-subject variability of each active compound, i.e., levodopa, carbidopa and entacapone was evaluated both for the test and the reference treatments.

Methodology:

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

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

T = test treatment, levodopa/carbidopa/entacapone 50/12.5/200 mg combination tablet
R = reference treatment, ½ Sinemet 100/25 mg tablet with Comtess 200 mg tablet

- The treatments were administered with 200 ml of water after an overnight fast.
- Test treatment, dose and mode of administration: Single dose of ½ tablet of levodopa/carbidopa/entacapone 50/12.5/200 mg , Orion Pharma, Finland, (Batch. no. BCA002-2; Batchsize: [redacted] administered orally.
- Reference treatment, dose and mode of administration: Sinemet 25-100 mg tablet, Merck & Co, USA (Batch. no.HL 14820-Halved) with Comtess 200 mg tablet, Orion Pharma, Finland (Batch. no. ZL012) administered orally.

PK measures:

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