

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-485

ADMINISTRATIVE DOCUMENTS

**13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE
DRUG (21 U.S.C. 355 (b) or (c))**

The applicant, Orion Corporation, represents that entacapone, the drug subject of this application for which approval is being sought, is protected by the following patents:

1. Drug Substance Patent(s)

U.S. Patent No. 5,446,194. Expiry date: August 29, 2012.
Patent holder: Orion-yhtymä Oy, Orionintie 1, FIN-02200 Espoo, Finland

U.S. Patent No. 5,135,950. Expiry date: October 31, 2010.
Patent holder: Orion-yhtymä Oy, Orionintie 1, FIN-02200 Espoo, Finland

2. Drug Product Patent(s)

U.S. Patent No. 4,963,590. Expiry date: November 27, 2007.
Patent holder: Orion-yhtymä Oy, Orionintie 1, FIN-02200 Espoo, Finland

3. Method of Use Patent(s)

U.S. Patent No. 5,112,861. Expiry date: May 12, 2009.
Patent holder: Orion-yhtymä Oy, Orionintie 1, FIN-02200 Espoo, Finland

Orion-yhtymä Oy is a parallel business name to Orion Corporation.

The US agent of the patent holder and applicant, authorized to receive notice of patent certification under section 505 (b)(3) and (j)(2)(B) of the act and §314.52 and §314.95 of 21CFR, is:

Burns, Doane, Swecker & Mathis
P.O.Box 1404
Alexandria, Virginia 22313-1404

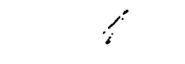
Formulation Declaration:

The undersigned declares that Patent Nos. 5,135,950, 4,963,590 and 5,112,861 cover the formulation, composition and/or method of use of entacapone. This product is the subject of this application for which approval is being sought.

Espoo, Finland March 21, 2002

ORION CORPORATION


Esa Heinonen
Senior Vice President


Esa Soppi
Vice President

EXCLUSIVITY SUMMARY for NDA # 21-485

Trade Name: STALEVO

Generic Name: carbidopa/ levodopa/ entacapone 12.5/50/200,
carbidopa/levodopa/entacapone 25/100/200, and
carbidopa/levodopa/entacapone 37.5/150/200 Tablets

Applicant Name: Orion Pharma, Inc. HFD-120

Approval Date June 11, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES/ X / NO / /
- b) Is it an effectiveness supplement? YES / / NO / X /
- If yes, what type (SE1, SE2, etc.)?
- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor was informed during the Pre-NDA meeting that only bioequivalence studies would be needed.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

- d) Did the applicant request exclusivity?

YES / / NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this

particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 17-555 Sinemet
 NDA # 20-796 Comtan

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or

2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #

NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #
Investigation #__, Study #
Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant

should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

CDR Teresa Wheelous

June 20, 2003

Signature of Preparer
Title: Sr. Regulatory Management Officer

Date

Signature of Office or Division Director

Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00



March 7, 2003

DEBARMENT CERTIFICATION

Orion Corporation ORION PHARMA, hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Orion Pharma, Inc.

By: 

Name: **Ilkka Larva, M.Sc. (Pharm.)**

Title: **Vice President, Drug Regulatory Affairs, Orion Pharma, Inc.
U.S. Agent for Orion Corporation ORION PHARMA**

April 16, 2002

DEBARMENT CERTIFICATION

ORION CORPORATION hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Orion Corporation
ORION PHARMA

By: *Gunilla Wilén-Rosenqvist*
Name: Gunilla Wilén-Rosenqvist
Title: Senior Regulatory Adviser,
International Regulatory Affairs

By: *Inge-Britt Lindén*
Name: Inge-Britt Lindén
Title: Vice President, International
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5 Page(s) Withheld

MEMORANDUM

NDA 21-485 STALEVO

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Combination Drug Product for the Treatment of Parkinson's Disease

DATE: April 24, 2003

Stalevo is a new combination drug product. It combines levodopa, carbidopa, and entacapone. Three dosage strengths are proposed for marketing. Each includes the same 200mg dose of entacapone. The doses of carbidopa and levodopa will be made available in the same 1:4 ratio in each dosage strength: 12.5mg/50mg, 25mg/100mg, and 37.5mg/150mg. The 3 tablet strengths will all be the same color, but will differ in size and shape.

The primary support for this application comes from 3 bioequivalence studies, 1 study for each of the proposed dosage strengths of Stalevo. In each of these studies, a dose strength of Stalevo was compared to the marketed Comtan (entacapone) plus marketed carbidopa/levodopa.

Dr. Wendy Chou performed the biopharmaceutics review. Dr. Eric Bastings performed the clinical review. Dr. Paul Roney was the pharmacology/toxicology reviewer. Dr. Martha Heiman was the chemistry reviewer.

Nomenclature

The proposed name, Stalevo, was reviewed by the nomenclature group and found acceptable. Note that in the original nomenclature consult, DMETS (Division of Medication Errors and Technical Support) evaluated the name with all 3 component strengths listed on the prescription. Subsequently, the sponsor proposed listing the name in the How Supplied section and on carton/container labeling with a numeric suffix to differentiate the 3 dosage strengths. That numeric suffix would mimic the dose of the component levodopa only: Stalevo 50, Stalevo 100, and Stalevo 150. I have discussed this proposal with Jerry Phillips from the Office of Drug Safety. He believes the numeric suffix in this case can only help to differentiate the product, so he does not believe a re-review by DMETS is needed. Because the numeric suffix is intended to be written on prescriptions, Jerry Phillips believes it should be considered part of the "proprietary name" for listing purposes (in the Orange Book). Therefore, any action letter should clearly list all 3 products: Stalevo 50, Stalevo 100, and Stalevo 150. The Orange Book listings will follow from the action letter.

Inspections

DSI performed inspections of 2 clinical sites and analytical sites. At one of the sites, a deficiency was identified in that samples of the actual product administered were not maintained. I am told by the biopharmaceutics group that this is a minor deficiency.

Chemistry

Dr. Heiman believes an Approval action is appropriate.

Pharm/Tox

With the combination product, several new carbidopa impurities were identified. The potential toxicity of these impurities was investigated in a new toxicology study. Dr. Roney has reviewed that study and had no new concerns.

Bioequivalence Studies

Bioequivalence, compared to the marketed products, was demonstrated for all 3 dosage strengths of Stalevo based on AUC. In one study, Study 96, the 90% confidence interval for C_{max} of entacapone included 1.35, outside the usually accepted range of 0.80-1.25. The sponsor argues that this was due in large part to the low plasma levels of entacapone following reference treatment in one period of the crossover study. Dr. Bastings agrees with this observation and adds that the C_{max} of entacapone in the test group in question was similar to the C_{max} seen for the control in other bioequivalence studies. Also, bioequivalence for levodopa was demonstrated in all studies and no concerning safety issues were identified in Study 96.

Labeling

The sponsor has proposed labeling for Stalevo that is, for the most part, a combination of approved labeling for Comtan and Sinemet. Because Sinemet is a fairly old product, the parts of the Clinical Pharmacology section for Stalevo, dealing with carbidopa and levodopa, required extensive revision based on Dr. Chou's review.

The Dosage and Administration section was expanded to describe in more detail the reductions in carbidopa/levodopa dosage in the clinical trials of entacapone, subsequent to the addition of entacapone to a regimen including carbidopa/levodopa. This seems particularly important for Stalevo labeling because it highlights the potential difficulty in transitioning from carbidopa/levodopa directly to a fixed-dose product, Stalevo, without first independently adjusting the doses of entacapone and carbidopa/levodopa. The review team believes this new information would also be helpful in the labeling for Comtan and encourages the sponsor to submit a labeling supplement for Comtan, incorporating this change.

Conclusions

Stalevo, a fixed dose product, provides a reasonable alternative to the use of the two marketed products, Comtan and carbidopa/levodopa.

Recommendations

The sponsor should be sent an Approvable Letter with draft labeling.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

John Feeney
4/24/03 01:33:17. PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 20, 2001
TIME: 9 AM
LOCATION: WOC II Conference Room E
APPLICATION: 60,554 Comtan Combination Products
TYPE OF MEETING: Pre-NDA
MEETING CHAIR: Dr. Russell Katz

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name	Title	HFD
Dr. Russell Katz	Division Director	120
Dr. John Feeney	Group Leader	120
Dr. Leonard Kapcala	Medical Reviewer	120
Dr. Barry Rosloff	Pharmacology Team Leader	120
Dr. Paul Roney	Pharmacology Reviewer	120
Dr. Wendy Chou	Clinical Pharmacology & Biopharmaceutics Reviewer	860
Dr. Ramana Uppoor	Clinical Pharmacology & Biopharmaceutics Team Leader	860
Ms. Teresa Wheelous	Project Manager	120

ORION CORPORATION / ORION PHARMA ATTENDEES AND TITLES:

Name	Title
Dr. Kari Reinikainen	V. P. – Neurological Projects
Dr. Inge-Britt Linden	V. P. , Regulatory Affairs
Ms. Helena Heikkinen	Clinical Team Leader / Project Manager
Dr. Harri Kanerva	Head of Dept. of Pharmacokinetics
Ms. Eva Saukko	Assist. V. P. Product Development
Dr. Mervi Niskanen	Head of Dept. of Pharmaceutical
Ms. Leena Sopenen	Manager, Toxicological Laboratory
Mika Leinonen	Project Statistician
Ullamari Kanerva	Regulatory Affairs Manager
Mr. Ilkka Larma	V. P. Drug Regulatory Affairs

NOVARTIS PHARMA AG

Name	Title
Ms. Nemecek	Regulatory Affairs
Dr. Sabri Markabi	Exec. Director, Clinical Research, Nervous System
Dr. Martina Struck	Assoc. Director, Regulatory Affairs

BACKGROUND:

The pre-IND / EOP2 meeting for this product was held on March 27, 2000. The new IND was received on June 29, 2000 and the study was allowed to proceed on July 28, 2000. The August 27, 2001 Pre-NDA meeting request was granted and subsequently

rescheduled for December 20, 2001. The NDA, planned for submission 3rd quarter 2002, will be based upon bioequivalence with the approved products, Comtan and Sinemet.

MEETING OBJECTIVES:

1. To provide the Agency with a summary of the contents of the dossier and status of the development program.
2. To seek FDA concurrence on the completeness of the dossier for a fileable NDA.

DISCUSSION POINTS:

CMC

Question 1

The applicant suggests the following specifications for degradation products in levodopa/carbidopa/entacapone (L/C/E) 50/12.5/200 mg (L/C/E) 100/25/200, and (L/C/E) 150/37.5/200 mg tablets. Does the Agency agree with the specifications for degradation products?

Test	Method ¹	Specifications
Degradation products of levodopa — unspecified Total	(Method 1)	Max — Max — may need to justify or tighten
Degradation products of Carbidopa — — — — unspecified Total	(Method 1)	Max — Max — Max — Max — Max — may need to justify or tighten
Degradation products of entacapone — unspecified Total	(Method 2)	Max — Max — Max — may need to justify or tighten

1. IND Annual report June 29, 2000 – June 28, 2001

Method 1: pages 62-71 for 50/12.5/200 mg tablet, pages 98-107 for 100/25/200, and pages 134-143 for 150/37.5/200 mg tablet.

Method 2: pages 72-77 for 50/12.5/200 tablet, page 108-113 for 100/25/200 tablet, and pages 144-149 for 150/37.5/200 mg tablet.

- To be discussed at a separate CMC telecon

Question 2

The applicant suggest the following specifications for dissolution of active ingredients from L/C/E 50/12.5/200, 100/25/200, AND 150/37.5/200 tablets. Does the Agency agree with the specifications for dissolution?

- Since dissolution method development report has not been submitted, the agency will only comment on the appropriateness of the dissolution method and specification when NDA is submitted. However, we note that you suggest different dissolution methods and specifications for three active ingredients and the dissolution profiles appeared to be different across 3 different strengths for all three active ingredients.

- Please incorporate in your NDA submission the following: (1) full report on the development of dissolution methods and specifications showing that the selected method is adequately discriminatory to detect sub-optimal batches, (2) justification of using different dissolution methods and specifications, (3) individual dissolution data for biobatches, (4) specifications across 3 strengths, (5) formulation of 3 different strengths.

Question 3

The applicant suggests to validate the manufacturing process and to report the process validation studies for each tablet strength to be available before the launch of the products. Does the Agency agree?

- To be discussed during a separate telecon

Nonclinical Pharmacology and Toxicology Issues

Question 4

Does the Agency agree that the non-clinical toxicology program (as described on page 27 of the briefing book) conducted with the combination of levodopa, carbidopa, and entacapone is sufficient for filing of the NDA for the triple combination product?

- The current preclinical package appears adequate for submission of the NDA.

Question 5

Does the Agency agree that the toxicological program as presented on page 29 of the briefing book is sufficient for qualification purposes of carbidopa related impurities/degradation products?

- The ongoing toxicological studies appear adequate for qualification of the impurities in carbidopa. Final acceptability of the studies will depend on detailed review of the studies.

Human Pharmacokinetics and Biopharmaceutics Issues

Question 6

Does the Agency agree that the bioequivalence (BE) studies as presented in Appendix 2 of this briefing book are adequate to allow the filing of the NDA for all three developed levodopa/carbidopa/entacapone strengths?

- See reply to # 7 below.

Question 7

Does the Agency agree that the bioequivalence results of the L/C/E triple combination strength of 150/37.5/200 mg are adequate for filing?

- 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.
- Commenting on the adequacy of the results is a review issue, the Agency will review the results when the NDA is submitted.
- The proposed extended limit of C_{190} to define bioequivalence is not acceptable. In your NDA submission, you should address (1) the variability seen in the studies, and (2) the clinical relevance from a safety point of view at the highest recommended daily dose regarding the two values that fell outside of the recommended values.

Question 8

Can the Agency confirm the acceptability of the proposed format of presenting the data for the pivotal bioequivalence studies (studies # 2939093, # 2939095, and # 2939096)?

- See reply to number 9.

Question 9

Does the FDA confirm the acceptability of submitting data for medical and statistical review in an electronic form as follows: Pharmacokinetic and safety data from four bioequivalence studies (#2930985, # 2939093, #293095, #2939096) will be provided as SAS transport files following the format and structure suggested by the FDA guidance documents for electronic submissions?

- You should follow the format and structure suggested by the FDA guidance “documents for electronic submissions” and submit the electronic data for all the 5 BE studies as SAS transport files.
- In addition to what was proposed in the briefing package, you should provide individual data of each measure including demographics, PK parameters and safety measurements in the “Human Pharmacokinetics and Bioavailability” section. Following information should be included in the electronic submission and hard copy as appropriate: subject #, demographics, individual concentrations, PK parameters (C_{max} & AUC), sequence, treatment, period along with other measurements. This could be used to explore effects of age or gender on PK if necessary.

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

/s/

Russell Katz
1/30/02 07:39:39 AM

PRE-IND MEETING MINUTES

MEETING DATE: March 27, 2000
DRUG NAME: Entacapone/Levodopa/Carbidopa Combination
SPONSOR: Orion Corporation
TYPE OF MEETING: PRE - IND

ATTENDEES

FDA Attendees & Titles:

Dr. R. Katz – Division Director
Dr. L. Kapcala – Medical Reviewer
Dr. G. Fitzgerald – Pharmacology Team Leader
Dr. P. Roney – Pharmacology Reviewer
Dr. M. Guzewska – CMC Team Leader
Dr. Heimann – CMC Reviewer
Dr. S. Al-Habet – Biopharmaceutics Reviewer
Ms. T. Wheelous – Project Manager

Orion Corporation Attendees & Titles

K. Varkila – Clinical / Regulatory
Inge-Britt Linden - Regulatory
E. Saukko – Regulatory
I. Larma – Regulatory
M. Ritalia – CMC
M. Niskanen – CMC
L. Sopanen - Toxicology
H. Heikkinen - Clinical
K. Reinikainen – Clinical

Novartis Attendees & Titles

M. Struck - Regulatory
S. Markabi – Clinical
R. Dodsworth – Regulatory

MEETING OBJECTIVES: To discuss the studies necessary to obtain market approval of a combination product containing Comtan and levodopa/carbidopa.

QUESTIONS:

- 1** Does the Agency agree to the proposed three strengths 50/12.5/200mg, 100/25/200mg, and 150/37.5/200mg for the triple combination levodopa/carbidopa/entacapone?
 - Since entacapone is labeled for use as an adjunct with Sinemet type products (i.e., levodopa/carbidopa) it is reasonable to request administration of a single product containing all three ingredients. The possible problems to be considered with fixed dose products is an increase in the incidence of product confusion and that these combinations will not be appropriate in all patients.
 - Orion intends to market the combination product as a stand-alone therapy and not for use as an adjunct. Therefore, those patients on high doses of levodopa, the more severe, will not be able to take advantage of the fixed dose combination.
 - The three proposed strengths are acceptable.

- 2** The target is to register the proposed three different combination tablets strengths (later called combination product) based on pharmacokinetic equivalence between

the combination tablet and the reference therapy. The reference therapy consists of Comtan 200 mg (Orion Pharma) with three different doses of Sinemet 25/100mg(DuPont Pharma/MSD). Does the Agency consider the registration of the combination product based on the demonstration of pharmacokinetic equivalence to be an appropriate approach?

- Studies showing pharmacokinetic equivalence of the fixed dose combination products as compared to Comtan and three different strengths of Sinemet are acceptable to support an NDA.

3 The proposed test and reference treatments for the bioequivalence testing of each triple combination strength are presented in Section 3.4 (Tablet 6) of the briefing book. Does the Agency agree on the proposed reference treatment for each triple combination strength?

Tablet 6. Test vs. reference treatment for the three proposed levodopa-carbidopa-entacapone combinations.

Strength of the Combination Tablet Tested	Test Treatment	Reference Treatment (Sinemet 100/25 mg* with Comtan/Comtess 200 mg**)	
Levodopa/Carbidopa /Entacapone (mg)	Combination of each strength	Sinemet 100/25 mg	Comtess 200 mg
50/12.5/200	1 tablet of 50/12.5/200 mg	0.5 tablet	1 tab
100/25/200	1 tablet of 100/25/200	1 tablet	1 tab
150/37.5/200	1 tablet of 150/37.5/200	1.5 tablets	1 tab

* Sinemet 100/25 mg (MSD) on the market in Finland.

** Comtess 200 mg is the same product as Comtan 200 mg registered in the U.S.

- If every ingredient of the component were proportionally equal then only one bioequivalence study would be necessary. We know that the ingredients are not proportionally equal, the ratios of the 3 combination products are different. Therefore, three different studies must be performed.
- There is a draft replicate design study in the meeting package; however, a detailed replicate design study should be submitted to the Agency for a statistical consult. The sponsor was requested to initiate / open an IND for this combination product and the protocol would be consulted to statistics and biopharmaceutics.

4 Does the Agency agree, that Sinemet 25/100 (MSD), which is on the Finnish market can be used as the reference product?

- The Finnish product should be bioequivalent to the U.S. product. In establishing

bioequivalence of the two products assess for quantitative composition equivalence and comparable plasma levels.

- Orion should also develop a dissolution program for the various strengths of their combination products.

5 Entacapone is known to be a highly variable drug. Does the Agency agree that extended CI_{90} limits (70 – 143%) can be applied regarding C_{max} values for entacapone in the bioequivalence study of each triple combination strength?

- This drug is highly variable and there is no guidance for extending the CI_{90} limits at this time, therefore, we can not agree.
- AUC and C_{max} should be within the CI_{90} limits of 80 – 125% to confirm bioequivalence for the three components.
- If bioequivalence testing fails by a small percentage, it may be acceptable to base approval upon clinical efficacy equivalence. Justification for using clinical equivalence as criteria for approval should be provided by the sponsor.

6 Does the Agency agree that the study design proposed in Appendix II of the Briefing Book is adequate to answer sufficiently the question of bioequivalence of the test and reference treatments?

- The proposed study is designed for healthy volunteers between 18 and 40 years of age.
- The sponsor should include both male and female, and include older subjects since Parkinson's patients are generally over 40 years of age.

7 The antiparkinsonian effect of the proposed combination product is produced solely by levodopa. If the test and reference products are bioequivalent regarding levodopa but the bioequivalence criteria are not fully met regarding carbidopa or entacapone, does the Agency agree that a repeated dose pharmacokinetic study in PD patient evaluating the equivalence of the test and referenced product based on the AUC of levodopa after single and repeated dosing is sufficient to support the equivalence of the test and reference products? The proposed study design is enclosed in Appendix III of the Briefing Book.

- It may be possible to show therapeutic equivalence by levodopa concentration. However, a small percent of entacapone can get into the CNS and may alter therapeutic equivalence. There are literature articles published suggesting that, depending on dose, the extent of central COMT inhibition with entacapone may vary and might be of therapeutic significance. Orion should address this issue and

particularly address whether the extent of central penetration and activity of entacapone may alter the therapeutic effect.

- Pharmacokinetic /pharmacodynamic (PK/PD) relationship will be difficult to show.

8 Our aim is to perform the stability program by using bracketing and /or matrixing design for each single strength. Does the Agency agree that the bracketing and/or matrixing design approach is applicable?

- Submit the protocol with available stability data for comment. Orion should refer to the ICH and FDA guidelines for requirements.
- Bracketing design on strength will probably not be permitted. Bracketing of container sizes is allowable
- Orion should indicate the total amount of stability data to be available at the time of the NDA submission. Of key importance is the early submission of the degradant assessment.
- A statistical consult will be needed.

9 Does the Agency agree that the planned documentation for Nonclinical Pharmacology and Toxicology data section (summarized below) is sufficient for registration of the proposed triple combination product?

- Segment 2 teratology studies have not yet been submitted, but Orion plans to submit them in the next annual report.
- A mouse dose ranging study to select doses for the repeat mouse bioassay is ongoing and a draft report is to be available in October 2000. If possible, Orion should add the combination dose group to the mouse carcinogenicity study. Otherwise, provide justification explaining why the combination data are not needed when submitting the carcinogenicity study protocol.
- The previous micronucleus assay used a low dose of levodopa (40 mg/kg). This test should be repeated using higher doses.

10 Finally, the Sponsor would like to discuss the type, contents, and the submission schedule of the application with the Agency.

- The sponsor should submit an IND containing a detailed protocol for bioequivalence and statistical analysis plan. Additional CMC information about the formulations of the three strengths should be included.

ACTION ITEMS

1. Meeting Minutes will be exchanged between Orion and the Agency.
2. Orion will submit an IND with the requested information for statistical and biopharmaceutics review.

Signature, minutes preparer:

Concurrence Chair:

Cc:

HFD-120

Katz

Kapcala

Fitzgerald

Roney

Guzewska

Heimann

Wheelous

HFD-8650/AI-Habet

Draft: May16, 2000 \ July 10, 2000 \ July 27, 2000

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11 Page(s) Withheld

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187 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Orion Corporation	DATE OF SUBMISSION 4/16/03
TELEPHONE NO. (Include Area Code) 011-358-10-4291	FACSIMILE (FAX) Number (Include Area Code) 011-358-10-4291-4341
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 65 FIN-02101, Espoo, FINLAND	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Ilkka Larma, M.SC. (Pharm.) 25A Vreeland Road, Suite 100, Florham Park, NJ 07932 Tel: (973) 377-1444 Fax: (973) 377-8814

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-796		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Carbidopa/Levodopa/Entacapone		PROPRIETARY NAME (trade name) IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) See Attachment 1		CODE NAME (If any) OR-611
DOSAGE FORM: Tablets	STRENGTHS: 50/12.5/200 mg-100/25/200mg- 150/37.5/200mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Adjunct to Levodopa in patients with idiopathic Parkinson's Disease

PRODUCT DESCRIPTION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b)(1)	<input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug _____	Holder of Approved Application _____	
TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO PENDING APPLICATION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION FDA's request for information		
PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attachment 2

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See Attachment 3

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) FDA's request for information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

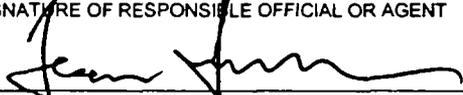
1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT



TYPED NAME AND TITLE

Ilkka Larma, M. Sc. (Pharm.), Vice President, Drug Regulatory Affairs, ORION PHARMA, Inc., USA

DATE:

4/16/03

ADDRESS (Street, City, State, and ZIP Code)

25A Vreeland Road, Suite 100, Florham Park, NJ 07932

Telephone Number

(973) 377-1444

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-39
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFM-94
12420 Parklawn Dr., Room 3045
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

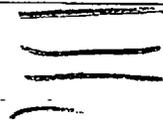
Section 4 - CMC

Question (United States of America) (US015)

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	Specification	Method
		LCE 50	LCE 100	LCE 150	
Levodopa	Sponsor proposed	Q=  at 45 min	Q=  at 45 min	Q=  at 45 min	Apparatus 1 /basket 50rpm 750 ml, 0.1 M HCl, 37° C
	Agency recommends	Acceptable	Acceptable	Q=  at 45 min	Acceptable
Carbidopa	Sponsor proposed	Q=  at 45 min	Q=  at 45 min	Q=  at 45 min	Apparatus 1 /basket 50rpm 750 ml, 0.1 M HCl, 37° C
	Agency recommends	Acceptable	Acceptable	Q=  at 45 min	Acceptable
Entacapone	Sponsor proposed	Q=  at 45 min	Q=  at 45 min	Q=  at 45 min	
	Agency recommends	Q=  at 45 min	Q=  at 45 min	Q=  at 45 min	Acceptable

Response:

Orion Pharma agrees to tighten the dissolution specifications for all three moieties as the Agency recommends. The updated specifications are as follows:

Moiety		Specification	Specification	Specification	Method
		LCE 50	LCE 100	LCE 150	
Levodopa	Proposed specifications in NDA	Q= _____ at 45 min	Q= _____ at 45 min	Q= _____ at 45 min	Apparatus 1 /basket 50rpm 750 ml 0.1 M HCl, 37° C
	Updated specifications	Q= _____ at 45 min	Q= _____ at 45 min	Q= _____ at 45 min	Apparatus 1 /basket 50rpm 750 ml 0.1 M HCl, 37° C
Carbidopa	Proposed specifications in NDA	Q= _____ at 45 min	Q= _____ at 45 min	Q= _____ at 45 min	Apparatus 1 /basket 50rpm 750 ml 0.1 M HCl, 37° C
	Updated specifications	Q= _____ at 45 min	Q= _____ at 45 min	Q= _____ at 45 min	Apparatus 1 /basket 50rpm 750 ml 0.1 M HCl, 37° C
Entacapone	Proposed specifications in NDA	Q= _____ at 45 min	Q= _____ at 45 min	Q= _____ at 45 min	_____ _____ _____
	Updated specifications	Q= _____ at 45 min	Q= _____ at 45 min	Q= _____ at 45 min	_____ _____ _____

This application contains the following items: <i>(Check all that apply)</i>		
<input checked="" type="checkbox"/>	1. Index	
<input checked="" type="checkbox"/>	2. Labeling <i>(check one)</i>	<input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
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<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
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<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
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<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
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<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input type="checkbox"/>	20. OTHER <i>(Specify)</i>	

CERTIFICATION

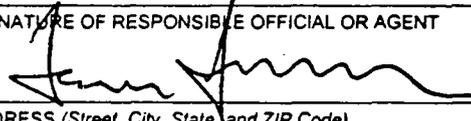
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Ilkka Larma, M. Sc. (Pharm.), Vice President, Drug Regulatory Affairs, ORION PHARMA, Inc., USA	DATE: 4/9/03
ADDRESS <i>(Street, City, State, and ZIP Code)</i> 25A Vreeland Road, Suite 100, Florham Park, NJ 07932		Telephone Number (973) 377-1444

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3C46
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

CHEMICAL NAME

Levodopa: L-Dihydroxyphenylalanine

Carbidopa: Benzenepropanoic acid

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

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT INFORMATION

US regulatory contact: Mr. Ilkka Larina, Vice-President, Drug Regulatory Affairs,
Orion Pharma Inc.
Telephone no. (973) 377-1444 Telefax no. (973) 377-8814

NAMES AND ADDRESSES OF THE MANUFACTURERS

_____ DMF No. _____

Contact: _____

_____ DMF No. _____

Contact: _____

Entacapone drug substance

Orion Corporation Fermion Orion Corporation Fermion
Hanko Plant Espoo Plant
Orioninkatu 2 Koivu-Mankkaantie 6 DMF No. _____
FIN-10900 Hanko FIN-02200 Espoo CFN #FCFI 023
FINLAND FINLAND

Both of these manufacturing facilities are ready for inspection by the FDA.
Contact: Dr. Stig Lindholm, Vice President, Orion Corporation Fermion
Telephone no. +358 10 4291 Telefax no. +358 9 452 1764

Bulk drug product: Orion Corporation ORION PHARMA
Espoo Plant
Orionintie 1 CFN #FCFI 022
FIN-02200 Espoo,
FINLAND

This facility is ready for inspection by the FDA.
Contact: Mr. Esko Taskila, Vice President, Quality Assurance
Telephone: +358 (50) 429 2830 Telefax: +358 (10) 429 3131

Final drug product:
(packaging, labeling and
release)

Novartis Pharmaceuticals Corporation
Suffern plant
25 Old Mill Road
Suffern, New York 10901
USA. CFN #2416082

This facility is ready for inspection by the FDA.
Contact: Mr. Karl Hornung, Head, Quality Assurance
Telephone: (845) 368-6060

**APPEARS THIS WAY
ON ORIGINAL**

CROSS REFERENCES

Drug Substance	Manufacturer	DMF number	Authorization letter date
██████████	██████████	██████████	April 25, 2002
██████████	██████████	██████████	March 25, 2002
Entacapone	Orion Corporation, Fermion, Finalnd	██████████	March 15, 2002
██████████	Manufacturer	DMF number	Authorization letter date
██████████	██████████	██████████	April 18, 2002
██████████	██████████	██████████	Feb. 22, 2002
██████████	██████████	██████████	Feb. 26, 2002
██████████	██████████	██████████	Feb. 22, 2002
██████████	██████████	██████████	Feb. 26, 2002
██████████	██████████	██████████	Feb. 26, 2002
██████████	██████████	██████████	Feb. 19, 2002
██████████	██████████	██████████	Feb. 26, 2002
██████████	██████████	██████████	April 18, 2002
██████████	██████████	██████████	April 18, 2002
██████████	██████████	██████████	Feb. 19, 2002
██████████	██████████	██████████	Feb. 26, 2002
██████████	██████████	██████████	April 18, 2002
██████████	██████████	██████████	April 18, 2002
Type of document	Holder	Reference Number	Subject
IND	Orion Corporation Orion Pharma Orionintie 1 02200 ESPOO FINLAND	# 60, 554	Entacapone Combi - levodopa /carbidopa/entacapone combination tablets 50/12.5/200mg, 100/25/200mg, and 150/37.5/200mg
NDA	Orion Corporation Orion Pharma Orionintie 1 02200 ESPOO FINLAND	# 20-796	Comtan ® (entacapone) 200mg tablet

45 Draft Labeling Page(s) Withheld

CONSULTATION RESPONSE

**Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)**

DATE RECEIVED: Dec. 16, 2002

DUE DATE: March 24, 2003

ODS CONSULT #: 02-0020-2

TO: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Teresa Wheelous
Project Manager
HFD-120

PRODUCT NAME:
Stalevo
(Carbidopa, Levodopa, and Entacapone Tablets)
12.5 mg/50 mg/200 mg,
25 mg/100 mg/200 mg, and
37.5 mg/150 mg/200 mg

SPONSOR: Orion Pharma, Inc.

NDA #: 21-485

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Stalevo" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objection to the use of the proprietary name "Stalevo". Additionally the sponsor should withdraw the proprietary name . DMETS recommends revising the labels and labeling as described in section III of this review. Please forward copies of the final printed labels and labeling when they are available. The firm should be notified that this name with its associated labels and labeling must be re-evaluated 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 28, 2003

NDA NUMBER: 21-485

NAME OF DRUG: **Stalevo**
(Carbidopa, Levodopa, and Entacapone Tablets)
12.5 mg/50 mg/200 mg,
25 mg/100 mg/200 mg, and
37.5 mg/150 mg/200 mg

NDA SPONSOR: Orion Pharma, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products, for an assessment of the proprietary name "Stalevo" regarding potential name confusion with other proprietary or established drug names. The container labels, carton labels, and package insert labeling for Stalevo was reviewed for possible interventions in minimizing medication errors.

This is the third name proposed name for this product. DMETS previously found the primary proposed name '————' unacceptable, and the secondary proposed name '————' acceptable (ODS Consult # 02-0020). However, the sponsor is encountering problems with the global use of the name '————'. The sponsor has indicated, however, that they would like to keep '————' as a possible name, but also requested that the name Stalevo be assessed, with the option of deciding which name to use at a later date.

PRODUCT INFORMATION

Stalevo is a combination of carbidopa, levodopa, and entacapone, and is indicated for the treatment of Parkinson's disease and syndrome. Stalevo is administered orally '————'. Individual tablets must not be fractionated and only one tablet should be administered at each dosing interval. The optimum daily dosage of Stalevo must be determined by careful titration in each patient. It is recommended that the dose be optimized using one of the available tablet strengths. The maximum daily dose of Stalevo is based on the recommendation that the dosage of the carbidopa component should not exceed 200 mg per day and the entacapone component should not exceed 1600 mg per day. This maximum daily dose is equivalent to eight tablets of the 25 mg/100 mg/200 mg dosage strength **OR** five tablets of the 150 mg/37.5 mg/200 mg. Stalevo will be available as a tablet in strengths of 12.5 mg/50 mg/200 mg, 25 mg/100 mg/200 mg, and 37.5 mg/150 mg/200 mg.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databasesⁱⁱⁱ for existing drug names which sound alike or look alike to “Stalevo” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database^{iv} and the data provided by Thomson & Thomson’s SAEGISTM Online Service^v were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Stalevo. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns with Stalevo in regard to promotional claims.
2. The Expert Panel identified three medication names that have potential for confusion with Stalevo. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

ⁱ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

^{iv} WWW location <http://www.uspto.gov>.

^v Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Stalevo	Levodopa, Carbidopa, and Entacapone Tablets 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, and 150 mg, 37.5 mg, 200 mg	Individualized dosage. Maximum per day is 200 mg carbidopa and 1600 mg entacapone.	
Strattera	Atomoxetine Hydrochloride Capsules 10 mg, 18 mg, 25 mg, 40 mg, and 60 mg	<u>Children up to 70 kg:</u> Initially 0.5 mg/kg, and increase after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg in the morning, or in evenly divided doses in the morning and later afternoon/early evening. <u>Adults and Children Over 70 kg:</u> Initiate at a total daily dose of 40 mg and increase after a minimum of 3 days to a target daily dose of approximately 80 mg administered as a single daily dose in the morning or as evenly divided doses in the morning and later afternoon.	**L/A
Stadol	Butorphanol Tartrate Injection 1 mg/mL and 2 mg/mL	<u>Intravenous:</u> 1 mg (dosage range 0.5 mg to 2 mg) repeated every 3 to 4 hours as necessary. <u>Intramuscular:</u> 2 mg (dosage range 1 mg to 4 mg) every 3 to 4 hours as necessary. Do not exceed single doses of 4 mg.	**L/A
Stadol NS	Butorphanol Tartrate Nasal Spray 10 mg/mL	1 mg (1 spray in 1 nostril). If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given. The initial 2 dose sequence may be repeated in 3 to 4 hours as needed.	**L/A
Staticin	Erythromycin Topical Solution 1.5 %	Apply morning and evening to affected areas with fingertips or applicator. Wash hands after use.	**L/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Stalevo with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Stalevo (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of

the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

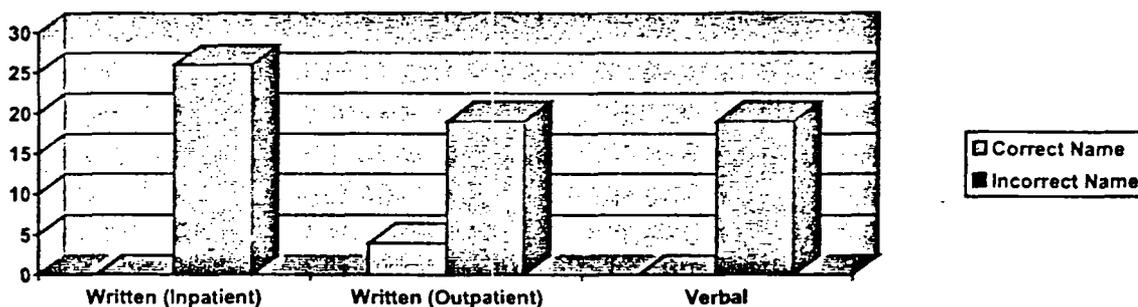
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p>Stalevo 37.5/150 t. q 3^o max: 8/day #200</p>	<p>Stalevo 37.5/150, take 1 every 3 hours to a maximum of 8 per day. Dispense #200.</p>
<p><u>Inpatient RX:</u></p> <p>Increase Stalevo to 100's</p>	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	39	26 (67%)	0	26 (100%)
Written Outpatient	35	23 (66%)	4 (17%)	19 (83%)
Verbal	32	19 (59%)	0	19 (100%)
Total	106	68 (64%)	4 (6%)	64 (94%)



Among the verbal prescription study participants for Stalevo, 100% of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of “Stalevo”. The incorrect responses were *Stelevo (5)*, *Stolevo (3)*, *Stelivo (2)*, *Stilevo (2)*, *Staleevo (1)*, *Stalero (1)*, *Stalivo (1)*, *Stellevo (1)*, *Sileavo (1)*, and *Stolivo (1)*. None of the interpretations are similar to a marketed drug product.

Among the written prescription study participants for Stalevo, 45 of 49 (92%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of “Stalevo”. The incorrect responses were *Staleno (15)*, *Stalevr (4)*, *Stalerio (3)*, *Stalerno (2)*, *Stalens (2)*, *Stalenz (2)*, *Stalever (2)*, *Stalevor (2)*, *Stalesco (1)*, *Stalereo (1)*, *Stalero (1)*, *Stalesso (1)*, *Stallereo (1)*, *Stallno (1)*, *Stallreo (1)*, *Stallvo (1)*, *Stalevir (1)*, *Stalent (1)*, *Stalert (1)*, *Stalev (1)*, and *Staleva (1)*. None of the interpretations are similar to a marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name “Stalevo”, the primary concerns raised were related to three look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Strattera, Stadol, and Staticin.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Strattera, Stadol, or Staticin. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Stalevo. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Strattera and the proposed name Stalevo look similar when written (see page 7). Strattera contains atomoxetine, and is indicated for the treatment of attention-deficit hyperactivity disorder (ADHD). In children up to 70 kg, the initial dose is 0.5 mg/kg, which is increased after a minimum of three days to a target total daily dose of approximately 1.2 mg/kg. In adults and children over 70 kg, the initial dose is 40 mg, which is increased after a minimum of 3 days to a target total daily dose of approximately 80 mg. Strattera is taken as a single daily dose in the morning, or as evenly divided doses in the morning and in the late afternoon or early evening. Both names consist of three syllables, and beginnings of the names differ only by the addition of one letter (“Stra” vs. “Sta”). Additionally, the endings of the names (“tera” vs. “levo”) can look similar when scripted. However, the names differ in number of letters (seven vs. nine). Also, the “tt” letter combination in the name “Strattera” is prominent, and helps to further

distinguish the names from each other when written. Strattera and Stalevo also differ in strength (10 mg, 18 mg, 25 mg, and 60 mg vs. 12.5 mg/50 mg/200 mg, 25 mg/100 mg/200 mg, and 37.5 mg/150 mg/200 mg). Lastly, the dosing for each product is individualized, and titrated, based on the factors such as the patient's weight, and response to the medication. These differences help to minimize the possibility of confusion between the two products.

Strattera

Stalevo

Strattera *Stalevo*

Stadol and the proposed name Stalevo have the potential to look similar (see below). Stadol contains butorphanol, and is indicated for the management of pain, including postoperative and preoperative analgesia, to supplement balanced anesthesia, and for relief of pain during labor. The usual dose of Stadol is 1 mg every 3 to 4 hours as necessary intravenously, and 2 mg every 3 to 4 hours as needed intramuscularly. The usual dose of Stadol NS, the nasal preparation, is 1 mg (1 spray in one nostril), which can be repeated within 60 to 90 minutes if adequate pain relief is not achieved. Both names begin with identical letter combinations ("Sta"), however the endings of the name are clearly distinguishable when written ("dol" vs. "levo"). Stadol and Stalevo also differ in dosage form (solution for injection and nasal spray vs. tablets), strength (1 mg/mL, 2 mg/mL and 10 mg/mL vs. 12.5 mg/50 mg/200 mg, 25 mg/100 mg/200 mg, and 37.5 mg/150 mg/200 mg), and route of administration (intravenous, intramuscular and nasal inhalation vs. oral). These differences, in addition to the differences in the look alike characteristics of the names help to minimize the potential of confusion between Stadol and Stalevo.

Stadol

Stalevo

Stadol *Stalevo*

Staticin has the potential to look similar to the proposed name, Stalevo, because the names share identical letters at the beginning of each name ("Sta"). Staticin contains erythromycin, and is indicated for the topical treatment of acne vulgaris. Staticin is applied to the affected areas with the finger tips or applicator in the morning and in the evenings. However, the endings of the names are clearly different from each other when written ("ticin" vs. "levo"). The products also differ in dosage form (topical solution vs. tablets), route of administration (topical vs. oral), and strength (1.5% vs. 12.5 mg/50 mg/200 mg, 25 mg/100 mg/200 mg, and 37.5 mg/150 mg/200 mg). These differences, in addition to the lack of convincing look-alike characteristics minimize the potential for confusion between Staticin and Stalevo.

Staticin

Stalevo

Staticin *Stalevo*

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container labels, carton labels for Stalevo, DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified the following areas of possible improvement.

A. CONTAINER LABEL

1. The ~~statement~~ statement on all the container labels is more prominent than the ~~statement~~ Please increase the prominence of the ~~statement~~ and likewise, decrease the prominence of the ~~statement~~
2. We note that there are two expressions of strength. Please revise the strength to read in one of the following manners:

~~_____~~
~~_____~~
~~_____~~

~~_____~~
~~_____~~
~~_____~~
~~_____~~

(In the second example, note that the ~~_____~~ is removed from beneath the ~~_____~~

3. Please clarify the need for the ~~_____~~ Generally this tablet quantity is not routinely used for ~~_____~~

B. CONTAINER LABEL (~~_____~~)

See comment A-2.

C. PACKAGE INSERT LABELING

HOW SUPPLIED

Please express the strength ~~_____~~ Additionally, please insert "mg" following each strength. For example, please revise to read ~~_____~~ mg rather than ~~_____~~

IV. RECOMMENDATIONS

- A. DMETS has no objection to the use of the proprietary name "Stalevo".
- B. DMETS recommends implementation of the labeling revisions described in Section III.
- C. DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Tia Harper-Velazquez
3/27/03 11:36:57 AM
PHARMACIST

Alina Mahmud
3/27/03 01:27:13 PM
PHARMACIST

Carol Holquist
3/28/03 08:14:54 AM
PHARMACIST

Jerry Phillips
3/28/03 09:00:07 AM
DIRECTOR

CONSULTATION RESPONSE

**Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)**

DATE RECEIVED: 1-28-2002

DUE DATE:
7-18-2002

ODS CONSULT #:
02-0020

TO: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Teresa Wheelous, Project Manager
HFD-120

PRODUCT NAME:
—— (Primary)
—— (Alternate)
(Carbidopa, Levodopa, and Entacapone Tablets)
12.5 mg/50 mg/200 mg,
25 mg/100 mg/200 mg, and
37.5 mg/150 mg/200 mg

SPONSOR: Orion Pharma, Inc.

NDA # 21-485

SAFETY EVALUATOR: Marci Ann Lee, PharmD

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names '——' and '——' to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proprietary name '——'. DMETS has no objection to the use of the proprietary name '——'. DMETS recommends revising the labels and labeling as described in section III of this review. Please forward copies of the final printed labels and labeling when they are available.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

16 Page(s) Withheld

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this page is the manifestation of the electronic signature.

/s/

Marci Ann Lee
7/16/02 01:59:13 PM
PHARMACIST

Carol Holquist
7/16/02 02:03:12 PM
PHARMACIST

NDA ACTION PACKAGE CHECKLIST

Vol. 1

Application Information		
NDA: 21-485	STALEVO 50, 100,150	
Drug: Levodopa/Carbidopa/ Entacapone Tablets 50/12.5/200, 100/25/200 & 150/37.5/200		Applicant: ORION CORPORATION
RPM: CDR Teresa Wheelous	HFD-120	Phone # 594-5504
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates April 26, 2003		
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input type="checkbox"/> Verified
❖ B Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ C Exclusivity Summary (approvals only)		

Vol. 1

Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	June 9, 2003 – AE vs. AP label comparison
General Information	
❖ E Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE – 4/25/03
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ F Public communications	
• Press Office notified of action (approval only)	() Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ G Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ H Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ I Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ J Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ K Memoranda and Telecons 10/30/00	
❖ L Minutes of Meetings	
• EOP2 meeting (indicate date) – SEE PRE-IND MEETING 3/27/00	
• Pre-NDA meeting (indicate date) 12/20/01	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other: Filing 8/13/02 Pre-IND 3/27/00	
❖ Advisory Committee Meeting N/A	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) N/A	

Vol. 2

Clinical and Summary Information

❖ M Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	
❖ N Clinical review(s) <i>(indicate date for each review)</i>	
❖ O Microbiology (efficacy) review(s) <i>(indicate date for each review)</i> N/A	
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	
❖ O Statistical review(s) <i>(indicate date for each review)</i>	
❖ P Biopharmaceutical review(s) <i>(indicate date for each review)</i>	
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i> N/A	
❖ Q Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	

CMC Information

❖ R CMC review(s) <i>(indicate date for each review)</i>	
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ S Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i> N/A	
❖ CAC/ECAC report	

MODE = MEMORY TRANSMISSION

START=JUN-12 09:29

END=JUN-12 09:37

FILE NO. = 021

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
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***** -FDA/DNDP - ***** 301 594 2958- *****



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: June 12, 2003

To: Pamela Shaneen	Teresa Wheelous
Company: Orion Pharma	From: Division of Division of Neuropharmacological Drug Products
Fax number: (973) 377-8814	Fax number: (301) 594-2859
Phone number:	Phone number: (301) 594-2850
Subject: NDA 21-485 STALEVO APPROVAL LETTER	

Total no. of pages including cover:

Pamela,
The following is a copy of the Stalevo approval letter and labeling. Please confirm receipt of this facsimile.

Thank you,
Teresa

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Wheelous, Teresa A

From: Schaneen, Pamela [Pamela.Schaneen@orionpharma.com]
ant: Friday, March 07, 2003 11:42 AM
To: 'Wheelous, Teresa A'
Subject: RE: NDA 21-485 Entacapone Triple Combination - FDA request for information

Dear Teresa,

I am in receipt of your request and will try to provide you with an answer as soon as possible.

Kind regards,
Pamela Schaneen
Sr. Regulatory Affairs Associate
ORION PHARMA INC

-----Original Message-----

From: Wheelous, Teresa A [mailto:WHEELOUST@cder.fda.gov]
Sent: Friday, March 07, 2003 11:37 AM
To: 'Schaneen, Pamela'
Subject: RE: NDA 21-485 Entacapone Triple Combination - FDA request for information

Pam,

Can you tell me where in the NDA I can locate the following:

Debarment certification: verified that qualifying language was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.

The Debarment Certification that I have, pg. 68 of the NDA, doesn't seem to have a the U.S. agent's signature unless either Inge-Britt Linden or Gunilla Wilen-Rosengvist is not the U.S. agent. Please provide either a new Debarment Certification with the U.S. agent's signature or inform which of the two signatures is the U.S. agent.

Thanks much,
Teresa

-----Original Message-----

From: Schaneen, Pamela [mailto:Pamela.Schaneen@orionpharma.com]
Sent: Wednesday, March 05, 2003 2:55 PM
To: 'Wheelous, Teresa A'
Subject: RE: NDA 21-485 Entacapone Triple Combination - FDA request for information

Dear Teresa,

Thank you for your quick reply and I will forward this request to Finland.

As soon as I hear back from them when we can expect to receive this information, I will contact you.

Kind regards,
Pamela

-----Original Message-----

From: Wheelous, Teresa A [mailto:WHEELLOUST@cder.fda.gov]
Sent: Wednesday, March 05, 2003 2:48 PM
To: 'Schaneen, Pamela'
Subject: RE: NDA 21-485 Entacapone Triple Combination - FDA request for
information

Dear Ms. Schaneen,

My replies follow your questions below.

Teresa

I wish to acknowledge the receipt of your voice mail to me this morning requesting additional information for the Nomenclature Committee regarding STALEVO and

In your voice mail, you had indicated that the Nomenclature Committee would like to receive copies of the container labels and package insert with STALEVO and in place of what has previously been submitted to the Agency in the NDA.

We would like to clarify the following:

Does the Committee want both STALEVO and in place of what was submitted previously?

Please submit with your preferred first choice name. If there is not preferred choice, then submit both.

2. What format does the Committee want this information in: Paper, Electronic (Microsoft Word and PDF Rendition)?

There is not preference, but if you can provide one sooner than the other, then that would be the preferred method.

3. Will copies of these documents be sufficient or do you want to see final printed labels?

Copies are acceptable.

4. How many copies of the requested information would the Committee like to receive?

The committee requires only one copy, but you should also send a copy to the NDA. If you submit the electronic version to the Electronic Document Room, then a paper version is not needed.

We will try to submit this information to you as soon as we receive clarification of the above questions.

Please contact me at (973) 377-1444 if you have any additional requests or

would like to discuss the above with me.

Thank you for your assistance,

Amela Schaneen
r. Regulatory Affairs Associate
ORION PHARMA, INC. USA
(973) 377-1444 (PHONE)
(973) 377-8814 (FAX)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE #1

FACSIMILE TRANSMITTAL SHEET

DATE: 04/15/03

To: Ilkka Larman	From: Merril J. Mille, R.Ph.
Company: Orion Pharma	Division: Division of Neuropharmacological Drug Products, HFD-120
Fax number: 973-377-8814	Fax number: 301-594-2859
Phone number:	Phone number: 301-594-5528
Subject: In-vitro Dissolution methods & specifications	

Total no. of pages including cover: 2

Comments: Specifications for all 3 moieties should be tightened.

Document to be mailed: YES NO

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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= at 45 min	Q= at 45 min	Q= at 45 min	Apparatus 1 /basket 50rpm 750ml, 0.1 MHC1 37°C
	Agency recommends	Acceptable	Acceptable	Q= at 45 min	Acceptable
Carbidopa	Sponsor proposed	Q= at 45 min	Q= at 45 min	Q= at 45 min	Apparatus 1 /basket 50rpm 750ml, 0.1 MHC1 37°C
	Agency recommends	Acceptable	Acceptable	Q= at 45 min	Acceptable
Entacapone	Sponsor proposed	Q= at 45 min	Q= at 45 min	Q= at 45 min	_____ _____ _____
	Agency recommends	Q= at 45 min	Q= at 45 min	Q= at 45 min	Acceptable

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/s/

Merril Mille
4/15/03 02:56:53. PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: March 31, 2003

To: Ilkka Larma	From: Teresa Wheelous
Company: Orion Pharma	Division of Division of Neuropharmacological Drug Products
Fax number: (973) 377-8814	Fax number: (301) 594-2859
Phone number:	Phone number: (301) 594-2850
Subject: NDA 21-485 DMETS Nomenclature Comments for Stalevo	

Total no. of pages including cover:

Ilkka,

The following are OPDRA comments regarding the proposed name Stalevo for NDA 21485:

- A. DMETS has not objection to the use of the proprietary name "Stalevo".
- B. DMETS recommends implementation of the labeling revisions described on the following page.

Document to be mailed: YES NO

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LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container labels, carton labels for Stalevo, DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified the following areas of possible improvement.

A. CONTAINER LABEL

1. The _____ statement on all the container labels is more prominent than the _____. Please increase the prominence of the _____ and likewise, decrease the prominence of the _____.

2. We note that there are _____ Please revise the _____ to read in one of the following manners:

OR

3. Please clarify the need for the _____ Generally this tablet quantity is not routinely used for _____

B. CONTAINER LABEL

See comment A-2.

C. PACKAGE INSERT LABELING

HOW SUPPLIED

Please express the strength with _____ Additionally, please insert "mg" following each strength. For example, please revise to read _____ rather than _____



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE: March 31, 2003

To: Ilkka Larma, M.Sc.	From: Martha R. Heimann, Ph.D.
Company: Orion Pharma, Inc	Division of Division of Neuropharmacological Drug Products
Fax number: (973) 377-8814	Fax number: (301) 594-2858
Phone number: (973) 377-1444	Phone number: (301) 594-5570
Subject: Information request letter for NDA 21-485	

Total no. of pages including cover: 4

Comments: Ilkka:

The points we discussed this morning are covered in the attached information request letter. I am working on the _____ DMF's but do not foresee any problems. We are discussing what to do about foreign inspections, such as the one that was planned for the Teva facility last week, within the Agency.

Sincerely,
 Martha

Document to be mailed: YES NO

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Attachment

Please submit following pre-study bioassays validation study reports:

#2939093

..... Determination of levodopa and carbidopa in human plasma by
Validation Report: Orion Pharma; 28 January 2002. Study
PRE011137.

4. Validation report: Determination of entacapone in human plasma by
Orion Pharma; 30 January 2002 Study PRE011135.

#2939096

REFERENCES

- [1] study no.: 3/01-05.LC, bioanalytical report: „Development and validation of a sensitive method with for determination of levodopa and carbidopa in human plasma“, 31.07.2001, final version
- [2] study no.: 1/01-03.LCE, bioanalytical report: „Determination of levodopa and carbidopa concentrations in human plasma by
..... 03.08.2001, 1st draft

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/s/

Teresa Wheelous :
2/20/03 04:31:27 PM
CSO

MODE = MEMORY TRANSMISSION

START=NOV-05 08:43

END=NOV-06 08:44

FILE NO. = 165

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2002

To: Ilkka Larma	Teresa Wheelous
Company: Orion Pharma	From: Division of Division of Neuropharmacological Drug Products
Fax number: (973) 377-8814	Fax number: (301) 594-2859
Phone number:	Phone number: (301) 594-2850
Subject: NDA 21-485 - Biopharm Information Request	

Total no. of pages including cover:

Ilkka,

Previously we requested the following information, but we are not sure if you have already submitted it. Please provide the following information as soon as possible.

1. Submit additional copy of the selection and justification of proposed different dissolution methods and specifications for 3 active ingredients. The sponsor indicated that they were submitted under CMC section 4 A III 8 the "Validation of the dissolution method for levodopa and carbidopa" and "Validation of the dissolution method for entacapone".
2. Submit additional copy of volume 64, 163-167 where the references for label in the sections of Clinical Pharmacology, drug interactions, and Dosage/Administration are located.
3. Provide in electronic format of the annotated "Microsoft Word" version of proposed label with side-by side comparisons with the approved Sinemet and Entacapone labels.

Please confirm receipt of this facsimile.

Thank you,

Teresa

Document to be mailed: YES NO

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MODE = MEMORY TRANSMISSION

START=AUG-01 16:26

END=AUG-01 16:27

FILE NO. = 070

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-FDA/DNDP

***** - ***** - 3015942859- *****



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: August 1, 2002

To: Ilkka Larma	Teresa Wheelous
Company: Orion Pharma	From: Division of Division of Neuropharmacological Drug Products
Fax number: (973) 377-8814	Fax number: (301) 594-2859
Phone number:	Phone number: (301) 594-2850
Subject: NDA 21-485 DMETS Nomenclature Comments	
Total no. of pages including cover: 3	

Ilkka,

The following are OPDRA comments regarding the proposed names for NDA 21485:

DMETS does not recommend the use of the proprietary name '_____'. We have no objection to the use of the proprietary name '_____'. DMETS recommends revising the labels and labeling as described below.

Please forward copies of the final printed labels and labeling when they are available.

Mr. DEB

COMMENTS TO BE PROVIDED TO THE SPONSOR

DMETS has no objection to the use of the proprietary name, [redacted]
DMETS does not recommend use of the proprietary name, [redacted] See below for a
description of some of the potential look-alike and sound-alike names that were identified.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

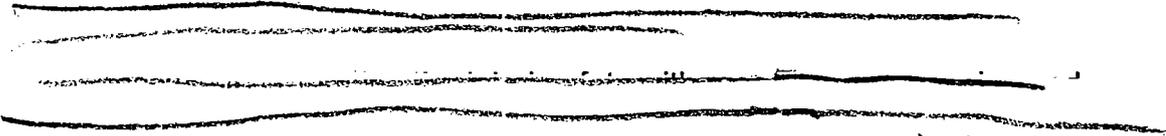
In the review of the container labels, sample container labels/carton labeling and insert labeling for [redacted], DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified the following areas of possible improvement.

A. GENERAL COMMENT

It is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used on the marketplace (i.e. color, placement of name, etc.). Please forward copies of the final printed labels and labeling when they are available.

B. CONTAINER LABEL (12.5 mg/50 mg/200 mg, 25 mg/100 mg/200 mg, and 37.5 mg/150 mg/200 mg)

[redacted]



C. SAMPLE CONTAINER AND CARTON

1. See above recommendations.

D. INSERT LABELING

1. In addition to the statement in DRUG INTERACTIONS, consider adding a statement about the safe use of _____ in patients with biliary obstruction to _____ PRECAUTIONS.
2. Modify the end of the HOW SUPPLIED section to list the manufacturer information for _____, in place of Comtan

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: October 30, 2000

APPLICATION NUMBER: IND 60,554, Comtan Combination Products (entacapone)

FDA Attendees & Titles:

Dr. R. Katz – Division Director
Dr. L. Kapcala – Medical Reviewer
Dr. J. Feeney – Group Leader
Dr. G. Fitzgerald – Pharmacology Team Leader
Dr. P. Roney – Pharmacology Reviewer
Dr. I. Mahmood – Biopharmaceutics Reviewer
Ms. T. Wheelous – Project Manager

Orion Pharm. Attendees & Title:

Dr. Ilkka Larma – Reg. Affairs
Several Finnish Participants

PURPOSE: To discuss the Agency's August 28, 2000, facsimile containing one Biopharmaceutics comment and eight clinical comments regarding the newly proposed Comtan combination protocol, IND 60,554.

DISCUSSION:

The sponsor of this new IND was notified in a July 28, 2000, telephone voice message that the proposed study may proceed. In that voice message the sponsor's representative was informed that there is one biopharmaceutical comment which is to add an additional blood sample at 12 hours post dose and that additional clinical comments would be relayed at a later date (the August 28, 2000, facsimile). Orion responded to the facsimile with a written submission dated, September 11, 2000.

Biopharmaceutics Comment from Facsimile

Orion's response, provided in the September 11, 2000 submission, to the Agency's request to add a blood sample at 12 hours is acceptable.

Clinical Comments from Facsimile

Point #1

Expand the upper age for healthy volunteers beyond 40 years old so that older subjects are also studied. Many patients with PD who would be exposed to this drug are likely to be significantly older than 40. This suggestion had also been made at the time of the Pre-IND meeting. It would be important to study a significant number of older subjects especially in the 60-80 year old range.

- There is an official guidance that issued October 27, 2000 addressing this issue. The guidance (available on the FDA web site) states that if the intended use of the product is predominantly in the elderly, then the sponsor should include as many subjects greater than or equal to 60 years of age as possible.
- Since, the majority of Parkinson's patients are elderly, elderly subjects (≥ 60) should be enrolled in the trial.

- Orion offers the possibility of conducting a separate trial in the elderly and conducting a bioequivalence trial in younger subjects.
- Bioequivalence in the elderly is a requirement for U.S. approval. However, if Orion would like to study only a small number of elderly, given the difficulty in knowing the adequate power for such a small study, then an argument must be provided for review by the division.

Point #2

Collect orthostatic vital sign data to characterize potential orthostatic effects. Ideally, heart and blood pressure should be measured while supine and after standing (at least after 2 minutes) to characterize the maximal potential change. Temperature and ventilatory rate should also be collected along with the heart rate/blood pressure.

- Since T_{max} occurs at one to two hours post dose, orthostatic vital signs (including pulse and blood pressure) should be taken near T_{max} at both one and two hours post dosing. These data might be used as supporting safety information should C_{max} fail slightly on the high side.

Point #3

Study ECGs at 0,1,2 and 9 hours after treatment. T_{max} is most likely expected between 1-2 hours. QTc adjustments to correct QT should be made in view of DNDP recommendations which will be communicated to sponsor.

- Since T_{max} occurs at one to two hours post dose, ECGs would be desirable at both one and two hours after dosing. As applicable to point #2, these data could be used as supporting safety information should C_{max} fail slightly on the high side.

Point #6

Include C_{max} as a primary study endpoint along with AUC₀₋₁₀ for levodopa/carbidopa/entacapone.

- C_{max} should be included as a standard for determining bioequivalence.
- The usual bioequivalence standards are AUC_{0-infinity} and C_{max}.

Separate Preclinical Question

Orion proposes that a high combination Sinemet/Comtan dose should not be included in the mouse carcinogenicity study. A rationale should be provided explaining the reason for waiving the Sinemet/Comtan combination dose. The division will consider the proposal at that time.

Dr. R. Katz
Division Director

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/s/

Teresa Wheelous
5/14/01 03:36:28 PM
CSO

Russell Katz
5/22/01 12:31:10 PM
MEDICAL OFFICER