CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-485

CORRESPONDENCE

ORION PHARMA

April 16, 2003
Page (1) 3

Russell Katz, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Control Room 4008
1451 Rockville Pike, Room 4039
Rockville, MD 20852

RE: **Orion Corporation NDA #21-485**
Combination Tablet of Carbidopa/Levodopa/Entacapone (Stalevo™)
150/37.5/200, 100/25/200, 50/12.5/200 Tablet

FDA's fax of April 15, 2003 from Mr. Merril J. Mille
In-vitro Dissolution Methods and Specifications

Dear Dr. Katz:

Reference is made to the NDA #21-485 for carbidopa/levodopa/entacapone (Stalevo™) tablets submitted to the Agency on June 24, 2002. Mr. Merril Mille, Consumer Safety Officer, had sent us a fax on April 15, 2003 informing us that the proposed dissolution methods for each moiety is acceptable. Mr. Mille had suggested, based on the dissolution profiles from biobatches, the specifications for all three moieties should be tightened.

Orion Pharma agrees to tighten the dissolution specifications for all three moieties as the Agency recommends. The updated specifications can be found on the attached pages.

Should you have additional questions, please feel free to contact the undersigned at (973) 377-1444.

Sincerely yours,

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

Attachments:

ORION PHARMA, INC.
25A Vreeland Rd., Suite 100
Florham Park, NJ 07932, USA

Tel. (973) 377-1444
Fax (973) 377-8814

cc:

1. Mr. Merril Mille (*desk copy*)
   Consumer Safety Officer
   Division of Neuropharmacological Drug Products
   Center for Drug Evaluation and Research (HFD-120)
   Food and Drug Administration
   1451 Rockville Pike, Room 4039, 4th Floor
   Rockville, MD 20852

2. Ms. Teresa Wheelous (*desk copy*)
   Consumer Safety Officer
   Division of Neuropharmacological Drug Products
   Center for Drug Evaluation and Research (HFD-120)
   Food and Drug Administration
   1451 Rockville Pike, Room 4039, 4th Floor
   Rockville, MD 20852

3. Dr. Ramana Uppoor (*desk copy*)
   Biopharm Reviewer
   Division of Neuropharmacological Drug Products
   Center for Drug Evaluation and Research (HFD-120)
   Food and Drug Administration
   1451 Rockville Pike, Room 4039, 4th Floor
   Rockville, MD 20852

ORION PHARMA

Russell Katz, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Control Room 4008
1451 Rockville Pike, Room 4039
Rockville, MD 20852

Re: Orion Corporation, NDA #21-485
Combination Tablet of Carbidopa/Levodopa/Entacapone – (Stalevo™)
150/37.5/200, 100/25/200, 50/12.5/200 Tablet

FDA Fax requests of March 31, 2003 by Ms. Teresa Wheelous
(on behalf of DMETS) and Dr. Martha Heimann/CMC reviewer

Dear Dr. Katz,

Reference is made to the NDA #21-485 for carbidopa/levodopa/entacapone (Stalevo™) tablets submitted to the Agency on June 24, 2002 and to the requests by Ms. Teresa Wheelous and Dr. Martha Heimann on March 31, 2003.

Referring to this request, we have made the following revisions to all Stalevo labeling as follows:

Container Lables

1. The prominence of the [redacted] has been increased and the [redacted] has been decreased.

2. We have revised the [redacted] to now read:

Example

[redacted]

ORION PHARMA, INC.
25A Vreeland Rd., Suite 100
Florham Park, NJ 07932, USA

Tel. (973) 377-1444
Fax (973) 377-8814

3. We have added the following wording under the [redacted]

4. [redacted] has been added to each label

5. [redacted] are on all labels

Container Label – [redacted]

We are enclosing the [redacted] to replace the [redacted] that were previously submitted for review on March 13, 2003.

We have reported the packages with tablet counts of [redacted] 100 and 250 in the CMC section of the NDA.

Colored Package and Container Label Mock-ups

- Colored mock-ups of Stalevo labels as follows:

37.5/150/200 mg strength - includes labels for:

1. 250 Tablet Trade Label
2. 100 Tablet Trade Label
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]

25/100/200 mg strength – includes labels for:

1. 250 Tablet Trade Label
2. 100 Tablet Trade Label
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7.

12.5/50/200 mg strength– includes labels for:

1. 250 Tablet Trade Label
2. 100 Tablet Trade Label
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]

Justification for the [redacted]

[redacted]

Should you have any questions, please contact the undersigned at (973) 377-1444.

Sincerely,

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

Enclosures:

cc: 1. Teresa Wheelous (*desk copy*)
Project Manager
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Food and Drug Administration
1451 Rockville Pike, Room 4039, 4th floor
Rockville, MD 20852

2. Martha Heimann, Ph.D. (*desk copy*)
   Division of Neuropharmacological Drug Products
   Center for Drug Evaluation and Research (HFD-120)
   Food and Drug Administration
   1451 Rockville Pike, Room 4039, 4th Floor
   Rockville, MD 20852

3. Martina Struck, Ph.D. (*letter only*)
   Associate Director
   Novartis Pharmaceuticals Corporation
   59 Route 10
   East Hanover, NJ 07936-1080

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-485

Orion Pharma
Attention: Pamela Schaneen
Sr. Regulatory Affairs Associate
25A Vreeland Road, Suite 100
Florham Park, NJ 07932

Dear Ms. Shaneen:

We acknowledge receipt on May 5, 2003 of your May 2, 2003 resubmission to your new drug application for Stalevo 50 (carbidopa/ levodopa/ entacapone 12.5/50/200), Stalevo 100 (carbidopa/levodopa/entacapone 25/100/200), and Stalevo 150 (carbidopa/levodopa/entacapone 37.5/150/200) Tablets.

We consider this a complete, class 1 response to our April 25, 2003 action letter. Therefore, the user fee goal date is July 5, 2003.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander
Supervisor, Regulatory Health Management Officer
Division of Neuropharmacological Drug Products
Office of Drug Evaluation 1
Center of Drugs Evaluation and Research

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/s/

Robbin Nighswander
5/21/03 10:45:19 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-485

INFORMATION REQUEST LETTER

Orion Pharma, Inc., U.S.
Attention: Mr. Ilkka Larma M.Sc.
Vice President, Drug Regulatory Affairs
25A Vreeland Road, Suite 100
Florham Park, New Jersey 07932

Dear Mr. Larma:

Please refer to your June 24, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stalevo™ (carbidopa, levodopa and entacapone) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We note a discrepancy in the test procedures for [redacted] Under [redacted] listed as the [redacted] The amounts given in the instructions for preparing [redacted] however, are only correct if the [redacted] is used. Please verify [redacted] is actually used and correct the test instructions accordingly.

2. The proposed expiration dating period of [redacted] is not supported by statistical analysis submitted in the application or by sufficient long-term stability data for the primary batches. Based on the statistical analysis and the available primary and supportive stability data we will accept a tentative 24 month expiration dating period. This may be extended as additional real time data is collected. Extension of the expiration dating period may be reported in the next annual report.

3. We note discrepancies between the [redacted] Section 9.3.1) and the [redacted] Appendix 7). Specifically, the [redacted] protocol for each strength indicates that Novartis Pharmaceuticals Corporation commits to [redacted] are not the same. Please clarify.

4. You propose [redacted] Although such a protocol may be proposed after a significant body of stability data is available for commercial production batches, it is not appropriate at this time. Please submit a revised

which conforms to the recommended testing frequency, i.e., at allowed by testing at intervals. When the expiration dating period has been confirmed on commercial production batches, you may submit a prior approval supplement to modify the by deletion of time points.

5. There is a discrepancy between CMC information on package configurations (00 and 250 count) and draft container labeling (00 and 250 count). If you intend to use the count package, please amend the CMC section and provide justification for the change.

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Maryla Guzewska, Ph.D.
Chemistry Team Leader, Neurology Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Maryla Guzewska
3/31/03 02:19:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-485

Orion Pharma
Attention: Ilkka Larma
Vice President, Drug Regulatory Affairs
25A Vreeland Road, Suite 100
Florham Park, NJ 07932

Dear Mr. Larma:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: —— (levodopa/carbidopa/entacapone) Tablets

Review Priority Classification: Standard (S)

Date of Application: June 24, 2002

Date of Receipt: June 26, 2002

Our Reference Number: NDA 21-485

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 24, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 26, 2003 and the secondary user fee goal date will be June 26, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Teresa Wheelous
7/9/02 03:21:01 PM
Teresa Wheelous (for) John S. Purvis