CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-485

CHEMISTRY REVIEW(S)

NDA 21-485

Stalevo™ (carbidopa, levodopa and entacapone) Tablets

Orion Corporation

Martha R. Heimann, Ph.D.
Division of Neuropharmacological Drug Products

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APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. **NDA 21-485**

2. **REVIEW #: 1**

3. **REVIEW DATE: 22-APR-2003**

4. **REVIEWER: Martha R. Heimann, Ph.D.**

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Information Request	21-MAR-2003

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original NDA	24-JUN-2002
Amendment (BL)	13-MAR-2003
Amendment (BC)	04-APR-2003
Amendment (BL)	09-APR-2003
Amendment (BC)	16-APR-2003
Amendment (BL)	21-APR-2003

7. **NAME and ADDRESS OF APPLICANT:**

Name:	Orion Corporation
Address:	P.O. Box 65 FIN-02101, Espoo, Finland
Representative:	Mr. Ilkka Larma, M.Sc. 25A Vreeland Road, Suite 100 Florham Park, NJ 07932
Telephone:	(973) 377-1444 (973) 377-8814

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Stalevo
b) Non-Proprietary Name (USAN): Carbidopa, levodopa and entacapone tablets
c) Code Name/#: LCE
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: S

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9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGICAL CATEGORY:

Treatment of end-of–dose "wearing off" in patients with idiopathic Parkinson's disease.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 12.5 mg/50 mg/200 mg, 25 mg/100 mg/200 mg, and 37.5 mg/150 mg/200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ **Rx** ___ **OTC**

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

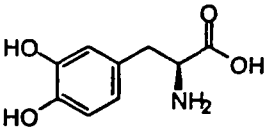
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Levodopa

L-Dihydroxyphenylalanine; (*S*)-(3,4-Dihydroxyphenyl)alanine

Molecular formula: $C_9H_{11}NO_4$

Molecular weight: 197. —

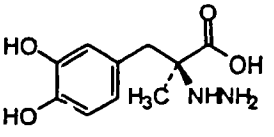


Carbidopa

(*S*)-α-Hydrazino-3,4-dihydroxy-α-methyl-benzenepropanoic acid monohydrate

Molecular formula: $C_{10}H_{14}N_2O_4 \cdot H_2O$

Molecular weight: 244.2 (monohydrate); — (anhydrous)

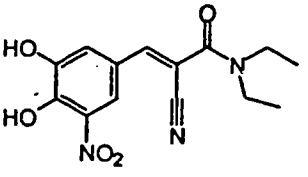


Entacapone

(*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl-*N,N*-diethyl-2-propenamide

Molecular formula: $C_{14}H_{15}N_3O_5$

Molecular weight: 305. —



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	REVIEWED BY/ COMMENTS
[redacted]	II	[redacted]	[redacted]		Adequate	1/13/2003 4/3/2003	D. Maldonado, M. Heimann
[redacted]	II	[redacted]	[redacted]	3, 4	Adequate	10/25/1999	R. Rajagopalan
[redacted]	II	[redacted]	[redacted]	3	Adequate	1/9/2002	M. Zarifa
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/18/2000	S. Kelly
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/19/2000	S. Kelly
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/20/2000	S. Kelly
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/19/2000	S. Kelly
[redacted]	III	[redacted]	[redacted]	3	Adequate	3/24/2000	D. Klein
[redacted]	III	[redacted]	[redacted]	1	Adequate	2/28/2003	M. Heimann
[redacted]	III	[redacted]	[redacted]	3	Adequate	8/10/1999	J. Piechocki

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20,796	Comtan® (entacapone) Tablets
IND	60,554	Carbidopa, levodopa and entacapone combination

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18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	--	--
EES	Overall Acceptable	22-APR-2003	CDER Compliance
Pharm/Tox	Approval	03-MAR-2003	P. Roney, Ph.D., D.A.B.T.
Biopharm	Revision of dissolution criteria is recommended.	14-APR-2003	W. Chou, Pharm.D., Ph.D.
LNC	N/A	--	--
Methods Validation	Pending—request sent on 04-APR-2003		Philadelphia and San Juan District Laboratories
DMETS (formerly OPDRA)	Tradename, Stalevo is acceptable. Revision of container labels was recommended.	27-MAR-2003	T. Harper-Velazquez, Pharm D.
EA	Categorical exclusion	22-APR-2003	M. Heimann, Ph.D.
Microbiology	N/A	--	--

The Chemistry Review for NDA 21-485

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls (CMC) perspective, approval of the application is recommended..

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed product, Stalevo™ Tablets, is a new immediate release, combination tablet containing three previously marketed active agents, carbidopa, levodopa and entacapone, for the treatment of Parkinson's disease. The combination formulation is based on the marketed 25 mg/100 mg strength of carbidopa/levodopa tablets, e.g., Sinemet®, and Comtan® (entacapone) tablets. The product will be marketed in three strengths, which are designated, based on levodopa content, as LCE 50, LCE 100 and LCE 150 in this review. Although all three strengths contain the same inactive ingredients, the tablet formulations are not compositionally proportional. Each strength consists of a 1:4 ratio of carbidopa to levodopa and 200 mg of entacapone. Stalevo Tablets are brownish- or grayish-red film coated tablets which are differentiated by shape and code as indicated below:

- Tablets containing 12.5 mg of carbidopa, 50 mg of levodopa and 200 mg of entacapone are round, bi-convex shaped and [redacted] 'LCE 50" on one side.
- Tablets containing 25 mg of carbidopa, 100 mg of levodopa and 200 mg of entacapone are oval-shaped and [redacted] LCE 100" on one side.
- Tablets containing 37.5 mg of carbidopa, 150 mg of levodopa and 200 mg of entacapone are elongated-ellipse shaped and [redacted] LCE 150" on one side.

Stalevo Tablets will be marketed in 100- and 250-count HDPE bottles with child resistant, tamper-evident closures. [redacted]

Two of the active ingredients of Stalevo™ Tablets, carbidopa, USP and levodopa, USP, are obtained from [redacted] s obtained from [redacted]

and all CMC information is incorporated by cross-reference to Drug Master File (DMF) No [redacted] is obtained from [redacted] CMC information on [redacted] incorporated by cross-reference to DMF No. [redacted]; however, limited information; i.e., test methods and identification of process impurities was duplicated in the NDA submission. Entacapone is manufactured by an Orion Corporation subsidiary, Orion Fermion. DMF No. [redacted] is cross-referenced for CMC information on entacapone.

Carbidopa is slightly soluble in water but dissolve readily in dilute mineral acids. Solubility also increases above pH 7. According to the Biopharmaceutics classification system (BCS), the solubility of carbidopa is considered high. Carbidopa is used as the monohydrate, which exists in a stable crystal form. Although carbidopa is stable as the bulk drug substance, it degrades readily in solution to form [redacted] which is also observed as the primary degradation product in the finished tablet. Carbidopa may undergo Michael addition to entacapone to form additional degradation products. Degradation via this pathway is minimized by the tablet manufacturing process, in which carbidopa and entacapone are [redacted]

Levodopa is slightly soluble in water but solubility increases below pH 3 and above pH 8. According to the BCS, it is classified as Class I, high solubility and high permeability. Anhydrous levodopa, which is used in the manufacture of Stalevo Tablets, exists in a stable crystal form (β-form).

Entacapone is practically insoluble in water, however, solubility is slightly higher above pH 7. The bulk drug substance is [redacted] to enhance bioavailability. Entacapone exists in a stable crystalline form [redacted]

The proposed commercial products are identical to the formulations used in bioequivalence studies presented in the application. No efficacy studies were performed with the triple combination products.

B. Description of How the Drug Product is Intended to be Used

The product is intended for treatment of Parkinson's disease patients who experience end-of-dose "wearing off". Patients currently taking immediate release 25 mg/100 mg (1:4) carbidopa tablets (Sinemet or generic equivalents) with Comtan (entacapone) may be switched directly to the corresponding strength of Stalevo Tablets. The product may also be used as a replacement for 1:4 carbidopa/levodopa therapy in patients who experience "wearing off" by replacing carbidopa/levodopa with the corresponding dose of Stalevo Tablets. The product should not be used as a replacement for therapy with 1:10 ratio carbidopa/levodopa tablets, regardless of whether they are taken with or without entacapone. The maximum recommended daily dose of Stalevo is 8 tablets per day, with no more than one tablet taken at each dosing administration. If necessary, additional carbidopa/levodopa can be added by use of carbidopa/levodopa only products together with a Stalevo tablet.

Based on stability data provided in the application and the sponsor's statistical analysis, a tentative expiration dating period of 24 months, when stored at controlled room temperature (20 - 25°C), is established for all strengths and bottle sizes.

C. Basis for Approvability or Non-Approval Recommendation

From a CMC perspective, the sponsor has provided adequate documentation, either in the original application or in response to information requests made during the review, of the composition of the proposed drug products, control of ingredients, the manufacturing process, control of critical manufacturing steps and control of the finished product. Adequate validation data to support the proposed regulatory methods was provided. The sponsor has agreed to tighten dissolution criteria for all three active moieties, as requested by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). Although the sponsor proposed a longer expiration dating period, the firm has agreed to the expiry proposed by the Agency.

All establishment inspections have been completed. The CDER Office of Compliance issued an overall acceptable recommendation for the application on April 22, 2003.

Although not an issue affecting the approvability of this application, the action letter should contain the standard paragraph regarding cooperation in completing validation of regulatory analytical procedures.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

See electronic signatures in DFS.

C. CC Block

See DFS.

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/s/

Martha Heimann
4/24/03 10:01:05 AM
CHEMIST

Hasmukh Patel
4/24/03 10:50:26 AM
CHEMIST

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