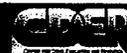


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-479**

**CHEMISTRY REVIEW(S)**



**NDA 21-479**

**ZELAPAR<sup>TM</sup> (selegiline hydrochloride)  
Orally Disintegrating Tablets**

**Valeant Pharmaceuticals International**

**David J. Claffey, Ph.D  
Office of New Drug Quality Assessment**

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On Original*



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P DRUG PRODUCT [Name, Dosage form].....	<b>Error! Bookmark not defined.</b>
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# Chemistry Review Data Sheet

1. NDA 21-479
2. REVIEW #:4
3. REVIEW DATE: 9 June 2005
4. REVIEWER:David J. Claffey, Ph.D.

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	29-MAR-2002
Amendment (BC)	09-SEP-2002
Amendment (BC)	08-OCT-2002
Amendment (NC)	03-MAY-2002
Amendment (BC)	11-JUN-2002
Amendment (BC)	21-JAN-2003
Amendment (BL)	16-MAY-2003
Amendment (BC)	31-OCT-2003
Amendment (BM)	15-DEC-2004
CMC Review #1	31-JAN-2003
CMC Review #2	29-MAY-2003
CMC Review #3	04-JUN-2004

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Ammendment (AL)	13-DEC-2005



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Valeant Pharmaceuticals International  
Address: 3300 Hyland Avenue, Costa Mesa, CA 92626  
Representative: William L. Schary, Ph.D., RAC  
Telephone: 800-548 5100

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) **Proprietary Name:** ZELAPAR™
- b) Non-Proprietary Name (USAN): selegiline hydrochloride
- c) Code Name/# (ONDC only): DRG-0237; FPF1100
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: **Adjunct treatment in Parkinson's patients exhibiting deterioration in their response to levodopa/carbidopa therapy.**

11. DOSAGE FORM: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: 1.25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
          SPOTS product – Form Completed



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

X  Not a SPOTS product

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

(-)-(R)-N- $\alpha$ -Dimethyl-N-2-propylphanethylamine hydrochloride

Mol. Weight: 223.75

Mol. Formula: (C<sub>13</sub>H<sub>17</sub>N).HCl

b(4)

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
					Adequate	23-JAN-2003	Reviewed by M. Guzewska
					Adequate	06-MAY-1999 (original submission) 16-JUL-2002 (update)	Update (stability only) reviewed by M. Zarifa

b(4)

<sup>1</sup> 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")**

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



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	47,005	ng Seleginine Zydys Tablet

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology			

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:

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# The Chemistry Review for NDA 21-479

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

APPROVAL of NDA 21-479 is recommended from a CMC perspective pending an overall acceptable recommendation from the CDER Office of Compliance. It should be noted that only package labeling was evaluated in review; the remainder of the application was found to be adequate in prior reviews.

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

No Phase 4 commitments or risk management steps are indicated from a CMC perspective.

### II. Summary of Chemistry Assessments

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

The drug product, ZELAPAR (selegiline HCl) Orally Disintegrating Tablet (1.25 mg) is a solid dosage form that disperses on the tongue within seconds without the need for water. During manufacture.

It should be noted that different drug product labels will be used at product launch than will be used thereafter. These initial labels will not have incorporated the changes recommended in the AE letter of SEPT 2005 or the forthcoming action letter.

The active ingredient, selegiline hydrochloride is a well known and well characterized drug substance which was first reported in Chem Abstracts in 1965 and patented in 1966 (Netherlands). Selegiline is: (R)-(-)-N,-(-)-dimethyl-N-2-propynylphenethylamine with CAS registry number 14611-51-9. It is a white to almost white crystalline powder. The drug substance is reported to be the R enantiomer only. It is freely soluble in water, chloroform, methanol, and is proposed for the Selegiline hydrochloride drug substance.

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

ZELAPAR (selegiline HCl) Orally Disintegrating Tablet (1.25 mg) will be administered orally. The drug is supplied as tablets in blisters and sachets. Based on stability data provided in DMF an expiration dating period of when stored at 25 °C (77 °F) is established for



**Executive Summary Section**

the 1.25 mg tablets packaged in blisters and sachets. An expiration dating period of three months is established for the tablets packaged in blisters without sachets when stored at 25 °C (77 °F).

**C. Basis for Approvability or Not-Approval Recommendation**

From a CMC perspective, the applicant has provided adequate documentation of the composition of the proposed drug product, control of ingredients, the manufacturing process, and control of the finished product. Stability data are adequate to support the proposed expiration periods. The sponsor provided an adequate response (N-BC, 21 OCT 203) to a request to establish an ~~\_\_\_\_\_~~ specification (CMC review #3). Establishment inspections were not complete at time of completion of this review; therefore an overall approval recommendation from a CMC perspective was made pending an acceptable compliance recommendation.

**b(4)**

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

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David Claffey  
6/14/2006 01:12:26 PM  
CHEMIST

Ramesh Sood  
6/14/2006 01:32:45 PM  
CHEMIST

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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120  
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

**NDA 21-479**

CHEM. REVIEW #3

REVIEW DATE 4 JUN 2004

SUBMISSION TYPE  
ORIGINAL  
AMENDMENT N-BC

DOCUMENT DATE  
29-MAR-2002  
31-OCT-003

CDER DATE  
08-APR-2002  
3-NOV-2003

ASSIGNED DATE  
  
17-MAR-2004

**NAME AND ADDRESS OF APPLICANT:**

Valeant Pharmaceuticals International  
3300 Hyland Avenue  
Costa Mesa, CA 92626

**DRUG PRODUCT NAME**

Proprietary:  
Nonproprietary/USAN:  
Code Name/Number:  
Chem. Type/Ther. Class:

ZELAPAR™  
selegiline hydrochloride  
DRG-0237; FPF1100

**PHARMACOLOGICAL CATEGORY/INDICATION**

Adjunct treatment in Parkinson's patients  
exhibiting deterioration in their response to  
levodopa/carbidopa therapy.

**DOSAGE FORM**

**STRENGTHS**

**ROUTE OF ADMINISTRATION**

**DISPENSED**

**SPECIAL PRODUCTS**

Orally Disintegrating Tablets

1.25 mg

Oral

RX

OTC

Yes

No

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA**

(-)-(R)-N- $\alpha$ -Dimethyl-N-2-propylphanethylamine  
hydrochloride

Mol. Weight: 223.75

Mol. Formula: (C<sub>13</sub>H<sub>17</sub>N).HCl

CAS Registry 14611-51-9

b(4)

**SUPPORTING DOCUMENTS:**

**RELATED DOCUMENTS:**

**CONSULTS:**

**REMARKS/COMMENTS:** This amendment is in response to a commitment by the sponsor (21 JAN 2003) to develop a ~~new~~ HPLC assay method for the drug product, and to establish a specification for ~~the drug product~~ in Zelapar Orally Disintegrating Tablets unless ~~the sponsor~~ is demonstrated to be insignificant during manufacture of the tablets and on storage. The sponsor was reminded of this commitment in an approvable letter dated 7-FEB-2004. An analytical method with a detection limit of ~~0.1 mg/g~~ for the ~~drug product~~ was developed and validated (no details on validation provided) ~~for the drug product~~ patch of drug substance ~~and~~ recent lots of drug product, and ~~lots of drug product on stability study (25°C/60%RH)~~ were analyzed. ~~The drug product~~ was not detected in any of these samples. The sponsor states that this demonstrates that ~~the drug product~~

b(4)

b(4)

b(4)

**CONCLUSIONS & RECOMMENDATIONS:** This response is acceptable as it meets the requirements of the ICH guidance on stereospecific testing (Q6A).

David J. Claffey, Ph.D., Chemist

cc: Orig. NDA 21-479  
HFD-120/Division Files  
HFD-120/DClaffey  
HFD-120/TWheelous  
HFD-120/MGuzewska  
R/D Init by: MEG

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Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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David Claffey  
6/8/04 09:45:15 AM  
CHEMIST

Maryla Guzewska  
6/8/04 09:47:23 AM  
CHEMIST

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**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

**NDA#: 21-479**

**CHEMISTRY REVIEW: # 2**

**DATE REVIEWED: 29-MAY-03**

<b>Submission Type</b>	<b>Document Date</b>	<b>CDER Date</b>	<b>Assigned Date</b>
ORIGINAL	29-MAR-02	08-APR-02	
AMEND. N-BL	16-MAY-03	19-MAY-03	25-MAY-03

**NAME AND ADDRESS OF APPLICANT:** Elan Pharmaceuticals, Inc.  
7475 Lusk Blvd.  
San Diego, CA 92121

**DRUG PRODUCT NAME:**  
**Proprietary:** ZELAPAR™  
**Nonproprietary/Established/USAN:** selegiline hydrochloride  
**Code Name/#:** DRG-0237; FPF1100  
**Chem. Type/Therapeutic Class:** 3 S

**DESI/PATENT STATUS:**

**PHARMACOLOGICAL CATEGORY / INDICATION:** Adjunct treatment in Parkinson's patients who are exhibiting deterioration of their response to levodopa/carbidopa therapy

**DOSAGE FORM:** Orally Disintegrating Tablets  
**STRENGTH(S):** 1.25 mg  
**ROUTE OF ADMINISTRATION:** Oral  
**DISPENSED:** XX Rx      \_\_\_ OTC  
**SPECIAL PRODUCTS:** No

**CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:**

(-)-(R)-N- $\alpha$ -Dimethyl-N-2-propylphenethylamine hydrochloride  
Molecular Formula: C<sub>13</sub>H<sub>17</sub>N HCl  
Molecular Weight: 223.75

**SUPPORTING DOCUMENTS:** DMF ~~IND 47,005 (Selegiline Zydys Tablet)~~ DMF

**RELATED DOCUMENTS:** N/A

**CONSULTS:** MV (To be submitted), DMETS-ODS for Revised Container Labeling, submitted 28-MAY-03 (Pending)

**REMARKS / COMMENTS:** This submission provides revised container labeling for Zelapar (selegiline HCl) Orally Disintegrating Tablets. This labeling reflects changes recommended in the February 7, 2003 AE letter.

**CONCLUSIONS AND RECOMMENDATIONS:** The revised container labeling is acceptable form a CMC perspective. Note that the DMETS-ODS evaluation of the revised container labeling is pending.

cc: Orig. NDA 21-479  
HFD-120/Division File  
HFD-120/DChristodoulou  
HFD-120/TWheelous  
HFD-120/MGuzewska/R/D Init.by: MG  
HFD-810/JSimmons

Danae D. Christodoulou, Ph.D., Review Chemist

Filename: N21479.N-BL.doc

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Maryla Guzewska  
6/17/03 11:12:06 AM  
CHEMIST

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**NDA 21-479**

**ZELAPAR™ (selegiline hydrochloride)  
Orally Disintegrating Tablets**

**Elan Pharmaceuticals, Inc.**

**Mona Zarifa, Ph.D.  
Haripada Sarker, Ph.D.**

**Division of Neuropharmacological Drug Products**

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# CHEMISTRY REVIEW

Chemistry Assessment Section

## Chemistry Review Data Sheet

1. NDA 21-479  
2. REVIEW #1  
3. REVIEW DATE: January 31, 2003  
4. REVIEWER: Mona Zarifa/Haripada Sarker  
5. PREVIOUS DOCUMENTS: N/A  
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	29-MAR-02
Amendment (BC)	09-SEP-02
Amendment (BC)	08-OCT-02
Amendment (NC)	03-MAY-02
Amendment (BC)	11-JUN-02
Amendment (BC)	21-JAN-03

7. NAME & ADDRESS OF APPLICANT:

Name: Elan Pharmaceuticals, Inc.  
Address: 7475 Lusk Blvd., San Diego, CA 92121  
Representative: Donald G. Grilley, Director, Regulatory Affairs  
Telephone: (858)-457-7457

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zelapar®  
b) Non-Proprietary Name (USAN): Selegiline hydrochloride  
c) Code Name/# (ONDC only): DRG-0237; FPF1100;  
d) Chem. Type/Submission Priority (ONDC only):

b(4)

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Eldepryl Tablets, 5 mg by Somerset Pharmaceuticals, approved June 5, 1989.  
10. PHARMACOL. CATEGORY: Adjunct treatment in Parkinson's patients who are exhibiting deterioration of their response to levodopa/carbidopa therapy  
11. DOSAGE FORM: Orally Disintegrating Tablets  
12. STRENGTH/POTENCY: 1.25 mg  
13. ROUTE OF ADMINISTRATION: Oral  
14. Rx/OTC DISPENSED:  Rx  OTC  
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:  
 SPOTS product - Form Completed  Not a SPOTS product  
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**(-)-(R)-N, alpha-Dimethyl-N-2-propynylphenethylamine hydrochloride and its structural formula is:**

b(4)

**Its empirical formula is C<sub>13</sub>H<sub>17</sub>N HCl, representing a molecular weight of 223.75.**

# CHEMISTRY REVIEW

## Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
				7	Adequate	23-JAN-03	Reviewed by M. Guzewska
					Adequate	06-MAY-99 (original submission) 16-JUL-02 (update)	Update (stability only) reviewed by M. Zarifa

b(4)

<sup>1</sup> 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")

<sup>2</sup> 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
IND	47,005	mg Selegiline Zydis Tablet

b(4)

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Approvable	16-JAN-03	Fanhui Kong
EES	Acceptable	07-NOV-02	S. Adams, Office of Compliance
Pharm/Tox	N/A	N/A	N/A
Biopharm	Acceptable with Phase 4 Commitments	17-JAN-03	Veneeta Tandon
LNC	ZELAPAR (selegiline hydrochloride) Orally Disintegrating Tablets, or ZELAPAR (selegiline hydrochloride orally disintegrating tablets)	27-JAN-03	Daniel Boring
Methods Validation	MV request will be sent after receiving corrections to the MV package		Haripada Sarker
DMETS, ODS	No objections to the use of the proprietary name ZELAPAR. Recommendations for revisions to container labels and PI were communicated to the sponsor on 7/15/2002.	05-JUL-02	Scott Dallas
EA	N/A Categorical Exclusion claim is acceptable	13-JAN-03	Nancy Sager
Microbiology	Approval	13-JAN-03	Bryan Riley



## CHEMISTRY REVIEW

### Chemistry Assessment Section

It is freely soluble in water, chloroform, methanol, \_\_\_\_\_  
\_\_\_\_\_ is proposed for the Selegiline hydrochloride drug  
substance.

b(4)

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## CHEMISTRY REVIEW

### Chemistry Assessment Section

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

ZELAPAR (selegiline HCl) Orally Disintegrating Tablet (1.25 mg) will be administered orally. The drug is supplied as tablets in blisters and sachets. Based on stability data provided in DMF ~~an~~ an expiration dating period of ~~6 months~~ when stored at 25 °C (77 °F) is established for the 1.25 mg tablets packaged in blisters and sachets. An expiration dating period of three months is established for the tablets packaged in blisters without sachets when stored at 25 °C (77 °F).

b(4)

#### C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, the applicant has provided adequate documentation of the composition of the proposed drug product, control of ingredients, the manufacturing process, and control of the finished product. Stability data are adequate to support the proposed expiration periods. Establishment inspections have been completed, and an overall acceptable compliance recommendation was received (refer to page 8 of this review).

### III. Administrative

#### A. Reviewer's Signature

See electronic signature in Division File System (DFS)

#### B. Endorsement Block

See electronic signatures in DFS

#### C. CC Block

See DFS

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Maryla Guzewska  
2/4/03 03:10:18 PM  
CHEMIST

Maryla Guzewska  
2/4/03 03:12:35 PM  
CHEMIST

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